Procedure-specific postoperative pain treatment

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Procedure-specific postoperative pain treatment

Procedure-specifieke postoperatieve pijnbehandeling

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PART I

Introduction

CHAPTER 1

General introduction

Postoperative pain remains a major problem, as many surgical patients still suffer from severe pain after surgery, which, in turn, contributes to both short- and long-term negative outcomes. In addition to the unpleasantness of feeling pain and possible dissatisfaction with suboptimal pain treatment, patients with severe postoperative pain are at higher risk to develop postoperative morbidity from pulmonary and cardiac complications.[1–3] Delayed postoperative ambulation due to pain can increase both length of hospital stay and hospital readmissions, and consequently increases health-care costs. Furthermore, severe acute pain has been identified as a relevant risk factor for the development of chronic postoperative pain.[4] Much research on this association has been performed in recent years, but the pathophysiology is not completely understood und preventive pain treatment strategies have produced contradictory results. Thus, successfully preventing the development of chronic postoperative pain syndromes is one of the major challenges of perioperative pain treatment.

In the last two decades, many new strategies to control postoperative pain were developed and their efficacy has been evaluated using various study designs. A number of co-analgesics such as pregabalin, gabapentin, ketamine, corticosteroids, and magnesium were analyzed in the setting of various surgical procedures. Regional analgesia was enhanced by new techniques such as local anesthetic infiltration of the wound using catheters and additional types of blocks such as the transversus abdominis plane block. The ever increasing resolution of ultrasound imaging to locate neural structures has improved the success rate of regional anesthesia. Furthermore, the quality of acute pain services has increased and in many hospitals improved processes are now in place such as routine documentation of pain scores and wider use of patient-controlled analgesia (PCA).

Whenever possible, "multimodal" or „preventive" analgesia, a combination of various systemic, local, and regional pain treatments, is regarded as the most favorable method due to the additive and synergistic effects that reduce the need for analgesic drugs and, consequently, side effects.[5] However, as many combinations of non-medicinals (e.g. cold packs, transcutaneous nerve stimulation or acupuncture), analgesic medication, and regional anesthesia techniques are possible, only a few types of surgery have been well studied to determine the best combination. Risks and costs must also play a role in decision-making.

Altogether, despite all the efforts to date, many studies indicate that large numbers of patients still suffer from severe postoperative pain.[6,7] and that outcomes have improved only slightly over the last years.[6]

What problems need to be dealt with to further improve postoperative pain therapy?

Several issues are still unclear and we need to identify the knowledge gaps that impede improvement of the structures and processes needed for optimal postoperative pain management.

A number of trials have shown that medical staff tend to underestimate the pain the patient is experiencing,[8,9] and newer literature confirms that this problem has not improved in recent years.[10] A major difficulty is the fact that medical staff are often uncertain as to the average painfulness of a particular type of surgery. Although guidelines have been given for some specific surgical procedures, for most operations the level of postoperative pain has never been studied. The majority of studies focused mainly on the surgeries that are most frequently performed or are known to produce severe pain. For instance, a review in 2008 identified 247 randomized, controlled trials (RCTs) dealing with pain treatment following knee-replacement surgery.[11] Similarly, numerous RCTs have been done for pain after cesarean section, another common type of surgery. However, the information regarding acute pain intensity, morphine consumption, and pain-treatment options after internal fixation of the elbow [12] or calcaneus [13] is scarce and of low quality. In addition, a major obstacle in comparing postoperative pain studies are the varied definitions of pain intensity employed. Average pain, lowest pain, worst pain, pain during movement or during coughing, and measurements at various postoperative time points (from directly after the procedure to several days after surgery) makes comparison of the study results problematic.

The most important determinant for postoperative pain is the type of surgery. Therefore, procedure-specific recommendations for pain treatment were developed. These have resulted in pain-treatment proposals such as the Dutch,[14] Australian,[15] American,[16] or German guidelines [17] and those from the PROSPECT project.[18] Although the degree of adherence to these guidelines in daily practice is not known, it is well known from other examples that full implementation of such recommendations takes a long time and is often inadequate. Furthermore, it is difficult to estimate how long moderate-to-severe postoperative pain continues

in order to decide whether, for instance, a costly PCA pump rather than oral analgesics or a peripheral pain catheter instead of single-shot regional anesthesia is indicated.

Only a few cohort studies exist on acute postoperative pain in daily clinical practice for specific types of surgery. Larger cohort studies have analyzed only mixed surgical groups.[7,19–21]using predictors that can be easily documented in a preoperative setting. A cohort of surgical inpatients (n=1416 While our knowledge of the pain intensity associated with specific types of surgeries is mainly based on the results of RCTs, these studies may lead to the impression that certain types of surgery are not particularly painful due to relatively low measured pain scores. Failure to consider the artificial setting of such trials can contribute to reluctant administration of analgesics in daily practice. Close monitoring of the patient, rapid access to the study drug and availability of rescue medication (PCA is often provided to both the control and intervention group even for surgeries that do not normally receive this device), and exclusion of patients with comorbidities, opioid use, or drug addiction may all contribute to considerable underestimation of the average pain experienced by patients in a regular postoperative ward setting.

Some risk factors for severe postoperative pain have been proposed, but clear conclusions cannot be drawn from these studies,[19,22] and it is unclear whether pain treatment should be modified based on their findings. There is some evidence that younger age might be related to more severe pain, while only dichotomous analyses of age categories have been performed so far. Female gender is regularly cited as an important risk factor, but definitive evidence is still lacking. A meta-analysis of experimental pain studies including 172 RCTs could not confirm a significant gender difference.[23] The question whether pain treatment should be gender-adapted is still unanswered, in part because we are not adequately informed about the situation in daily practice. A high level of preoperative pain has been described in some studies as a risk factor for more severe postoperative pain, but other studies could not confirm this relation.

Longer duration of surgery is presumed to increase pain intensity, possibly because of more extensive tissue damage or longer duration of noxious spinal cord stimulation. However, this hypothesis is mainly derived from large cohort studies with heterogeneous groups of operations.[20,21,24]and pain relief was defined as a

visual analog scale score of 30 mm or less. Patients were divided into two groups: young and elderly (age > or = 70 yr Such a relation appears plausible, as longer-lasting surgeries are indeed often associated with more extensive tissue damage. However, it is unknown whether the duration of surgery within a specific surgical group can make a difference in terms of pain intensity.

To achieve optimal pain treatment it is important to clearly specify the aims of such treatment, in particular all desired outcomes, because optimal pain treatment comprises much more than simply reducing patient-reported pain scores. The efficacy of analgesics can be measured, for example, by the number needed to treat (NNT) for a 50% reduction of pain intensity or the time until analgesic rescue medication is requested. There are, however, other desired outcomes of postoperative pain treatment such as minimizing side effects (nausea, vomiting, itching, and dizziness), ability for deep breathing to prevent atelectasis, achieving pain levels that enable ambulation, or a good quality of sleep. Thus, the outcome quality of pain treatment is complex, and no score has yet been developed that reliably indicates the overall quality of postoperative pain therapy.
There is no consensus as to the target pain intensity that should be aimed for after surgery. Many different, arbitrarily-defined cut-off values have been applied in clinical studies, but it is questionable whether those values all correspond to the wish of the patient for more analgesics. In any case, using different end points among studies impairs comparison of their results.

To obtain answers to these questions, a comparison of all kinds of surgical procedures is needed. Two projects, the "Quality Improvement of Postoperative Pain Treatment" (QUIPS)[25] and the European project from 14 countries "Improvement in Postoperative PAIN OUTcome" (PainOut)[26] have been used for analysis. Validated questionnaires are filled in by the patient on the first postoperative day and information about surgery, anesthesia, and pain treatment are collected.

OBJECTIVES OF THIS THESIS

The aims of this thesis are:

- To give an overview of one of the serious consequences of acute pain – the transition to chronic pain.
- To measure and rank pain intensity in a large number of surgical groups in order to define the surgical groups where pain treatment is insufficient and those where pain control is adequate.
- To determine possible reasons for inadequate pain relief
  - to identify patient and surgical factors that are associated with postoperative pain intensity
  - to analyze whether their influence is dependent on the type of surgery.
- To obtain a better insight into patient's pain perception and the impact of acute pain by analyzing different pain outcome variables next to pain intensity

OUTLINE OF THIS THESIS

Acute postoperative pain is known to be the most important risk factor for the development of chronic postoperative pain. **Chapter 2** reviews the transition from acute to chronic postoperative pain and its consequences.

Chapter 3 describes and compares pain intensity, pain treatment, and anesthesia technique of 179 different surgical groups.

In **Chapter 4,** more than 800 cesarean-section patients are analyzed and compared to more than 2,400 hysterectomy patients with respect to anesthesia and analgesic techniques, to identify potential causes of insufficient pain treatment after cesarean section.

In **Chapter 5** the procedure-specific influence of gender, age, and preoperative chronic pain intensity on postoperative pain scores is investigated using the 30 most frequently performed surgeries involving over 22,000 patients.

Chapter 6 further examines the potential role of gender in the development of postoperative pain. In addition to pain intensity, other relevant outcomes such as wish for more analgesics or pain-related interferences are used to indicate the clinical relevance of gender-specific pain perception.

Chapter 7 analyzes the influence of the duration of surgery on postoperative pain.

In **Chapter 8,** the factors influencing satisfaction with postoperative pain treatment are analyzed based on data from the PainOut registry.

Chapter 9 aims to define optimal cut-off values to divide the 11-item numeric rating scale (NRS 0-10) of postoperative pain intensity into three frequently used categories (mild, moderate, and severe pain).

In **Chapter 10** results of the studies are discussed and directions for improvement and future studies on postoperative pain treatment are outlined.

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CHAPTER 2

Transition from acute to chronic postsurgical pain. Physiology, risk factors, and prevention

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ABSTRACT

Chronic post-surgical pain (CPSP) is defined as pain persisting for longer than 3 months postoperatively. The incidence ranges from 5 % to 60 % in all types of surgery, and 1%-3 % of patients with CPSP will suffer from severe pain and pain-related interference with daily activities. The pathological mechanisms that lead to the development of CPSP are complex and have not yet been analyzed. Neuropathic pain after surgical nerve lesions has been reported. Many patients with CPSP, however, do not present with any neuropathic pain characteristics. Peripheral and central sensitization are the essential mechanisms of pain chronification in the postoperative period. As treatment of CPSP is demanding, attempts should be made to prevent central sensitization before CPSP develops. New scientific findings on the development of CPSP, perioperative risk factors, and the potential use of preventative interventions are discussed.

INTRODUCTION

Chronic post-surgical pain (CPSP) represents a major health-economic problem. Nearly 15 million operations are performed annually in Germany; it is estimated that 1%-3% of patients will experience severe pain-related impairment postoperatively. While certain procedures are associated with a significantly higher risk of producing persistent pain, CPSP can occur after any operation. Since the treatment of CPSP is frequently difficult once it has developed, its prevention is of particularly great importance.

Definition

Various synonyms have been used to describe chronic pain following surgery:

- "chronic postsurgical pain (CPSP)",
- "chronic postoperative pain (CPOP)", or
- "persistent postoperative pain (PPP)".

Individual names have also become established for subgroups, such as „post-thoracotomy pain" or post-sternotomy pain". Phantom and stump pain after amputations are also categorized as forms of CPSP.

There is no generally recognized definition of CPSP at present. The purely time-related definition as pain persisting for more than 3, 6, or 12 months following surgery is too simple to characterize the multidimensionality and complexity of the pain-chronification process. In 2001, Macrae[1] defined CPSP as pain

1. that originates after an operation,
2. persists for more than 2 months after an operation,
3. for which other causes have been excluded, and
4. is not the result of a continuing, pre-existing problem.

Recent studies have recommended using a time frame of 6 or even 12 months, since postoperative pain can prove to be self-limiting even after many months.

Table 1. Incidence of severe postoperative pain and CPSP and percentage of neuropathic pain associated with CPSP

Severe acute post-operative pain[a] (%)	CPSP (%)	Neuropathic pain with CPSP (%)	Severe acute post-operative pain[a] (%)
Lower leg ampuation	23	50-80	80
Mamma-Ablation	12	47	65
Thoracotomy	23	25-60	45
Sternotomy	25	7-17	-
Lung transplantation	-	18	-
Knee replacement	28	13	6
Inguinal hernia	12	10	80
Mamma augmentation	30	10	38
Cesarean sectio	33	5-10	50
Craniotomy	11	7-30	25
Melanom resection	-	9	-

[a] Percent of patients with pain score > 8 on the numeric rating scale (NRS) during the first 24 h after surgery (analysis of the German QUIPS data bank with 120 participating German hospitals). CPSP=chronic postsurgical pain; QUIPS=Quality Improvement in Postoperative Pain Therapy.

EPIDEMIOLOGY

The incidence of CPSP has been reported as 5%-60%, depending on the surgical procedure. Severe, disabling CPSP occurs in 1%-10% of cases, independent of the type of procedure. The incidences associated with individual operations vary considerably, however, in particular because different definitions of CPSP are applied. For example, postoperative time frames of 3, 6, or 12 months are examined, and pre-existing preoperative pain has often not been excluded.

A large, cross-sectional population study showed a 40% prevalence of CPSP after surgeries during the past 3 years. [2] On average, 20% of patients in German pain clinics indicated that their chronic pain had been caused, among other things, by a surgical procedure.

Over the last few years, a wide range of operations has increasingly been studied in regard to CPSP. It has become apparent that CPSP is a complication that can occur after virtually every surgical procedure, including minor interventions such as melanoma resection (CPSP-Incidence: 9% [3]). Early studies of CPSP in children revealed an incidence of 13% [4]. Numerous studies, however, examined only the incidence, but not pain intensity or pain-related impairment due to CPSP. Future research must also investigate the degrees of pain chronification more closely in

order to permit a better evaluation of preventive measures. The incidences of CPSP associated with a variety of surgical procedures are shown in Table 1.

PATHOPHYSIOLOGY

The mechanisms involved in the development and persistence of CPSP are complex and are only partly understood at the present time. Procedure-related injuries to tissues and nerves are the main causes of CPSP. Neuropathic pain, persistent inflammatory reactions, and peripheral and central sensitization can lead to pain that lasts far beyond the normal phase of wound-healing.

Neuropathic pain

The incidence of neuropathic pain varies markedly among different operations. The variance is due in part to the differing methods of history-taking and examination for neuropathic pain [6]. In order to standardize the neuropathic component of CPSP, studies employ either a screening questionnaire for neuropathic pain or quantitative sensory testing (QST).

A survery of more than 2,000 patients after a variety of operations showed an incidence of CPSP of 40%, with 22% of the patients reporting mild, 11% moderate, and 7% severe pain.[2]

Hypoesthesia and/or hyperesthesia of the surgical scar area persisted in 25% of cases, and these were the most relevant independent risk factors for CPSP: 55% of patients with hypoesthesia, 72% with hyperesthesia, and 89% with a combination of hypo- and hyperesthesia reported having CPSP. However, 30% of patients with CPSP did not show any somatosensory dysfunction at the surgical site.[2] In addition, not all persisting postoperative somatosensory disorders were associated with CPSP: 20% of patients who had undergone hernia repair, 43% who had had a sternotomy, and 38% who had had augmentation mammoplasty had neural disturbances without persistent pain.

In addition to mechanically-caused neuropathies, an inflammatory-immunologic component of CPSP has also been under discussion. Superficial sensory nerves were biopsied in 21 CPSP patients with postoperative neuropathies after various operations without evidence of intraoperative mechanical nerve lesions.[7] Post-surgical inflammatory neuropathies were identified in all cases. A further indication of an inflammatory-immunologic process is the low prevalence and

intensity of CPSP after lung transplantation as opposed to lung resection. It has been proposed that this could be due to the immune-suppressive medication used following transplantation. The significance of the inflammatory-immunologic reaction on CPSP and the frequency with which post-surgical inflammatory neuropathies resp. neuropathic pain develop is not known at present.

Peripheral sensitization

Peripheral sensitization is defined as increased sensitivity of peripheral nociceptive neurons that develops following a tissue lesion. It is caused by various mediators, neurotransmitters, and molecules such as ATP, nitrogen monoxide, histamine, bradykinin, and pro-inflammatory cytokines that are released by the injured tissue. These substances lower the stimulation threshold and lead to signal amplification, which results in the clinical finding of .primary hyperalgesia, or increased sensitivity to painful stimuli at the surgical site. Over time, adjacent nociceptors that did not previously respond to mechanical stimuli can suddenly begin to transmit painful impulses as well.

Central sensitization

Central sensitization is an amplification of neuronal signals in the central nervous system (CNS) that produces hypersensitivity to pain.[8] Nociceptive stimuli due to tissue trauma normally trigger a reversible hyperexcitability of the CNS. At the spinal level there is increased excitability of the dorsal-horn neurons, which is intensified in particular by substance P and glutamate. This can lead to short-term changes at the synapses, such as phosphorylation of the ion channels and receptor proteins, but also to long-term changes due to alterations of gene expression, which in turn have been proposed as a basis for spinal long-term potentiation (LTP). LTP at the dorsal-horn synapses is closely linked to hyperalgesia, and is a principal focus of scientific research aimed at finding new ways of preventing and treating chronic pain.[8,9]

The descending pain-inhibitory system, which arises in the periaqueductal gray matter of the midbrain cavity and transmits its antinociceptive effect via the reticular nuclei and the locus caeruleus to the interneurons in the dorsal horn, also plays an important role in the development of CPSP. The function and effectiveness of this endogenous pain-inhibiting system can be assessed by means of the Conditioned Pain Modulation (CPM) paradigm, which was formerly called "diffuse noxious inhibitory control" (DNIC). A painful stimulus - the conditioned

stimulus that activates endogenous pain inhibition - is applied to one side of the body. A second painful stimulus, the test stimulus, is then applied at a different site. It has been demonstrated that in patients with a variety of chronic pain disorders the endogenous pain-reducing system diminished the painfulness of the test stimulus less effectively than in normal probands. For the first time, this effect could also be shown in CPSP: Thoracotomy patients with ineffective preoperative CPM had developed CPSP more frequently after 6 months.[10]

Central sensitization can also be associated with changes at the cortical level, as occurs, for example, after traumatic nerve lesions or in phantom pain. The so-called cortical plasticity is due to neuroplastic changes in somatotopic areas and neighboring regions that correspond to the site of the peripheral lesion.

The following symptoms are typical of central sensitization, although they may not occur in all patients:[8]

- Dynamic-mechanical allodynia (non-painful contact with intact skin is perceived as painful);
- Secondary hyperalgesia (increased sensitivity to pain from a painful stimulus to the area directly around the wound);
- Wind-up phenomenon (pain amplification from a series of painful stimuli. In QST testing, the skin is stimulated with a needle for 1 s ten times [256 Nm]). Temporal summation is a similar phenomenon in which continuous stimulation, e.g., a thermal stimulus, produces increasing pain intensity.

Patients with CPSP more frequently show clinical signs of central sensitization than those without CPSP. After surgery for inguinal hernia, the wind-up phenomenon could be demonstrated in 50% of patients with CPSP and only 15% of those without CPSP. In addition, hyperalgesia to pressure pain in the contralateral inguinal region was found in 50% of CPSP patients, but in none of those without CPSP.[11, 12] It is possible that this finding may also be related to central sensitization.

RISK FACTORS

Risk factors for the development of CPSP can be divided into pre-, intra-, and postoperative factors. These are:

- Demographic,
- Clinical,

- Psychosocial, and
- Surgical-technical.

Most of the factors that exert a negative influence on acute postoperative pain are also related to a higher incidence and/or intensity of CPSP. These influencing parameters are shown in **Tab. 2**, and will be discussed in more detail in the following sections.

Table 2. Risk factors for the development of chronic postoperative pain

Preoperative risk factors	Intraoperative risk factors	Postoperative risk factors
• Preoperative chronic pain • Younger age • Female gender • Fear • Pain-related catastrophizing • Hyperalgesia • Limited descending pain inhibition • (genetic disposition)	• Nerve lesions • Open vs. minimally-invasive procedure	• Severe acute postoperative pain • Wound infection • Early postoperative secondary hyperalgesia • Early postoperative neuropathic pain • Perceived lack of control of the acute pain

PREOPERATIVE RISK FACTORS

Preoperative pain

Preoperative chronic pain, both within and external to the surgical site, is a risk factor for CPSP.[13,14,15] In addition to the pain intensity, a higher stage of pain chronification according to the Mainz classification also correlates significantly with a higher incidence of CPSP.[13] The total number of different preoperative pain sites also corresponds to the probability of developing CPSP.[13,16] Central sensitization can be demonstrated in a large number of painful disorders such as back pain, fibromyalgia, and chronic headaches.[14] Among patients who underwent herniated lumbar disc resection, those who had chronic back pain showed preoperative hyperalgesia that was still present 1 week after the surgery while those without chronic pain did not.[17]

Psychosocial factors

Preoperative anxiety and pain-related catastrophizing are among the most relevant psychological factors that impact the development of severe acute postoperative pain.[18] These are also risk factors for the development of CPSP: A recent meta-

analysis demonstrated a positive correlation in 16 of 29 studies.[19] A number of sub-analyses resulted in a pooled odds ratio (OR) between 1.55 [95% confidence interval (CI): 1.10–2.20] und 2.10 (95%-CI: 1.49–2.95). Catastrophizing was associated with a greater influence on the occurrence of CPSP than anxiety. Depression was only identified as a significant predictor in 5 of 16 CPSP studies[19] Additional factors found to be associated with the development of CPSP include:

- A low degree of social and familial support [20],
- Excessive stress and strain during the 6 months prior to surgery [21],
- Psychosomatic dysfunction [13], and
- Limited pain coping [22]

Age

In the acute postoperative phase, younger age represents a significant risk factor for severe pain.[18] Younger age is also described as a risk factor in the majority of studies on CPSP.[14] At the present time, the causes for this effect are unclear. Acute and chronic postoperative pain are thus distinct painful conditions, since in many other chronic painful disorders the incidence and intensity of the pain increase with increasing age.[23]

Gender

In numerous studies, female patients reported having CPSP more frequently compared to males.[14] Many hypotheses as to the causes of this gender difference were proposed; reports of genetic, psychological, socio-cultural, pharmacodynamic, and pharmacokinetic gender differences have been published. The consequences of a possibly greater incidence of CPSP in females with regard to prophylaxis or therapy, however, remain obscure at the present time.

Preoperative hyperalgesia

In order to predict the occurrence of CPSP, preoperative sensitivity to painful experimental stimuli was examined. Patients who reported higher pain intensity from electrical stimulation prior to total knee replacement surgery [24] or from thermal stimulation prior to inguinal herniorrhaphy [11] more frequently developed CPSP.

Insufficient descending inhibition

In addition to the pro-nociceptive influence of peripheral sensitization on central sensitization, reduced descending inhibition („CPM“) of dorsal-horn neurons

has also been identified as a risk factor: Patients with insufficient CPM reported having CPSP more frequently than normal probands after thoracotomy.[10]

Genetic disposition

To date, numerous genetic variants have been demonstrated to have a correlation with pain phenomena. While there have been no genetic studies of CPSP as yet, this topic is a focus of ongoing studies.[25]

INTRAOPERATIVE RISK FACTORS

Surgical techniques

Nerve lesions represent a significant risk factor for the development of CPSP, and thus, any factor that is associated with a nerve lesion is also a risk factor for CPSP. The various different surgical techniques play a major role, and are dependent on the particular procedure. As examples, inguinal herniorrhaphy and thoracotomy will be discussed in more detail, as they have been studied most extensively in regard to the surgical approach.

In a meta-analysis of inguinal hernia operations, laparoscopic techniques led to chronic inguinal pain significantly less often than open approaches [26]. In the sub-group analysis of the laparoscopic operations, CPSP occurred significantly less often after transabdominal preperitoneal mesh implantation (TAPP) than after total extraperitoneal herniaplasty (TEP). These advantages must, however, be weighed against the higher hernia recurrence rate after TEP and the greater incidence of complications after TAPP as compared to the open approach.[26]

Since nerves can be trapped by surgical clips as the mesh is fixed over the abdominal-wall defect, fixation with tissue glue has been studied as an alternative method in TEP procedures. In a meta-analysis, the occurrence of CPSP dropped significantly after this modification without an increase in the incidence of recurrence.[27] In contrast to the numerous studies that propagate nerve-sparing, a meta-analysis of four randomized, controlled trials (RCT) recommended prophylactic dissection of the ilioinguinal nerve for the prevention of CPSP.[28] Two of the four RCTs revealed an advantage of nerve transection and two did not show any difference in outcome. The studies were extremely heterogeneous, however, and did not investigate the presence of neuropathic pain.

Although thoracotomies are among the operations with the highest incidence of CPSP, only retrospective data are available for comparing the open thoracotomy techniques.[29]. One study indicates that the posterolateral approach leads to CPSP less often when the latissimus dorsi muscle is spared. In two studies, the anterior approach was associated with a lower incidence of CPSP. In two RCTs, video-assisted thoracotomy did not show any advantage over the posterolateral technique in regard to the development of CPSP. Sparing rather than dissection of the intercostal nerve was associated with a significantly lower incidence of CPSP.[31] An intracostal suture, via a borehole in the rib, can also prevent pressure from the suture on the intercostal nerve, and thus significantly reduce the development of CPSP.[32]

POSTOPERATIVE RISK FACTORS

Acute postoperative pain

Acute postoperative pain is the most consistent risk factor that is associated with CPSP in nearly all CPSP studies.[14]

Since acute pain is extremely relevant to the development of CPSP, current studies have been directed at categorizing the clinical course of pain intensity over the initial postoperative days. In one study of pain intensity during the first 4 days after sternotomy, acute pain severity decreased in only 29% of the patients. In the others, it remained constant or even increased.[33] Future studies are needed in order to determine the extent to which different changes in pain trends may influence CPSP.

Secondary hyperalgesia

The skin around a surgical wound is hyperalgesic postoperatively, and the hyperalgesic area enlarges over at least the first 3 days. A number of studies could demonstrate a relationship between acute postoperative hyperalgesia and CPSP, for example, after mastectomy, prosthetic hip implantation, and maxillofacial and inguinal-hernia operations.[34,35,36] In addition, early postoperative hyperalgesia is intensified by the presence of chronic preoperative pain.[17] Secondary hyperalgesia is mediated by central sensitization.

Acute postoperative neuropathic pain

In most studies, the presence of neuropathic pain was not analyzed until 3 or 6 months after surgery, and not in the early postoperative period. Screening for neuropathic pain during the initial days can be very useful, however, in identifying patients who are at high risk for developing CPSP.

Among patients examined by an acute pain service, 3% were found to have neuropathic pain. After 6 months, 78% of these patients and after 12 months 56% complained of persisting pain.[37] Similarly, neuropathic pain during the initial days after open nephrectomy [38] and iliac crest bone-graft removal was also associated more frequently with CPSP.[39]

Psychological factors

Patient-perceived poor control of acute pain was significantly associated with the development of CPSP.[40]

Recently, risk scores to evaluate the risk of CPSP have been published based on a mixed surgical patient population [21] and patients undergoing inguinal hernia operations [11] However, none of these scores has been validated to date.

Preoperative screening would be advantageous to enable primary prophylactic treatment of patients at high risk for CPSP. Chronic preoperative pain, younger age, an open surgical approach, and procedures associated with a high risk of CPSP could motivate clinicians to consider the use of preventive measures (see below) in everyday practice.

If primary prophylactic measures are not used, severe acute pain and, in particular, acute neuropathic pain are clear warning signals that are indications for starting secondary prophylactic measures while the patient is still in the hospital.

PREVENTION

Treatment of CPSP is often difficult, so that urgent preventive measures are needed to avoid its occurrence and/or mitigate its intensity. The primary goal is to block or diminish peripheral and central sensitization This can be accomplished by:

- Inhibition of peripheral nociception,
- Blocking pro-nociceptive excitatory input to the dorsal horn, or
- Augmenting the descending inhibitory system.

The concept of pre-emptive analgesia has become obsolete; this was a method of simply applying analgesic treatment at different time periods. The pre-emptive study group received the analgesic intervention prior to, and the other group after the surgical incision.[41] Preventive analgesia, on the other hand, aims to minimize the sensitization that is induced by pre-, intra-, and postoperative stimuli perioperatively. A preventive effect is defined as pain reduction that lasts 5.5 times longer than the half-life of the analgesic agent. The time when it is administered is unimportant; thus, it can also be given postoperatively.[41]

In the following sections, the analgesic methods and agents whose preventive effects on CPSP have been studied to date will be described.

Regional anesthesia

A recent Cochrane analysis examined the preventive effects of local anesthetics (LA) and regional anesthesia on the development of CPSP after 6 and 12 months.[42] Of the 23 studies selected, only 3 that examined thoracotomy using epidural analgesia (EA) and 2 on breast surgery with paravertebral block (PVB) could be pooled for analysis. The remainder of the studies had included a variety of analgesic methods and diverse operations.

EA significantly reduced the incidence of CPSP after thoracotomy (OR: 0.34; 95%-KI: 0.19–0.60), as did PVB prior to breast-tumor surgery (OR: 0.37; 95%-KI: 0.14–0.94] [43, 44]).

While the incidence of CPSP after open colon resection could be significantly reduced by using EA[45] this was not the case for major open gynecologic operations (OR: 0.81; 95%-KI: 0.35–.,88). [46]

The indication for perioperative EA for thoracic and major abdominal surgeries is clear, as is the use of PVB for major breast-resection procedures. It is not known to what degree the use of EA is reasonable for preventing CPSP after "medium-sized" operations in which EA is not generally used (e.g., laparoscopic procedures). No studies are currently available that examine the effects of peripheral nerve blocks in general or bolus administration versus catheter techniques

Wound infiltration

Wound infiltration with LA was found in some cases, such as inguinal herniorrhaphy (OR: 0.01; 95%-CI: 0.00–0.09)[47] or vasectomy (OR: 0.02; 95%-KI: 0.00–0.33),[48] to decrease the incidence of CPSP after 6 or 12 months. Other studies

could demonstrate a positive trend from wound infiltration, e.g., after iliac-crest graft excision (OR: 0.22; 95%-KI: 0.03–1.42])[49] or cesarean section.[50]
Even in operations where the incidence of CPSP has not been shown to be reduced, wound infiltration can be recommended, as it is a safe and inexpensive measure that can have a positive effect on acute postoperative pain.

Topical LA

EMLA® is a cream that contains lidocaine and prilocaine and can anesthetize the skin to a depth of several millimeters. The cream was applied perioperatively at the sternal border, the wound area, and the axilla in patients with breast cancer through the 3rd postoperative day. After 3 months, the incidence and intensity of pain in the chest wall and axilla were significantly less compared to controls.[51]

Gabapentin and pregabalin

After regional anesthesia, the co-analgesics gabapentin and pregabalin have been most frequently studied in regard to the prevention of CPSP. In addition to their widespread application for neuropathic pain, they have also been employed in acute postoperative pain therapy. A meta-analysis of pregabalin studies did not show any reduction in acute postoperative pain intensity during the first 24 h, however, there was a significant dose-dependent reduction in opioid use.[52] Visual disturbances occurred significantly more often in these patients. A Cochrane analysis showed that only 15% of patients reported a pain reduction of 50% within the first 6 h after surgery when 250 mg gabapentin was given as acute pain therapy (number needed to treat =11), so that this substance is less effective than other analgesics.[53]
A total of 11 RCTs - 8 with gabapentin and 3 with pregabalin - were included in a recent meta-analysis. CPSP was defined as pain that was present more than 2 months after the surgery.[54] Three studies dealt with breast surgery, while 8 different operative procedures were examined in the others. Differing therapeutic methods that varied in regard to dosage and duration of treatment (from a single dose to 10-day treatment) were utilized. Both drugs led to a significant reduction in the occurrence of CPSP, with a pooled OR of 0.52 (95%-KI: 0.27–0.98) for gabapentin and 0.09 (95% CI: 0.02–0.52) for pregabalin. In 4 of 6 studies, improvement in the functional outcome was also observed.[54]
Three studies showed a significant reduction in CPSP after a single dose of 1,200 mg gabapentin was given 1-2 h preoperatively; however, in 2 other studies a single

600-mg dose 1-2 h preoperatively was not effective. Of the 3 additional studies in which gabapentin was also administered in the postoperative phase, only 1 showed a reduction in CPSP.

Despite these positive preliminary results, the findings must be interpreted with caution, since nearly all the studies did not include sufficient numbers of patients. The authors of the meta-analysis analyzed a potential publication bias that might have overestimated the benefit of the two substances. Since the optimal dosage and duration of application for different surgical procedures are still not known, gabapentin and pregabalin cannot as yet be generally recommended for the prevention of CPSP. If gabapentin is used, 1,200 rather than 600 mg should be given preoperatively.

Ketamine

The studies regarding ketamine are extremely heterogeneous, as differing time points, intervals, and dosages as well as varying multimodal therapeutic schemes were employed. Contradictory results have been described for the i.v. administration of ketamine after thoracotomy. In one study, persistent neuropathic pain could not be decreased by a bolus of 1 mg/kg at induction followed by a 24-h infusion (0.04 mg/kg/h),[55] whereas in others a ketamine dose of 0.05 mg/kg/h for 48 h perioperatively resulted in a significantly lower incidence of CPSP and a reduction in analgesic use 3 months after surgery.[56] Similarly, 0.25 mg/kg/h after rectum resection [57] and an 0.5 mg/kg bolus followed by 0.012 mg/kg/h for 24 h after prosthetic hip implantation [58] were also associated with less occurrence of CPSP. However, a ketamine bolus followed by a 24-h infusion of 0.018 mg/kg/h showed no benefit 3 months after prosthetic knee replacement surgery.[59] The addition of ketamine to EA had no influence on the development of CPSP.[57,60]

Although the benefit of administering sub-anesthetic i.v.ketamine for CPSP prevention is not yet clear, its use should be considered for patients at high risk of developing CPSP, since a Cochrane analysis has at least demonstrated a significant reduction in pain intensity, opioid requirement, and postoperative nausea and vomiting in the acute-pain phase.[61] Among these patients at high risk are in particular those with preoperative opioid use, as the advantages of ketamine on acute and chronic postoperative pain can be especially useful in these cases.[62]

I.V. lidocaine

A meta-analysis of 29 RCTs has shown that continuous perioperative i.v. infusion of lidocaine can contribute to a reduction in acute pain and opioid requirement after abdominal and thoracic surgery.[63] A long-term effect on postoperative pain 3 months after breast-cancer surgery has also recently been demonstrated:[64] a bolus of 1.5 mg/kg 1% lidocaine was administered prior to incision and 1.5 mg/kg/h infused until 60 min after the end of surgery. Secondary hyperalgesia was also significantly reduced.

An additional opoid-sparing effect, a reduction in nausea and vomiting, and improved postoperative bowel function are also associated with i.v. lidocaine. It cannot be recommended for the prophylaxis of CPSP, however, as the optimal dosage scheme and side effects have not been studied sufficiently.

Nitrous oxide

Nitrous oxide (N2O) interacts with GABAergic and opioid receptors, and is also a competitive antagonist at the N-Methyl-D-Aspartate (NMDA) receptor. To date, only one study has examined the effect of N2O on CPSP: N2O was found to significantly reduce the incidence of CPSP after major non-cardiac procedures.[65]

Remifentanil

Dose-dependent opoid-induced hyperalgesia in the acute postoperative period has been described in experimental and clinical studies after the use of remifentanil.[66] A recent study has now shown a long-term negative effect of remifentanil administration 1 year after sternotomy[67] Persistence of pain was significantly associated with higher cumulative as well as body-weight-adapted doses of remifentanil.

α_2-Agonists

Although the analgesic effects of α_2-agonists on acute postoperative pain have been extensively studied, no study has as yet examined their effects on CPSP.[68]

Combination therapy

Further RCTs are needed in order to define the optimal doses, dosage schemes, and surgical indications for the individual analgesics and regional anesthesia techniques. In future studies, different combination therapies must be investigated so as to achieve optimal CPSP prevention. An initial example could

be polypragmatic pain therapy with gabapentin, EMLA® cream, and LA wound infiltration, which significantly reduced the incidence of CPSP after 3 months in comparison with placebo.[69]

TIPS FOR THE CLINICIAN

CPSP is a complication with highly variable incidence that can occur after any surgical procedure.

- Risk factors for CPSP include:
  - Younger age
  - Chronic preoperative pain
  - Preoperative anxiety
  - Pain-related catastrophizing
  - Open surgical techniques (versus laparoscopic procedures)
  - Intraoperative nerve damage
  - Perioperative hyperalgesia and
  - Severe acute postoperative pain.
- Although a number of interventions can decrease the occurrence of CPSP, it is difficult to make specific recommendations for its prevention, since differing dosages, dosage schemes, and drug combinations are employed for different operations.
- Epidural analgesia for thoracotomies and paravertebral blocks for major breast resections can be recommended.
- Wound infiltration with local anesthetic can be included as a part of multimodal treatment.
- For certain procedures, perioperative ketamine infusion and the administration of gabapentin and pregabalin may have a preventive, analgesic effect, however, the optimal prophylactic dosages must be analyzed more thoroughly.
- Future studies must be concerned with effective combinations for multimodal therapy. In addition, operation-specific analyses are needed, as the currently known preventive measures do not show the same effects for all procedures.

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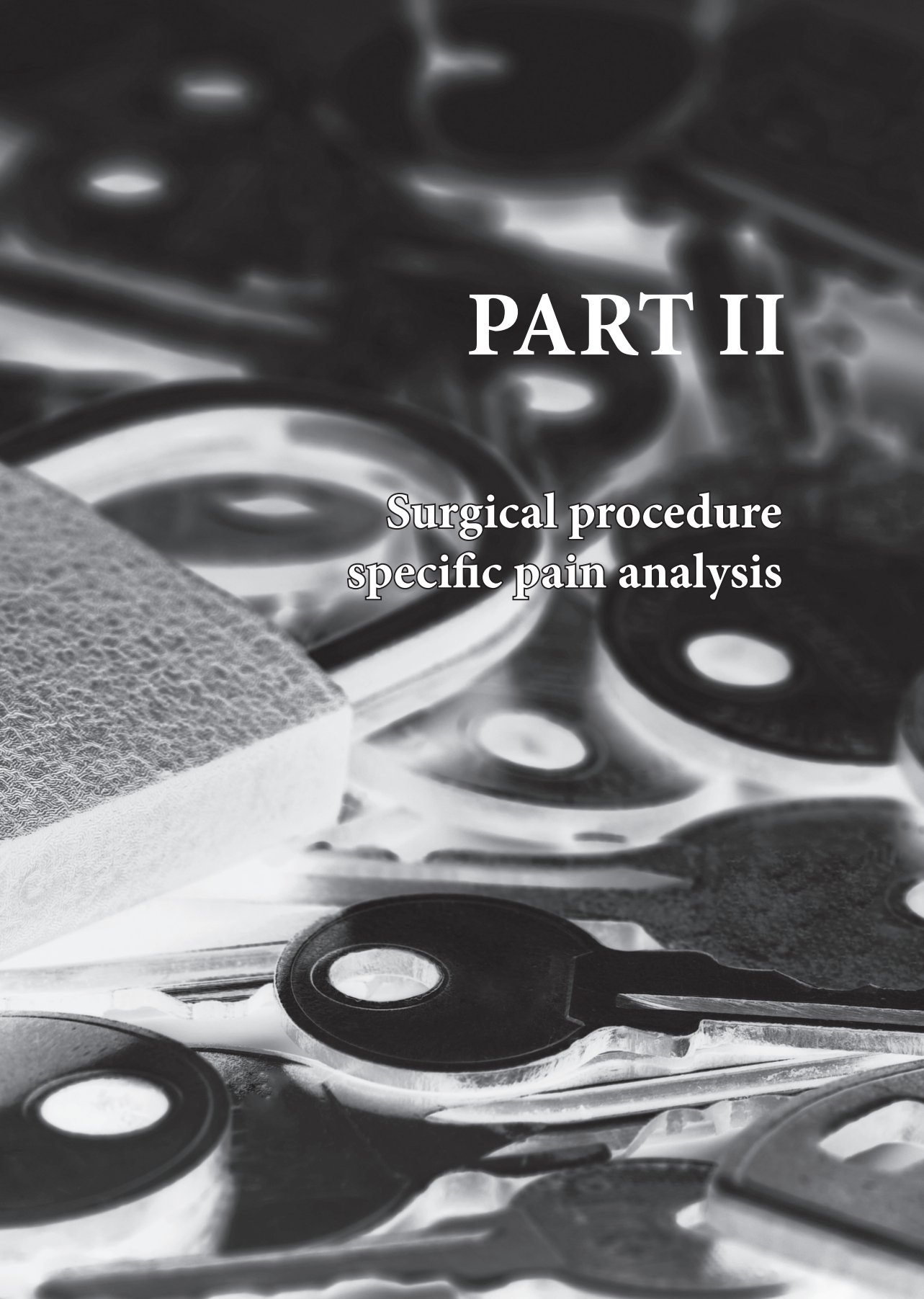

PART II

Surgical procedure specific pain analysis

CHAPTER 3

Pain intensity on the first day after surgery – A prospective cohort study comparing 179 surgical procedures

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ABSTRACT

Background

Severe pain after surgery remains a major problem, occurring in 20% to 40% of patients. Despite numerous published studies, the degree of pain following many types of surgery in everyday clinical practice is unknown. To improve postoperative pain therapy and develop procedure-specific, optimized pain-treatment protocols, types of surgery that may result in severe postoperative pain in everyday practice must first be identified.

Methods

This study considered 115,775 patients from 578 surgical wards in 105 German hospitals. A total of 70,764 patients met the inclusion criteria. On the first postoperative day patients were asked to rate their worst pain intensity since surgery (numeric rating scale 0 to 10). All surgical procedures were assigned to 529 well-defined groups. When a group contained less than 20 patients the data were excluded from analysis. Finally, 50,523 patients from 179 surgical groups were compared.

Results

The 40 procedures with the highest pain scores (median numeric rating scale 6 to 7) included 22 orthopedic/trauma procedures on the extremities. Patients reported high pain scores after many "minor" surgical procedures, including appendectomy, cholecystectomy, hemorrhoidectomy, and tonsillectomy, which ranked among the 25 procedures with highest pain intensities. A number of "major" abdominal surgeries resulted in comparatively low pain scores, often due to sufficient epidural analgesia.

Conclusions

Several common minor- to medium-level surgical procedures, including some with laparoscopic approaches, resulted in unexpectedly high levels of postoperative pain. To reduce the number of patients suffering from severe pain, patients undergoing so-called minor surgeries should be monitored more closely and postsurgical pain treatment needs to comply with existing procedure-specific pain-treatment recommendations.

INTRODUCTION

Severe postoperative pain remains a widespread but still underestimated problem. Extensive studies have demonstrated that despite present-day improvements in pain treatment, many patients still suffer from moderate to severe postoperative pain.[1;2] Severe pain is associated with decreased patient satisfaction, delayed postoperative ambulation, the development of chronic postoperative pain,[3] an increased incidence of pulmonary[4;5] and cardiac complications[6], and increased morbidity and mortality.[7] Therefore, it is of great importance that surgical procedures that result in severe pain and optimal analgesic strategies for these procedures can be identified.

To date, no comprehensive comparison of pain intensities among surgical procedures has been performed. One reason is a lack of pain studies for surgical procedures that are performed infrequently or for "minor" procedures that have been assumed to result in little or no postoperative pain. Another problem is the variability of pain assessment methods between studies, including different time periods for data collection and/or different types of pain measurements such as "pain on movement" or "pain at rest".[8]

We hypothesized that a systematic and standardized comparison of pain after all types of surgery might identify procedures where patients suffer from severe postoperative pain and could benefit from additional pain-treatment modalities such as regional anesthesia (RA).

In this cohort study, we aimed to provide an estimate of pain intensities that can be expected after most types of surgical procedures in relation to the applied pain treatment and to identify procedures where current pain therapy is likely to be insufficient.

MATERIALS AND METHODS

QUIPS registry

The present cohort study was part of the "Quality Improvement in Postoperative Pain Treatment" registry (QUIPS). The QUIPS registry was started as a benchmark initiative to compare pain outcome parameters among participating German hospitals. This study was supported by the German Society of Anesthesiologists, the German Society of Surgeons, and their professional organizations.[9] Each surgical

patient completed the validated 15-item QUIPS questionnaire. Worst pain intensity since surgery and pain during movement were measured using a numeric rating scale (NRS) of 0 to 10 (0 = no pain, 10 = worst pain imaginable). Further information on the type of surgery, anesthesia, and pain treatment was collected by study nurses. The personnel were trained to collect data in a standardized manner and were not part of the responsible surgical or anesthesia team. To reduce selection bias, data collection took place on randomly selected days. These dates were not known in advance to the medical staff, and on a survey day all patients who had been operated upon the day before were considered for inclusion. Approval was obtained from the University Ethics Committee of the University of Jena. All patients gave their written informed consent before entering the study.

Patients

All patients admitted between May 2004 and May 2010 were included in this analysis. Exclusion criteria as defined by the QUIPS project were as follows: The patient: (1) has been transferred to another ward after surgery; (2) is not present in his/her room at the time of data collection or has been discharged; (3) refuses participation in the study; (4) cannot communicate in German; (5) has cognitive deficits; or (6) is sedated or asleep. Additional exclusion criteria for this study were: (7) missing or incorrect German Surgical Procedure Coding (OPS), which precisely defines the kind of surgery performed; (8) age younger than 18 years; and (9) only patients who completed the questionnaire on the first postoperative day were included.

Definition and selection of surgical procedures

In order to compare pain intensities from various types of surgery, homogeneous surgical groups were created. The type of surgery was documented using the OPS, which includes some 21,000 surgical codes. These OPS codes were assigned to 529 surgical groups based on the extent of tissue lesions of the specific anatomic site as well as the surgical access method (laparoscopic, open, endoscopic, etc.). Minor differences in the extent of surgical lesions were assigned to one surgical group (e.g., partial, hemi-, total thyroidectomy). Very rare surgeries such as retrosternal thyroidectomy with sternotomy were disregarded. The type of material used for fixation of fractures or type of prosthesis was not taken into account.

Surgical groups were selected for comparison when they contained at least 20 procedures. In selected cases the minimum number of patients was set at 10 in

order to allow comparison between open and laparoscopic surgeries and to permit procedures with particularly high pain scores (median worst pain NRS ≥ 6) to be shown.

For eight organ systems and surgical sites (among others: eye, ear, and brain and skull surgery), insufficient numbers of patients were available to create homogeneous surgical groups. However, in order to permit analysis of as broad a spectrum of surgeries and surgical disciplines as possible, exceptions were made by pooling different types of these surgeries into heterogeneous groups.

The surgical codes of all patients were individually examined for the presence of multiple procedures. Thus, patients were excluded from the cholecystectomy group if an additional appendectomy was performed. Patients were also not included if they underwent a more extensive procedure than the one precisely defined by the surgical group (e.g., left hemicolectomy with an additional sigmoid resection).

Analgesics

Morphine equivalents were calculated to compare pain treatments for the different surgical procedures. The opioid consumption on the surgical ward after discharge from the post-anesthetic care unit (PACU) was measured. To calculate oral morphine equivalents, the following conversion factors were used: intravenous (i.v.) morphine (3x), oral oxycodone (2x), piritramide (2x), tramadol (0.1x), meperidine (0.4x), oral hydromorphone (7.5x), i.v. hydromorphone (22.5x), and i.v. fentanyl (100x).The use of non-opioids was analyzed by comparing the application of none, one, or two different analgesics.[10;11]

Statistical analysis

The primary analysis of pain scores was descriptive. For each surgical group medians and interquartile ranges (IQR) are presented. The surgical groups are ranked by their median worst pain intensity since surgery. Surgical groups with the same median pain score were sub-ranked according to their mean pain score. For the initial ranking of pain intensities of surgery, the type of anesthesia was not considered because it was our aim to mirror the true everyday clinical situation. As RA is generally thought to result in lower pain scores, in a separate analysis surgeries with general anesthesia alone (GA without any RA) and surgeries with RA (with or without GA) were examined separately. When information on the type of anesthesia was missing, patients were excluded from the comparison between the RA and GA groups. RA included: a) epidural anesthesia (EA) with a catheter

technique; b) peripheral nerve block (PNB; local anesthetic [LA] administered as a single injection or continuously via a catheter); and c) spinal anesthesia. To avoid very small patient groups, pain intensities of patients with RA were only shown when RA groups contained at least 10 patients. For analysis statistical software package SPSS 20 was used.

RESULTS

Data were collected from 115,775 surgical patients on 578 surgical wards in 105 German hospitals. Participating centers included primary, secondary, and tertiary hospitals.

Numbers and reasons for exclusion are presented in figure 1. A total of 70,518 patients were eligible for further analysis. Gender and age distribution are listed in table 1. The median worst pain intensity since surgery was NRS 5.0 (3.0; 7.0) and pain during movement NRS 4.0 (2.0; 5.0). GA alone was applied in 53,066 patients (75.3%), RA with or without GA in 6,015 (8.5%), and information on the type of anesthesia was missing for 11,437 patients (16.2% of the cases).

Table 1. Demographic data (n = 70,518)

	n	%
Gender		
Female	38,823	55.0
Age (years)		
18-20	1,811	2.6
21-30	5,360	7.6
31-40	6,779	9.6
41-50	12,248	17.4
51-60	13,628	19.3
61-70	15,772	22.4
71-80	12,110	17.1
81-90	2,810	4.0

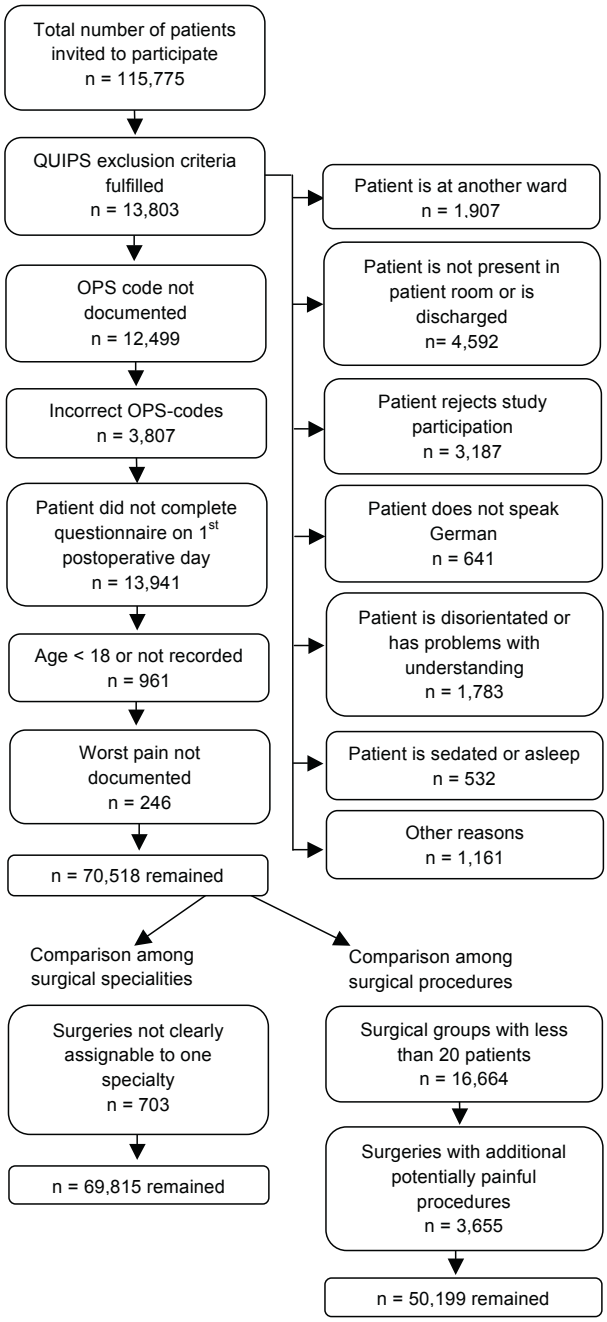


Figure 1. Exclusion criteria for comparison of postoperative pain intensities among surgical wards and surgical procedures

QUIPS = Quality Improvement in Postoperative Pain Treatment Benchmarking; OPS = German Surgical Procedure Coding

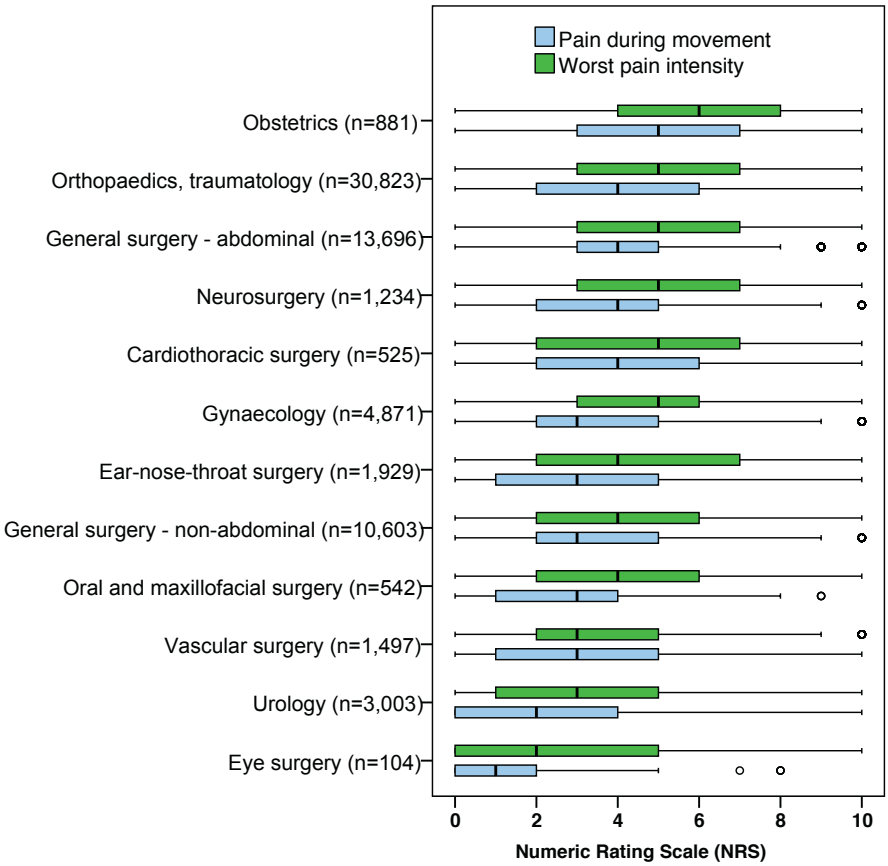


Figure 2. Comparison of pain intensities among surgical specialties. Worst pain and pain during movement since surgery were assessed on the first postoperative day.

Comparison between surgical specialties

For comparison of surgical specialties, 69,815 patients were analyzed. In 703 cases the surgical procedure could not be assigned to a particular department, e.g., biopsies, skin debridement, or diagnostic procedures. These were mainly minor surgical procedures. Pain intensities according to surgical discipline are presented in figure 2. The high pain intensity of neurosurgery was mainly associated with spinal surgery. Tonsillectomies considerably influenced the otolaryngological (ENT) group, as this was by far the most frequently performed procedure (n = 402; 21.4%) and the one that resulted in the highest pain scores (median worst pain NRS 6.0 [5.0; 7.0]). Excluding tonsillectomies, the ENT group would have had a median worst pain score of NRS 3.0 (2.0; 4.0).

Comparison between surgical groups

A total of 50,199 patients were selected for comparison of pain intensities in 179 surgical groups. These included: (1) 164 homogeneous surgical groups comprising more than 20 patients; (2) 7 groups with less than 20 patients; and (3) 8 heterogeneous groups (figure 3). The distributions of pain scores for all 179 surgeries as well as fractions of patients with NRS ≥ 6 and ≥ 8 has been calculated (see table, Supplemental Digital Content 1, which is a table listing the distribution of the pain scores of all 179 surgical procedures).

Analgesic use

Data on opioid use were recorded in 72% of cases. Patients without RA received opioids on the ward after discharge from the PACU in 38% of cases, compared to 39% of patients with RA.

In 79% of the cases data on non-opioid use were available. Among these patients, none, one, and two non-opioid analgesics (acetaminophen, metamidazol, non-steroidal anti-inflammatory drugs, cycoloxygenase-2-inhibitors) were used in 16.4%, 58.2%, and 25.4% of cases, respectively. In general, the higher the postoperative pain intensity, the more often one or two non-opioids were administered. In 49 of 179 surgical procedures, more than 20% of the patients did not receive non-opioid analgesics. These procedures were predominantly less painful surgeries that lay within the lowest one-third of the pain ranking list. Orthopedic and trauma patients most frequently received a second non-opioid analgesic.

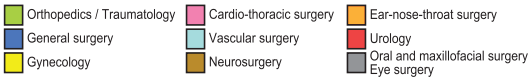
"Major" thoracic / abdominal surgery

For a number of "major" open thoracic and abdominal surgeries low pain scores with NRS ≤ 4 were reported. In those surgeries, the percentage in which EA was used was high, often 50% and more. The average opioid consumption of patients without EA in most of these surgical groups was greater than 35 mg: open left hemicolectomy (rank 109); open lung resection (rank 118); (sub)total gastrectomy (rank 120), rectum resection (rank 133); open adrenal surgery (rank 136); total bladder resection (rank 142); or radical prostatectomy (rank 163).

Laparoscopic surgery

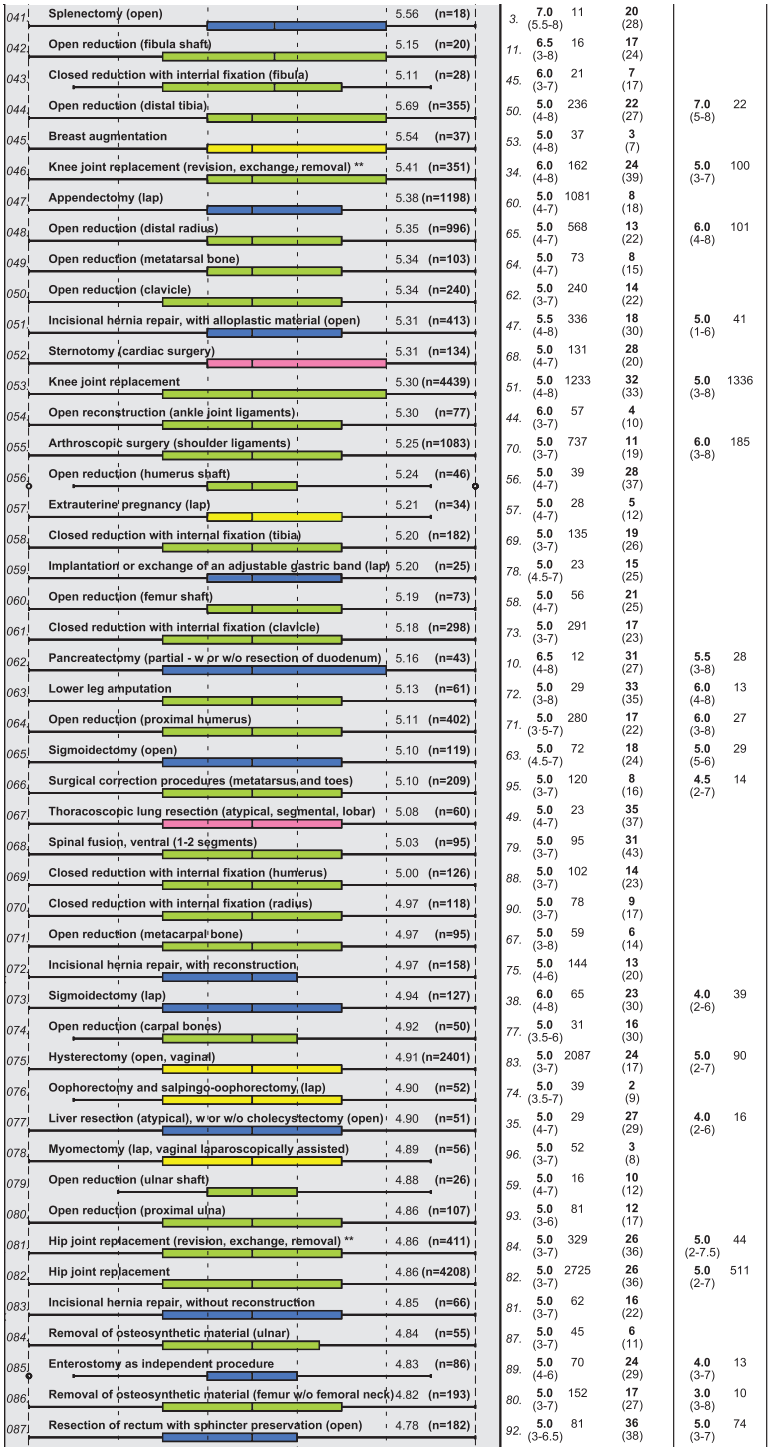
In laparoscopic surgeries with high postoperative pain scores comparably low opioid doses were used. These included incisional hernia repair (rank 29: 15 mg,

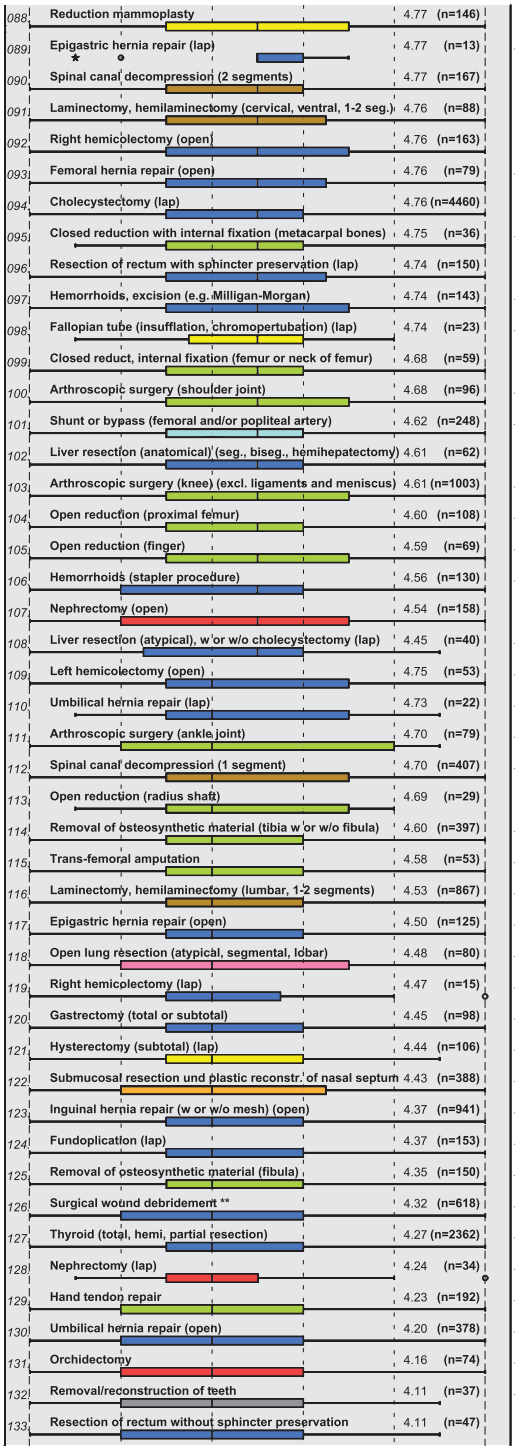
SD 23); appendectomy (rank 47: 7 mg, SD 18); extrauterine pregnancy (rank 57: 5 mg, SD 12); salpingo-oophorectomy (rank 76: 2 mg, SD 9); myomectomy (rank 78: 3mg, SD 8); and cholecystectomy (rank 94: 10 mg, SD 25). In the above-mentioned laparoscopic groups, on average 72% of the patients did not receive any opioids.



Worst pain since surgery (NRS 0-10)

Rank	All patients (general and regional anesthesia) NRS 0–10	Mean (NRS)		General anesthesia only NRS Median (IQR)	n	Morphine equivalent mg (mean) (SD)	Regional-anesthesia w or w/o general anesthesia NRS Median (IQR)	n
001.	Open reduction (calcaneus)	6.68	(n=90)	7.0 (5-8)	65	40 (32)		
002.	Spinal fusion, dorsal (1-2 segments)	6.61	(n=126)	7.0 (5-8)	126	37 (89)		
003.	Spinal fusion, dorsal (3 or more segments)	6.55	(n=40)	7.0 (5.5-9)	40	27 (39)		
004.	Myomectomy (open)	6.47	(n=36)	7.5 (6-8)	32	24 (29)		
005.	Proctocolectomy (open)	6.29	(n=14)	4.0 (4-7)	5	28 (32)		
006.	Complex spinal reconstruction (e.g. scoliosis)	5.84	(n=37)	7.0 (4-8)	37	29 (36)		
007.	Arthrodesis (foot joint)	6.23	(n=77)	6.0 (4.5-8)	44	12 (20)		
008.	Arthrodesis (metacarpophalangeal, interphalangeal joints)	6.14	(n=112)	6.0 (4-8)	61	10 (20)	7.0 (6-10)	13
009.	Caesarean section	6.14	(n=818)	6.0 (4.5-8)	203	27 (33)	6.0 (4-8)	253
010.	Open reduction (acetabulum and head of femur)	6.13	(n=31)	6.0 (4-8)	26	31 (27)		
011.	Hand resection arthroplasty	6.13	(n=78)	6.0 (5-8)	25	11 (17)	7.0 (5-8)	19
012.	Shoulder joint replacement	6.09	(n=79)	6.0 (5-7)	25	25 (23)	7.0 (5-9)	29
013.	Arthrodesis (ankle joint)	6.06	(n=124)	6.0 (4-8)	82	19 (22)	6.0 (4-7)	13
014.	Pancreatectomy (partial - Whipple)	6.06	(n=18)	7.0 (5-7)	3	18 (8)	6.0 (5-7)	14
015.	Open refixation and reconstruction (knee ligaments)	6.05	(n=148)	6.0 (5-8)	105	26 (32)		
016.	Open reduction (tibia shaft)	6.04	(n=49)	6.5 (4.5-8)	32	12 (25)		
017.	Open reduction (patella)	5.98	(n=55)	6.0 (4-8)	37	19 (26)		
018.	Open reduction (proximal radius)	5.96	(n=76)	6.0 (4-8)	51	10 (15)		
019.	Appendectomy (open)	5.95	(n=227)	6.0 (4-8)	196	14 (22)		
020.	Open reduction (proximal tibia)	5.95	(n=141)	6.0 (4-8)	104	23 (28)		
021.	Open reconstruction (shoulder joint ligaments)	5.91	(n=633)	6.0 (4-8)	349	26 (32)	5.0 (4-7)	109
022.	Partial shoulder joint replacement (humerus)	5.91	(n=113)	6.0 (4-8)	63	24 (26)	6.0 (5-8)	16
023.	Hemorrhoids (plastic reconstruction)	5.91	(n=67)	6.0 (5-8)	65	13 (22)		
024.	Tonsillectomy	5.89	(n=402)	6.0 (5-7)	401	7 (15)		
025.	Cholecystectomy (open)	5.83	(n=335)	6.0 (4-8)	285	28 (33)	6.0 (4-8)	11
026.	Kidney transplantation	5.81	(n=43)	6.0 (4-9)	38	17 (23)		
027.	Hysterectomy (subtotal) (open)	5.79	(n=19)	7.5 (6-8)	14	30 (44)		
028.	Vertical sleeve gastrectomy with duodenal switch (open)	5.73	(n=15)	6.0 (5-8)	14	53 (35)		
029.	Incisional hernia repair, with alloplastic material (lap)	5.69	(n=132)	6.0 (4-8)	123	16 (23)		
030.	Open reduction (pelvic rim and ring) **	5.63	(n=127)	6.0 (4-8)	96	21 (29)		
031.	Oophorectomy and salpingo-oophorectomy (open)	5.62	(n=21)	6.0 (5-8)	17	19 (24)		
032.	Arthrodesis (toe joint)	5.59	(n=70)	6.0 (3-8)	37	16 (25)	5.0 (3-8)	17
033.	Open reduction (distal humerus)	5.58	(n=55)	6.0 (3-7)	40	24 (39)		
034.	Open reduction (distal fibula)	5.55	(n=677)	5.0 (3-8)	461	17 (23)	7.0 (5-8)	49
035.	Small-bowel resection (open)	5.45	(n=49)	6.0 (5-8)	29	22 (25)	4.0 (2-6)	12
036.	Arthroscopic surgery (knee ligaments)	5.41	(n=633)	6.0 (4-8)	396	13 (21)	6.0 (3.5-7)	60
037.	Vertical sleeve gastrectomy with duodenal switch (lap)	5.37	(n=164)	6.0 (4-7)	162	19 (28)		
038.	Arthroscopic surgery (hip joint)	5.30	(n=27)	6.0 (4-7)	21	3 (8)		
039.	Arthroscopic revision (wrist joint)	5.09	(n=32)	6.0 (3-7)	29	7 (19)		
040.	Open reduction (distal femur)	5.00	(n=29)	5.5 (2.5-6)	20	32 (39)		


041 Splenectomy (open) 5.56 (n=18) 3. 7.0 (5.5-8) 11 20 (28)
042 Open reduction (fibula shaft) 5.15 (n=20) 11. 6.5 (3-8) 16 17 (24)
043 Closed reduction with internal fixation (fibula) 5.11 (n=28) 45. 6.0 (3-7) 21 7 (17)
044 Open reduction (distal tibia) 5.69 (n=355) 50. 5.0 (4-8) 236 22 (27) 7.0 (5-8) 22
045 Breast augmentation 5.54 (n=37) 53. 5.0 (4-8) 37 3 (7)
046 Knee joint replacement (revision, exchange, removal) ** 5.41 (n=351) 34. 6.0 (4-8) 162 24 (39) 5.0 (3-7) 100
047 Appendectomy (lap) 5.38 (n=1198) 60. 5.0 (4-7) 1081 8 (18)
048 Open reduction (distal radius) 5.35 (n=996) 65. 5.0 (4-7) 568 13 (22) 6.0 (4-8) 101
049 Open reduction (metatarsal bone) 5.34 (n=103) 64. 5.0 (4-7) 73 8 (15)
050 Open reduction (clavicle) 5.34 (n=240) 62. 5.0 (3-7) 240 14 (22)
051 Incisional hernia repair, with alloplastic material (open) 5.31 (n=413) 47. 5.5 (4-8) 336 18 (30) 5.0 (1-6) 41
052 Sternotomy (cardiac surgery) 5.31 (n=134) 68. 5.0 (4-7) 131 28 (20)
053 Knee joint replacement 5.30 (n=4439) 51. 5.0 (4-8) 1233 32 (33) 5.0 (3-8) 1336
054 Open reconstruction (ankle joint ligaments) 5.30 (n=77) 44. 6.0 (3-7) 57 4 (10)
055 Arthroscopic surgery (shoulder ligaments) 5.25 (n=1083) 70. 5.0 (3-7) 737 11 (19) 6.0 (3-8) 185
056 Open reduction (humerus shaft) 5.24 (n=46) 56. 5.0 (4-7) 39 28 (37)
057 Extrauterine pregnancy (lap) 5.21 (n=34) 57. 5.0 (4-7) 28 5 (12)
058 Closed reduction with internal fixation (tibia) 5.20 (n=182) 69. 5.0 (3-7) 135 19 (26)
059 Implantation or exchange of an adjustable gastric band (lap) 5.20 (n=25) 78. 5.0 (4.5-7) 23 15 (25)
060 Open reduction (femur shaft) 5.19 (n=73) 58. 5.0 (4-7) 56 21 (25)
061 Closed reduction with internal fixation (clavicle) 5.18 (n=298) 73. 5.0 (3-7) 291 17 (23)
062 Pancreatectomy (partial - w or w/o resection of duodenum) 5.16 (n=43) 10. 6.5 (4-8) 12 31 (27) 5.5 (3-8) 28
063 Lower leg amputation 5.13 (n=61) 72. 5.0 (3-8) 29 33 (35) 6.0 (4-8) 13
064 Open reduction (proximal humerus) 5.11 (n=402) 71. 5.0 (3-5-7) 280 17 (22) 6.0 (3-8) 27
065 Sigmoidectomy (open) 5.10 (n=119) 63. 5.0 (4.5-7) 72 18 (24) 5.0 (5-6) 29
066 Surgical correction procedures (metatarsus and toes) 5.10 (n=209) 95. 5.0 (3-7) 120 8 (16) 4.5 (2-7) 14
067 Thoracoscopic lung resection (atypical, segmental, lobar) 5.08 (n=60) 49. 5.0 (4-7) 23 35 (37)
068 Spinal fusion, ventral (1-2 segments) 5.03 (n=95) 79. 5.0 (3-7) 95 31 (43)
069 Closed reduction with internal fixation (humerus) 5.00 (n=126) 88. 5.0 (3-7) 102 14 (23)
070 Closed reduction with internal fixation (radius) 4.97 (n=118) 90. 5.0 (3-7) 78 9 (17)
071 Open reduction (metacarpal bone) 4.97 (n=95) 67. 5.0 (3-8) 59 6 (14)
072 Incisional hernia repair, with reconstruction 4.97 (n=158) 75. 5.0 (4-6) 144 13 (20)
073 Sigmoidectomy (lap) 4.94 (n=127) 38. 6.0 (4-8) 65 23 (30) 4.0 (2-6) 39
074 Open reduction (carpal bones) 4.92 (n=50) 77. 5.0 (3.5-6) 31 16 (30)
075 Hysterectomy (open, vaginal) 4.91 (n=2401) 83. 5.0 (3-7) 2087 24 (17) 5.0 (2-7) 90
076 Oophorectomy and salpingo-oophorectomy (lap) 4.90 (n=52) 74. 5.0 (3.5-7) 39 2 (9)
077 Liver resection (atypical), w or w/o cholecystectomy (open) 4.90 (n=51) 35. 5.0 (4-7) 29 27 (29) 4.0 (2-6) 16
078 Myomectomy (lap, vaginal laparoscopically assisted) 4.89 (n=56) 96. 5.0 (3-7) 52 3 (8)
079 Open reduction (ulnar shaft) 4.88 (n=26) 59. 5.0 (4-7) 16 10 (12)
080 Open reduction (proximal ulna) 4.86 (n=107) 93. 5.0 (3-6) 81 12 (17)
081 Hip joint replacement (revision, exchange, removal) ** 4.86 (n=411) 84. 5.0 (3-7) 329 26 (36) 5.0 (2-7.5) 44
082 Hip joint replacement 4.86 (n=4208) 82. 5.0 (3-7) 2725 26 (36) 5.0 (2-7) 511
083 Incisional hernia repair, without reconstruction 4.85 (n=66) 81. 5.0 (3-7) 62 16 (22)
084 Removal of osteosynthetic material (ulnar) 4.84 (n=55) 87. 5.0 (3-7) 45 6 (11)
085 Enterostomy as independent procedure 4.83 (n=86) 89. 5.0 (4-6) 70 24 (29) 4.0 (3-7) 13
086 Removal of osteosynthetic material (femur w/o femoral neck) 4.82 (n=193) 80. 5.0 (3-7) 152 17 (27) 3.0 (3-8) 10
087 Resection of rectum with sphincter preservation (open) 4.78 (n=182) 92. 5.0 (3-6.5) 81 36 (38) 5.0 (3-7) 74



088	Reduction mammoplasty	4.77	(n=146)	98.	**5.0**	(3-7)	135	**4**	(13)			
089	Epigastric hernia repair (lap)	4.77	(n=13)	108.	**5.0**	(2-6)	10	**4**	(9)			
090	Spinal canal decompression (2 segments)	4.77	(n=167)	99.	**5.0**	(3-6)	158	**38**	(49)			
091	Laminectomy, hemilaminectomy (cervical, ventral, 1-2 seg.)	4.76	(n=88)	97.	**5.0**	(3-6.5)	88	**26**	(36)			
092	Right hemicolectomy (open)	4.76	(n=163)	61.	**5.0**	(4-7)	80	**34**	(41)	**4.0**	(2-7)	60
093	Femoral hernia repair (open)	4.76	(n=79)	117.	**4.0**	(3-6)	66	**6**	(12)			
094	Cholecystectomy (lap)	4.76	(n=4460)	91.	**5.0**	(3-6)	4091	**10**	(25)	**3.5**	(2-6)	12
095	Closed reduction with internal fixation (metacarpal bones)	4.75	(n=36)	134.	**4.0**	(2-5.5)	19	**4**	(5)			
096	Resection of rectum with sphincter preservation (lap)	4.74	(n=150)	76.	**5.0**	(4-7)	107	**23**	(26)	**3.5**	(2-6)	38
097	Hemorrhoids, excision (e.g. Milligan-Morgan)	4.74	(n=143)	112.	**4.5**	(3-7)	136	**12**	(21)			
098	Fallopian tube (insufflation, chromopertubation) (lap)	4.74	(n=23)	111.	**4.5**	(3-6)	22	**0**				
099	Closed reduct, internal fixation (femur or neck of femur)	4.68	(n=59)	94.	**5.0**	(3-6)	46	**15**	(26)			
100	Arthroscopic surgery (shoulder joint)	4.68	(n=96)	102.	**5.0**	(3-7)	61	**15**	(22)	**5.0**	(3-9)	13
101	Shunt or bypass (femoral and/or popliteal artery)	4.62	(n=248)	100.	**5.0**	(3-6)	175	**18**	(57)	**4.0**	(2-6)	34
102	Liver resection (anatomical) (seg., biseg., hemihepatectomy)	4.61	(n=62)	54.	**5.0**	(5-7)	21	**27**	(31)	**5.0**	(3-6)	37
103	Arthroscopic surgery (knee) (excl. ligaments and meniscus)	4.61	(n=1003)	124.	**4.0**	(3-6)	634	**6**	(14)	**5.0**	(3-6)	96
104	Open reduction (proximal femur)	4.60	(n=108)	105.	**5.0**	(3-6)	87	**24**	(31)			
105	Open reduction (finger)	4.59	(n=69)	123.	**5.0**	(3-7)	35	**6**	(11)			
106	Hemorrhoids (stapler procedure)	4.56	(n=130)	106.	**5.0**	(2-6)	124	**6**	(15)			
107	Nephrectomy (open)	4.54	(n=158)	52.	**5.0**	(4-8)	49	**35**	(33)	**4.0**	(0-6)	76
108	Liver resection (atypical), w or w/o cholecystectomy (lap)	4.45	(n=40)	107.	**5.0**	(2-5.5)	36	**14**	(38)			
109	Left hemicolectomy (open)	4.75	(n=53)	115.	**4.0**	(3-7)	21	**40**	(45)	**5.0**	(2-8)	20
110	Umbilical hernia repair (lap)	4.73	(n=22)	116.	**4.0**	(3-7)	21	**12**	(22)			
111	Arthroscopic surgery (ankle joint)	4.70	(n=79)	143.	**3.0**	(2-6)	44	**6**	(12)	**7.0**	(3-8)	13
112	Spinal canal decompression (1 segment)	4.70	(n=407)	119.	**4.0**	(3-6.5)	399	**24**	(71)			
113	Open reduction (radius shaft)	4.69	(n=29)	85.	**5.0**	(3-5)	25	**8**	(13)			
114	Removal of osteosynthetic material (tibia w or w/o fibula)	4.60	(n=397)	101.	**5.0**	(3-6)	293	**9**	(17)	**3.0**	(3-5)	13
115	Trans-femoral amputation	4.58	(n=53)	120.	**4.0**	(2-6)	37	**41**	(54)	**4.0**	(4-6)	11
116	Laminectomy, hemilaminectomy (lumbar, 1-2 segments)	4.53	(n=867)	122.	**4.0**	(3-5)	865	**19**	(28)			
117	Epigastric hernia repair (open)	4.50	(n=125)	125.	**4.0**	(3-6)	114	**13**	(30)			
118	Open lung resection (atypical, segmental, lobar)	4.48	(n=80)	142.	**3.0**	(2.5-7)	19	**72**	(77)	**3.5**	(1.5-8)	20
119	Right hemicolectomy (lap)	4.47	(n=15)	109.	**4.5**	(4-7)	8	**26**	(28)			
120	Gastrectomy (total or subtotal)	4.45	(n=98)	110.	**4.5**	(3-6.5)	36	**38**	(40)	**5.0**	(2.5-6)	47
121	Hysterectomy (subtotal) (lap)	4.44	(n=106)	121.	**4.0**	(3-6)	89	**5**	(9)			
122	Submucosal resection und plastic reconstr. of nasal septum	4.43	(n=388)	126.	**4.0**	(2-6.5)	388	**1**	(5)			
123	Inguinal hernia repair (w or w/o mesh) (open)	4.37	(n=941)	127.	**4.0**	(3-6)	714	**6**	(14)	**4.0**	(3-6)	37
124	Fundoplication (lap)	4.37	(n=153)	129.	**4.0**	(3-6)	149	**5**	(13)			
125	Removal of osteosynthetic material (fibula)	4.35	(n=150)	113.	**4.5**	(2-6)	118	**6**	(14)			
126	Surgical wound debridement **	4.32	(n=618)	128.	**4.0**	(2-6)	490	**13**	(56)	**5.0**	(3-8)	25
127	Thyroid (total, hemi, partial resection)	4.27	(n=2362)	130.	**4.0**	(3-6)	2358	**7**	(17)			
128	Nephrectomy (lap)	4.24	(n=34)	118.	**4.0**	(3-5.5)	12	**19**	(22)			
129	Hand tendon repair	4.23	(n=192)	104.	**5.0**	(2-6)	94	**9**	(17)	**3.0**	(2-5)	15
130	Umbilical hernia repair (open)	4.20	(n=378)	131.	**4.0**	(2-6)	345	**4**	(12)			
131	Orchidectomy	4.16	(n=74)	135.	**4.0**	(2-5.5)	52	**9**	(24)			
132	Removal/reconstruction of teeth	4.11	(n=37)	132.	**4.0**	(2-6)	37	**0**				
133	Resection of rectum without sphincter preservation	4.11	(n=47)	86.	**5.0**	(3.5-6)	23	**29**	(34)	**3.0**	(2-5)	18

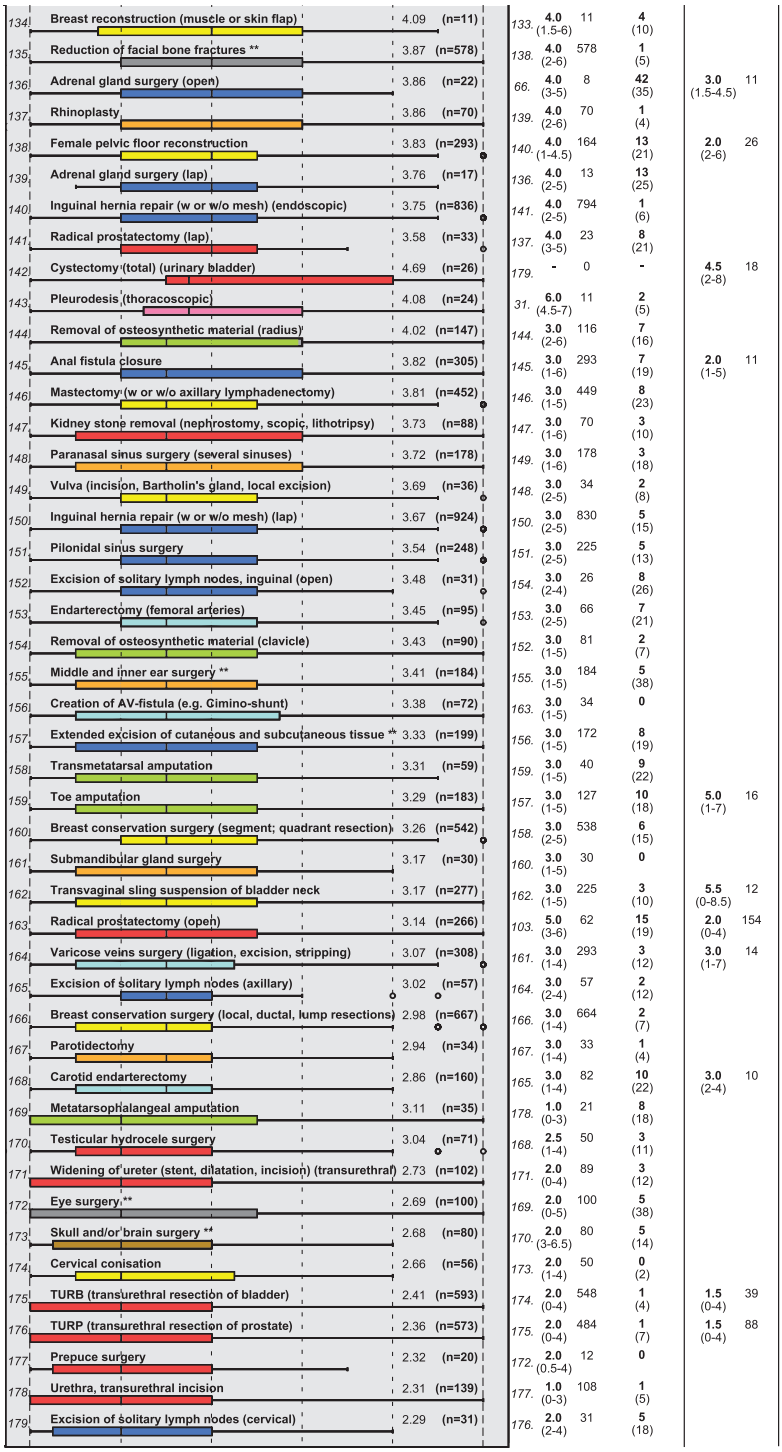

134 Breast reconstruction (muscle or skin flap) 4.09 (n=11) 133. 4.0 (1.5-6) 11 4 (10)
135 Reduction of facial bone fractures ** 3.87 (n=578) 138. 4.0 (2-6) 578 1 (5)
136 Adrenal gland surgery (open) 3.86 (n=22) 66. 4.0 (3-5) 8 42 (35) 3.0 (1.5-4.5) 11
137 Rhinoplasty 3.86 (n=70) 139. 4.0 (2-6) 70 1 (4)
138 Female pelvic floor reconstruction 3.83 (n=293) 140. 4.0 (1-4.5) 164 13 (21) 2.0 (2-6) 26
139 Adrenal gland surgery (lap) 3.76 (n=17) 136. 4.0 (2-5) 13 13 (25)
140 Inguinal hernia repair (w or w/o mesh) (endoscopic) 3.75 (n=836) 141. 4.0 (2-5) 794 1 (6)
141 Radical prostatectomy (lap) 3.58 (n=33) 137. 4.0 (3-5) 23 8 (21)
142 Cystectomy (total) (urinary bladder) 4.69 (n=26) 179. - 0 - 4.5 (2-8) 18
143 Pleurodesis (thoracoscopic) 4.08 (n=24) 31. 6.0 (4.5-7) 11 2 (5)
144 Removal of osteosynthetic material (radius) 4.02 (n=147) 144. 3.0 (2-6) 116 7 (16)
145 Anal fistula closure 3.82 (n=305) 145. 3.0 (1-6) 293 7 (19) 2.0 (1-5) 11
146 Mastectomy (w or w/o axillary lymphadenectomy) 3.81 (n=452) 146. 3.0 (1-5) 449 8 (23)
147 Kidney stone removal (nephrostomy, scopic, lithotripsy) 3.73 (n=88) 147. 3.0 (1-6) 70 3 (10)
148 Paranasal sinus surgery (several sinuses) 3.72 (n=178) 149. 3.0 (1-6) 178 3 (18)
149 Vulva (incision, Bartholin's gland, local excision) 3.69 (n=36) 148. 3.0 (2-5) 34 2 (8)
150 Inguinal hernia repair (w or w/o mesh) (lap) 3.67 (n=924) 150. 3.0 (2-5) 830 5 (15)
151 Pilonidal sinus surgery 3.54 (n=248) 151. 3.0 (2-5) 225 5 (13)
152 Excision of solitary lymph nodes, inguinal (open) 3.48 (n=31) 154. 3.0 (2-4) 26 8 (26)
153 Endarterectomy (femoral arteries) 3.45 (n=95) 153. 3.0 (2-5) 66 7 (21)
154 Removal of osteosynthetic material (clavicle) 3.43 (n=90) 152. 3.0 (1-5) 81 2 (7)
155 Middle and inner ear surgery ** 3.41 (n=184) 155. 3.0 (1-5) 184 5 (38)
156 Creation of AV-fistula (e.g. Cimino-shunt) 3.38 (n=72) 163. 3.0 (1-5) 34 0
157 Extended excision of cutaneous and subcutaneous tissue ** 3.33 (n=199) 156. 3.0 (1-5) 172 8 (19)
158 Transmetatarsal amputation 3.31 (n=59) 159. 3.0 (1-5) 40 9 (22)
159 Toe amputation 3.29 (n=183) 157. 3.0 (1-5) 127 10 (18) 5.0 (1-7) 16
160 Breast conservation surgery (segment; quadrant resection) 3.26 (n=542) 158. 3.0 (2-5) 538 6 (15)
161 Submandibular gland surgery 3.17 (n=30) 160. 3.0 (1-5) 30 0
162 Transvaginal sling suspension of bladder neck 3.17 (n=277) 162. 3.0 (1-5) 225 3 (10) 5.5 (0-8.5) 12
163 Radical prostatectomy (open) 3.14 (n=266) 103. 5.0 (3-6) 62 15 (19) 2.0 (0-4) 154
164 Varicose veins surgery (ligation, excision, stripping) 3.07 (n=308) 161. 3.0 (1-4) 293 3 (12) 3.0 (1-7) 14
165 Excision of solitary lymph nodes (axillary) 3.02 (n=57) 164. 3.0 (2-4) 57 2 (12)
166 Breast conservation surgery (local, ductal, lump resections) 2.98 (n=667) 166. 3.0 (1-4) 664 2 (7)
167 Parotidectomy 2.94 (n=34) 167. 3.0 (1-4) 33 1 (4)
168 Carotid endarterectomy 2.86 (n=160) 165. 3.0 (1-4) 82 10 (22) 3.0 (2-4) 10
169 Metatarsophalangeal amputation 3.11 (n=35) 178. 1.0 (0-3) 21 8 (18)
170 Testicular hydrocele surgery 3.04 (n=71) 168. 2.5 (1-4) 50 3 (11)
171 Widening of ureter (stent, dilatation, incision) (transurethral) 2.73 (n=102) 171. 2.0 (0-4) 89 3 (12)
172 Eye surgery ** 2.69 (n=100) 169. 2.0 (0-5) 100 5 (38)
173 Skull and/or brain surgery ** 2.68 (n=80) 170. 2.0 (3-6.5) 80 5 (14)
174 Cervical conisation 2.66 (n=56) 173. 2.0 (1-4) 50 0 (2)
175 TURB (transurethral resection of bladder) 2.41 (n=593) 174. 2.0 (0-4) 548 1 (4) 1.5 (0-4) 39
176 TURP (transurethral resection of prostate) 2.36 (n=573) 175. 2.0 (0-4) 484 1 (7) 1.5 (0-4) 88
177 Prepuce surgery 2.32 (n=20) 172. 2.0 (0.5-4) 12 0
178 Urethra, transurethral incision 2.31 (n=139) 177. 1.0 (0-3) 108 1 (5)
179 Excision of solitary lymph nodes (cervical) 2.29 (n=31) 176. 2.0 (2-4) 31 5 (18)

Figure 3 Pain scores on the first postoperative day after 179 surgical procedures. Horizontal box plots indicate "worst pain since surgery" on a numeric rating scale (NRS) from 0 = "no pain at all" to 10 = "worst pain imaginable". Box edges indicate 25th and 75th percentiles. Whiskers indicate 5th and 95th percentiles.

Columns to the right of box plots indicate pain scores in patients receiving only general anesthesia (GA) and patients receiving regional anesthesia (RA) with or without GA. Procedures are ranked in descending order of median pain severity. Mean scores (also shown) were used to rank surgical groups with identical median NRS scores.

Opioid concentration was calculated as oral morphine equivalents. Opioid doses are presented only for patients under GA without RA.

Open reduction of distal or proximal bones means that fracture includes joint region.

** Heterogeneous surgical group (pooled on basis of surgery on an organ system or surgical site).

w or w/o = with or without; IQR = interquartile range

"Major" orthopedic surgery

Three of the 6 surgeries with a median pain score of NRS 7 were major spinal procedures. Among the 40 highest ranked surgeries (median NRS 6 or 7) were 22 orthopedic/trauma surgeries on the extremities. In these groups, RA was used in only 537 of 3,462 cases (15.5%).

"Minor" orthopedic surgery

A number of hand and foot surgeries resulted in high pain scores. The average morphine equivalent dose administered was below 10 mg in all of the following surgical groups: arthrodesis of foot joint (rank 7); arthrodesis of metacarpophalangeal joints (rank 8); hand resection arthroplasty (rank 11); arthroscopic wrist revision (rank 39); open reduction of metatarsal bone (rank 49); open reconstruction of ankle ligaments (rank 54); and surgical correction of metatarsus and toes (rank 66).

DISCUSSION

To our knowledge, this is the largest prospective cohort study to date comparing standardized

pain intensity scores obtained after a wide range of surgical procedures performed in a large number of hospitals. This standardized assessment provides insight into the painfulness of everyday surgical interventions in relation to the treatment provided.

Our findings show that, depending on the pain treatment received, in many surgical procedures the incision size and extent of tissue trauma were not related to postoperative pain intensity. On the one hand, above-knee amputation, open lung resection, total gastrectomy, mastectomy, or radical prostatectomy, which are certainly major procedures in terms of the extent of tissue trauma, all received sufficient pain treatment as they resulted in median worst-pain scores of NRS 4 or less and ranked lower than position 115 for pain intensity. On the other hand, tonsillectomy, hemorrhoidectomy with plastic reconstruction, open appendectomy, and open cholecystectomy ranked among the highest 25 surgeries. The mainstay of good acute pain treatment is careful individual titration of analgesics while minimizing adverse effects. It has repeatedly been demonstrated that medical staff commonly misjudge the pain intensity that patients are experiencing.[12;13] Therefore, the administration of analgesics should be adjusted according to the individual patient's reported pain scores and desire for additional medication. In the present study we were able to demonstrate that patients undergoing minor surgeries typically received no or low doses of opioids. However, many patients indicated high pain scores. It is thus conceivable that high pain intensities were often ignored or not taken seriously, so that analgesic administration was delayed and/or insufficient.

In most surgical groups pain intensities after laparoscopic access were lower compared to the open route, as would be expected.[14-16] However, some laparoscopic surgeries were nevertheless associated with high postoperative pain intensities: After laparoscopic appendectomy, patients' pain ratings were similar to those after knee-joint replacement and sternotomy. After many laparoscopic surgeries patients often reported severe pain, but did not receive any opioids at all or only in low doses, which supports the presumption that the painfulness of some laparoscopic interventions is underestimated.

Similar results were observed in "minor" surgeries of the hand and foot in orthopedics and traumatology: low amounts of opioid use indicate inadequate titration of analgesics and low percentages of RA demonstrate possibilities for future improvement of pain treatment in those surgeries.

Good pain relief was achieved after many major abdominal surgeries: a high incidence of use of EA and oral morphine equivalent doses of around 30 to 50 mg after discharge from the PACU resulted in acceptable worst-pain scores of NRS 4 for many procedures.

In contrast, major orthopedic surgery was frequently associated with high pain scores. Pain treatment after major spinal surgery (fusions and scoliosis surgery: ranks 2, 3, and 6) was commonly insufficient. EA had not been used, and mean opioid doses were low compared to those in trials using patient-controlled i.v. analgesia (PCA) that demonstrated an average consumption of 150 mg oral morphine equivalents within the first 24 hours.[17;18] Even though open reduction of the calcaneus – the procedure with the highest pain score in this study - was associated with a comparatively high opioid administration of 40 mg, another trial demonstrated that patients used on average 167 mg i.v. morphine via PCA (about 500 mg oral morphine equivalents) during the first 24 hours.[19]

EA and PNBs are known to reduce postoperative pain intensity.[20] For many procedures, especially those that are known to cause severe postoperative pain, guidelines from many countries recommend the use of RA for postoperative pain control.[21-24] Interestingly, however, for some procedures such as open reduction of a calcaneus fracture, which was ranked highest, effective pain-treatment alternatives such as sciatic nerve block were not used.[19] Additional examples where RA was neglected included open reconstruction of knee ligaments (ranked 15th) and hemorrhoid resections with plastic reconstruction (ranked 23rd), which are both known to be painful procedures. While randomized, controlled trials (RCTs) have demonstrated clinically significant pain reduction after femoral nerve blocks[25] and wound infiltration with LA,[26] in our study population these techniques were hardly ever employed.

There are some limitations of this study: (1) we measured postoperative pain in surgical patients treated in hospitals from a single western European country. Thus, it was not possible to evaluate cross-national cultural influences on pain perception. (2) Pain after reduction of fractures must be interpreted with care, as the type of fracture and soft-tissue damage are likely to influence postoperative pain. (3) Participation in the benchmarking survey was entirely voluntary, and was associated with additional effort for the hospital. This factor may have resulted in a selection that influenced the generalizability of our findings, because the participating hospitals may be more actively striving to improve their postoperative pain management. This type of selection could have led to underestimation of the true incidence of inadequate postoperative pain relief. (4) For the majority of the surgical groups, many different hospitals contributed patient data sets (see

figure 3). Exceptions included sternotomy, laparoscopic and open vertical-sleeve gastrectomy, laparoscopic radical prostatectomy, and kidney transplantation, which were performed only in a subset of hospitals.

A number of risk factors are known to increase postoperative pain intensity, e.g., younger age, female gender, and the presence of preoperative pain.[27-29] Pain scores were intentionally not adjusted for these variables, since pain intensities within a surgical group should represent all patients who are typical of this patient cohort; otherwise, pain intensity in older men undergoing radical prostatectomy might be corrected to erroneously high scores, whereas younger patients after appendectomy might show erroneously low pain scores.

A strength of the presented data is that the German invoicing system for hospitals is based on OPS codes; hence, the accuracy of OPS documentation is strictly monitored in each hospital by the financial control system. Furthermore, incentives for hospitals to report lower pain scores than those reported by the patients in the QUIPS registry are unlikely, as the collected data are for internal use only and comparisons between hospitals are performed anonymously.

Pain intensities collected in cohort studies may differ from those obtained in RCTs. A RCT can be considered "state of the art" for identifying the best analgesic modality for a specific type of surgery. However, RCTs are of limited use to ascertain the degree of postoperative pain after a particular procedure in everyday clinical practice, as estimates obtained from RCTs may be considerably biased. For example, RCT participants usually have easy access to rescue medication or receive additional i.v. PCA pumps. Most RCTs have generous exclusion criteria, e.g., medical and mental comorbid conditions. These more favorable terms limit the generalizability of many RCTs that deal with postoperative pain. Integrating the results of RCTs with our results should demonstrate where the implementation of RCT recommendations may result in particular advantages for the patient and where this might not be the case. On the one hand, the use of sciatic-nerve catheters after reduction of calcaneus fractures[19] or epidural catheters after spinal fusion and scoliosis surgery[30] (the two surgeries with the highest pain scores in this study population) may be of particular benefit. On the other hand, paravertebral nerve blocks have been shown in a meta-analysis to be superior to systemic analgesics after mastectomy surgery;[31] however, in our study, patients without RA had low median worst-pain scores of NRS 3.

The aim of our pain ranking is not to assign a specific rank to a particular surgical procedure, as many procedures were associated with only minimal differences in mean pain scores. Consequently, the exact rank number has no clinical significance, but is intended to simplify comparison among the large number of surgeries included in the study. The results offer a comprehensive and impartial view of postoperative pain intensity ratings. Estimates of postsurgical pain by medical staff members are mainly based on their clinical experience. Physicians and nurses may underestimate the patient's requirement for analgesic medication, especially after so-called minor surgical procedures. Awareness of the average postoperative pain intensity after various procedures may thus contribute to improved postoperative care by facilitating the implementation of procedure-specific pain-treatment protocols.

In conclusion, this cohort study demonstrates that for a large number of everyday surgical procedures, many patients experience high postoperative pain intensities. Some laparoscopic procedures and "minor" surgeries involving small incisions require additional vigilance. This study reveals a number of surgeries associated with high pain scores where more frequent adherence to evidence-based pain-treatment recommendations could improve quality of care. By incorporating these measures into comprehensive postoperative pain protocols, the adverse effects of inadequate pain control may be reduced or prevented.

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CHAPTER 4

Quality of pain treatment after Caesarean section – Results of a multicentre cohort study

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ABSTRACT

Introduction

A large cohort study recently reported high pain scores after Caesarean section (CS). The aim of this study was to analyse how pain after CS interferes with patients' activities and to identify possible causes of insufficient pain treatment.

Methods

We analysed pain scores, pain-related interferences (with movement, deep breathing, mood and sleep), analgesic techniques, analgesic consumption, adverse effects, and the wish to have received more analgesics during the first 24 hours after surgery. To better evaluate the severity of impairment by pain, the results were compared with those of patients undergoing hysterectomy.

Results

CS patients (n=811) were compared to patients undergoing abdominal, laparoscopic-assisted vaginal or vaginal hysterectomy (n=2406, from 54 hospitals). Pain intensity, wish for more analgesics and most interference outcomes were significantly worse after CS compared to hysterectomies. CS patients with spinal or general anaesthesia and without patient-controlled analgesia (PCA) received significantly less opioids on the ward (62% without any opioid) compared to patients with PCA ($p<0.001$). Patients with PCA reported pain-related interference with movement and deep breathing between 49% and 52% compared to patients without PCA (between 68% and 73%) (p-values between 0.004 and 0.013; not statistically significant after correction for multiple testing).

Conclusion

In daily clinical practice pain after CS is much higher than previously thought. Pain management was insufficient compared to patients undergoing hysterectomy. Unfavourable outcome was mainly associated with low opioid administration after CS. Contradictory pain treatment guidelines for patients undergoing CS and for breastfeeding mothers might contribute to reluctance of opioid administration in CS patients.

INTRODUCTION

A recent analysis of more than 70,000 patients revealed that women after caesarean section (CS) ranked 9th for pain severity among 179 different surgical procedures (Gerbershagen et al., 2013). This was an unexpected result, as many randomized trials (RCT) dealing with different analgesic approaches indicated lower postoperative pain scores after CS (Alhashemi et al., 2006; Belavy et al., 2009; Bonnet et al., 2010; Bozkurt et al., 2009; Fassoulaki et al., 2004; Kanazi et al., 2010; Loane et al., 2012; Matsota et al., 2011; McDonnell et al., 2010; Munishankar et al., 2008; Nayar and Sahajanand, 2009; Ngan Kee et al., 1997, 2002; Reza et al., 2010; Schewe et al., 2009; Shahin and Osman, 2010; Wolfson et al., 2012). In these studies, NRS scores at rest ranged from 1.9 to 4.2 and pain during coughing from 3.0 to 6.0 during the first 24 hours after surgery. However, due to selective inclusion and somewhat artificial conditions of randomized controlled trials (e.g., rescue intravenous patient controlled analgesia), these rarely represent typical everyday care and the normal course of acute postoperative pain.

Next to the unpleasantness of pain, insufficiently treated acute pain after CS can contribute to long-term negative outcomes such as chronic postoperative pain (Eisenach et al., 2008; Kainu et al., 2010; Nikolajsen et al., 2004), a threefold risk of developing postpartum depression, a risk for delayed breastfeeding, and a feeling of guilt if the woman is not able to care for her newborn (Eisenach et al., 2008; Woods et al., 2012). Persistent maternal pain and depression have also been demonstrated to impair cognitive processes and might induce later behavioural disturbances in the child (Evans et al., 2007; Grace et al., 2003; Wrate et al., 1985). Despite the large number of RCTs to date, national guidelines are equivocal in their recommendations for perioperative pain management for CS consequently there is no "gold standard" (Gizzo et al., 2014; Kuczkowski, 2010; McDonnell et al., 2009). Subsequently surveys reveal not only large differences of pain treatment strategies between countries but also within those countries (Aluri and Wrench, 2014; Van Houwe et al., 2006; Jacques et al., 2013; Marcus et al., 2011). Specifically, there seems to be a reluctance of recommending the use of opioids after CS. Concerns specifically aim at the potential risk of drug transmission to the newborn during breastfeeding. Regional anaesthesia is propagated as the technique of choice for CS and spinal anaesthesia became the anaesthesia technique most frequently used for scheduled CS in Germany as well as in many other countries.

The aim of this prospective multicentre cohort study was to assess the quality of pain treatment after CS in daily clinical practice. Therefore we analysed various pain-related variables and compared these with other surgeries of the uterus. A further aim of the study was to identify potential causes of insufficient postoperative pain treatment. Thus, the effects of different analgesic techniques on pain outcomes were compared.

METHODS

For this study data from the Quality Improvement in Postoperative Pain Treatment project (QUIPS) which were collected between 2004 and 2010 were used. QUIPS is a benchmark initiative to compare pain outcome parameters among participating hospitals. This project is supported by the German Societies of Anaesthesiologists and the German Societies of Surgeons (Meissner et al., 2008).
The project was approved by the ethics committee as well as the data security board of Jena University Hospital, Jena, Germany and all participating sites obtained approval from their respective ethics committees. Patients were informed in written form as well as orally by the study personnel. Participation was voluntary and withdrawal was possible at any time. Strict anonymization of the data was performed by data entry into the web-based QUIPS data base. Inclusion criteria were patients' age ≥18 and voluntary completion of the questionnaire on the first postoperative day after scheduled surgery. Informed consent was documented by filling in the questionnaire. Exclusion criteria as defined by the QUIPS project were as follows: the patient refused participation, could not communicate in German, had cognitive deficits or was sedated or asleep. Additionally, patients that had been transferred to another ward after surgery, that were not present in their room at the time of data collection or had been discharged were not enrolled.
The validated 15-item questionnaire asked for worst and least pain intensities since surgery using a numeric rating scale (NRS: 0 = no pain, 10 = worst pain imaginable) (Rothaug et al., 2012). Pain-related interference was assessed using the four items: pain-related interference with movement, pain-related interference with deep breathing or coughing; waking-up due to pain, and pain-related interference with mood. Side effects like nausea, vomiting, and severe tiredness were further items as well as the question for preexisting chronic pain and the wish to have received more analgesics.

The trained study personnel in charge of data collection were not involved in anaesthesia and postoperative care. They documented variables related to anaesthesia, surgery and pain treatment, the use of analgesics and the doses of the different opioids administered. Opioid doses were converted to intravenous morphine equivalents using conversion factors described elsewhere (Gerbershagen et al., 2013). As a huge amount of different non-opioids were used and a calculation of equianalgesic doses is not feasible, only the item whether non-opioids were used or not was evaluated.

For the current study data on all women who were registered with caesarean section as the main procedure in the QUIPS registry were analysed. We compared characteristics of these women to those of patients after abdominal hysterectomy (AH), laparoscopic-assisted vaginal hysterectomy (LAVH), and vaginal hysterectomy (VH). These three types of surgeries were chosen as these are also lower abdominal surgeries performed on the uterus.

Statistical analysis

Data are presented as mean and standard deviation (SD) and as median and 1st/3rd quartile where appropriate. In a first step four different types of surgery (CS, AH, LAVH, VH) and in a second step five different analgesia / anaesthesia techniques used in CS patients were compared. For CS we compared the following five analgesic regimens: general anaesthesia (GA) with and without postoperative i.v. patient-controlled analgesia (PCA), spinal anaesthesia (SA) with and without PCA and epidural analgesia (EA).

To analyse differences in opioid consumption after the various uterine surgeries pair-wise Mann-Whitney tests were used with CS as the reference group comparing the 4 surgical procedures. Spinal anaesthesia with PCA was used as the reference group when comparing the 5 pain treatment procedures after CS.

General linear models were applied to compare worst pain and pain during movement among CS, AH, LAVH, and VH patients and the five pain treatment groups in CS patients. Crude data and data adjusted for the well-described confounders age and preoperative chronic pain were calculated. Adjustment for these confounders was not applied in CS patients comparing different analgesic treatments due to very low incidences of chronic pain and small differences in age.

Binomial regression analysis was applied when analysing the items 'wish to have received more analgesics', the four pain-related interferences (interference with mood, sleep, deep breathing, and movement) and side effects (nausea, vomiting,

and severe tiredness). Due to multiple comparisons the significance level was adjusted to p <0.001. Data were analysed using SPSS 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Comparison between CS and hysterectomies

A total of 811 patients undergoing CS from 34 obstetric departments and 2,406 hysterectomies from 54 gynaecological departments were included in this study. The 34 hospitals that included the CS patients have also contributed 65% of the hysterectomy study population. Table 1 shows the demographic and anaesthesia related data as well as the incidence of preoperative existing chronic pain. Patients undergoing hysterectomy more often reported preexisting chronic pain before surgery than CS-patients. Main anaesthetic technique was SA for CS and GA for hysterectomies (table 1).

Analgesic treatment and side effects

In 610 CS patients (75.2%) opioid use could be analysed. The majority of these patients (n = 384, 63.0%) did not receive any opioids on the surgical ward after discharge from the recovery room. Pairwise analyses demonstrated that CS patients received significantly less opioids compared to patients of each of the hysterectomy groups (each comparison p < 0.001) (table 2).

Data entry for non-opioids used after surgery was complete for 688 (84.8%) of the CS and 2000 (83.1%) of the hysterectomy patients. Non-opioids were administered to 85.3% of CS patients. Frequency of non-opioid administration in the three hysterectomy groups ranged between 84.6% and 87.5%.

Postoperative pain intensity

Worst pain intensity and pain during movement were significantly higher after CS compared to the three hysterectomy groups (p < 0.001) (table 2). Generalised linear models also indicated significantly higher scores for worst pain and pain during movement after adjusting for age and preoperative chronic pain (p < 0.001) compared to VH and LAVH with no difference to worst pain after AH (table 2).

Table 1. Demographic and clinical data

	Caesarean section n = 811		Abdominal hysterectomy n = 682		Vaginal hysterectomy (lap-assisted) n = 226		Vaginal hysterectomy n = 1498	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age (years)								
18-30	442	(54.5)	3	(0.4)	1	(0.4)	8	(0.5)
31-40	343	(42.3)	75	(11.0)	27	(11.9)	163	(10.9)
41-50	24	(3.0)	327	(47.9)	126	(55.8)	695	(46.4)
51-60	-	-	161	(23.6)	37	(16.4)	258	(17.2)
61-70	-	-	79	(11.6)	22	(9.7)	230	(15.4)
> 70	-	-	31	(5.4)	13	(5.8)	144	(9.1)
Missing data	2	(0.2)	-		-	-	-	-
Preoperative chronic pain								
No pain	724	(89.3)	543	(79.6)	171	(75.7)	1180	(78.8)
Pain	20	(2.6)	96	(14.1)	41	(18.1)	262	(17.5)
Missing data	67	(8.3)	43	(6.3)	14	(6.2)	56	(3.7)
Type of anaesthesia								
Epidural	67	(8.3)	-	-	-	-	-	-
Spinal	470	(58.0)	-	-	-	-	-	-
General (GA)	202	(24.9)	579	(84.9)	220	(97.3)	1287	(86.0)
GA+epidural	-	-	49	(7.2)	1	(0.4)	16	(1.1)
Missing data	72	(8.9)	54	(7.9)	5	(2.2)	195	(12.9)
PCA	151	(18.6)	82	(12.0)	15	(6.6)	155	(10.3)
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Duration of surgery (min)	37	30;47	90	70;115	105	83;133	61	45;85

PCA (intravenous patient-controlled analgesia), lap-assisted (laparoscopic-assisted), epidural (epidural anaesthesia with catheter placement), IQR = interquartile range

Wish to have received more analgesics

On the first postoperative day, 14.1%, 12.8%, 11.2%, and 9.2% of the CS, AH, LAVH, and VH patients respectively reported that they wished to have received more analgesics since surgery. A significant difference was only present between CS and VH in crude regression analysis (table 2). After correction for age and preoperative chronic pain however no statistical significant differences were seen.

Pain-related interference

Patients after LAVH and VH reported less pain-related interference with movement compared to CS (table 2). Patients after CS and AH reported that their

movement was interfered by pain in 69% and 72% of cases, which resulted in a significant difference after adjusting for age and preoperative chronic pain.
Pain interference with coughing and deep breathing was significantly more often present after CS (66%) compared to all three types of hysterectomy (ranging between 30 – 56%). After adjustment for age and preoperative chronic pain, however, the differences between CS and AH were no longer significant.
Waking up due to pain occurred significantly more often in CS patients (47%) compared to the three hysterectomy groups (between 31% and 36%). However, again, after adjusting for age and preoperative chronic pain no differences remained between these groups (table 2). Mood was similarly impaired by pain in all surgical groups (incidences between 17% and 21%).

Table 2. Comparison of analgesics use, pain intensities, wish to have received more analgesics and four pain interference variables during the first 24 postoperative hours of cesarean section with abdominal, vaginal laparoscopic-assisted , and vaginal hysterectomy

	Caesarean section n = 811		Abdominal hysterectomy n = 682				Vaginal hysterectomy laparoscopic-assisted n = 226				Vaginal hysterectomy n = 1498			
ANALGESICS						p-value				p-value				p-value
Morphine iv (mg) (median, IQR)	0	(0;10)	7 (0;13)			<0.001	10 (0;13)			<0.001	5 (0;12)			<0.001
No opioids received (%)	63		34			<0.001	34			<0.001	43			<0.001
PAIN INTENSITY	NRS	99.9% CI	NRS		99.9% CI	p-value	NRS		99.9% CI	p-value	NRS		99.9% CI	p-value
Worst pain	6.2	5.9;6.4	5.3		5.0;5.6		4.4		3.8;4.9		4.8		4.6;5.1	
Unadjusted						<0.001				<0.001				<0.001
Adjusted						0.081				<0.001				<0.001
Pain during movement	5.2	4.9;5.4	4.4		4.1;4.6		3.5		3.0;4.0		3.5		3.3;3.7	
Unadjusted						<0.001				<0.001				<0.001
Adjusted						0.848				<0.001				0.003
	%	Ref	%	RR	99.9% CI	p-value	%	RR	99.9% CI	p-value	%	RR	99.9% CI	p-value
Wish for more analgesics	14		13				11				9			
Unadjusted		1		0.90	0.60;1.36	0.428		0.80	0.42;1.52	0.276		0.66	0.45;0.95	<0.000
Adjusted		1		1.38	0.80;2.38	0.071		1.25	0.61;2,55	0.335		1.03	0.61;1,73	0.864
INTERFERENCES														
Pain interferes with movement	69		72				50				44			
Unadjusted		1		1.05	0.95;1.16	0.149		0.72	0.58;0.90	<0.001		0.64	0.57;0.72	<0.001
Adjusted		1		1.23	1.07;1.42	<0.001		0.83	0.64;1.05	0.015		0.75	0.64;0.88	<0.001
Pain interferes with deep breathing or coughing	66		56				37				30			
Unadjusted		1		0.85	0.74;0.97	<0.001		0.56	0.43;0.75	<0.001		0.46	0.39;0.53	<0.001
Adjusted		1		1.01	0.83,1.23	0.860		0.64	0.47;0.89	<0.001		0.54	0.44;0.67	<0.001
Waking up due to pain	47		33				31				36			
Unadjusted		1		0.70	0.57;0.86	<0.001		0.66	0.47;0.92	<0.001		0.76	0.65;0.89	<0.001
Adjusted		1		0.87	0.67;1.13	0.100		0.79	0.55;1.15	0.052		0.95	0.76;1.20	0.518
Pain interferes with mood	19		22				17				18			
Unadjusted		1		1.19	0.87;1.64	0.088		0.94	0.57;1.56	0.696		0.95	0.71;1.26	0.947
Adjusted		1		1.61	1.08;2.41	<0.001		1.27	0.74;2.18	0.174		1.27	0.87;1.86	0.053

CI = confidence interval; RR = relative risk; Ref = reference group; NRS = numeric rating scale;
Morphine dosage calculated as iv morphine equivalent dosage (comparison with pairwise Mann-Whitney test)
For comparison of pain intensities general linear models were used; Adjusted analysis: adjusted for age and presence of preoperative chronic pain
Following Bonferroni correction for multiple comparison significance level was adjusted to $p < 0.001$; corresponding to a 99.9% CI

2. Comparison of CS patients with five different analgesic treatments

Use of analgesics in CS patients

Patients with PCA after SA and GA administered similarly high doses of intravenous morphine equivalents: median 30 mg (IQR 26-38) and 28 mg (IQR 18-30) (table 3). In contrast, when no PCA was used after SA and GA administered opioid doses were significantly lower ($p < 0.001$). The majority of the two groups without PCA (SA 81%, GA 59%) did not even receive any opioids after discharge from the recovery room (table 3). Non-opioid analgesics were administered on the ward in patients with PCA (SA and GA) in 60% only whereas patients without PCA (SA and GA) received non-opioids in 91% of the cases

Pain intensity

Worst pain intensities after GA and SA with or without PCA were between NRS 5.8 and 6.4 and pain during movement between NRS 4.7 and 5.4. Only in patients with epidural analgesia the two pain intensity scores were significantly lower (table 3).

Wish to have received more analgesia

The wish to have received more analgesics was reported after SA with and without PCA in 7% and 16%, after GA with and without PCA in 7% and 15%, and in patients with EA in 12% of the cases (table 3).The large differences in opioid doses between patients with and without PCA and the resulting wish to have received more analgesics are illustrated in figure 1. However, the differences in the wish to have received more analgesics between the five analgesics groups were not statistically significant.

Pain-related interferences

No significant differences in pain-related interferences were observed between the five analgesic groups (table 3). However, patients after SA and GA with PCA reported similar pain-inferences with movement and deep breathing with incidences around 50%. In contrast, patients after SA and GA without PCA had higher incidences around 70% regarding pain-interferences with movement and deep breathing. Comparisons between SA with PCA and SA and GA without PCA did not differ statistically significant (p values ranged between 0.004 and 0.013).

Waking up due to pain occurred between 30% and 50% of the participants with lowest scores in the EA group. Mood was interfered by pain in patients with SA and PCA in 7% and after SA without PCA in 22% ($p = 0.013$) (table 3).

Table 3. Comparison of pain intensities, wish to have received more analgesics, four pain interference variables, and analgesic use during the first 24 postoperative hours after cesarean section among different analgesic treatment groups

	Spinal anesthesia						General anesthesia						Epidural analgesia			
	with PCA n = 69			without PCA n = 401			with PCA n = 46			without PCA n = 156			n = 67			
ANALGESICS						p-value			p-value			p-value				p-value
Morphine iv (mg) (median; IQR)	30	26; 38		0	0; 0	<0.001	28	18; 30	0.007	0	0; 10	<0.001	0	0; 7		<0.001
No opioids received (%)	0			81			0			60			54			
PAIN INTENSITY	NRS	99.9% CI		NRS	99.9% CI	p-value	NRS	99.9% CI	p-value	NRS	99.9% CI	p-value	NRS	99.9% CI		p-value
Worst pain	6.3	5.5; 7.0		6.4	6.0; 6.7	0.782	5.8	4.8; 6.8	0.278	6.2	5.6; 6.8	0.815	5.0	3.8; 6.2		0.001
Pain during movement	5.3	4.5; 6.1		5.4	5.0; 5.7	0.763	4.7	4.0; 5.5	0.190	5.0	4.4; 5.5	0.303	4.0	3.1 ;5.0		0.001
	%	ref	%	RR	99.9% CI	p-value	%	RR	99.9% CI	p-value	%	RR	99.9% CI	p-value	%	RR	99.9% CI	p-value
Wish for more analgesics	7	1	16	2.17	0.54; 8.66	0.082	7	0.90	0.10; 8.01	0.881	15	2.12	0.49; 9.11	0.109	12	1.65	0.31; 8.89	0.358
INTERFERENCE																		
Movement	52	1	73	1.41	0.97; 2.03	0.004	52	1.00	0.57; 1.76	1.000	73	1.40	0.95; 2.06	0.007	52	1.00	0.60; 1.67	0.994
Deep breathing	49	1	68	1.37	0.93; 2.03	0.013	50	1.02	0.56; 1.83	0.939	72	1.47	0.97; 2.21	0.004	55	1.12	0.67; 1.87	0.488
Waking up	55	1	49	0.90	0.62; 1.30	0.363	50	0.91	0.51; 1.60	0.598	42	0.77	0.49; 1.20	0.066	30	0-54	0.28; 1.06	0.005
Mood	7	1	22	3.00	0.76; 11.7	0.013	15	2.10	0.38; 11.70	0.180	16	2.23	0.52; 9.50	0.087	15	2.06	0.41; 10.33	0.520
SIDE EFFECTS																		
Nausea	28	1	15	0.55	0.27; 1.12	0.009	20	0.71	0.23; 2.15	0.339	17	0.63	0.28; 1.41	0.077	18	0.65	0.24; 1.79	0.188
Vomiting	10	1	6	0.60	0.17; 2.13	0.213	7	0.62	0.08; 4.87	0.477	7	0.68	0.16; 2.81	0.394	6	0.57	0.09; 3.70	0.353
Severe tiredness	64	1	41	0.64	0.46; 0.90	<0.001	69	1.08	0.71; 1.64	0.568	58	0.92	0.64; 1.30	0.431	34	0.54	0.30; 0.98	<0.001

CI = confidence interval; RR = relative risk; ref = reference group; PCA = intravenous patient controlled analgesia; IQR = interquartile range; NRS = numeric rating scale

Movement = pain-related interferes with movement; deep breathing = pain-related interferes with deep breathing or coughing; waking up = waking up due to pain; mood = pain-related interference with mood

Opioid dosage calculated as i.v. morphine equivalent dose (pairwise comparisons with "Spinal anesthesia with PCA" using Mann-Whitney test). Morphine dose and "no opioids received" were registered on the surgical ward after discharge from recovery room.

For comparison of pain intensities general linear models were used

Following Bonferroni correction for multiple comparisons significance level was adjusted to $p < 0.001$; corresponding to a 99.9% CI

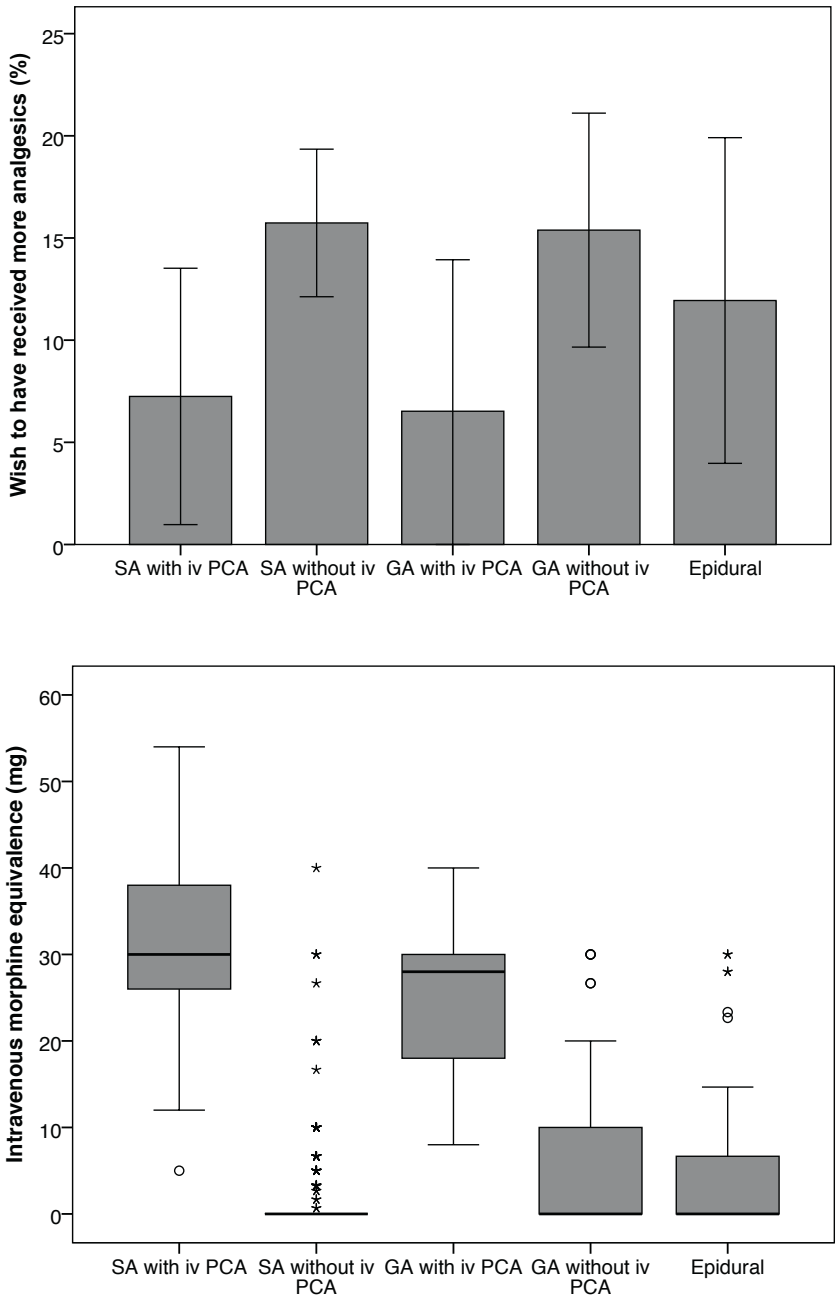

Figure 1. A) Comparison of intravenous morphine equivalents and 1B) wish to have received more analgesics between patients having received spinal anaesthesia (SA) with and without postoperative i.v. patient controlled analgesia (PCA), was well as general anaesthesia (GA) with and without postoperative i.v. PCA or epidural analgesia.

Side effects

Differences in side effects, nausea, vomiting and severe tiredness between the treatment groups were analysed and compared to patients with SA and PCA as a reference group. Among the five different pain treatment groups only severe tiredness was significantly lower in the SA without PCA group and in patients with epidural analgesia ($p < 0.001$) (table 3).

DISCUSSION

This multicentre, prospective cohort study demonstrates that many women still receive insufficient pain treatment after CS. Compared to three different types of hysterectomy CS-patients reported significantly higher pain scores and were more interfered by pain while receiving significantly less opioids. This study demonstrates that pain scores after CS were much higher in clinical practice than would have been expected from many RCTs.

Analyses of different analgesic treatments after CS revealed that patients following SA and GA without PCA received very low amounts of opioids, if any, on the obstetric ward. Although the anaesthesia/analgesia groups indicated non-statistically significant differences in pain-related interferences the distribution among patients with and without PCA independent of the anaesthesia technique is noticeable. In all women receiving a PCA-device for pain control pain-related interferences with movement as well as with deep breathing were around 50% in contrast to 70% in those without a PCA device. The p-values ranged between 0.004 and 0.013 and thus did not reach the conservative significance level of $p < 0.001$. Overall, EA resulted in the significantly lowest pain scores.

Pain intensity scores are widely used to assess quality of postoperative pain treatment and arbitrary cut-off values (e.g. NRS > 4) are often applied to identify patients with inadequate analgesia. However, such cut-offs cannot differentiate 'sufficient' from 'insufficient' pain treatment or detect patients who are in need for more analgesics (van Dijk et al., 2014; Gerbershagen et al., 2011; Schwenkglenks et al., 2014). Furthermore, quality of postoperative pain treatment and postoperative recovery does not only comprise pain intensity, but is regarded as a multidimensional outcome (Gerbershagen et al., 2009; Neville et al., 2014; Schwenkglenks et al., 2014) Thus, in the present study not only pain

scores but also pain related impairment were studied. As these measures have not been used before in obstetric pain studies a comparison to patients undergoing hysterectomies was performed. Patients undergoing hysterectomy are, however, typically older than patients undergoing caesarean section. Younger age and preoperative chronic pain have been shown to be significant risk factors for severe postoperative pain (Gerbershagen et al., 2014; Ip et al., 2009). After adjusting for these risk factors CS was still significantly associated with higher pain scores compared to the hysterectomies and reported more impairment when moving or taking deep breaths. These unfavourable pain-related measures after CS together with a lower opioid use compared to the hysterectomy patients suggest substantial shortcomings in the quality of postoperative pain treatment after CS.

To elucidate the reasons for the worse outcome after CS, different analgesic treatments in the cohort were compared. In our study pain scores were high compared to many RCTs with the exception of patients receiving EA. The study protocols for these RCTs typically allowed prompt availability of rescue analgesic therapy, most often in the form of PCA. Also, they use stringent exclusion criteria. To our knowledge, our analysis is the first cohort study that evaluated pain experience after CS in the everyday clinical setting.

Morphine use via PCA could be as low as 2.7 mg within 24 hours when using sufficient regional anaesthesia (Loane et al., 2012). However, in most of the above-mentioned studies, patients with a PCA and without regional analgesia consumed 30 to 55 mg i.v. morphine during the first 24 hours after CS (Bozkurt et al., 2009; Fassoulaki et al., 2004; Munishankar et al., 2008; Ngan Kee et al., 1997, 2002; Paraskeva et al., 2009, 2012). This concurs with our findings in patients with SA and GA and i.v. PCA, who self-administered about 30 mg of i.v. morphine. However, in our study 62% of the patients did not receive any opioids after discharge from the recovery room when they did not have a PCA. Even those patients without a PCA pump but who received opioids on the ward had relatively low median i.v. morphine equivalent doses of 13 mg (IQR 8-30 mg) compared to the studies cited above with 30-55 mg i.v. morphine.

Due to our conservative statistical correction for multiple comparisons, differences in pain-related interferences with movement, deep breathing, and mood (p-values between 0.004 and 0.013) were not statistically significant. Furthermore, because PCA use was infrequent, group sizes were small, contributing to large confidence intervals and statistically non-significant results. However, the absolute differences

in pain-related interferences were large and likely indicate clinically important differences in favour of patients provided with PCA and EA.
The same applies to the 'wish for more analgesics'. Patients without PCA reported a wish for more analgesics twice as frequent (16%) as PCA users (7%). Comparing the wish for more analgesics between 179 different types of surgery from the QUIPS benchmarking study (more than 70,000 patients) (Gerbershagen et al., 2013), patients after CS with PCA would rank 44 whereas patients without PCA would rank 124 in their wish for more analgesics.

The question arises why patients after CS are particularly at risk to develop severe pain in daily clinical practice. Recent literature points out that there is no gold standard for pain treatment after CS (Kuczkowski, 2010; McDonnell et al., 2009). In the comprehensive German acute pain treatment guidelines no specific recommendations are given for pain treatment after CS. Furthermore, contradictory guidelines and considerations for opioid use during breastfeeding have been published. German guidelines recommend avoiding the use of morphine in the breastfeeding period and using other opioids such as piritramide for "compelling reasons" only (Laubenthal et al., 2008). The British National Formulary guidelines advise that therapeutic doses of morphine given to the breastfeeding mother are unlikely to affect the newborn (Soltanifar and Russell, 2012). The elaborate acute pain treatment guidelines of the Australian and New Zealand College of Anaesthetists consider morphine to be safe in the lactating patient (Macintyre et al., 2010). This concept has recently been supported by a review that found no single case report of infant opioid toxicity when the mother was using morphine (Hendrickson and McKeown, 2011. According to the recently updated American guidelines of The Academy of Breastfeeding Medicine morphine is preferred due to its limited transfer in milk and its poor oral bioavailability in infants (Montgomery and Hale, 2012).
Due to these conflicting guidelines and recommendations, medical staff may opt to restrict the administration of opioids following the principle 'primum non nocere', leaving many women without adequate pain therapy after CS. Furthermore, if new mothers who are pointed to potential side effects of opioids in their newborn or necessity of discarding milk, it can be assumed that they will avoid such medication and instead bear also severe pain. Remarkably, when offering PCA, and thus bypassing nurse-controlled opioid administration, the patients used opioids in amounts comparable to those in many RCTs on analgesia

after CS. Furthermore, the high incidence of women wishing more analgesics after CS suggests that undertreatment in this population is not solely caused by patients' refusal to receive pain medication. These results point out that education of both, the caregivers and the young mothers is essential to improve postoperative pain treatment after CS.
Possible other reasons for withholding opioids from CS patients might be poor overall process quality of pain treatment on the wards. This is not highly likely, as women after open and laparoscopic hysterectomies received considerably more opioids, even when reporting lower pain scores.

This study has some limitations. It is a single-country study and clinical practice in Western countries might differ. The doses of the different non-opioid analgesics used could not be evaluated and variations in the use of these substances may have influenced our findings.
As intrathecaly administered opioids were not documented, we cannot assess whether this had an influence on postoperative analgesia. Intrathecal morphine for example has a long lasting effect (average of 12 hours) compared to fentanyl (2 hours) (Pöpping et al., 2012)1932 of whom received opioids. However, a survey revealed that intrathecal morphine is administered in only 4% of the German hospitals (Marcus et al., 2011). Assuming that participating hospitals in the present study were also reluctant to use spinal morphine this would further support the hypothesis that patients were in need of more opioid treatment.
Though we could adjust for the known confounders age and preoperative chronic pain data on preoperative emotional status such as anxiety or depression were not available which could have influenced the results. Additionally, it has to be pointed out that patients undergoing CS are in a distinctly different emotional status than patients undergoing hysterectomy.
In recent studies transabdominal plain blocks demonstrated good results on pain intensity and opioid consumption in patients without neuraxial blocks. In our study population this regional anaesthesia technique has not been used (Mishriky et al., 2012; Wieczorek, 2014).
In conclusion, this study indicates that analgesic treatment after CS in the everyday clinical setting is often insufficient. Pain intensity and most pain-related interferences as well as wish for more analgesics were higher than in abdominal or vaginal hysterectomies. The majority of CS patients were not offered PCA after spinal or general anaesthesia. Those patients received very low doses of

opioids or no opioids at all. Unclear - or even contradictory - guidelines and recommendations for analgesia after CS might contribute to this problem. Use of epidural analgesia was associated with the most favourable relation of pain scores and side effects.

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PART III

Risk factors of postoperative pain

CHAPTER 5

Procedure-specific risk factor analysis for the development of severe postoperative pain

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ABSTRACT

Background

Many studies have analyzed risk factors for the development for severe postoperative pain with contradictory results. The association of risk factors with postoperative pain intensity among different surgical procedures has so far not been studied and compared.

Methods

We selected precisely defined surgical groups (at least 150 patients each) from prospectively collected perioperative data from 105 German hospitals (2004 to 2010). The association of age, gender, and preoperative chronic pain intensity with worst postoperative pain intensity was studied with multiple linear and logistic regression analyses. Pooled data of the selected surgeries were studied with random effect analysis.

Results

Thirty surgical procedures with a total number of 22,963 patients were compared. In each surgical procedure, preoperative chronic pain intensity and younger age was associated with higher postoperative pain intensity. A linear decline of postoperative pain with age was found. Females reported more severe pain in 21 of 23 surgeries. Analysis of pooled surgical groups indicated that postoperative pain decreased by 0.28 points (95% CI 0.26 to 0.31) on the numeric rating scale (0 to 10) per decade age increase and postoperative pain increased by 0.14 points (95% CI 0.13 to 0.15) for each higher score on the preoperative chronic pain scale. Females reported 0.29 points (95% CI 0.22 to 0.37) higher pain intensity.

Conclusions

Independent of the type and extent of surgery, preoperative chronic pain and younger age were associated with higher postoperative pain. Females consistently reported slightly higher pain scores regardless of the type of surgery. The clinical significance of this small gender difference has to be analyzed in future studies.

INTRODUCTION

Some 240 million surgical procedures are performed annually worldwide.[1] Severe pain after surgical procedures is a major factor causing patients' dissatisfaction, delayed recovery, immobility, and prolonged hospital stay in the postoperative period and is associated with severe complications, such as chronic pain.[2,3] A recent study indicated that severe pain is not only an issue after major but also after many minor surgeries.[4] Optimal perioperative pain management is not only an ethical, but also a medical as well as an economic issue. Much effort has been made to improve postoperative pain treatment: implementing guidelines on postoperative pain, providing acute pain services, and increasing the use of regional anesthesia techniques is known to be the most effective for reducing postsurgical pain. Despite these efforts, many patients continue to suffer severe postoperative pain.[3,5,6]

Some major reasons for this unsatisfactory situation have recently been elucidated, one of them being that different surgical procedures may have different mechanisms that produce pain and pain-related consequences. Surgical procedure-specific pain treatment is therefore regarded as the next step towards further improvement of pain management.[7-9] Another problem is that some patients may present certain risk factors for developing more severe postoperative pain than others.[10] The identification of patients at risk may help to permit effective treatment strategies to be initiated at an early stage in order to prevent severe pain in these patients.

Demographic, clinical, and psychological factors have been identified that could be relevant risk factors for the development of severe postoperative pain.[10] However, study designs were non-homogeneous and results were – at least for most risk factors - equivocal. Differences in associations of risk factors with postoperative pain between various types of surgical procedure have not been determined as yet. Risk-factor analyses for postoperative pain have mainly been performed in major abdominal and orthopedic procedures in which it was expected that patients would have severe postoperative pain. Risk factors have been analyzed in both, small cohorts of selected surgeries[11] or larger cohorts with mixed surgical procedures.[12] To date, however, no procedure-specific comparison of risk factors has been performed that might help to further determine optimal procedure and patient specific pain treatment.

The aim of this study was to analyze the associations of age, gender, and preoperative chronic pain with postoperative pain intensity and to compare these associations among various surgical procedures.

MATERIALS AND METHODS

QUIPS registry (Quality Improvement in Postoperative Pain Treatment)

The analysis was based on data from the QUIPS project, which was started as a benchmark initiative to compare pain outcome parameters among participating German hospitals. The QUIPS project is supported by the German Societies and Professional Associations of Anesthesiologists and Surgeons.[13] Patients completed the validated 15-item QUIPS questionnaire on the first postoperative day. Patient-reported data were completed by information on the type of surgery, anesthesia, and pain treatment. Data assessment was carried out by trained study personnel which was not involved in routine care, and pain data were collected in a standardized manner on randomly selected days that were not known to the medical staff prior to data collection. On the survey day, all patients who had been operated upon the day before were considered for inclusion. Patients were informed in written form as well as orally by the study personnel that data collection was voluntary and anonymous, and that they could refuse to be included at any time. Informed consent was documented by filling in the questionnaire. The project was approved by the Ethics Committee as well as the Data Security Board of Jena University Hospital, Jena, Germany and all participating sites obtained approval from their respective Ethics Committees.

Outcome factor and influencing variables

The outcome parameter was defined as worst pain intensity since surgery, measured with the numeric rating scale (NRS) of 0 to 10 (0 = no pain, 10 = worst pain imaginable). The association of age, gender, and preoperative chronic pain with worst postoperative pain intensity was analyzed. Age was documented as 10 year categories. Preoperative chronic pain was defined as persisting for longer than 3 months prior to surgery in any location.

Patients

All patients having completed the QUIPS questionnaire between May 2004 and May 2010 were used for analysis. The inclusion and exclusion criteria were defined by the QUIPS project. Broad inclusion criteria were the day after surgery and admission to a surgical ward. Exclusion criteria were: the patient (1) had been transferred to another ward after surgery; (2) was not present in his room or had been discharged

at the time of data collection; (3) refused to participate in the study; (4) could not communicate in German; (5) had cognitive deficits; or (6) was sedated or asleep. Additional exclusion criteria for the analysis of the present analysis were: (7) missing or incorrect German Surgical Procedure Coding (OPS), which precisely defines the kind of surgery performed; (8) age younger than 18 years; and (9) patients assessed later than the first postoperative day. Further exclusion factors for procedure-specific risk factor analysis were: (10) use of regional anesthesia; and (11) trauma surgery.

Selection of surgical procedures

In order to analyze risk factors for acute postoperative pain, precisely defined surgical groups were formed. The type of surgery was recorded using the OPS, which includes more than 21,000 surgical codes. Based on a specific surgical site, organ system, as well as surgical access, e.g., laparoscopic, open, and endoscopic, 529 detailed surgical groups were defined. Minor differences in the extent of surgical lesions were assigned to one surgical group, e.g., partial, hemi-, or total thyroidectomy. Very rare procedures such as retrosternal thyroidectomy with sternotomy were disregarded.

All patients assigned to one of the 529 groups were individually examined and excluded in case of multiple surgeries. Thus, for example, patients were excluded from the cholecystectomy group if an additional appendectomy was performed. Patients were also not included if they underwent a more extensive procedure than the one precisely defined by the surgical group, e.g., left hemicolectomy with an additional sigmoid resection.

As regional anesthesia regularly results in lower postoperative pain scores, only patients undergoing general anesthesia were included in order to generate comparable study groups. Trauma patients were excluded from procedure-specific risk factor analysis, as different types of fractures, differences in soft-tissue damage, and differing surgical techniques could have influenced postoperative pain scores. For the analysis, only surgical groups with more than 150 patients were included.

Statistical analysis

The influences of age, gender, and preoperative chronic pain intensity on worst postoperative pain were analyzed by multiple linear regression models containing these three variables as independent risk factors and worst postoperative pain as the outcome. To arrive at procedure-specific estimates this was done for each surgical group with more than 150 patients separately.

Patients with severe pain are of special interest, as they suffer the most and could benefit the most from sufficient pain treatment. Therefore, we also report the associations of the three risk factors with the development of severe postoperative pain (NRS ≥ 7). Logistic regression was used to represent the odds ratios (OR) of each influencing variable.

Patients from all surgical groups with more than 150 patients were pooled into one dataset to analyze the total effect of the influencing variables. Since clustering was expected on a procedural level because specific surgical procedures were likely to have their own specific pain profiles, additional linear and logistic mixed effect regression analyses were performed (glmer, lme4 library, (R software, 2013, R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org)). All three influencing factors were included as fixed effects. As the relationship among influencing variables and postoperative pain intensity was expected to be procedure-dependent (cluster-dependent), a random slope was included in the mixed-effects model for each of the three factors in addition to a random intercept. In addition to procedure–specific estimates for age, gender, and preoperative pain derived from separate models for each surgical procedure, we also included procedure-specific estimates directly derived from the random-effect model; obtained by combining fixed and random effects for each procedure.

Before statistical analyses, pre- and postoperative NRS variables were tested for nonlinearity using restricted cubic splines.[14] For this assessment, predicted postoperative NRS values as calculated from a simple regression model using preoperative NRS values were visually compared to predicted postoperative NRS values from a regression model using restricted cubic splines to model preoperative NRS values.

Missing data were multiply imputed (n = 10). Imputation of missing variables was based on risk factors, outcome variables, and other perioperative data.[15-17] The type of surgical procedure was added as an extra variable to the imputation model to take into account the multilevel structure of the data. Estimates from the imputation sets were combined using Rubin's rule.[18]

RESULTS

Data were collected from 115,437 surgical patients on 578 surgical wards in 105 German hospitals. The number and type of exclusion criteria are presented

in figure 1. For the procedure-specific risk factor analysis, the inclusion criteria were met by 30 surgical groups comprising 22,963 patients (13 general surgery, 6 gynecology, 4 orthopedics, 2 otolaryngological surgery, 2 neurosurgery, 2 urology, 1 vascular surgery) (figure 2). Demographic and clinical data are shown in table 1. The mean worst pain intensity since surgery for all included patients was NRS 4.6 (standard deviation [SD] 2.5). Overall, 24.5% of the 22,963 patients reported severe pain of NRS ≥ 7.

Table 1. Demographic and clinical data (n = 22,963)

	Raw data		Imputated data	
	n	%	n	%
Gender				
Male	9,211	40.1	9,224	40.2
Female	13,719	59.8	13,739	59.8
Missing	33	0.1	-	-
Preoperative chronic pain intensity				
no pain	13,603	59.2	14,987	65.3
NRS 1	141	0.6	156	0.7
NRS 2	302	1.3	329	1.4
NRS 3	619	2.7	675	2.9
NRS 4	725	3.2	786	3.4
NRS 5	1,024	4.5	1,115	4.9
NRS 6	889	3.9	958	4.2
NRS 7	1,022	4.5	1,101	4.8
NRS 8	1,365	5.9	1,466	6.4
NRS 9	592	2.6	646	2.8
NRS 10	688	3.0	744	3.2
missing	1,983	8.6	-	-
Age (years)				
18-20	516	2.2		
21-30	1,362	5.9		
31-40	2,137	9.3		
41-50	4,536	19.8		
51-60	4,597	20.0		
61-70	5,187	22.6		
71-80	3,843	16.8		
> 80	785	3.4		

NRS (numeric rating scale)

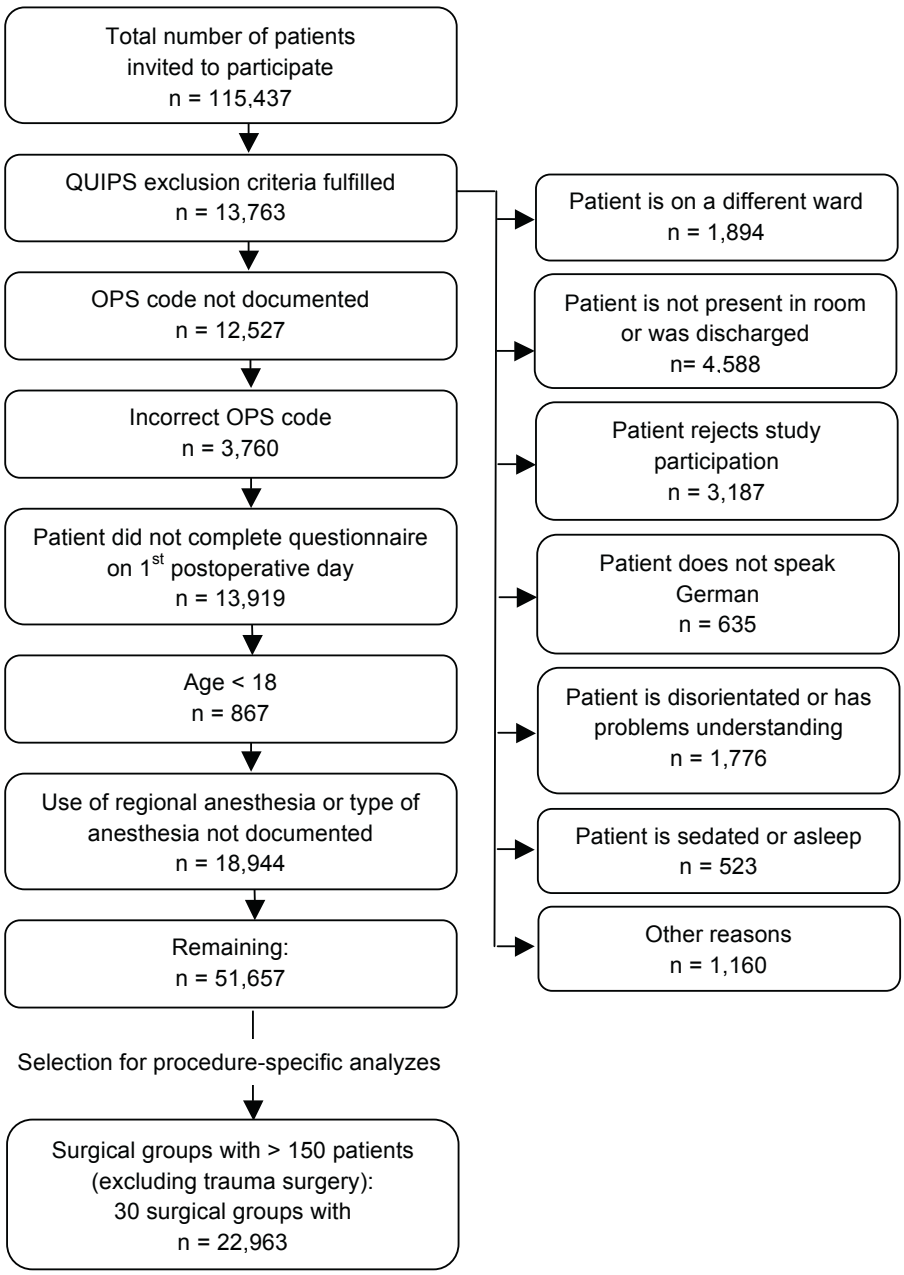

Figure 1. Number of patients and exclusion criteria. OPS = German; Surgical Procedure Coding; QUIPS = Quality Improvement of Postoperative Pain Treatment project.

Procedure-specific risk-factor analysis

In all 30 surgical groups preoperative chronic pain intensity was positively related to higher postoperative pain intensity (range of regression coefficients: 0.05 to 0.33) (figure 2). Twenty of the 30 surgical groups had regression coefficients between 0.1 and 0.25 (figure 2). Postoperative pain intensity decreased consistently with higher age categories for all surgical procedures. Regression coefficients ranked between -0.06 and -0.53. In 20 of the 30 surgical procedures the regression coefficients ranked between -0.15 and -0.35.

Females reported higher postoperative pain intensities for all but two surgical procedures: Pain intensity was 0.1 to 0.5 NRS points higher for 15 of 23 procedures (range of all surgical procedures: -0.31 to 0.71) (figure 2). Data per surgical group on pain intensity, frequency of preoperative pain, distribution between the sexes, and regression coefficients are presented as supplemental online material in web-based table 1.

The influence of the three risk factors on the development of severe pain defined as NRS ≥ 7 was calculated using logistic regression analyses. In figure 3 the adjusted OR for each of the three risk factors are presented per surgical procedure.

The relations between the three risk factors and postoperative pain are demonstrated by the findings for the total study population (figure 4) and the four most often performed procedures each including more than 1,200 patients (laparoscopic cholecystectomy, total hip replacement, thyroidectomy, and vaginal hysterectomy) (figure 5). In the total study population and in all of the four procedures, a nearly linear decline in pain intensity was observed with increasing age. The difference in postoperative pain intensity between chronic and non-chronic pain patients remained almost constant over the different age categories in all surgical groups. The higher pain intensities in females were observed consistently over all age groups and patients with preoperative chronic pain, as shown for the total population (figure 4), and were similar in the four largest surgical groups (data not shown).

Analysis of data from 30 pooled surgical groups

Thirty surgical procedures were included for procedure-specific risk factor analysis. The random effect analysis that adjusted for the type of surgery indicated significant associations of age, gender, and preoperative chronic pain with postoperative pain intensity. It was demonstrated that postoperative pain decreased by 0.28 NRS points (95% CI 0.26 to 0.31) per increase of one age category (decade) (figure 2). Postoperative pain intensity increased by 0.14 NRS points (95% CI 0.13 to 0.15) for each higher score on the preoperative chronic pain scale. Females reported 0.29 NRS points (95% CI 0.22 to 0.37) higher mean pain intensity than males.

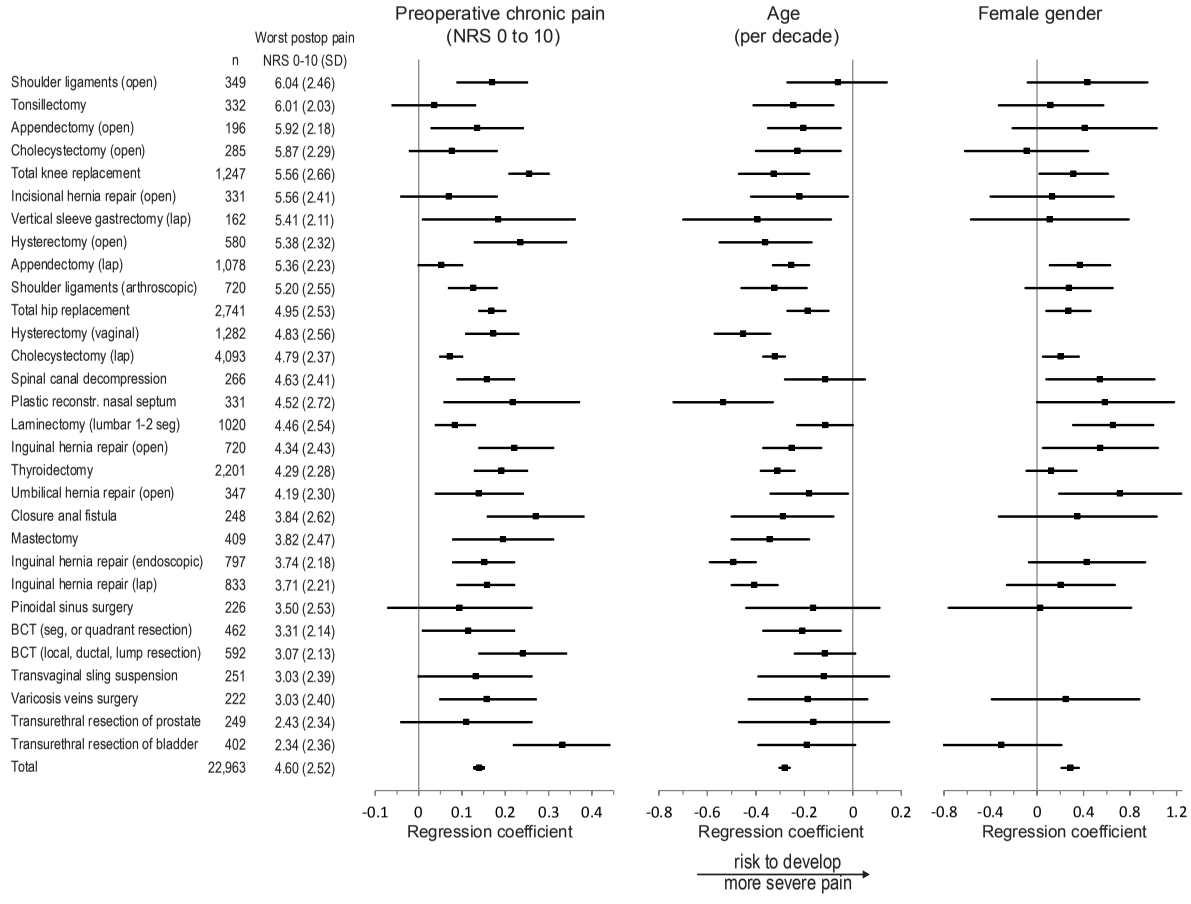

Figure 2. Comparison of the three risk factors age, preoperative chronic pain intensity, and female sex on postoperative pain intensity. The 30 surgical procedures that included more than 150 patients who received general anesthesia without regional anesthesia were selected. Plots show regression coefficients (95% CI) of multiple linear regression analysis of each surgical procedure. The analysis of the total study population (n = 22,963) is based on mixed-effect linear regression analysis with random slope and random intercept adjusting for the type of surgery. Age categories: 18–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80, and >80 yr. Preoperative chronic pain intensity: numeric rating scale (NRS) 0 to 10 (0 = no pain and 10 = worst pain imaginable). BCT = breast conservative therapy; lap = laparoscopic; OPS = German Surgical Procedure Coding; QUIPS = Quality Improvement in Postoperative Pain Treatment project; seg = segmental.

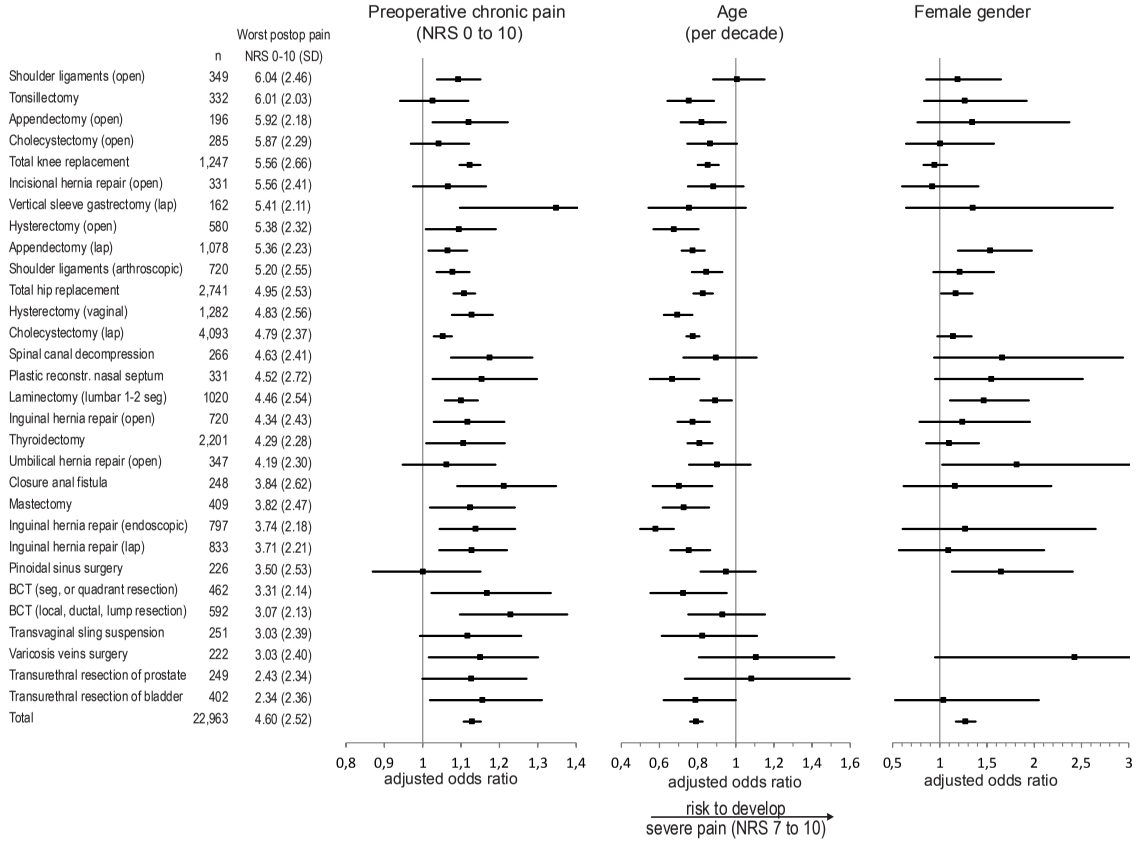

Figure 3. Comparison of the three risk factors age, preoperative chronic pain intensity, and female sex on postoperative pain intensity. The 30 surgical procedures that included more than 150 patients who received general anesthesia without regional anesthesia were selected. *Plots* show odds ratios (95% CI) for severe pain (NRS ≥7) for each surgical procedure. The analysis of the total study population (n = 22,963) is based on mixed-effect logistic regression analysis with random slope and random intercept adjusting for the type of surgery. Age categories: 18–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80, and >80 yr. Preoperative chronic pain intensity: numeric rating scale (NRS) 0–10 (0 = no pain, 10 = worst pain imaginable). Odds ratio for preoperative chronic pain in vertical sleeve patients is 1.35 (1.10–1.66) and for female sex in varicosis veins surgery is 2.43 (0.95–6.21). BCT = breast conservative therapy; lap = laparoscopic; OPS = German Surgical Procedure Coding; QUIPS = Quality Improvement in Postoperative Pain Treatment project; seg = segmental.

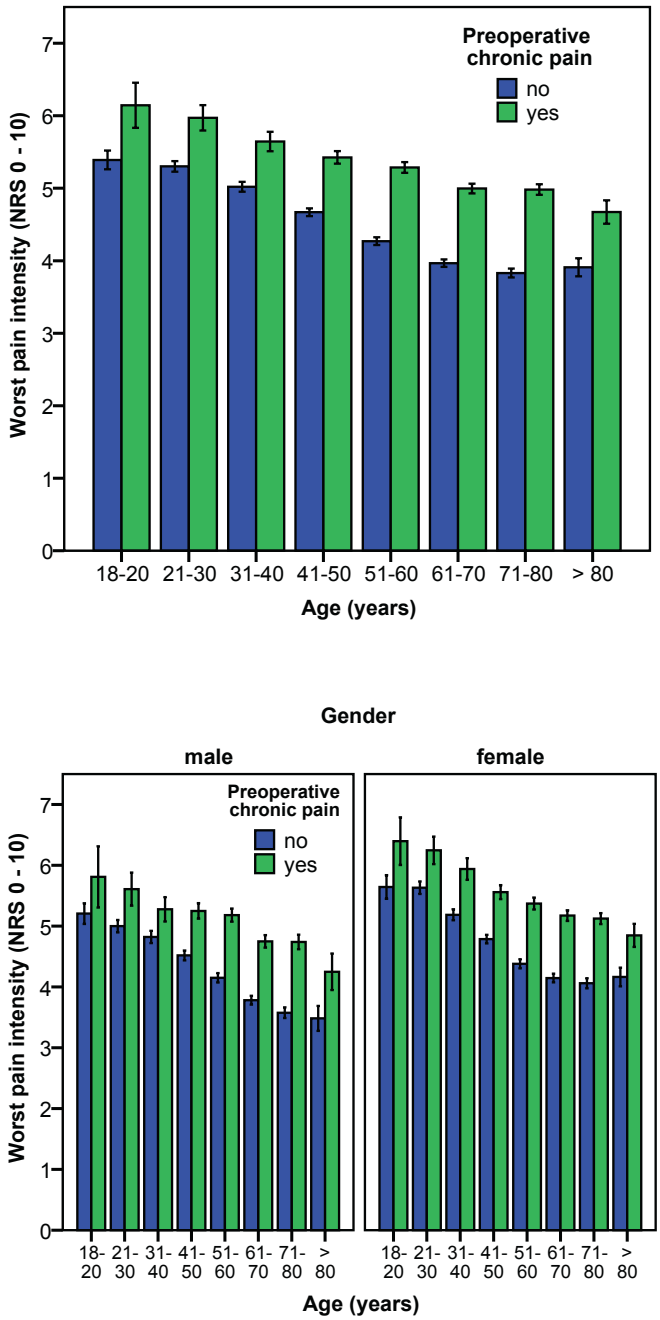

Figure 4. Associations between severe postoperative pain intensity (NRS > 7) since surgery on the first postoperative day and age, gender, and preoperative chronic pain intensity (NRS 0-10) of the total study population (n = 22, 963). Patients with regional anesthesia were excluded.

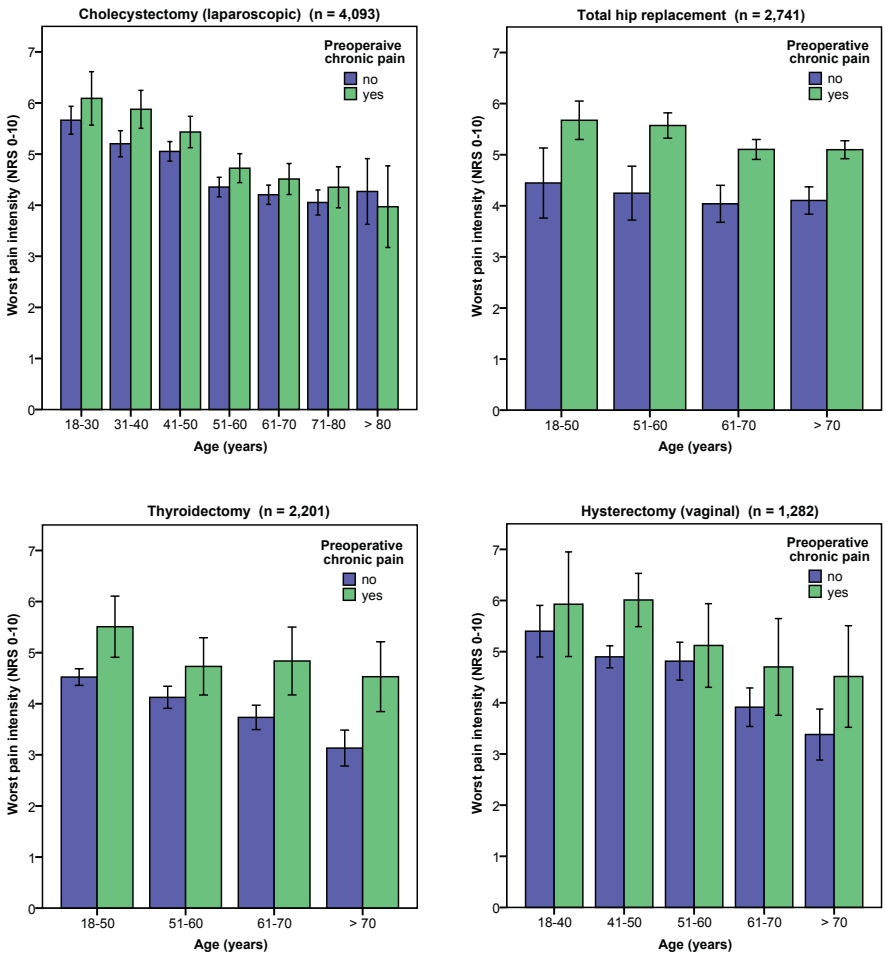

Figure 5. Associations between worst postoperative pain since surgery (numeric rating scale, NRS 0-10) on the first postoperative day, age, and preoperative chronic pain intensity (NRS 0-10). Patients undergoing general anesthesia are shown; those with regional anesthesia were excluded. The four most often performed procedures were selected for graphic presentation: (A) laparoscopic cholecystectomy, (B) total hip replacement, (C) thyroidectomy, and (D) vaginal hysterectomy. Error bars indicate 95% CI of the mean. Due to differences in age distribution in the various surgical procedures, differing age groups were combined.

The adjusted OR to develop severe postoperative pain (≥ NRS 7) was OR 1.13 (95% CI 1.11 to 1.15) with each point higher on the preoperative chronic pain scale (figure 3). Older age was associated with less pain (adjusted OR 0.79 [95% CI 0.76 to 0.82] for each 10 years of increase in age). The adjusted OR for severe pain in females was 1.27 (95% CI 1.17 to 1.38) compared to males (figure 3).

Derived from the random-effect model additional procedure-specific estimates for age, gender, and preoperative chronic pain for each of the 30 surgical procedures were analyzed (supplemental online table 2).

Preoperative chronic pain intensity

Data on preoperative chronic pain were available for 91.4 % of the patients (table 1). Of those with complete data, preoperative chronic pain in any location was reported by 40.6%. Postoperative pain intensity increased in proportion to preoperatively estimated chronic pain intensity. Patients without preoperative chronic pain reported mean postoperative pain scores of NRS 4.23 (95% CI 4.19 to 4.27), while patients with maximum preoperative chronic pain of NRS 10 reported mean scores of NRS 5.84 (95% CI 5.67 to 6.02) after surgery (figure 6).

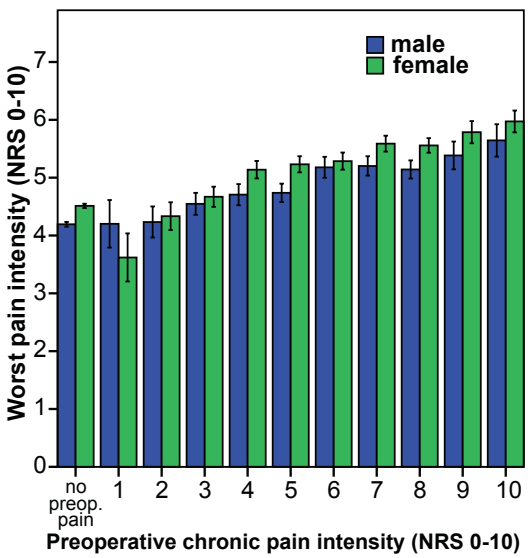

Figure 6. Association of preoperative chronic pain intensity (numeric rating scale, NRS 0-10) with worst postoperative pain intensity since surgery and gender (n = 22, 963).

DISCUSSION

In this study, we analyzed data from 22,963 surgical patients assessed in a highly standardized manner and identified preoperative chronic pain intensity, younger age, and female gender to be associated with higher postoperative pain

scores. These relations were consistently present in 30 precisely defined surgical procedures independent of the type of surgery, the surgical specialty, and the painfulness of the surgical procedure. Postoperative pain increased parallel to preoperative chronic pain intensity and decreased linearly with increasing age. These findings were comparable in both males and females. For each 1.0-point increase in preoperative chronic pain intensity, postoperative pain increased by 0.14 NRS points (95% CI 0.13 to 0.15); similarly, postoperative pain decreased by 0.28 points (95% CI 0.31 to 0.26) per decade older age. Females reported slightly higher mean pain intensities by 0.29 points (95% CI 0.22 to 0.37).

The adjusted OR to develop severe postoperative pain (≥ NRS 7) was OR 1.13 (95% CI 1.11 to 1.15) with each point higher on the preoperative chronic pain scale (figure 3); thus a patient with preoperative chronic pain of NRS 7 has a higher risk of OR 1.84 to have severe postoperative pain (≥ NRS 7) compared to a patient with preoperative chronic pain intensity of NRS 2. Older age was associated with less pain (adjusted OR 0.79 [95% CI 0.76 to 0.82] for each 10 years of increase in age); thus a 70 year old patient has a lower risk of OR 0.39 for postoperative pain of ≥ NRS 7 compared to a 30 year old patient. The adjusted OR for severe pain in females was 1.27 (95% CI 1.17 to 1.38).

Risk factors for the development of postoperative pain have been analyzed in many studies with contradictory results. A few studies have analyzed the influence of the type of surgery on postoperative pain. However, all previous studies assigned the types of surgery to broad anatomical regions or surgical disciplines such as abdominal, thoracic, laparoscopic, or minor and major surgery[12,19-21] or used the duration of surgery and incision length as surrogates for the extent of surgery and tissue damage,[22] which is of questionable validity for many types of procedures. Differences in the influence of age, gender, and preoperative chronic pain on postoperative pain intensity among various types of surgery by using the exact OPS codes for categorizing a specific surgical site, organ system, as well as surgical access have not previously been analyzed and compared. So-called minor surgeries in which low postoperative pain intensities are expected have not been analyzed with regard to risk factors for postoperative pain. Our results demonstrate that the impact of age, preoperative chronic pain, and gender on postoperative pain is similar among various types of surgery regardless of the postoperative pain intensity and type and extent of tissue trauma. A linear association between postoperative pain and age as well as preoperative chronic pain was exemplarily shown in the four largest surgical groups with more than 1,200 patients each.

Most of the larger studies on risk factors for postoperative pain have used different pain intensity cut-off points such as NRS ≥ 3, NRS ≥ 4, NRS ≥ 5, and NRS ≥ 8 as an outcome variable, which makes comparison of these groups difficult.[12,19-21] For primary data analysis we did not use an arbitrarily chosen cut-off point, as this would have resulted in loss of information.[23] However, as clinicians are often interested in patients with severe pain, we used the cut-off point of NRS ≥ 7 to calculate adjusted OR per risk factor and surgical procedure. Although the choice of such a cut-off point is always somewhat arbitrary, we have chosen the threshold value of 7 as this is commonly used.

A systematic review has demonstrated that preoperative pain is the most consistent risk factor for the development of severe postoperative pain (7 out of 8 studies).[10] Preoperative pain has been analyzed according to pain intensity (NRS 0 to 10),[12] the presence of preoperative pain (yes or no),[19-21,24] and the presence of preoperative chronic pain (yes or no).[19] Information on the duration of pain persistence and its location(s) as well as relation to the surgical site is generally missing, which also makes comparison difficult. In this study, preoperative pain was defined as chronic pain persisting for more than three months in any location. We could indicate that independent of the type of surgery preoperative chronic pain is related to more severe postoperative pain. Furthermore we could demonstrate that the intensity of preoperative chronic pain is correlated with more severe postoperative pain. This is in accordance with a previous study, showing the association between the degree of preoperative pain chronicity and postoperative pain intensity in radical prostatectomy patients.[25]

In the same systematic review, six studies showed decreasing pain with older age and three found no significant differences.[10] More recent studies were not able to clarify the question of age as a risk factor for severe postoperative pain.[20,21,24,26] However, the numbers of patients studied were rather low and various dichotomous cut-off points for the age groups were chosen, which may have contributed to the inconsistent results. To our knowledge, this study is the first to examine age not only as a dichotomous variable. We could demonstrate a continuous decrease in postoperative pain with increasing age: Pain decreased by 0.28 points (95% CI 0.31 to 0.26) per decade older age. A mean overall difference of 1.5 NRS points (22,963 patients) was shown between the youngest (18 to 20 years) and the oldest age group (> 80 years). This was, again, consistent throughout most surgeries as shown for the four major surgical procedures. Many factors could influence the pain differences with age, such as bio-psychosocial and life-stage factors [26]

as well as changes in the complex cascade of immune, inflammatory, and neural responses.[27] In addition to those factors, insufficient titration of analgesics should also be considered. It is well known that during the postoperative period younger patients generally need higher doses of opioids than older ones.[28,29] This fact may not have been considered in daily clinical practice if a fixed standard pain treatment regimen was followed without individual adaptation.

The review of Ip et al. as well as more recent studies did not find consistent results of the influence of gender on acute pain. Some indicated female gender to be associated with higher pain scores,[12,24,29-33] while others did not find statistical differences.[19-21,34,35] Only in one study did males report higher pain scores, however, females with minor gynecological surgeries were overrepresented.[22] Although some studies found statistical differences and others did not, in most studies females reported slightly higher pain scores. These results are in concordance with our data: In 21 of 23 surgical procedures females had higher pain scores, ranging between 0.13 and 0.73 NRS points. Thus, the negative findings in some studies are not surprising as the differences in NRS scores are small and statistical significance is dependent on sample size. Although the differences in pain intensities were small, it is of note that they were very consistent among our surgical groups. From the clinical point of view several causes of the gender differences could be hypothesized. First, pain intensity difference is a result of insufficient pain treatment in females compared to men. Second, as indicated by Schnabel et al.,[33] female patients may use (epidural) patient controlled opioid treatment less frequently because of increased side effects of the opioids compared to males. Third, slightly higher pain scores do not reflect less sufficient pain treatment in females but are related to causes such as different use of the NRS or social and cultural differences. The actual clinical significance of this small difference in pain intensity should be analyzed in future studies applying different postoperative quality-outcome factors such as side effects or patient satisfaction.

There are some limitations of this study: (1) We analyzed data from patients treated with systemic analgesia after surgery only. Thus, the influence of the risk factors cannot be generalized to patients with regional anesthesia. A recent large study indicated, similar to our present results, slightly higher pain scores in female patients when patient-controlled epidural anesthesia was used in the perioperative period.[33] Although gender differences were statistically significant, the difference of NRS score was small regardless what type of analgesia was used;

(2) Our study measured postoperative pain in surgical patients treated in hospitals from a single Western European country. Thus, it was not possible to evaluate cross-national cultural influences on the association between the risk factors and pain perception; and (3) Other risk factors such as psychological distress (anxiety, depression) and pain perception have not been included in this analysis, however, in a prediction model for postoperative pain intensity, preoperative pain and age have been shown to be the risk factors with the largest predictive values on postoperative pain.[12]

An open access to the QUIPS database is not possible. According to the consortium agreement of QUIPS data access is available for participants, only.

In conclusion, this study demonstrates that younger age, preoperative chronic pain intensity, and female gender are associated with higher postoperative pain intensities and that these associations are consistent over a large number of different types of surgeries. The clinical relevance of the statistically significant but only slightly higher pain scores in females compared to males will require further research.

ACKNOWLEDGEMENTS

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CHAPTER 6

Gender differences in postoperative pain intensity and pain-related outcomes – A prospective multicenter cohort study

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ABSTRACT

Background

Numerous studies have found slightly higher postoperative pain scores in females. The clinical significance of this small gender difference has not been examined as yet.

To evaluate the clinical relevance of pain-intensity differences, other outcome variables related to postoperative pain were compared between genders.

Methods

The most frequently performed surgeries from the German Postoperative Acute Pain Registry (QUIPS) were selected for gender-related procedure-specific comparison. On the first postoperative day worst pain intensity was recorded by means of the numeric rating scale 0-10 (NRS). Random effect logistic regression analysis was used

Results

Women scored 0.28 NRS points higher (NRS 4.83 (95%CI 4.79-4.87)) than men (NRS 4.45 (95%CI 4.41-4.49) $p<0.0001$; n=36,003. Twenty surgical procedures (each with > 150 patients) including 16,800 patients were available for surgical-procedure-specific comparison. In 18 procedures, women showed higher pain-intensity scores than men. Analysis of crude and adjusted data indicated no gender difference in the wish to have received more analgesics since surgery. Pain-related interference with movement, deep breathing, sleep, and mood showed significantly poorer outcomes in females, with odds ratios ranking between 1.10 (95%CI 1.02-1.18) and 1.16(95%CI 1.07-1.25). Oral morphine equivalents did not differ between genders.

Conclusion

Females reported consistently higher pain scores after various types of surgery; however, differences - although statistically significant - were rather small. As the wish for more analgesics and opioid use did not differ, higher pain scores in females do not appear to indicate insufficient pain treatment and, consequently, would not indicate a need for intensified pain therapy.

INTRODUCTION

In many studies, females report higher pain scores after surgery compared to males.[1–11] However, in most of these studies the differences in pain intensity scores between men and women were small, usually not exceeding 1 point on the Numeric Rating Scale (NRS: 0 = no pain; 10 = worst pain imaginable). We have confirmed in a recent large-scale study that females report more severe pain independent of the surgical procedure.[12] The pain intensity difference was small, at 0.29 points on the NRS.

Numerous studies addressing gender differences in postoperative pain have directed attention to determining differences in pain-intensity, or trying to identify causes for the higher pain scores in women. However, the clinical consequence of these results on pain treatment in females has not been studied as yet. Higher pain ratings in females after surgery may be related to "under-treatment" of females or "less responsiveness" to drugs compared to males. But the difference could also be due to pharmacodynamic, pharmacokinetic, hormonal, psychological (e.g., expectation, anxiety, coping strategies), genetic, social, cultural, or other reasons that do not automatically imply greater perceived pain with the need for more intense pain treatment. Furthermore, women are more often affected by side effects, such as nausea and vomiting. Female patients could be weighing the impact of side effects against the wish to ask for more pain medication, and this could consequently lead to higher pain scores in women. Although the Special Interest Group of the International Association for the Study of Pain has requested that studies should be undertaken to analyze how gender differences can influence the clinical management of pain, no such studies have been performed yet.[13]

The aim of this study was to assess whether postoperative pain treatment in women should be improved or changed due to their often reported higher pain scores compared to men. Therefore, in addition to differences in pain intensity between men and women, other pain-related outcome variables such as pain-related interferences and the wish to have received more pain treatment are analyzed. Furthermore, a surgical-procedure-specific comparison was performed to indicate whether the surgical site, painfulness of the procedure, or incidence of side effects might contribute to possible gender differences in various pain-related outcome variables.

METHODS

Patients

The data used were collected in the QUIPS project (Quality Improvement in Postoperative Pain Therapy).[14] The QUIPS project offers German hospitals the opportunity to compare their postoperative pain treatment outcomes anonymously by means of a 15-item validated questionnaire.[15] Before hospitals participate in the registry study, nurses are trained to perform standardized data collection. The project was approved by the Ethics Committee as well as the Data Security Board of Jena University Hospital, Jena, Germany. Patients were informed in written form as well as orally by the study personnel that data collection was voluntary and anonymous, and that they could refuse to be included at any time. Inclusion criteria were patients' age ≥18 years and voluntary completion of the questionnaire on the first postoperative day after scheduled surgery. Informed consent was documented by filling in the questionnaire. Data analyzed in this study were collected between May 2004 and May 2010 in 105 German hospitals.

Patients on a surgical ward were included when they had been operated upon for elective surgery one day previously. The type of surgery was recorded using the German Surgical Procedure Coding system (OPS), which includes more than 21,000 surgical codes.

Exclusion criteria were as follows: the patient (1) had been transferred to another ward after surgery; (2) was not present in his room or had been discharged at the time of data collection; (3) refused to participate in the study; (4) could not communicate in German; (5) had cognitive deficits; or (6) was sedated or asleep. Additional exclusion criteria were: (7) missing or incorrect OPS code, which precisely defines the kind of surgery performed; (8) age younger than 18 years; (9) use of regional anesthesia; and (10) surgeries in the urology, gynecology, obstetrics, and traumatology departments. Trauma patients were excluded because postoperative pain differs depending on the extent of soft-tissue damage, type of fracture, and surgical technique.

Outcome variables and confounders

Five outcome factors were selected to evaluate the clinical significance of pain intensity differences between genders. The wish to have received more analgesics was asked on the first postoperative day, covering the period since surgery. Additionally, patients were asked to evaluate if postoperative pain had interfered

with their movement, deep breathing or coughing, or mood, and if they woke up due to pain.

Age and preoperative chronic pain are known to be associated with severe postoperative pain and were considered as potential confounders (Gerbershagen 2014).[12] Postoperative side effects occur more often after surgery in women, and may keep the patient from asking for more pain medication, but also may lead to reluctance by the medical staff to administer more opioids if the patient is drowsy. Therefore, nausea, vomiting, and severe tiredness were additionally regarded as potentially confounding the relation of gender with the wish for more analgesics.

Pain treatment

Next to the patient questionnaire, further data on type of anesthesia and analgesia, pharmacological substances used, and doses were collected. In the present study, we excluded data from patients receiving peripheral nerve blocks or epidural analgesia in order to create a homogeneous cohort for gender comparison. Opioid consumption after discharge from the postoperative care unit (PACU) was calculated for each surgical procedure. Different opioid analgesics were converted to oral morphine equivalent doses. The conversion factors used to calculate oral morphine equivalents are presented elsewhere.[16]

Surgical-procedure-related analysis

For procedure-specific analysis, precisely defined surgical groups were formed based on the specific surgical site, organ system, as well as surgical access, e.g., laparoscopic, open, and endoscopic. A detailed description of selection and definition of surgical procedures is given in a recent publication.[16]

Statistical Analysis

In a first step, all patients fulfilling the inclusion criteria were used for comparison of pain intensity, the four pain-related interferences, the wish to have received more analgesics, and side effects between males and females using *t*-test or Fisher's exact test where appropriate. Significance level was defined as $p < 0.05$.

In a second step, the most frequently performed operations (> 150 patients per surgical group) were selected for a surgical-procedure-specific comparison of gender differences. Worst pain intensity, the four pain-related interferences, the wish to have received more analgesics, and opioid dose were analyzed for each of the selected surgical groups. For those surgical procedures the odds ratios

(ORs) were calculated by logistic regression analysis and presented in a forest plot. Regression analysis was adjusted for preoperative chronic pain and age.
The surgical-procedure-specific analysis was performed using logistic mixed-effects regression analysis since clustering was expected on a procedural level, as specific surgical procedures were likely to have their own specific pain profiles. Chronic preoperative pain and age were used as confounders. In the analysis of wish for more analgesics we additionally adjusted for the side effects (nausea, vomiting, and severe tiredness). As the relationships between gender and the outcome variables were expected to be procedure-dependent (cluster-dependent), a random slope for gender was included in addition to a random intercept in the mixed-effects model. Before data analysis, pre- and postoperative variables were tested for nonlinearity using restricted cubic splines.[17] Confounders were entered into the model as splines when non-linear. Missing data were multiply imputed (ten times). Imputation of missing variables was based on confounders, outcome variables, and other perioperative data.[18] The type of surgical procedure was added as an extra variable to the imputation model to take the multi-level structure of the data into account. Analyses were conducted in SPSS version 22 (IBM; United States, NY). For the mixed-effects models we used R version 3.1.2 (glmer, lme4 libraries).

RESULTS

A total of 36,003 patients met the inclusion criteria (figure 1), of which 15,485 were males and 20,516 were females. The mean of worst pain intensity on the first postoperative day differed significantly between males (mean NRS 4.45 (95% CI 4.41; 4.49) and females 4.83 (95% CI 4.79; 4.87) respectively ($p < 0.0001$). Pain during movement was rated by men as NRS 3.70 (95% CI 3.66; 3.73) and by women as NRS 4.00 (95% CI 3.97; 4.03) ($p < 0.0001$). Side effects were significantly more frequent in females than in males: nausea in 29.9% (95% CI 29.4; 30.5) vs. 14.0% (95% CI 13.5; 14.4), vomiting in 19.2% (18.7; 19.6) vs. 7.4% (95% CI 7.1; 7.7), and severe tiredness in 57.7% (95% CI 57.2; 58.3) vs. 43.2% (95% CI 42.5; 43.8) (all side effects: $p < 0.0001$). The incidence of nausea, vomiting, and severe tiredness in relation to postoperative pain intensity is presented in figure 2.

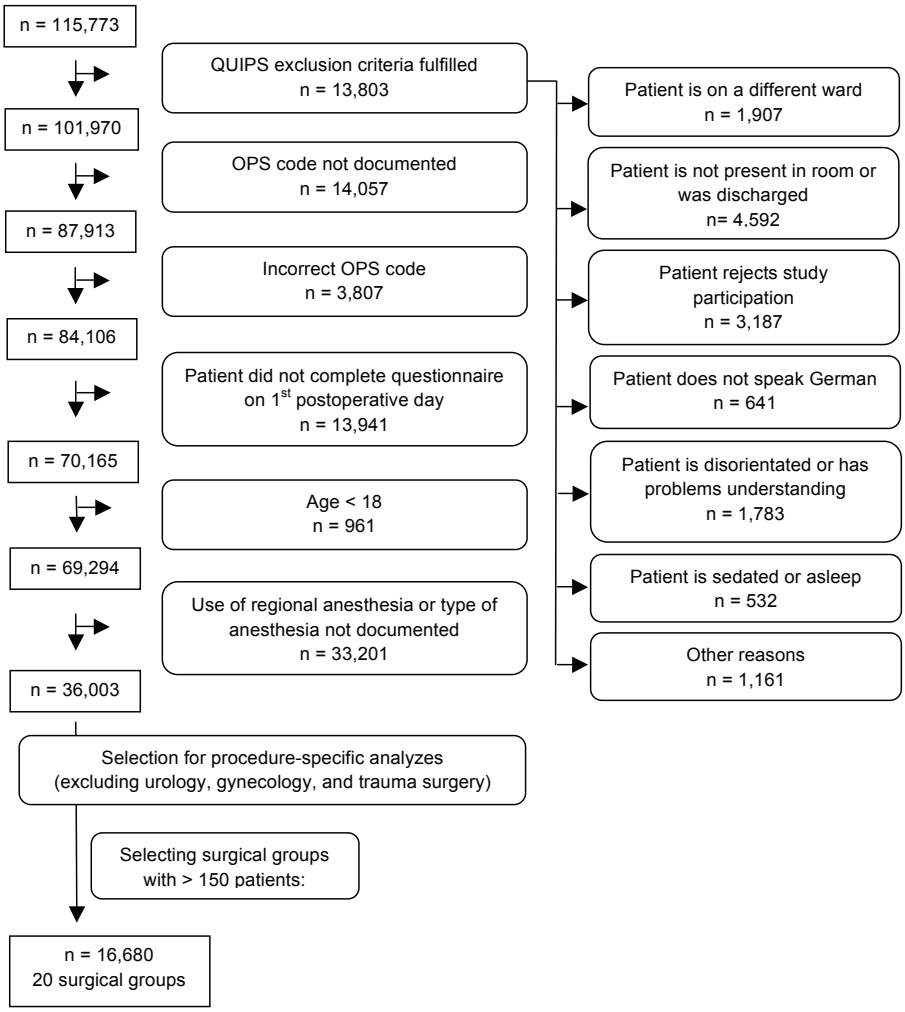

Figure 1. Flow chart for inclusion in the study population

Wish to have received more analgesics

The wish to have received more analgesics did not differ significantly, with 11.5% (95% CI 11.1; 12.0) in women and 11.9% (95% CI 11.4; 12.4) in men (p = 0.304). The associations between the wish for more analgesics, worst postoperative pain intensity score, and gender are shown in figure 3. If worst postoperative pain intensity remained lower than NRS 5, the wish for more analgesics was less than 10% (figure 3).

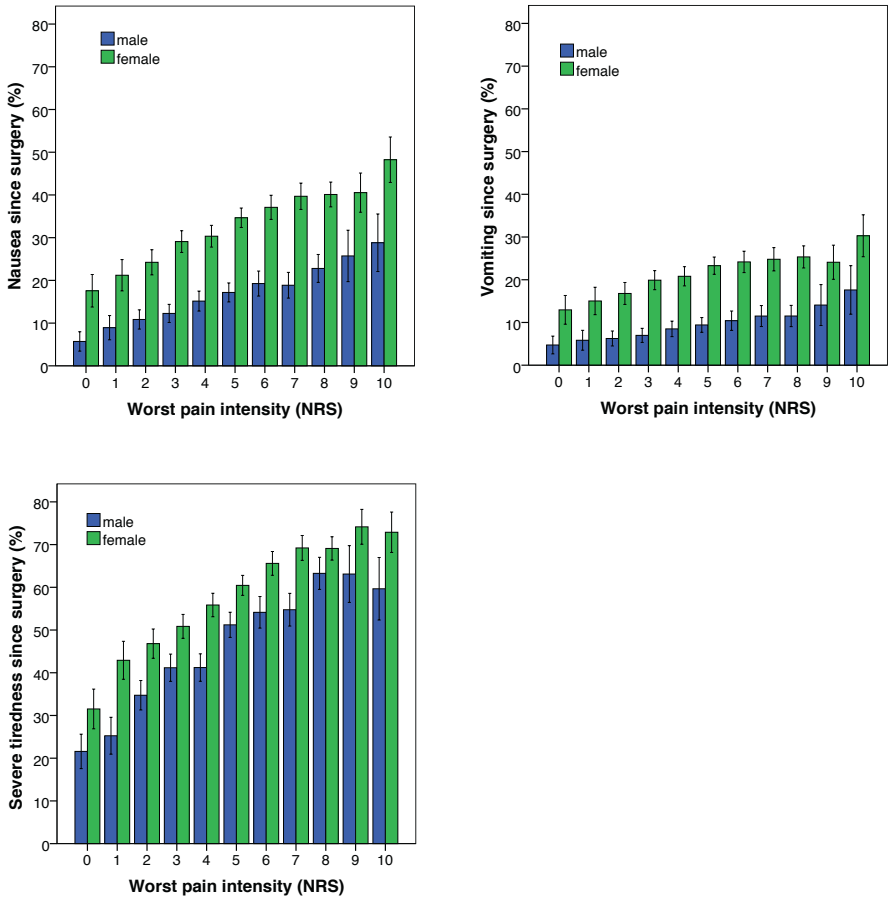

Figure 2. Incidence of side effects in females and males related to postoperative worst pain intensity: a) nausea; b) vomiting; c) severe tiredness

Gender differences for 'wish for more analgesics' were separately analyzed for the 20 most often performed surgical procedures (each > 150 patients) using logistic regression analyses (figure 4). Based on the crude analysis, only in the procedures "closure of anal fistula" and "transurethral resection of bladder" a significant difference between the genders was seen with respect to the wish to have received more analgesics since surgery (figure 4); in all other procedures no statistically significant differences were found. After adjusting for the confounders age and preoperative chronic pain intensity, only the difference for closure of anal fistula showed a statistically significant difference. After additional adjustment for nausea, vomiting, and severe tiredness, the wish for more analgesics did not differ between the genders in any of the 20 procedures. The random effect regression

analysis of the 20 selected procedures did not indicate any gender differences for either the crude or the adjusted data (table 2).

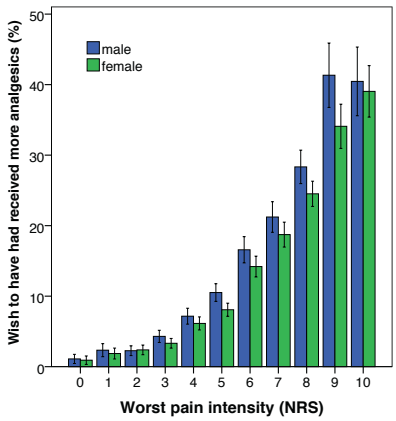

Figure 3. Gender differences in 'wish to have had received more analgesics since surgery' (n = 36,003)

In 18 of 20 procedure-specific comparisons, oral morphine equivalent doses did not differ between genders (figure 4). Males received more opioids after open cholecystectomy (32 mg (SD 36) vs. 23 mg (SD 29) (p = 0.027)) and hip-joint replacement (28.2 mg (SD 34) vs. 25 mg (SD 37), p = 0.020). In the overall group of all 20 selected surgical procedures, males were administered more opioids (14 mg (SD 27) vs. 15 mg (SD 32) p = 0.032).

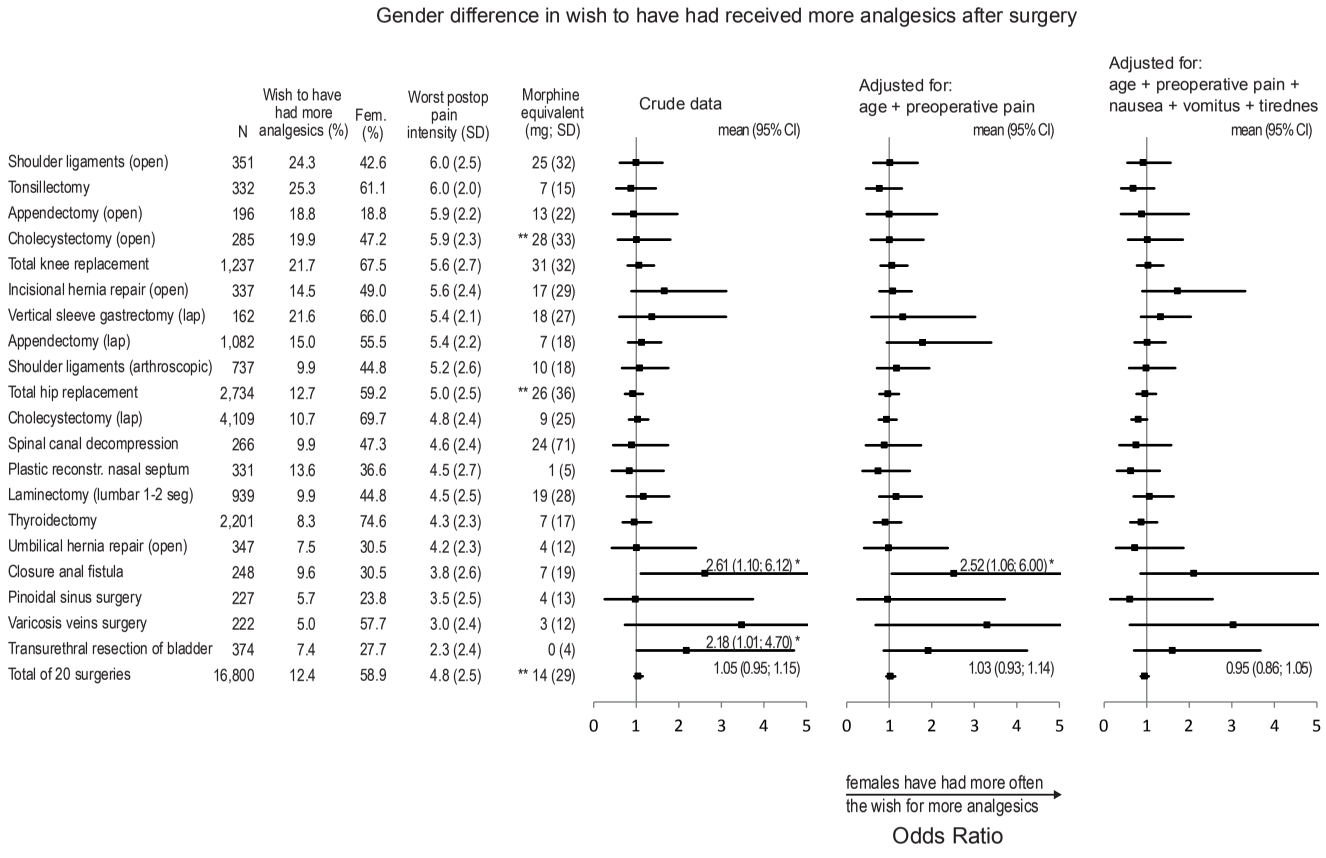

Figure 4. Gender differences in wish to have received more analgesics since surgery: 20 surgical procedures with more than 150 patients each were selected. Logistic regression analysis was used to calculate odds ratios for crude and adjusted association between gender and outcomes for each procedure. Random effect logistic analysis was applied to calculate odds ratios of the pooled data of the 20 surgeries.

The order of the surgeries is based on worst pain intensity scores. Different opioids used were converted into 'oral morphine equivalents'. * significant gender difference of wish to have received more analgesics ($p < 0.05$) ** significant gender difference of oral morphine equivalent dose ($p < 0.05$)

Pain-related interferences

The incidences of pain-related interference with movement, deep breathing/coughing, waking up due to pain, and mood in 36,003 patients were 56%, 31%, 34%, and 18%, respectively. Incidences in men and women are shown in table 1. The gender differences of the relations of all four pain-related interferences for different levels of pain intensity are presented in figure 5. For all four variables, impairment increased with increasing pain intensity.

All 16,800 patients who underwent those 20 procedures were pooled using a random-effect analysis to compare gender differences for the four pain-related interferences. The odds ratios for female gender are very similar in each of the four outcomes (table 2). Likewise, all four effect estimates were no longer statistically significant when additionally adjusted for the side effects of nausea, vomiting, and severe tiredness (table 2). For wish for more analgesics we additionally adjusted for side effects (nausea, vomiting, and severe tiredness), which yielded an odds ratio of 0.93 (0.85-1.02).Figure 6 shows the surgical-procedure-specific gender comparison for waking up due to pain and pain interfering with movement for the 20 most often performed surgeries.

Table 2. Gender differences of wish to have received more analgesics and four pain-related interferences (interference with movement, deep breathing, waking up due to pain and pain interfering with mood)

	Odds ratio: Crude data	Odds ratio: Adjusted for: age + preop. chronic pain
Wish for more analgesics	1.03 (0.94 - 1.12)	1.01 (0.92 - 1.11)
Waking up due to pain	1.14 (1.06 - 1.23)	1.10 (1.02 - 1.18)
Pain interfering with mood	1.20 (1.11 - 1.30)	1.17 (1.08 - 1.27)
Pain interfering with movement	1.18 (1.09 - 1.28)	1.16 (1.07 - 1.25)
Pain interfering with coughing or deep breathing	1.12 (1.04 - 1.12)	1.11 (1.03 - 1.20)

Odds ratio > 1 indicates higher risk for females

20 surgical procedures including more than 150 patients per procedure (n = 16,800). Odds ratio were analyzed with mixed effect logistic regression analysis

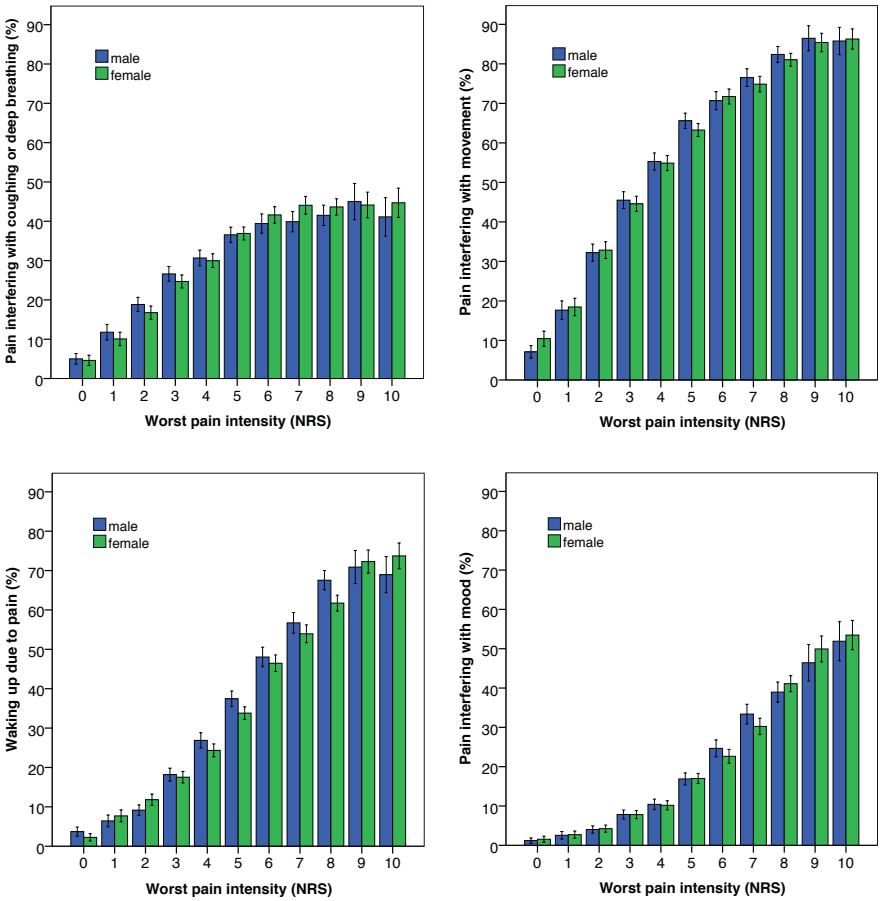

Figure 5. Incidences of pain-related interference factors: a) pain interfering with movement b) pain interfering with coughing or deep breathing c) waking up due to pain and d) pain interfering with mood (n = 36,003)

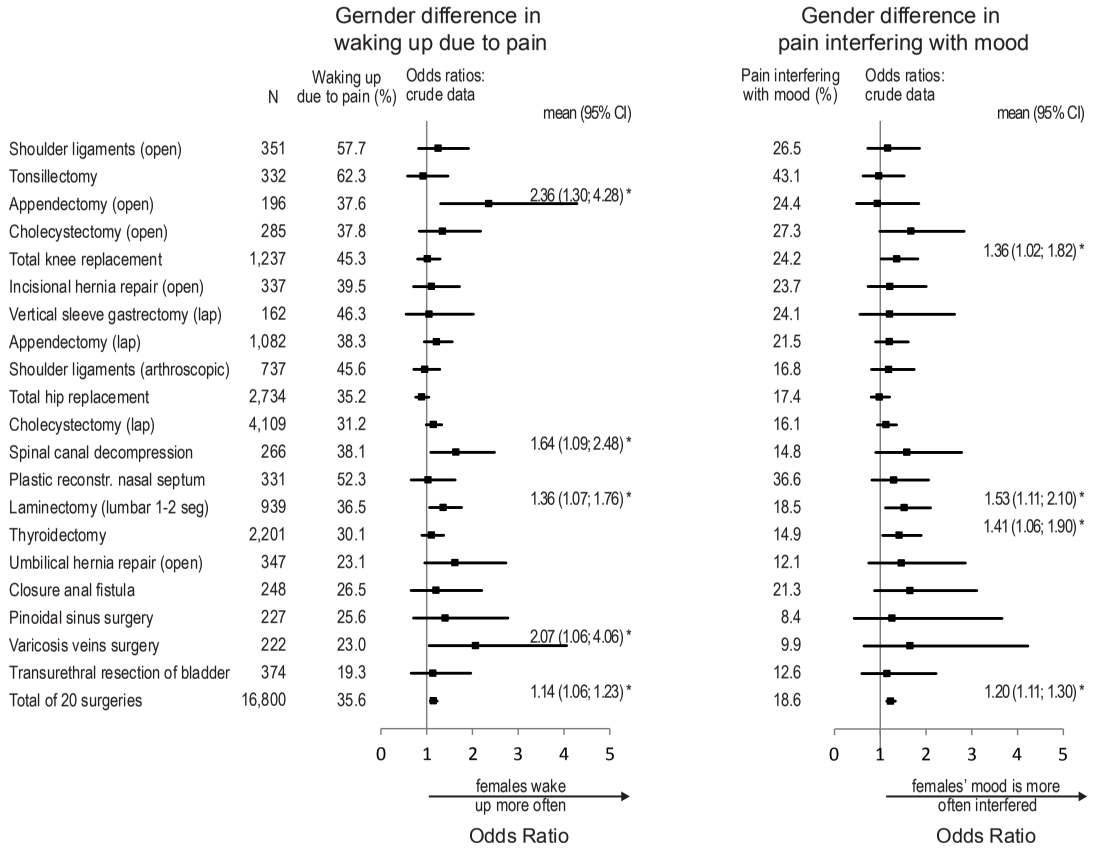

Figure 6. Gender differences of waking up due to pain and pain interfering with mood:

20 surgical procedures with more than 150 patients each were selected. Logistic regression analysis was used to analyze odds ratios for crude data of each of the surgical procedures. Random effect logistic analysis was applied to calculate odds ratios of the pooled data of the 20 surgeries.

The order of the surgeries is based on worst pain intensity scores.

* significant gender difference of waking up due to pain or pain interfering with mood ($p < 0.05$)

DISCUSSION

In concordance with a number of previous studies, we found slightly but significantly higher pain scores in females when compared to males. In the present study, we examined the clinical significance of this gender difference on the first day after surgery. A procedure-specific analysis of 20 different types of surgery comprising 16,800 patients that compared pain-related interference with sleep, mood, movement, and deep breathing also demonstrated poorer results in females. However, there was no difference between females and males in the wish to have received more analgesics since surgery in either the crude or adjusted analyses.

Many earlier studies as well as our own data have indicated slightly higher pain intensities in females.[1–11,19,20] These differences were small, however, and usually less than one NRS point on a scale from 0 to 10.
In a recent study, the authors demonstrated that females consistently reported more pain after various surgical procedures even after adjustment for type of surgery, age, and preoperative chronic pain intensity. In a previous study pooled data of 23 surgical groups showed that women scored 0.29 (95% CI 0.22; 0.37) points higher on the NRS for worst pain intensity.[12] A study from the United States including nearly 8,000 patients showed very similar results, with females reporting 0.22 (95% CI 0.16-0.28) points higher pain intensity.[20]
The impact of this difference in pain-intensity has thus far not been addressed in the literature. There is no standard to evaluate the clinical significance of pain intensity differences between the two gender groups. Studies in acute pain settings have indicated that a reduction of one-third of a pain intensity score is regarded as sufficient pain alleviation. However, this parameter cannot be used to evaluate differences between groups.
Therefore, we chose a different approach by comparing other pain-related outcome variables in order to better understand the differences in quality and perception of pain treatment between men and women.

A total of 11.7% of our patients reported the wish to have received more analgesics since surgery. No gender differences were demonstrated in either the crude or the adjusted data analysis. We consider the wish for more analgesics to be a strong indicator of the adequacy of acute pain treatment. Although a number of factors can influence the patient's answer, this question reflects the patient's perception of

exactly what the physician wants to know: Do we have to intensify pain treatment in this particular patient? The question regarding a patient's wish for more analgesics for postoperative pain has only rarely been examined. Van Dijk et al. reported that the wish for more opioids in the PACU was only expressed by 20% of patients with NRS 5 and 30% of patients with NRS 7.[21] The incidence of the wish for more analgesics by patients with the corresponding pain scores was even lower in our study. Van Dijk et al. demonstrated that patients with pain scores ≥ 5 and no wish for more analgesics reported in 62% of cases that their pain was tolerable.[21]
Female gender was strongly associated with higher incidences of nausea (30% vs. 14%) and vomiting (19% vs. 7%). These incidences are similar to other published data.[22] Female gender is the strongest risk factor for postoperative nausea and vomiting.[23] Accordingly, it might be expected that females could be more reluctant to ask for analgesics due to their higher incidence of nausea and vomiting.
Oral morphine equivalent doses on the ward (after discharge from the PACU) did not differ between genders in 18 of the 20 surgical groups. These results are consistent with a meta-analysis including 25 randomized, controlled trails indicating no gender difference in opioid administration.[24] In none of the 20 surgical procedures did the higher incidence of side effects lead to a less frequent wish for more analgesics in females. As the wish for more analgesics and opioid dose administered did not differ between genders, the current findings provide no rationale for gender-adapted postoperative pain treatment due to gender differences in pain intensity. However, as the reasons why men and women do or do not have a wish for more analgesics are probably not the same (e.g. difference in reluctance to take medication, fear of opioid addition), further analysis of these differences may facilitate improvement of pain treatment.
Furthermore, despite the large number of experimental studies, no clear and consistent pattern of gender differences in pain sensitivity could be determined (Racine 2012). However, most experimental and clinical studies have found variations in the severity of pain symptoms across the menstrual cycle.[25]

All analyses on interference with movement, deep breathing, mood, and sleep resulted in very similar, slightly higher ORs in females compared to males. ORs ranged between 1.12 and 1.20 in both crude analysis, and after being adjusted for age and preoperative pain. These results are in accordance with a recent study analyzing gender differences for sixteen postoperative symptoms (such as throat pain, headache, dyspnea, dry mouth, etc.). Females scored poorer in ten items,

whereas no differences were demonstrated for the others. Preoperative expectations of those ten postoperative conditions were also poorer in females. When adjusted for preoperative expectation, effect sizes were distinctively diminished for many factors, and surgical wound pain even became non-significant.[26] Thus, preoperative expectations could play a role in higher postoperative pain scores in women. Two other well known risk factors for more severe pain, namely anxiety and depression, could not be verified to cause the gender differences in pain scores.[27]
Despite the poorer postoperative outcomes in females, no gender difference in regard to satisfaction with postoperative pain treatment could be found in the largest multi-center study, which included almost 17,000 patients.[28] However, the wish for more analgesics played an important role in affecting patients' satisfaction with pain treatment.
Finally, social factors may also contribute to differences in postoperative pain scores. Gender-role expectations or perceived identification according to typical gender stereotypes (e.g., willingness to report pain or to ask for more pain medication) may affect postoperative pain-intensity scores. A generally higher reluctance toward medication use or fear of side effects may also contribute to pain-intensity differences. It is thus apparent that many factors – most of them not well understood - can play a role in the higher reported pain scores in females after surgery.

Our study has some limitations. Variables that may have had an influence on postoperative pain such as preoperative expectations or anxiety are not collected in the QUIPS database. Cultural or social gender differences could not be analyzed, as the study was performed in one country only. However, our findings with regard to pain-intensity differences between males and females were comparable to studies from different countries in the literature. We performed regression analyses adjusting for age and preoperative chronic pain, which are variables that are well known to influence postoperative pain.
In conclusion, the results of this study are consistent with many others that demonstrate slightly higher postoperative pain scores in females. Although pain-related interferences with movement, deep breathing, sleep, and mood were significantly higher in females, their wish for more analgesics did not differ from those of the male patients. These results were independent of age, preoperative chronic pain, type of surgery, and the painfulness of the surgical procedure. It thus appears that adaptation of postoperative pain treatment or pain-treatment protocols for females after surgery is not necessary.

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CHAPTER 7

The influence of duration of surgery on postoperative pain intensity – A prospective, multicenter cohort study

submitted
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ABSTRACT

Background

The influence of duration of surgery on postoperative pain intensity has been analyzed in cohort studies with heterogeneous groups of surgical procedures with contradictory results. The effect of duration of surgery on postoperative pain within specific types of surgery is unknown.

Methods

Data from the QUIPS registry (Quality Improvement of Postoperative Pain Treatment) was used to select surgical groups with more than 150 patients each. Worst postoperative pain since surgery (numeric rating scale 0-10, NRS) was evaluated at the first postoperative day. Mixed effects linear regression analysis was applied to the entire cohort to examine the overall effect of duration of surgery. To study the effect per surgical procedure, duration of surgery was split in procedure-specific quintiles with the middle quintile as reference.

Results

In total, 33 surgical procedures with each more than 150 patients from 105 German hospitals were included (n = 26,992 patients). Pain intensity increased significantly with 0.03 points (95% CI 0.022; 0.037) on the NRS per 10 min longer duration of surgery. A surgical procedure-specific analysis of each of the 33 surgical groups did not demonstrate a statistically significant effect on pain.

Conclusion

Analysis of the total cohort indicated a statistically significant, but small increase of pain intensity with duration of surgery that is unlikely to be of clinical relevance. A significant association of duration of surgery with postoperative pain intensity was not present within specific surgical groups.

INTRODUCTION

Over the past years there has been debate on the possible association between the duration of a surgical procedure and postoperative pain intensity, but the presence and magnitude of such an association remains unclear. More severe pain after prolonged surgery within a specific surgical group might be the result of a larger tissue lesion with correspondingly more severe inflammatory reaction or it could be due to local complications such as infection, adhesions, or bleeding. [1,2]

Generally, duration of surgery has been studied in two different types of studies. Some studies were restricted to one specific type of surgery; for example the influence of duration of surgery on pain after laparoscopic cholecystectomy has been investigated, but with contradictory results.[3–5] Other studies combined multiple types of surgery within one study population, however, these study results were also inconclusive.[6–14]

In risk-factor analyses of cohorts with different kinds of surgeries, statistical adjustment for the type of operation is usually not possible due to the large number of different procedures included. Therefore, the duration of surgery is often used as a proxy for the extent of the surgical lesion. This does not take into account, however, that there are a number of short-lasting surgeries that cause severe pain and some complex, long-lasting surgeries that are associated with minimal postoperative pain.

Furthermore, comparability of the studies is limited by arbitrarily chosen cut-off points for both the outcome (generally postoperative pain intensity) and for duration of surgery. It is not known whether identified positive relations are linear or if higher pain scores were only present in patients with very long duration of surgery. It is also not known whether this presumed association between duration of surgery and pain is a general phenomenon among all kinds of surgeries, or is specific to a certain subset of procedures. No standardized, procedure-specific comparison of this association has been published yet.

The aim of this study was to analyze the influence of duration of surgery on postoperative pain for individual, well-defined surgical procedures, and to compare the association between duration of surgery and pain intensity between different surgical procedures.

METHODS

Patients

Patient data were analyzed from the project "Quality Improvement in Postoperative Pain Treatment" (QUIPS).[15] The data were collected between 2004 and 2010 on 589 surgical wards in 105 German hospitals. Patients completed a validated questionnaire on the first day after surgery.[16] Additional information on the type of surgery and anesthesia, pain treatment, and duration of surgery was recorded. Approval was obtained from the University Ethics Committee of the University of Jena. All patients gave written informed consent before entering the study.

Inclusion criteria were elective surgery and age older than 18 years. A patient was excluded when he or she (1) had been transferred to another ward after surgery; (2) was not present in his room or had been discharged at the time of data collection; (3) refused to participate in the study; (4) could not communicate in German; (5) had cognitive deficits; or (6) was sedated or asleep. Additional exclusion criteria were: (7) missing or incorrect German Surgical Procedure Coding (OPS), which precisely defines the kind of surgery performed, and (8) use of regional anesthesia. Surgical procedures were precisely documented with one or several of the 21,000 codes of the OPS. Details of patient assignment to one of 529 different surgical groups have been described in a recent publication.[17]

Outcome variable, confounders, and pain therapy

The outcome variable was defined as worst postoperative pain intensity since surgery, assessed by the patient on the first postoperative day on a numeric rating scale (NRS) from 0 (= no pain) to 10 (= worst pain imaginable).

Gender, age, and preoperative chronic pain intensity are known to influence postoperative pain perception and were considered as potential confounders.[2,18,6,12] Postoperative opioid consumption after discharge from the post-anesthetic care unit (PACU) was documented on the surgical ward. Different opioids were transformed into oral morphine equivalent doses, using factors for these calculations described elsewhere,[18] and also included as potential confounders.

Statistical analysis

To give an overview of the association between duration of surgery and pain intensity between different types of operations all surgical groups with more than 20 patients were compared with respect to worst postoperative pain, expressed by

median NRS score. Selected surgical groups can be seen in a recent publication.[17] The surgical groups were ordered according to duration of surgery per 15 or 30 minutes.

The association between duration of surgery and postoperative pain was assessed using linear regression analysis, in a similar fashion as has been described before.[18] The shape of the association was verified for non-linearity using restricted cubic splines. Results of the linear regression analysis were expressed as change in NRS per ten minutes duration of surgery.

After crude estimates were obtained, the regression analyses were adjusted for age, gender and preoperative chronic pain (first adjustment) and subsequently also for morphine use, expressed as 0-10 mg, 10-30 mg, and more than 30 mg oral morphine equivalents (second adjustment). The analyses were repeated expressing duration of surgery as a dummy variable with categories (0-15, 16-30, 31-45, 46-60, 61-90, 91-120, >120 min). As clustering is expected within groups of patients undergoing the same surgical procedure, we repeated our analyses using a linear mixed model with random intercept and slope, and a model based on generalized estimation equations to verify our findings.

Next, we repeated these analyses for procedure-specific subgroups of surgical procedures with > 150 patients in our dataset. As the categories for duration may not be clinically relevant for all types of surgery (e.g., for tonsillectomy, almost 75% of the procedures lasted less than 30 minutes), we used procedure-specific duration categories, based on distribution of the data (quintiles) and clinically relevant thresholds (rounded per 5, 10, 15, 20 or 30 minutes, whichever was most appropriate). Threshold values that were used are provided in figure 2. Again, these procedure-specific duration categories were included in linear regression analysis, adjusting for gender (where appropriate), age, preoperative chronic pain, and morphine equivalent dose use.

Analyses were conducted using the statistical software SPSS version 22 (IBM; New York; United States). Throughout the analyses a level of significance of 0.05 was used.

RESULTS

Pain associated with duration of surgery between different procedures

A total of 161 surgical procedures including more than 20 patients each (n = 36,003) was selected to give an overview of pain intensity and duration of surgery between surgical groups. The median duration of surgery varied between 17 min (IQR 10; 30) for cervical lymph node resection and 240 min (IQR 204; 290) for pancreatectomy (figure 1). The order in which the surgeries are presented in figure 1 is based on their median duration. The mean worst pain intensity after the procedures ranged from NRS 2.0 (SD 2.8) for cervical lymph node resection to 6.9 (SD 2.4) for spinal fusion.

In general, many surgeries of very short duration resulted in low postoperative pain intensity, and many long-lasting surgeries caused severe pain. However, there was large variation. Surgeries of short duration that were particularly painful (NRS > 6) included procedures such as tonsillectomy or hemorrhoidectomy with plastic reconstruction. Long-lasting procedures that were relatively less painful (NRS < 4) included, for example, laparoscopic radical prostatectomy or femoral-artery endarterectomy.

After categorizing each surgical procedure in duration groups as given in figure 1 on the right side (i.e. < 30 min, 31-45min, 46-60 min etc.) it was evident that there is a large variability between pain intensities among all categories of short or long lasting types of surgeries. Surgical groups with an average duration of < 30 min scored a median NRS of 3.5. All other types of surgeries assigned to duration categories of more than 30 min ranged between NRS 4.5 and 5.5.

Pain associated with duration of surgery in individual surgical procedures

A total of 33 surgical procedures that each included more than 150 patients without regional anesthesia were identified, comprising a total of 26,992 patients. These procedures originated from 8 surgical disciplines: 12 general surgery, 6 gynecology, 4 orthopedics, 4 trauma surgery, 2 otolarnygology, 2 neurosurgery, 2 urology, and 1 vascular surgery.

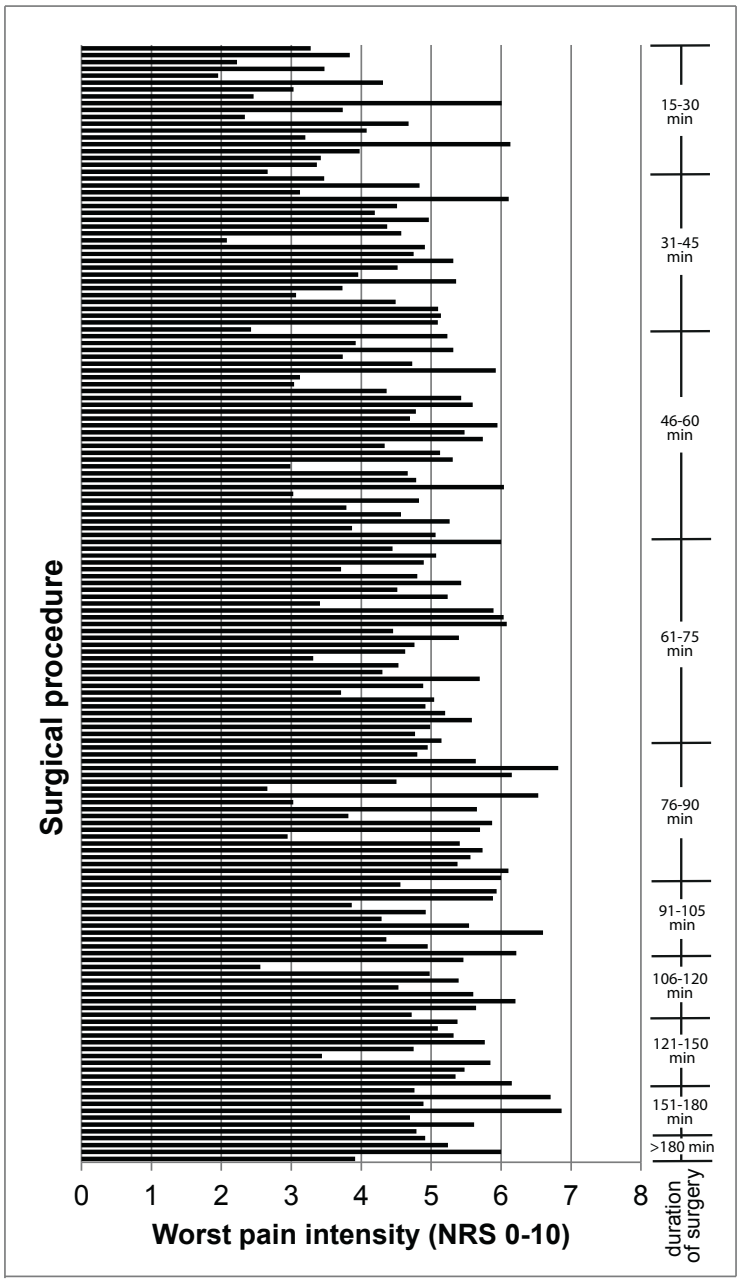


Figure 1. Comparison of the association of duration of surgery and worst postoperative pain between surgical procedures. 161 procedures including more than 20 patients each were selected (n = 36,003). Bars show median of worst postoperative pain intensity since surgery for each procedure. On the right side of the graph the duration of surgery is shown in 15-min or 30-min categories.

Table 1. Linear regression analysis of the influence of duration of surgery on worst postoperative pain during the first 24 hours after surgery in a cohort of 33 different surgical procedures (n=26,992). Age, preoperative chronic pain intensity, gender, and morphine equivalent dose were included as potential confounders.

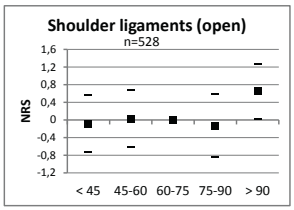
	Crude estimate	Adjusted for age, gender and preoperative pain	Adjusted for age, gender, preoperative pain and morphine use
Duration per 10 min	Regr.-Coef. (95% CI)	Regr.-Coef. (95% CI)	Regr.-Coef. (95% CI)
	0.030 (0.022; 0.038)	0.036 (0.029; 0.044)	0.030 (0.022; 0.037)
Duration category	Regr.-Coef. (95% CI)	Regr.-Coef. (95% CI)	Regr.-Coef. (95% CI)
0-15 min	0 (reference)	0 (reference)	0 (reference)
16-30 min	0.565 (0.319; 0.810)	0.533 (0.296; 0.769)	0.518 (0.283; 0.753)
31-45 min	0.661 (0.427; 0.895)	0.678 (0.453; 0.904)	0.643 (0.419; 0.867)
46-60 min	0.860 (0.628; 1.092)	0.913 (0.689; 1,137)	0.848 (0.626; 1.071)
61-90 min	0.984 (0.757; 1.210)	1.052 (0.833; 1.271)	0.956 (0.738; 1.174)
91-120 min	1.052 (0.816; 1.288)	1.126 (0.898; 1,354)	1.002 (0.775; 1.229)
>120 min	1.029 (0.784; 1.274)	1.148 (0.911; 1.384)	1.022 (0.786; 1,257)

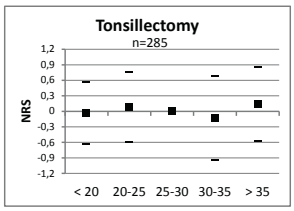
Regr.Coef = regression coefficient; CI = confidence interval

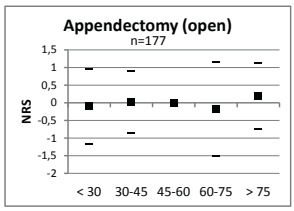
Results of the linear regression analysis comprising all patients are shown in table 1. A ten-minute increase in duration of surgery was associated with 0.030 (95% CI 0.022; 0.038) increase on the NRS pain scale. After adjustment for age, gender and preoperative chronic pain this was 0.036 (95% CI 0.029; 0.044). Further adjustment by morphine (equivalent) use resulted in an overall estimate of 0.030 (95% CI 0.022; 0.037). This increase is also reflected in the analyses where duration was included in categories. Restricted cubic splines did not improve model fit, hence duration of surgery was included in the models in linear fashion.

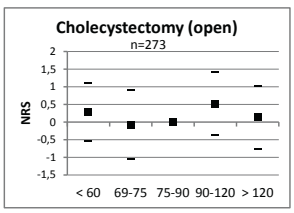
Figure 2 provides the adjusted estimates (age, gender where appropriate, preoperative pain and morphine equivalent use) for the procedure specific analyses. For each type of surgery, the categories of duration are shown, and the effect estimate on postoperative pain intensity expressed by NRS. In all of these analyses, the middle category was used as the reference; however, the actual threshold values for these categories vary between surgery types. In none of the 33 analyzed surgical groups a significant association between duration of surgery and postoperative pain was found defined by a significantly higher pain score of the 4th or 5th quintile or lower pain scores of the 1st or 2nd quintile. However, a comparison only to the middle quintile as reference group could mask a clinically relevant

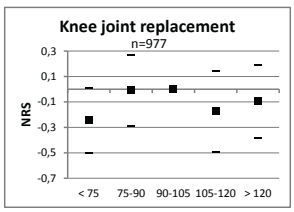
continuous increase of pain intensity over all quintiles. A possible association may be present in the laminectomy group (consisting of flavectomy, hemilaminectomy, and laminectomy on 1 or 2 segments) and arthroscopic surgery of shoulder ligaments (both with an almost steady increase in pain intensity). Unadjusted analysis only including duration of surgery categories indicated very similar results.

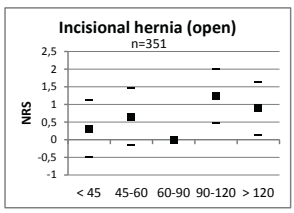

Shoulder ligaments (open)
n=528
NRS
1,6 1,2 0,8 0,4 0 -0,4 -0,8 -1,2
< 45 45-60 60-75 75-90 > 90

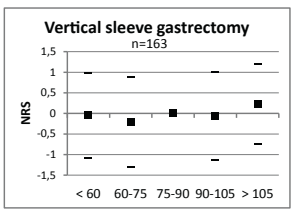

Tonsillectomy
n=285
NRS
1,2 0,9 0,6 0,3 0 -0,3 -0,6 -0,9 -1,2
< 20 20-25 25-30 30-35 > 35

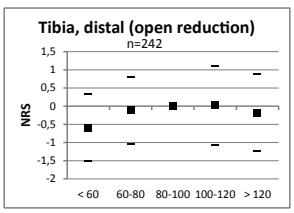

Appendectomy (open)
n=177
NRS
1,5 1 0,5 0 -0,5 -1 -1,5 -2
< 30 30-45 45-60 60-75 > 75

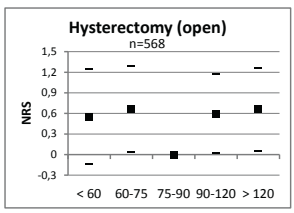

Cholecystectomy (open)
n=273
NRS
2 1,5 1 0,5 0 -0,5 -1 -1,5
< 60 69-75 75-90 90-120 > 120

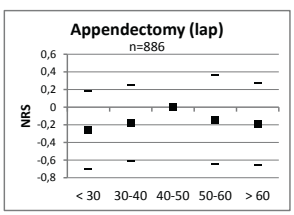

Knee joint replacement
n=977
NRS
0,3 0,1 -0,1 -0,3 -0,5 -0,7
< 75 75-90 90-105 105-120 > 120

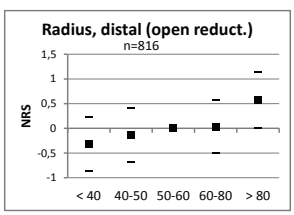

Incisional hernia (open)
n=351
NRS
2,5 2 1,5 1 0,5 0 -0,5 -1
< 45 45-60 60-90 90-120 > 120

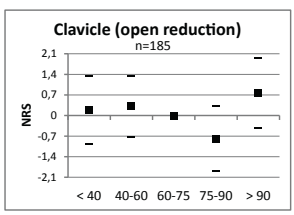

Vertical sleeve gastrectomy
n=163
NRS
1,5 1 0,5 0 -0,5 -1 -1,5
< 60 60-75 75-90 90-105 > 105

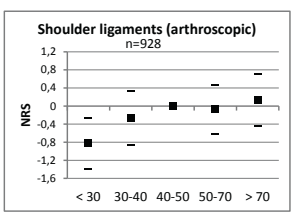

Tibia, distal (open reduction)
n=242
NRS
1,5 1 0,5 0 -0,5 -1 -1,5 -2
< 60 60-80 80-100 100-120 > 120

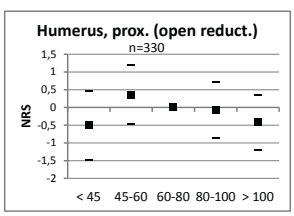

Hysterectomy (open)
n=568
NRS
1,5 1,2 0,9 0,6 0,3 0 -0,3
< 60 60-75 75-90 90-120 > 120

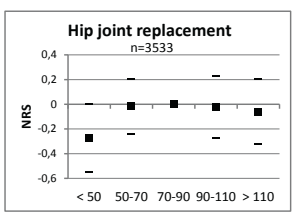

Appendectomy (lap)
n=886
NRS
0,6 0,4 0,2 0 -0,2 -0,4 -0,6 -0,8
< 30 30-40 40-50 50-60 > 60

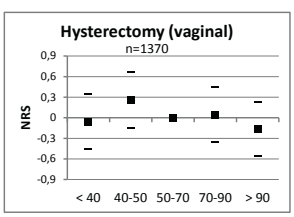

Radius, distal (open reduct.)
n=816
NRS
1,5 1 0,5 0 -0,5 -1
< 40 40-50 50-60 60-80 > 80

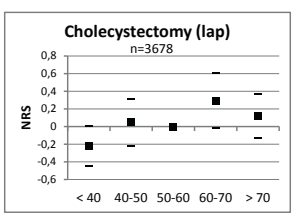

Clavicle (open reduction)
n=185
NRS
2,1 1,4 0,7 0 -0,7 -1,4 -2,1
< 40 40-60 60-75 75-90 > 90

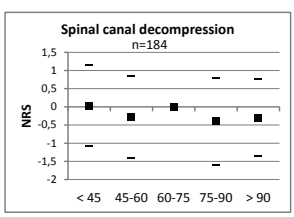

Shoulder ligaments (arthroscopic)
n=928
NRS
1,2 0,8 0,4 0 -0,4 -0,8 -1,2 -1,6
< 30 30-40 40-50 50-70 > 70


Humerus, prox. (open reduct.)
n=330
NRS
1,5 1 0,5 0 -0,5 -1 -1,5 -2
< 45 45-60 60-80 80-100 > 100


Hip joint replacement
n=3533
NRS
0,4 0,2 0 -0,2 -0,4 -0,6
< 50 50-70 70-90 90-110 > 110


Hysterectomy (vaginal)
n=1370
NRS
0,9 0,6 0,3 0 -0,3 -0,6 -0,9
< 40 40-50 50-70 70-90 > 90


Cholecystectomy (lap)
n=3678
NRS
0,8 0,6 0,4 0,2 0 -0,2 -0,4 -0,6
< 40 40-50 50-60 60-70 > 70


Spinal canal decompression
n=184
NRS
1,5 1 0,5 0 -0,5 -1 -1,5 -2
< 45 45-60 60-75 75-90 > 90

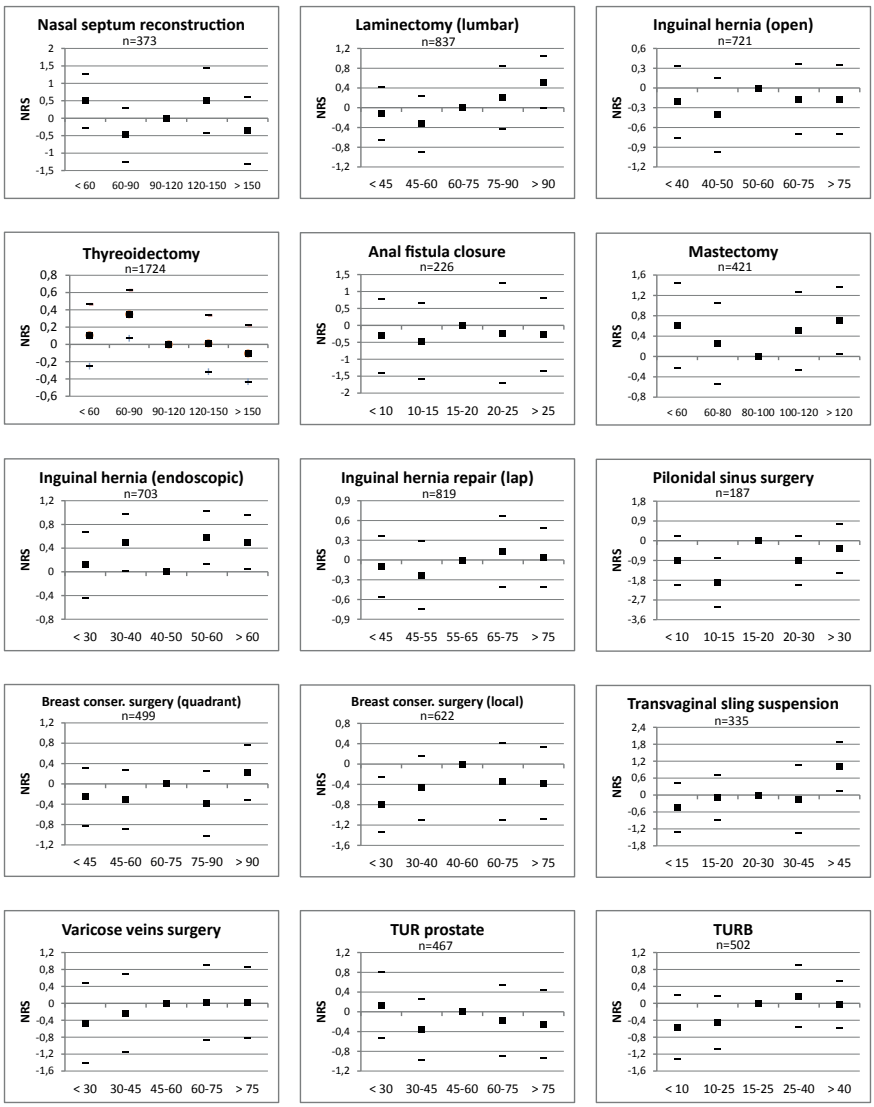


Figure 2. Surgical procedure-specific comparison of the association between duration of surgery and worst postoperative pain during the first 24 hours after surgery. All surgical groups with more than 150 patients were included. For comparison surgical groups were split into quintiles. The cut-offs were rounded to 5, 10, 15, 20 or 30 min. The actual threshold values for these categories vary between types of surgery. Effect estimates (95% confidence intervals) were analyzed with multiple linear regression adjusting for age, preoperative chronic pain intensity, and dose of morphine equivalents. The middle category was used as the reference. The order of the presented surgeries is based on worst pain intensity.

NRS = numeric rating scale; lap = laparoscopic; reconstr. = reconstruction; reduct. = reduction; quadrant = quadrant resection; TUR = transurethral resection; TURB = transurethral resection of the bladder

DISCUSSION

In this large cohort study we did not find a significant association between duration of surgery and postoperative pain intensity within all single 33 surgical procedures. When analyzing the 33 surgical groups as a total cohort (n = 26,992 patients) a statistical significant increase of postoperative pain by NRS 0.030 (95% CI 0.022; 0.037) per 10 minutes longer duration of surgery was found. However, this difference is so small that even after very long surgical procedures it likely is clinically negligible.

Our comparison of the association of duration of surgery and postoperative pain in 161 surgical procedures indicated large variations between procedures. When the duration of surgery was divided into 15-min categories, only very short procedures lasting less than 30 min turned out to be less painful (median NRS 3.5). Surgeries lasting longer than 60 min reached a plateau ranging between median worst pain scores between NRS 4.5 and 5.5. It is noteworthy that due to the large variation in pain intensities, it is not surprising that contradictory results were described in the literature. The combination of types of surgeries included in the study population will play a major role if the duration of surgery is significantly related to pain. In the prediction model of Kalkman et al., duration of surgery had no added predictive value, which was also confirmed in the validation study of this prediction model.[9]

A number of studies examining risk factors for severe postoperative pain have pooled patients with different types of surgical procedures. In those studies, it is virtually impossible to adjust for the type of surgery due to the large variety of procedures and the small number of patients per type of procedure. The duration of the surgical intervention has in those cases been used as a proxy for the extent of surgery. We identified nine such studies, of which four found [12,11,13,14] and five did not find [6,9,8,7,10] a relation between duration of surgery and postoperative pain. Various cut-off points for pain (NRS ≥ 4, ≥ 6, and ≥ 8) [6,12,9,8,10] and duration of surgery (100 min, 120 min, 180 min) [13,14,8,7] were utilized. Furthermore, two studies used a cut-off value of administered morphine dose instead of NRS scores to define severely painful surgeries.[13,14] Chung et al. defined moaning or writhing in pain at any time, initial nursing care dominated by pain control, or cases requiring more analgesics than ordered (~8 mg of morphine) as severely painful procedures.[11] Thus, a comparison based on the existing literature is not really possible.

The analysis of the total cohort including 33 surgical groups indicates a statistically significant effect in unadjusted data, that remained after adjusting for age, preoperative chronic pain and opioid dose. However the effect was so marginal in all analyses also after clustering for surgical groups that we consider this difference as not clinically relevant.

When analyzing duration of surgery within specific single types of surgery undergoing general anesthesia (excluding any regional anesthesia) hardly any association with postoperative pain was seen. A continuous increase of pain intensity from the shortest to the longest duration of surgery category (though not statistically significant) was only found in two surgical groups (arthroscopic shoulder ligament repair and lumbar laminectomy). However, this association may have also been induced by more tissue damage, as the extent of shoulder ligament surgery is not further defined. Likewise, the laminectomy group comprises flavectomy, hemilaminectomy and laminectomy on 1 or 2 lumbar levels. These are in itself different types of surgery, with different degree of tissue damage.

The effect of duration of surgery on postoperative pain has not yet been analyzed in a standardized manner for different types of surgery. Only a few studies have analyzed the effect of duration for a single type of procedure (laparoscopic cholecystectomy).[3–5] Our results in case of laparoscopic cholecystectomy are consistent with two RCTs indicating no relation between abdominal pain and duration of surgery.[4,5] However, an association between longer-lasting pneumoperitoneum and more frequent as well as more intense shoulder pain was found in another RCT.[3] In the QUIPS project the location of postoperative surgical pain is not documented. Other laparoscopic surgeries such as appendectomy, inguinal hernia repair, and vertical sleeve gastrectomy however were not associated with more pain in our study when surgery took a longer time.

There are some limitations of this study. Details of the surgery that may have caused longer surgical duration such as bleeding, abdominal adhesions due to former surgeries, or other intraoperative complications were not recorded. Additional trauma and soft-tissue lesions in patients with fractures were not documented, so that postoperative pain could have been influenced by other pathologies.

Our data describe for the first time the influence of duration of surgery on postoperative pain in a procedure-specific manner. Although postoperative pain must always be treated individually, knowledge about risk factors can enable clinicians to anticipate differences in postoperative pain intensity. Based on our

findings, adaptation of postoperative pain treatment guided by the duration of surgery seems not necessary.

In conclusion, the duration of surgery for a single, specific type of procedure most likely does not have an influence on postoperative pain. If prolonged surgical duration is associated with an extensive tissue damage or incision, as in orthopedic or trauma surgery, the duration of surgery may be associated with postoperative pain intensity.

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PART IV

Outcome measures of postoperative pain

CHAPTER 8

Determination of moderate to severe postoperative pain on the numeric rating scale – A cut-off point analysis applying four different methods

British Journal of Anaesthesia 2011 Oct;107(4):619-26

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Judith Rothaug
Cor Kalkman
Winfried Meissner

ABSTRACT

Background

Cut-off points of the numeric rating scale (NRS 0-10) are regularly used in postoperative pain treatment. However, there is insufficient evidence to identify the optimal cut-off point between mild and moderate pain.

Methods

A total of 435 patients undergoing general, trauma or oral and maxillofacial surgery were studied. To determine the optimal cut-off point for pain treatment, four approaches were applied: firstly, patients estimated preoperatively their tolerable postoperative pain intensity; secondly, 24 hours after surgery they indicated if they would have preferred to receive more analgesics; thirdly, satisfaction with pain treatment was analyzed, and fourthly, multivariate analysis was used to calculate the optimal cut-off point for pain intensities in relation to pain-related interference with movement, breathing, sleep, and mood.

Results

The preoperatively estimated tolerable postoperative pain was median NRS 4.0 (0-10). Patients who would have desired more analgesics reported significantly higher average pain since surgery (median NRS 5.0 (0-9)) when compared to patients without this request (NRS 3.0 (0-8)). Patients satisfied with pain treatment reported an average pain intensity of median NRS 3.0 (0-8) compared to less satisfied patients with NRS 5.0 (2-9). Analysis of average postoperative pain in relation to pain-related interferences indicated pain categories of NRS 0-2=mild, 3-4=moderate, and 5-10=severe pain.

Conclusions

Three of the four methods identified a treatment threshold of NRS ≥ 4 for moderate to severe pain intensity of postoperative average pain. This cut-off was rated as tolerable pain threshold and lay between patient groups regarding satisfaction and the wish for more analgesics.

INTRODUCTION

The numeric rating scale (NRS 0-10; 0 = no pain, 10 = worst pain imaginable) has been validated for measuring postoperative pain intensity.[1] This scale is often used to divide patients into groups who are in need of pain treatment (moderate and severe pain) and those who are not (mild pain). The presently used treatment threshold or cut-off point (CP) for moderate pain treatment is arbitrarily set at NRS ≥ 3,[2, 3] ≥ 4,[3, 4] or ≥ 5,[5-7] and even as high as NRS ≥ 6 in different studies.[8]

Different cut-off points in protocols for acute postoperative pain management lead to variations in treatment. In addition, such cut-off points are increasingly regarded as a quality indicator of postoperative pain control. The wide range of cut-off points used in different research studies makes the comparison of results difficult. It is possible that in some study protocols the threshold for pain treatment was selected to achieve the desired study result.

Initial attempts to define cut-off points were based on the assumption that the terms mild and moderate pain could distinguish patients requiring additional pain treatment. Pain descriptors of a verbal rating scale (VRS) (mild, moderate, and severe) were matched with the corresponding pain scores of the visual analogue scale (VAS) scores (0-100 mm).[9, 10] However, a large prospective study found a discrepancy between reports of severe pain and acceptability; 31% of patients who rated their pain as severe reported this pain as acceptable.[11] Thus, a simple match of the term 'moderate' on the VRS with the scores of the NRS or VAS does not seem appropriate for identifying the optimal cut-off point indicating a need for analgesic administration.

A different approach was introduced by Serlin and colleagues to calculate the optimal cut-off points for mild, moderate, and severe pain. These authors analyzed the association of pain intensity with pain-related interference in activities such as movement and sleep in cancer patients. Pain interference was measured with the Brief Pain Inventory (BPI).[12] In acute postoperative pain studies this method of calculation has only been applied twice, in a study of postoperative pain after hip and knee replacement surgery and after sternotomy. It is not clear if this method of calculating cut-offs between pain intensity and pain interference actually reflects the need for therapeutic intervention.

The aim of this study was to determine the optimal cut-off points between mild and moderate to severe pain intensities on the first postoperative day. There is no generally accepted gold standard to determine the optimal cut-off point on a NRS

and presently used cut-off point analysis methods are not known to be appropriate for postoperative pain. We applied and compared four different methods in order to arrive at the most valid approach to analyze cut-off points.

METHODS

Subjects

Data were collected following the guidelines of the QUIPS project (Quality Improvement in Postoperative Pain Management)[13] in the departments of general surgery, traumatology, and oral and maxillofacial surgery at the University of Jena, Germany, between November 2006 and November 2007. A total of 444 patients were included in the study. Inclusion criteria were age over 18 years and capability to understand German. Patients were excluded if they were undergoing a repeat surgical procedure and when postoperative mechanical ventilation was planned for more than 24 hours, as this was the time-point for pain assessment.[13] There was no restriction with regard to the type of surgery. All consecutive patients fulfilling the inclusion criteria were asked to take part in this study. After approval was obtained from the University Ethics Committee, all patients gave their written informed consent before entering the study.

QUIPS questionnaire

The QUIPS project was set up to analyze postoperative pain management and to anonymously compare outcomes among participating hospitals.[13] The standard QUIPS protocol is divided into sections dealing with (1) average and worst pain intensities during the last 24 hours since surgery (NRS 0-10); (2) pain-related interference with: physical strain (walking, movement); coughing and deep breathing, sleep, and mood during the last 24 hours since surgery (NRS 0-10); (3) pain-related awakening during the previous night; (4) nausea or vomiting since surgery; (5) wish to have had received additional doses of pain medication during the period since surgery; (6) patient satisfaction with postoperative analgesia recorded employing a 16-box NRS (0-15, 0 = very unsatisfied, 15 = very satisfied). Information on the type of surgery, anaesthesia, and postoperative pain treatment are also documented. In addition to the standard QUIPS questionnaire items patients were preoperatively asked to estimate their tolerable postoperative pain level (NRS 0-10).

Patient questionnaires were administered by study nurses who were neither associated with the particular departments nor involved in patients' care. Assessment was performed on the first postoperative day between 8 and 11 am.

Analysis of cut-off points

First, we asked patients preoperatively to indicate postoperative pain thresholds that they would consider 'tolerable'. Second, we evaluated the need for therapeutic interventions by asking patients 24 hours after surgery if they would have wished to have received additional postoperative analgesia and compared the NRS scores of patients who indicated a wish to have received more analgesia to patients who did not. Third, pain intensities in patients 'very satisfied' or 'satisfied' with pain treatment were compared to pain intensities in patients who were less satisfied. Fourth, we calculated cut-off points between mild and moderate to severe postoperative pain intensities in relation to pain-related interference with movement, taking deep breaths, sleep quality, and mood.

Statistical analysis

All variables measured with the NRS are reported as median (range). The Mann-Whitney test was applied to compare postoperative pain intensities between patients with presence and absence of the wish to have received more analgesics and between patients with low and high satisfaction with pain treatment. Furthermore, preoperatively estimated tolerable pain was compared between patients with mild and moderate to severe postoperative pain by means of the Mann-Whitney test.
Satisfaction with pain treatment (NRS 0-15) was graded using German school grade categories: 15-13 (very satisfied), 12-10 (satisfied), 9-7 (neither satisfied, nor dissatisfied), 6-4 (dissatisfied), and 0-3 (very dissatisfied). The scale was dichotomized in NRS ≥ 10 (very satisfied or satisfied) vs. lower scores. In all comparisons, two-sided tests were used with $p \leq 0.05$ to indicate statistical significance.
The fourth applied method to identify the optimal cut-off point is based on the relation between postoperative pain intensity since surgery and pain-related interference in the period since surgery. The statistical method described by Serlin and colleagues was used.[12] To identify the optimal cut-off point 28 different combinations of pain cut-off points from CP 1/2 to CP 7/8 of average and worst pain since surgery were analyzed. The upper limits for mild and moderate pain were used to describe the cut-off points, e.g. cut-off points 1-4, 5-6, 7-10 were termed CP 4/6.

The means of the four variables (interference with mood, deep breathing, sleep, and mood) were pooled to a total-interference score (NRS 0-10). The optimal cut-off points of mild, moderate, and severe pain were identified by multivariate analysis among pain-severity categories yielding the largest *F* ratio for the between-category effect on the total pain-related interference score as indicated by Pillai's trace, Wilks lambda, and Hotelling trace *F* statistics. Patients without any postoperative pain do have no pain-related interferences and are subsequently excluded from the cut-off point analysis based on between-category effects. Data were analyzed using the Statistical Package for the Social Sciences (SPSS© release 18.0, Chicago, IL, USA).

RESULTS

Demographic and clinical data

Inclusion criteria were met by 444 patients. Nine patients did not complete the questionnaire, leaving 435 for further statistical analysis. Approximately 56% of the patients were male; 55%, 24% and 21% were admitted to the traumatology, general surgery, or oral and maxillofacial surgery departments. The most frequent surgical procedures are listed in table 1.

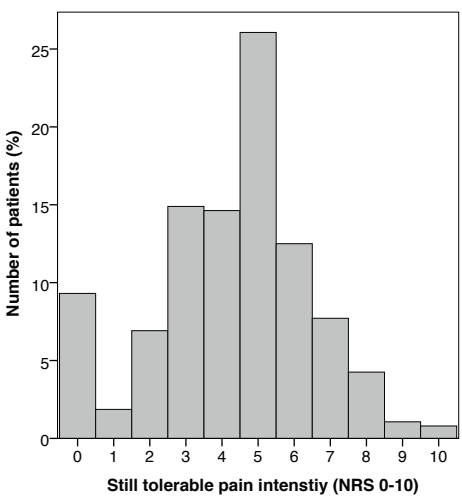

Figure 1. Distribution of preoperatively estimated tolerable postoperative pain intensities (NRS 0-10) of the entire study population (n = 435).

Preoperatively evaluated 'tolerable' postoperative pain intensity, the wish to have received more analgesics, and satisfaction with pain treatment

Before surgery, patients indicated a NRS score of median 4.0 (0-10) as the threshold for tolerable postoperative pain (figure 1).

Table 1. Demographic and clinical data (n = 435)

	n	(%)
Gender		
Female	192	(44.1)
Male	243	(55.9)
Age (yrs)		
18-20	38	(8,7)
21-30	75	(17.2)
31-40	88	(20.2)
41-50	96	(22.1)
51-60	87	(20.0)
61-70	49	(11.3)
71-80	2	(0.5)
Surgical department		
Traumatology	237	(54.5)
General surgery	106	(24.4)
Oral and maxillofacial surgery	92	(21.1)
Most frequent types of surgery		
Traumatology		
Osteotomy	50	(21.2)
Arthroscopy	42	(17.7)
Tendons, muscles of the hands	38	(16.0)
Metal removement	25	(10.5)
Others	82	(34.6)
General surgery		
Cholecystectomy	37	(34.9)
Thyroidectomy	23	(21.7)
Gastrointestinal surgery	22	(20.8)
Inguinal hernia repair	18	(17.0)
Others	6	(5.6)
Oral and maxillofacial surgery		
Osteotomy	60	(65.2)
Plastic surgery	17	(18.5)
Debridement	15	(16.3)

Patients were asked on the morning after surgery if they would have wished to receive additional doses of analgesics during the period from surgery to the time of the study nurse's interview. Eight of the 435 patients did not answer this question; 75 of the remaining patients (17.6%) indicated that they would have preferred to receive more analgesics. Patients without this demand reported an average pain intensity since surgery of median NRS 3.0 (0-8); whilst those who would have preferred additional analgesic doses reported significantly higher pain intensity of median 5.0 (0-9) ($p \leq 0.001$) (figure 2). Worst pain intensity since surgery recorded on the NRS also differed significantly ($p \leq 0.001$) between these two groups: median 6.0 (0-10) vs. median 8.0 (2-10).

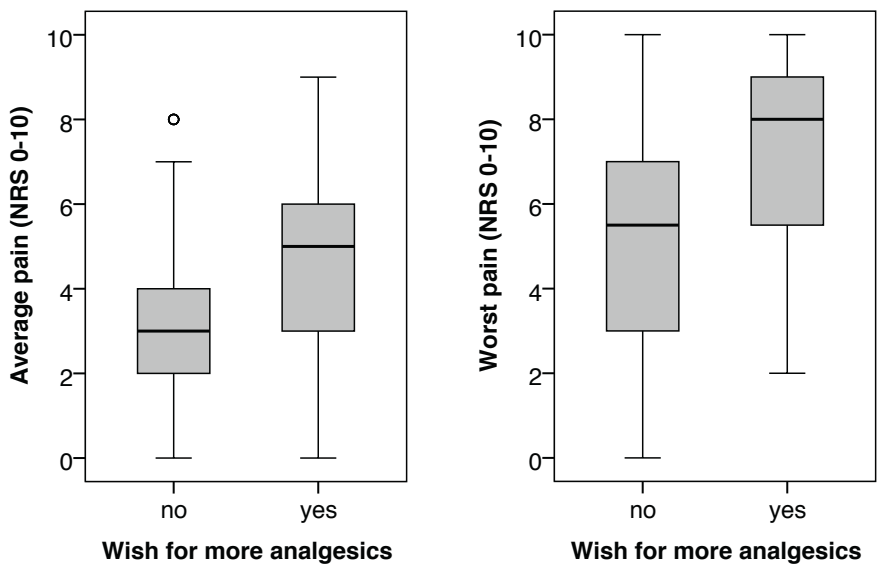

Figure 2. Differences in average and worst pain intensities among patients with and without the desire for more analgesics in the period from surgery to the first postoperative day.

Patients who graded their satisfaction with pain treatment as very satisfied or satisfied (83.7%) reported average postoperative pain intensity since surgery as median 3.0 (0-8) as compared with NRS 5.0 (2-9) in the less satisfied patient group (16.3%) (figure 3). The two groups differed significantly for average as well as for worst pain intensity since surgery ($p \leq 0.001$).

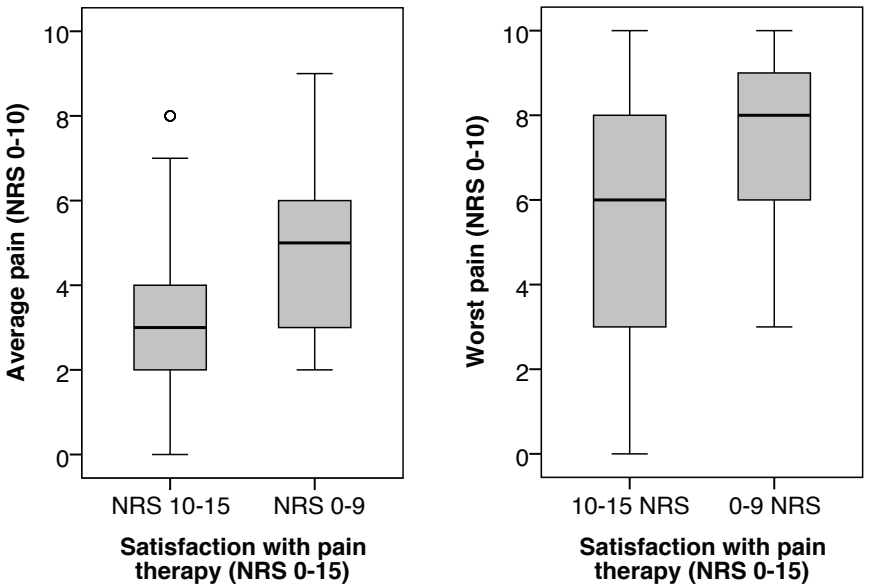

Figure 3. Average and worst pain intensities reported by patients very satisfied and satisfied with postoperative pain treatment (NRS 10-15) compared to patients who are less satisfied (NRS 0-9)

Relation between pain intensity and pain-related interferences

Movement, sleep, and mood were negatively impacted by pain with median scores on the NRS of 4.0, 3.0 and 2.0, all ranging from NRS 0-10. Deep breathing was not interfered by pain in 53% of the patients resulting in a pain-related interference score of median NRS 0 (0-10) The total pain-related interference score for movement, deep breathing and coughing, sleep, and mood was median NRS 2.5 (0-10). The relations of average and worst pain intensities during the time since surgery and the four pain-related interferences as well as the total pain-related interference score are shown in figure 4.

Patients without pain are excluded for the cut-off analysis based on pain-related interference. A total of 25 patients reported an average pain intensity of NRS 0 leaving 410 patients for further analysis. The optimal cut-off points between mild and moderate, and moderate and severe pain were defined when they had the largest between-category *F* ratio using Pillai's trace, Wilks λ, and Hotelling's statistic. The cut-off points for average pain during the first postoperative day were estimated to be 2/4 (NRS 1-2 = mild; 3-4 = moderate; 5-10 = severe) (figure 5).

Twelve patients reported a worst pain intensity of NRS 0 and were subsequently excluded for this analysis, leaving a total of 423 patients. For worst pain intensity the statistical analysis showed higher cut-off points of 4/7 (NRS 1-4 = mild; 5-7 = moderate; 8-10 = severe) (figure 5).

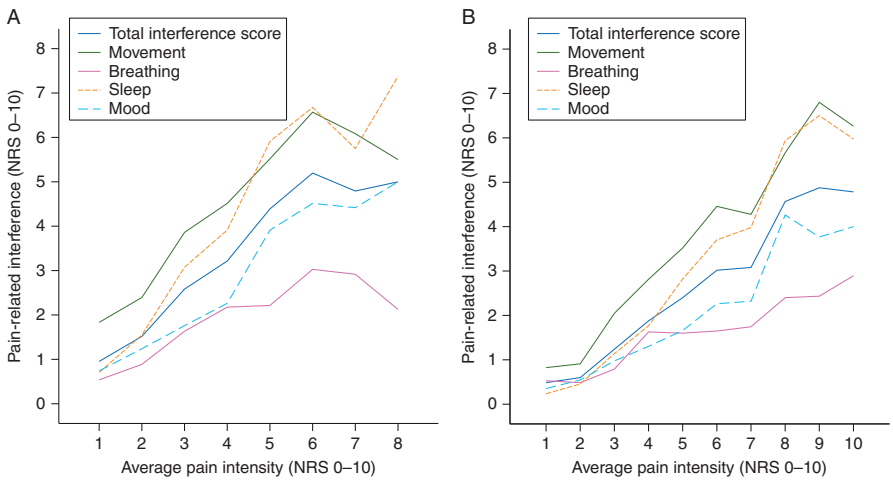

Figure 4. Relation between average and worst postoperative pain intensities (numeric rating scale (NRS) 0-10) since surgery and pain-related interference. Pain-related interferences (NRS 0-10) are measured (1) during movement; (2) when taking deep breaths or coughing; (3) with sleep, and (4) with mood. The mean of these four variables is shown as a total interference score.

The preoperatively estimated score for postoperative tolerable pain intensity was rated as NRS 4.0. Patients who did or did not have the wish for more analgesics since surgery as well as patients satisfied or not satisfied with pain treatment had a median of average pain since surgery of NRS 3.0 vs. 5.0. This implies that the optimal cut-off is best described at ≥ NRS 4 confirmed by the preoperative assessment. However, the relation between pain intensity and pain-related interference revealed a cut-off point at ≥ NRS 3.

With 3 out of the 4 applied methods identifying NRS ≥ 4 as the cut-off point we defined the latter as the optimal cut-off point. A comparison of preoperatively estimated tolerable pain intensity between patients with mild (NRS < 4) and moderate to severe pain (NRS ≥ 4) demonstrated no differences ($p = 0.826$). Thus, a different interpretation of the NRS between patients with mild and moderate to severe pain as a possible confounder can be excluded.

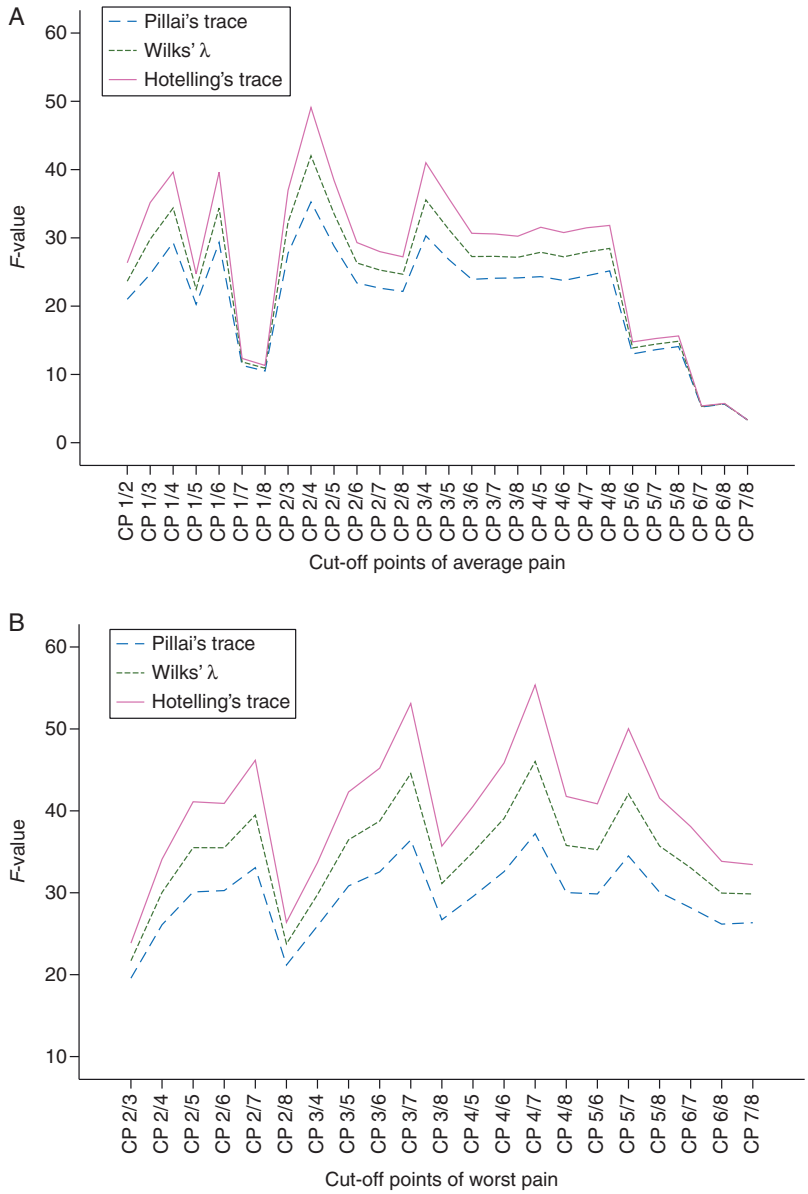

Figure 5. Average and worst pain intensities were each divided into three groups defined by their cut-off points (CP). CP 4/6 stands for NRS 1-4 = mild, NRS 5-6 = moderate, and NRS 7-10 = severe pain. For each CP multivariate analyses were used with different methods (Pillai's trace, Wilks lambda, and Hotellings trace) to calculate the best relation of each CP with the average of four pain-related interferences (movement, deep breathing, sleep, and mood). The highest F-values indicate the most significant relationship between pain interference and the corresponding CPs.

DISCUSSION

In this study we sought to determine the optimal cut-off point between mild and moderate to severe postoperative pain at the first day after surgery. Moderate pain was considered in this study as pain requiring analgesic intervention and leading to relevant pain-related interference with movement, sleep, mood, and deep breaths. The optimal cut-off point for average pain between mild and moderate intensity was NRS ≥ 4 indicated by 3 of the 4 applied methods.

In acute postoperative pain cut-off points are widely used as a basis for administering or withholding opioid analgesics but no consensus exists as to appropriate treatment thresholds. Consequently, various arbitrarily chosen cut-off points are used in clinical protocols and research. It is generally agreed that cut-off points only serve as a guideline. Pain treatment should be tailored to individual needs. However, an inappropriate cut-off point on a pain treatment protocol may carry a risk of over- or undertreatment.

Cut-off points are employed in various study designs. In clinical trials the aim of treatment may be the reduction of pain below a defined cut-off point. In such instances predefined doses of analgesics are titrated until the cut-off point is arrived at. This is usually done by selecting a NRS or VAS cut-off point.[4,7,9,14,15] Furthermore, cut-off points are used in aetiologic[5,16] and prognostic studies. In such studies factors are determined which predict the incidence of pain above a certain cut-off point.[17,18]

There is no agreement on the optimal cut-off point for pain treatment and there is no agreement on how to identify an optimal cut-off point on the NRS for postoperative pain. To maximize validity of our analyzed optimal cut-off point we compared several distinct outcome measures. Four methods were adopted to characterize the optimal NRS cut-off point. These were, 'tolerable pain intensity', 'patient's wish for more analgesic', 'satisfaction with pain therapy', and 'pain-related interference with movement, sleep, mood, and deep breaths'.

Three of the four methods identified a cut-off point of NRS ≥ 4 as optimal. Firstly, the preoperative evaluation of a tolerable postoperative pain threshold identified a cut-off point of 4.0 (0-10). Secondly, the cut-off point of NRS ≥ 4 lay between the median pain intensities of patients without further analgesic demands (NRS 3.0 (0-8)) and those who would prefer to have received additional pain medication NRS 5.0 (0-9). Thirdly, pain intensity between patient groups very satisfied or

satisfied compared to those less satisfied with pain therapy gave similar results (NRS 3.0 (0-8); vs. NRS 5.0 (2-9)). Fourthly, the relation between average pain intensity since surgery and pain-related interference with movement, sleep, mood, and deep breaths resulted in a lower threshold of NRS ≥ 3.

Previously two methods have been used to identify cut-off points for postoperative pain. The first method, an exclusive matching of VAS or NRS pain scores with the terms mild, moderate, and severe of the VRS were not been conducive.[9] A relationship between patients' verbal rating of moderate pain and need for analgesic treatment is often postulated[9] but has not been proven. In contrast, one large prospective study asked patients with acute pain about the acceptability of their pain.[11] Thirty-one percent of patients who reported severe pain on a VRS (mild, moderate, severe pain) rated their pain as acceptable.[11]

A second established method to identify cut-off points relates pain intensity to the extent of pain-related interference with activity, sleep and mood.[12] In our study this method gave rise to a lower cut-off point of NRS ≥ 3 as compared to a value of NRS ≥ 4 given by the other three methods. The method was primarily developed for cancer pain and its use may not be satisfactory in the acute postoperative situation. Transferring cut-off point derivation methods from chronic pain syndromes to acute postoperative pain conditions should be undertaken with caution.[12] The nature of chronic pain may result in different pain-related interferences[19] as compared to acute postoperative pain. Furthermore, therapeutic aims differ in acute and chronic pain therapy. Chronic pain therapy tries to improve physical and mental functioning, i.e. health-related quality of life. Thus, reduction of chronic pain intensity is not the only objective. Acute postoperative pain therapy primarily focuses on pain intensity reduction. This pain reduction allows for improved physical and mental functioning.

In our study population a cut-off for average pain intensity since surgery based on patients very satisfied or satisfied with pain treatment was identified as NRS ≥ 4. This cut-off value is consistent with a recent multicenter study including some 2200 patients.[20] Patients rating their pain treatment as very good or good on a 6 item scale scored their pain intensities at rest as NRS 3 or lower. Higher pain intensities (NRS ≥ 4) were associated with poorer satisfaction scores.

As in other pain studies, our results showed a large range of pain intensities experienced acceptable to patients.[9] This indicates that cut-off points do not

identify sharp changeover points. They describe a most optimal threshold, only. Consequently, pain thresholds alone should not be used separately as a quality outcome parameter as considered by some authors and authorities.[16] Furthermore, categorization of mild, moderate, and severe pain is reserved for treatment or study protocols and should never be used for therapeutic strategies in individual patients. The patient's perception of pain intensity and need for therapeutic intervention are extremely variable.[11, 15] In patient care a strict adherence to treatment protocols and 'absolute' VAS or NRS thresholds distract health personnel from administering individualized pain treatment.

Further limitations of cut-off points use in research studies include loss of statistical power and a risk of oversimplification when relating to other outcome or predictor variables.[21] It is important to notice that there are many published studies in which patients were inappropriately categorised by cut-off point. It has to be doubted that any additional knowledge is gained from arbitrarily selected groupings as long as there is no consensus on the classification of mild, moderate, and severe pain.[22]

Two studies have previously analyzed cut-off points in the postoperative period with regard to pain interference. Pain interference was measured using the modified Brief Pain Inventory that analyzes interferences with activity, walking, mood, sleep, and relation with others. One study examined pain intensities and pain-related interferences (5 items) in 77 patients after hip- or knee-replacement surgery.[22] The authors obtained the optimal cut-off points for average pain at CP 4/5 (our scores: CP 2/4) and for worst pain at CP 4/7 (same scores as in our study). The other study calculated pain cut-off points after coronary artery bypass graft (CABG) surgery.[23] The authors analyzed worst pain only during a 11 day period.[23] The CP 4/6 was optimal for 5 of the 11 assessment days and CPs 3/6 and 3/7 were optimal for three assessment days each.

There are several potential explanations for the discrepancies between our results and those of the two other postoperative cut-off point studies. In contrast to our study, selected types of cardiac or orthopaedic surgery were analyzed. This does lead to differences in pain-related interferences, e.g. with regard to mobility. Mendoza and co-workers analyzed only 'worst pain intensity' and only four possible CPs (3/6; 3/7; 4/6; 4/7) following sternotomy.[23] The study of orthopaedic surgery examined eight cut-off point combinations only, ranging from 3/5 to 5/8, actually not covering our identified cut-off points for average pain of 2/4. Our study is to

our knowledge the first to examine cut-off points for pain intensities in relation to pain-related interference during the first 24 hours after surgery. In the studies discussed above patients undergoing CABG were followed-up from postoperative day 4 to 14 and the orthopaedic patients were studied on postoperative day 3.

More recently, several study groups have employed multivariate analyses to study the relationship between pain intensity and pain-related interference in chronic pain patients including patients suffering from osteoarthritis pain,[24] back pain,[25] diabetic polyneuropathy,[26] amputation pain,[27] and pain following spinal cord injury.[28] In the majority of studies NRS ≥ 4 was reported to be the threshold for moderate pain in chronic pain patients, although cut-off points of ≥ 3 and ≥ 5 were also quoted.
A limitation of our study is that the wish for more analgesics during the time since surgery could have been influenced by a patient's general refusal of medication, fear of side effects, or fear of addiction. We did not analyze these factors.

In conclusion, the present study identified a threshold of NRS ≥ 4 between mild and moderate to severe pain of postoperative average pain intensity during the first 24 hours after surgery. This value was ascertained by means of four different methodological approaches. Three of these approaches arrived at the cut-off point of NRS ≥ 4.

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CHAPTER 9

Correlates of satisfaction with pain treatment in the acute postoperative period – Results from the international PAIN OUT registry

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ABSTRACT

Patient ratings of satisfaction with their postoperative pain treatment tend to be high even in those with substantial pain. Determinants are poorly understood and have not previously been studied in largescale, international datasets. PAIN OUT, a European Union-funded acute pain registry and research project, collects patient-reported outcome data on postoperative day 1 using the self-reported International Pain Outcome Questionnaire (IPO), and patient, clinical, and treatment characteristics. We investigated correlates of satisfaction and consistency of effects across centers and countries using multilevel regression modelling. Our sample comprised 16,868 patients (median age 55 years; 55% female) from 42 centers in 11 European countries plus Israel, USA, and Malaysia, who underwent a wide range of surgical procedures, for example, joint, limb, and digestive tract surgeries. Median satisfaction was 9 (interquartile range 7–10) on a 0–10 scale. Three IPO items showed strong associations and explained 35% of the variability present in the satisfaction variable: more pain relief received, higher allowed participation in pain treatment decisions, and no desire to have received more pain treatment. Patient factors and additional IPO items reflecting pain experience (eg, worst pain intensity), pain-related impairment, and information on pain treatment added little explanatory value, partially due to covariate correlations. Effects were highly consistent across centers and countries. We conclude that satisfaction with postoperative pain treatment is associated with the patients' actual pain experience, but more strongly with impressions of improvement and appropriateness of care. To the degree they desire, patients should be provided with information and involved in pain treatment decisions.

INTRODUCTION

A number of studies devoted to quality improvement of pain management in the acute postoperative period measured patient-reported pain intensity, satisfaction with pain treatment, and related elements.[3,4,8,13,18,21,25,27,29] Questionnaires developed by the American Pain Society (APS) were frequently used in this context.[3,4,13,18,28,29] Most studies noted high satisfaction ratings even in patients experiencing moderate to severe pain,[3,4,8,18,21,27-29], sometimes despite long waiting periods for medication and ineffective care.[19,29] It has been argued in response to this initially unexpected observation that patients may expect substantial pain after surgery and, therefore, not be dissatisfied if this expectation is met.[3,6,28] Expectation of a peak-and-trough pattern of pain intensity may make temporary relief achieved with medication more relevant than overall pain intensity.[18,29] Perceived clinician and staff support may influence satisfaction more than the actual pain experience.[17,29] Social desirability bias may play a role.[18]

Empirically, satisfaction with pain treatment has been associated with demographic and preoperative patient factors, expectations, actual postoperative pain experience, and the care environment. Specifically, patients of older age [18,27] and of male gender [27] were more satisfied. Associations with preoperative pain [2,13] and with expectation of postoperative pain[1,13] were inconsistent. Optimism had a positive influence [5] while preoperative fear [21], interference of pain with mood [18] and side effects of medication impacted negatively [17,20]. Perceived pain relief received was associated with higher satisfaction [4,17,27,29]. This was also true for lower pain intensity [5,13,14,18] but in some cases, the association was weak.[4,17,23,27,28] Availability of a pain service [19], staff valuing pain management [17,29] or expressing an intention to provide relief [3,28], and informing patients preoperatively [4,14,21,25,29] had positive influence. A systematic review showed no clear impact of choice of postoperative pain treatment techniques (e.g. epidural anesthesia, intravenous opioids).[17]

The emerging picture is that of a complex and possibly rather indirect relationship of patient satisfaction with actual pain experience. What patients refer to when they rate satisfaction is not entirely understood. There is currently no theoretical framework that would provide a comprehensive explanation.[4,18] Better management and reduction of pain have been demonstrated to improve clinical outcomes, irrespective of satisfaction.[3,4] Still, the priorities and perceptions of patients should be valued.[4] Moreover, the studies available to date were mostly

small and non-international, conducted in the USA, Canada, or single countries in Western and Northern Europe.

Data on a large number of patients from different geographies, covering many of the above-mentioned potential influences on satisfaction, enabled us to address some of the above mentioned issues on a larger scale than before. We aimed to contribute to a better understanding of how patients conceptualize satisfaction and ways to improve it. Specific objectives were to study correlates of patient-reported satisfaction with postoperative pain treatment in a large, international cohort of patients, to gain an understanding of the relative importance of observed effects and possible implications for the care process, and to examine potential variation in the direction and magnitude of these effects across centers and countries.

MATERIALS AND METHODS

PAIN OUT project

PAIN OUT is an international, European Union (EU)-funded registry and research project aimed to improve postoperative pain management (http://www.pain-out.eu). The overall set-up and approach have been previously described.[24,30] Between February 2010 and January 2012, 51 clinical centers in 17 countries participated in the PAIN OUT data collection. Inpatients from all surgical specialties could be enrolled; however, the eleven member sites of the EU-funded PAIN OUT consortium focused on orthopedic and general surgery for the first 300 patients, to facilitate initial validation. Patients had to be of consenting age (18 years in the majority of countries; 16 years in the United Kingdom) or over, not cognitively impaired, on postoperative day 1, back on the ward from the recovery room for at least 6 hours, available in their hospital room, and able to complete the study questionnaire. Postoperative day 1 was chosen because PAIN OUT does not only cover large surgeries but also the much larger number of smaller surgeries where pain may not be long-lasting and where patients may be discharged on day 2. Research assistants approached potentially eligible patients in their room. Where capacity was insufficient to approach all, PAIN OUT Standard Operating Procedures provided guidance on how to achieve a random selection. Based on a written information sheet, patients were asked to provide assent or written consent, as determined by the local institutional review board or ethics committee. Approval was obtained from all local institutional review boards or ethics committees.

Measures

The International Pain Outcomes Questionnaire (IPO) was developed on the basis of the most recent APS questionnaire [9] and forms the core of the PAIN OUT project. [24] It covers key aspects of outcome measurement in acute pain, namely pain severity, interference of pain with physical function and mood, side effects of pain treatment, and perception of care including satisfaction with postoperative pain treatment. Questions on the use of non-medicine methods of pain relief and on the presence and intensity of preoperative chronic pain are also included. The IPO mostly uses 11-point (0-10) numeric rating scale items and binary items. Two items addressing time in severe pain and pain relief received use percentage scales but were treated as numeric rating scales for the purpose of this analysis. Translation from English into 15 languages used state-of-the-art forward and backward translation procedures to ensure consistency between language versions.[24] A two-stage questionnaire validation process led to two slightly different versions being used during the data collection phase; both were successfully validated and fully consistent as previously described.[24] The final set of questionnaire items is shown in Table O-1, on-line. Self-completion of the IPO was the rule but patients could be interviewed if they were too ill, in too much pain, or unable to read or write due to their condition. The use of self-completion versus interview was recorded. Demographics, medical history information, International Classification of Diseases version 9 surgical procedure (ICD-9-CM) codes, time and duration of surgery, and techniques and drugs used for preoperative, intraoperative and postoperative anesthesia and pain treatment were extracted from the medical records and recorded on a separate case report form. For opioids and non-opioid pain drugs (but not for local anesthetics), dose was also recorded. A web-based tool was used to enter all data into a central database.

Analysis sets and explanatory variables

For the purpose of this analysis, data from centers which enrolled less than 25 eligible patients were excluded in order to reduce the *a priori* risk of inconsistency in the local approach to data collection. Data on female patients undergoing Cesarean section were also excluded to achieve a restriction to disease-related procedures. The resulting main analysis set encompassed patients who underwent a large variety of different surgeries. A second, restricted analysis set was confined to patients undergoing 15 frequently recorded and well-defined procedures, namely complete thyroidectomy (ICD-9-CM 06.40), laparoscopic appendectomy

(47.01), open cholecystectomy (51.22), laparoscopic cholecystectomy (51.23), total abdominal hysterectomy (68.40), open reduction of fracture with internal fixation, upper arm (79.31), open reduction of fracture with internal fixation, femur (79.35), shoulder arthroscopy (80.21), knee arthroscopy (80.26), excision of intervertebral disc (80.51), ankle fusion (81.11), total hip replacement (81.51), total knee replacement (81.54), resection of quadrant of breast (85.22) and unilateral simple mastectomy (85.41).

Potential correlates of satisfaction were pre-selected based on the grounds of either published evidence [1-5,13,14,17-21,25,27,29] or presumed logic. They included age, gender, weight and body mass index (BMI), medical history items indicative of respiratory, renal, psychiatric comorbidity and malignant disease, surgical procedure performed or body site of surgery (see Table O-2, on-line, showing ICD-9-CM codes used for this classification), duration of surgery, time from end of surgery to IPO completion, self-completion of the IPO or interview, IPO version and language used, and responses to the questionnaire items (including those addressing preoperative chronic pain). Indicators of type of anesthesia received intra-operatively distinguished general anesthesia, neuraxial (spinal or epidural) anesthesia, peripheral nerve block, and wound infiltration. Indicators of type of treatment received in the recovery room and on the ward covered neuraxial anesthesia, peripheral nerve block, opioids, and non-opioids. The role of non-medicine methods of pain relief was assessed on a summary basis, using a binary variable indicating any use versus none. While patients were the main units of observation, higher-level units of potential interest included ward, clinical center, country of clinical center or country group (7 geographic categories; Table 1). As 7 of 14 countries were only represented by a single clinical center, the country group variable was primarily used in multivariable regression analysis but the performance of the country variable was also assessed.

Statistical analysis

Variables were described by frequencies and percentages, or medians and ranges, as appropriate. For IPO items using 0-10 numeric rating scales, medians and interquartile ranges were reported. Univariable analysis was based on Spearman's rank correlation coefficient, Mann-Whitney U tests and Kruskall-Wallis tests, and was used to screen for potential influences on patient satisfaction. Covariates that showed no trend of an association (i.e., $p > 0.25$) in the main analysis set were dropped from subsequent analysis.

The remaining covariates were further assessed using multivariable regression techniques. In order to correctly take into account the hierarchical nature of the data (i.e., clustering of patient data within higher-level units such as clinical center or country), and as consistency of effects across higher-level units was of explicit interest, a multilevel modeling framework was chosen.[7] We used multilevel (mixed-effects) normal response models based on iterative generalized least squares regression, with a low potential for estimation problems.

Our multilevel modeling approach was similar to that of Hox.[12] An intercept-only model with no explanatory variables was estimated based on the main analysis set to gain an understanding of the amount of higher-level variation present in the data and to select a higher-level unit of primary interest. Explanatory variables were added to the resulting random-intercept model, as fixed effects. Two criteria needed to be fulfilled for inclusion, namely statistical significance based on Wald tests and reduction of the Bayesian Information Criterion (BIC). Reduced BIC values indicate better predictive ability and model fit. The BIC implies a relatively strong penalization for over-complexity and was selected to exclude effects which would contribute little explanatory value to the models despite being significant in our large dataset. A modification of the BIC appropriate for multilevel modeling was used.[22] Higher order terms (i.e., squared or cubic terms; centered to avoid estimation problems) and first order interaction terms were treated in the same way.

After completion of the fixed part of the model, we studied higher-level variation around patient-level effects. Significant random slopes representing such higher-level variation were added in descending order of the reduction in deviance achieved. Covariance terms were freely estimated and fixed to zero if non-significant.

In a final step, the degree of higher-level variation was assessed graphically. The covariate representing country group was added to the model and we tested for interaction between country group and patient-level effects showing higher-level variation. Graphical presentation was used to gain initial insights into patterns of effect variation across country groups.

Statistical analyses were performed using Stata/MP, version 12.1 (StataCorp, College Station, Texas) and MLwiN, version 2.27 (Centre for Multilevel Modelling, University of Bristol, UK). Integration of MLwiN into Stata was achieved using the *runmlwin* command (Centre for Multilevel Modelling, University of Bristol, UK). For effect estimates representing combinations of linear predictors, standard errors (SE) were calculated using Stata's *lincom* command.

Additional analyses

A series of additional analyses were conducted to complement and support the findings based on the main analysis set and considering all IPO items as covariates. The items of the IPO were excluded in alternative regression models because we anticipated them to potentially mask upstream effects. (For example, the influence of type of intraoperative anesthesia on satisfaction may be mediated by postoperative pain experience. If both type of anesthesia and IPO items representing postoperative pain experience are included as covariates in multivariable regression models, the influence of type of anesthesia – occurring earlier, upstream – may be absorbed into the effect of the IPO items, and may hence become invisible.) Most regression analyses (with the exception of the final graphical assessment of multilevel variation) were also performed on the restricted analysis set to assess consistency. Parallel least squares regression models allowed an approximate quantification of the explanatory value of model covariates, based on the R squared statistic and standardized regression coefficients. They were also used as a basis for assessing the impact of influential observations and the presence of collinearity. As satisfaction was defined on an 11-point (0-10) numeric rating scale and showed a skewed distribution (Fig. 2), parallel models using Huber and White robust standard errors (relaxing the assumption of homoscedasticity and other assumptions of standard normal response models), [26] ordered logistic regression models, and logistic regression models of satisfaction rating < 8 versus ≥ 8 were estimated for the purpose of validation.

RESULTS

Of 24,145 patients assessed, 18,009 (74.6%) were eligible for PAIN OUT, provided informed assent or consent and answered the IPO (Fig. 1). The main analysis set for this study comprised 16,868 (93.7%) of these patients from 42 clinical centers (median number of patients per center, 164; range, 25 – 1305 and median number of centers per country, 2; range, 1 – 11). The restricted analysis set comprised a subset of n = 4,733 patients from 40 clinical centers (median number of patients per center, 62; range, 1 – 549 and median number of centers per country, 2; range, 1 – 11). Patients underwent a wide range of surgical procedures; the vast majority had trauma, orthopedic, abdominal, gynecological or thyroid surgery. Patient and procedure characteristics for the main and restricted analysis sets are shown in Table 1.

Patient-reported satisfaction and pain experience

Patient-reported satisfaction with postoperative pain treatment showed a very similar, skewed distribution for the main and restricted analysis sets (Fig. 2 and Table 2). Results for other IPO items were also similar for both sets (Table 2). In univariable analysis, most covariates demonstrated an association with satisfaction at p values ≤ 0.25. Exceptions were medical history items representing respiratory, renal or malignant comorbidity, and the binary covariate indicating any use of non-medicine methods of pain relief.

Hierarchical data levels and attributable variance

In a four-level (patient, ward, clinical center, and country group level) intercept only model based on the main analysis set, with no additional explanatory variables, 94.3% of the total variance present in the satisfaction variable occurred at the patient level (i.e., the lowest level). Higher-level variance at the ward, clinical center, and country group levels amounted to 1.1%, 3.7%, and 0.8%, respectively, of the total variance. Clinical center showed the highest degree of random variation and was subsequently used as the higher-level unit of interest in two-level analysis. In the following, we present two-level, multivariable regression models based on the main analysis set, including and then excluding IPO items. A final section addresses models based on the restricted analysis set and supportive models estimated for the purpose of validation.

Table 1. Demographics and procedural characteristics of patients included in the main and restricted analysis sets

	Main analysis set (n = 16,868)[a]	Restricted analysis set (n = 4,733)[b]
Age, years (n = 16,770/4,706)	55 (16-100)	59 (18-99)
Female gender (n = 16,797/4,722)	9,178 (54.6)	3,023 (64.0)
Weight, kg (n = 16,330/4,654)	75 (22-202)	75 (39-173)
Body mass index, kg/m^2 (n = 8,505/2,498)[c]	26.4 (14.4-72.1)	27.5 (16.2-52.2)
Chronic pain prior to surgery (n = 16,733/4,698)	7,359 (44.0)	2,594 (55.2)
Chronic pain intensity (n = 7,089/2,512)[d]	6 (1-10)	7 (1-10)
Opioid use prior to surgery (n = 15,549/4,442)[d]	979 (6.3)	331 (7.5)
Body site of surgery (n = 15,425/4,733)		
Limbs	7,316 (47.4)	2,700 (57.0)
Abdomen	4,357 (28.2)	1,087 (23.0)
Female reproductive organs and urinary tract	1,001 (6.5)	151 (3.2)
Thyroidal gland	700 (4.5)	503 (10.6)
Breast	659 (4.3)	292 (6.2)
Spine	424 (2.7)	--
Skin and subcutaneous tissue	397 (2.6)	--
Male reproductive organs and urinary tract	323 (2.1)	--
Lymphatic system	215 (1.4)	--
Cardiovascular system	33 (0.2)	--
Intraoperative anesthesia (n = 16,433/4,733)[e]		
General anesthesia	13,223 (80.5)	3,981 (84.1)
Neuraxial anesthesia (spinal, epidural)	3,190 (19.4)	812 (17.2)
Peripheral nerve block	2,457 (15.0)	831 (17.6)
Wound infiltration	1,671 (10.2)	550 (11.6)
Pain medication in recovery room (n = 16,124/4,612)[f]		
Neuraxial anaesthesia	710 (4.4)	111 (2.4)
Peripheral nerve block	1,202 (7.5)	658 (14.3)
Systemic opioids	5,972 (37.0)	1,846 (40.0)
Non-opioids	5,435 (33.7)	1,775 (38.5)
None	7,281 (45.2)	1,827 (39.6)
Pain medication on ward (n = 16,438/4,713)[f]		
Neuraxial anaesthesia	791 (4.8)	114 (2.4)
Peripheral nerve block	1,071 (6.5)	578 (12.3)
Systemic opioids	8,659 (52.7)	2,705 (57.4)
Non-opioids	13,385 (81.4)	3,994 (84.7)
None	1,503 (9.1)	351 (7.4)

Table 1. Continued

	Main analysis set (n = 16,868)[a]	Restricted analysis set (n = 4,733)[b]
Country of clinical site		
Central Western Europe	6,103 (36.2)	1,881 (39.7)
Germany	3,194 (18.9)	756 (16.0)
Switzerland	1,746 (10.4)	576 (12.2)
France	1,163 (6.9)	549 (11.6)
Southern Europe	4,958 (29.4)	1,445 (30.5)
Italy	3,630 (21.5)	983 (20.8)
Spain	1,328 (7.9)	462 (9.8)
Eastern Europe	1,930 (11.4)	456 (9.6)
Romania	1,203 (7.1)	314 (6.6)
Ukraine	362 (2.1)	57 (1.2)
Serbia	219 (1.3)	18 (0.4)
Moldavia	146 (0.9)	67 (1.4)
Northern Europe and British Isles	1,708 (10.1)	411 (8.7)
Sweden	1,129 (6.7)	322 (6.8)
United Kingdom	579 (3.4)	89 (1.9)
Israel	950 (5.6)	259 (5.5)
Malaysia	716 (4.2)	82 (1.7)
USA	503 (3.0)	199 (4.2)

Data are median (range) or n (%). [a] All kinds of surgeries. [b] Fifteen frequently performed surgeries; see text. [c] Body mass index only available for the second phase of the data collection. [d] Based on patients responses to corresponding International Pain Outcome Questionnaire items; see Table O-1, on-line. [e] Percentages add up to more than 100% because categories were not mutually exclusive. [f] Percentages add up to more than 100% because categories other than "none" were not mutually exclusive.

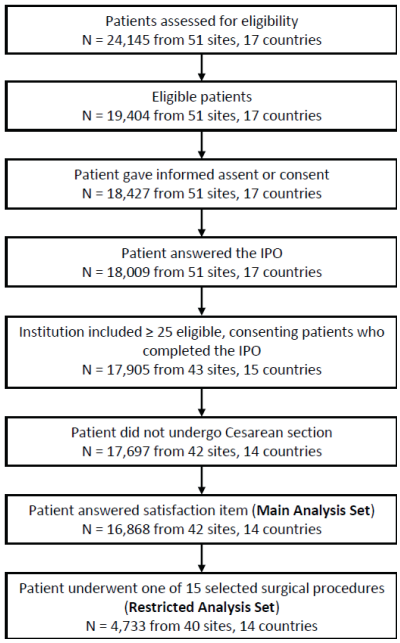

Figure 1. Patient accountability.
IPO = International Pain Outcome questionnaire.

Table 2. Satisfaction with pain treatment and responses to key International Pain Outcome questionnaire items in the main and restricted analysis sets

	Main analysis set (n = 16,868)[a]	Restricted analysis set (n = 4,733)[b]
Satisfaction	9 (7-10)	9 (7-10)
Worst pain intensity since surgery (n = 16,793/4,708)	5 (3-8)	6 (3-8)
Least pain intensity since surgery (n = 16,750/4,697)	2 (0-3)	2 (0-3)
Time in severe pain (n = 16,522/4,621)	2 (1-4)	2 (1-5)
Pain relief received (n = 16,054/4,504)	7 (5-9)	7 (5-9)
Desire to have received more pain treatment (n = 16,621/4,665)	2,938 (17.7)	784 (16.8)
Pain interference with		
activities in bed (n = 16,576/4,623)	4 (2-7)	4 (2-7)
sleep (n = 16,614/4,648)[c]	2 (0-5)	2 (0-5)
Emotional impairment		
Anxiety (n = 16,670/4,668)	1 (0-4)	1 (0-4)
Helplessness (n = 16,534/4,624)	0 (0-4)	1 (0-4)
Adverse effects		
Nausea (n = 16,739/4,689)	0 (0-3)	0 (0-4)
Drowsiness (n = 16,700/4,676)	2 (0-5)	2 (0-5)
Itching (n = 16,656/4,659)	0 (0-0)	0 (0-0)
Dizziness (n = 16,705/4,674)	0 (0-3)	0 (0-3)
Received information on pain treatment options (n = 16,686/4,681)	10,214 (61.2)	3,020 (64.5)
Allowed to participate in decision making (n = 16,191/4,525)	7 (1-10)	7 (1-10)

Data are median (interquartile range) for 11-point numeric rating scales or n (%) for binary items. Most numeric rating scales used a range of 0-10. Time in severe pain and pain relief received used a range 0-100% but are expressed as 0-10 in the table). [a] All kinds of surgeries. [b] Fifteen frequently performed surgeries; see text. [c] The first IPO version used two sleep-related items which were highly correlated. For the purpose of this study, the average score was used when both items were answered.

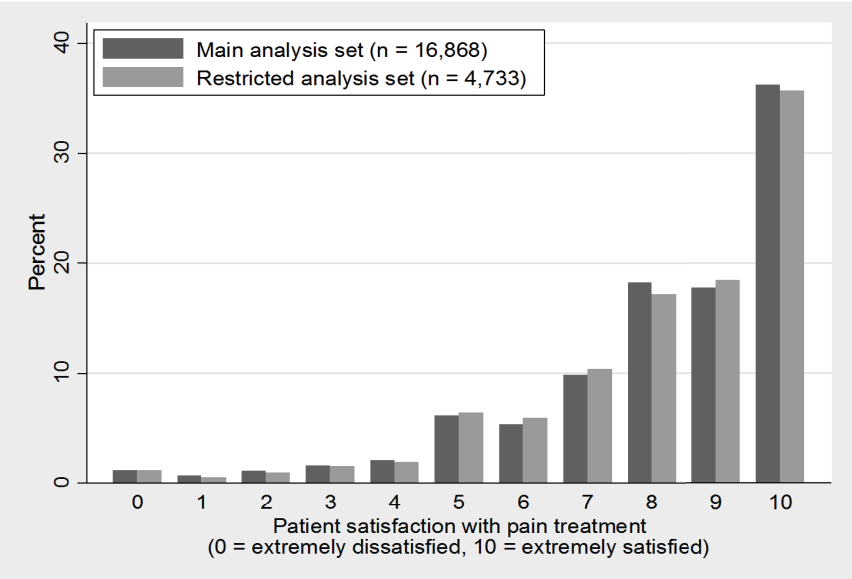

Figure 2. Distribution of responses to the International Pain Outcome questionnaire item representing patient satisfaction with postoperative pain treatment.

Two-level normal response model based on the main analysis set, including IPO items

The final two-level normal response model based on the main analysis set (Table 3, first column; including the patient level and clinical center as the higher level) achieved a BIC of 54,201 compared to 60,488 for a corresponding two-level random intercept-only model, indicating substantial explanatory value of the included covariates. Higher satisfaction was most strongly associated with responses to three IPO items indicating higher pain relief received, more allowed participation in pain treatment decisions and no desire to have received more pain treatment. The underlying relationships with pain relief received and allowed participation were curved (Fig. 3, rows C and D). Therefore, combinations of linear and squared terms were required to represent these items in the model. Satisfaction was lowest at pain relief and allowed participation scores of 0% and 3, respectively. In comparison with these reference points, pain relief and allowed participation scores of 70% and 7, representing the observed medians, increased satisfaction by 0.91 (SE 0.14) and 0.47 (SE 0.03), respectively, on the 0-10 scale. Maximum pain relief and participation scores of 100% and 10 increased satisfaction by 1.83 (SE 0.14) and 1.37 (SE 0.07). No desire to have received more pain treatment increased

Table 3. Two-level normal response models of satisfaction with pain treatment based on the main and restricted analysis sets, with IPO items related to pain experience and pain-related impairment

	Main analysis set (n = 14,086)[a]		Restricted analysis set (n = 3,927)[b]	
	Coefficient (SE)	P Value[c]	Coefficient (SE)	P Value[c]
FIXED-EFFECTS PARAMETERS				
IPO items describing pain experience and pain-related impairment				
Worst pain intensity since surgery[d]	-0.023 (0.007)	0.001	-0.035 (0.013)	0.009
Time in severe pain[d]	-0.048 (0.008)	< 0.001	-0.035 (0.015)	0.018
Pain interference with sleep[d]	-0.036 (0.006)	< 0.001	-0.059 (0.011)	< 0.001
Emotional impairment[d,e]	-0.057 (0.010)	< 0.001	-0.022 (0.013)	0.085
Adverse event: drowsiness[d]	0.023 (0.006)	< 0.001	0.036 (0.010)	0.001
Adverse event: itching[d]	-0.020 (0.008)	0.019	-0.026 (0.018)	0.133
Adverse event: nausea[d]	-0.021 (0.009)	0.018	-0.021 (0.016)	0.182
Desire to have received more pain treatment	-1.185 (0.068)	< 0.001	-1.246 (0.121)	< 0.001
Pain relief (linear term)[d]	0.183 (0.014)	< 0.001	0.147 (0.021)	< 0.001
Pain relief (squared term)[d,f]	0.017 (0.003)	< 0.001	0.024 (0.006)	< 0.001
IPO items describing perception of pain treatment				
Allowed participation (linear term)[d]	0.118 (0.008)	< 0.001	0.110 (0.008)	< 0.001
Allowed participation (squared term)[d,f]	0.026 (0.002)	< 0.001	0.030 (0.003)	< 0.001
Information on pain treatment options received	0.222 (0.033)	< 0.001	0.122 (0.063)	0.050
Patient, procedure and site characteristics				
Age (decades)	0.018 (0.009)	0.045	0.015 (0.018)	0.393
Body site of surgery	Non-significant in models with IPO items related to pain experience and pain-related impairment			
Duration of surgery (hours)				
Systemic opioids in recovery room				
Opioid use prior to surgery				
Chronic pain intensity prior to surgery	0.025 (0.006)	< 0.001	0.010 (0.008)	0.236
Data collected in phase 2[g]	-0.113 (0.049)	0.020	-0.093 (0.059)	0.115
Constant	6.150 (0.139)	< 0.001	6.453 (0.217)	< 0.001
RANDOM-EFFECTS PARAMETERS	See Table O-3, on-line			

The dependent variable is satisfaction with pain treatment, expressed on an 11-item (0-10) numeric rating scale forming part of the International Pain Outcomes Questionnaire (IPO). Only those independent variables are shown that met the inclusion criteria for one of the statistical models presented in Tables 3 and 4. Model statistics: Bayesian Information Criterion (BIC) = 54,201 (main analysis set) / 15,227 (restricted analysis set). ns = non-significant or no decrease in BIC. SE = standard error. [a] All kinds of surgeries. [b] Fifteen frequently performed surgeries; see text. [c] Based on Wald tests of fixed effects parameters. [d] Expressed on an 11-item (0-10 or 0-100%) numeric rating scale forming part of the IPO. [e] Mean score of IPO questionnaire items representing anxiety and helplessness. Items were combined due to very similar behavior in the regression models. [f] Squared terms were centered around 5, i.e. the middle of the scale, to avoid collinearity effects. [g] Data collected in phase 2 of the PAIN OUT data collection.

satisfaction by 1.19 (SE 0.07). (In complementary least squares regression, these three effects alone explained 35% of the variability present in the satisfaction variable, i.e. they achieved an R squared value of 0.35. Standardized regression coefficients in the full model ranged from 0.21-0.23 for the three linear terms. They reached 0.09 and 0.14, respectively, for the terms representing relief squared and participation squared.) Higher satisfaction was also associated with older age, higher chronic pain intensity prior to surgery, enrollment during the first phase of the PAIN OUT data collection, and responses to a number of additional IPO items indicating lower worst pain intensity, less time spent in severe pain, less pain interference with sleep, less emotional impairment (helplessness and anxiety), more drowsiness, less itching, less nausea, and information on pain treatment received. (In complementary least squares regression, adding these covariates increased the R squared to 0.37. Standardized regression coefficients for worst pain intensity, time spent in severe pain, pain interference with sleep and emotional impairment had absolute values of 0.04-0.06. These covariates showed substantial correlations with pain relief received and desire to have received more pain treatment; Spearmen correlation coefficients had absolute values of 0.30-0.44. Drowsiness had a standardized regression coefficient of 0.06 and the remainder of covariates had standardized regression coefficients with absolute values of 0.04 or smaller.) A third group of variables, including female gender, no opioid use prior to surgery and shorter duration of surgery, were nominally associated with higher satisfaction but of minimal explanatory value. They did not improve model fit and missed criteria for inclusion in the final model. Association but no improvement of model fit was also observed for country group treated as a covariate. Country of center behaved similarly but performed marginally worse. The same was true for patient-level descriptors of language of questionnaire used, country of birth, and nationality. The remainder of candidate covariates, e.g. those describing co-morbidity, were not significant.

A number of the aforementioned effects showed significant higher-level variation between clinical centers; this was the case for emotional impairment, nausea, desire to have received more pain treatment, pain relief received (linear and quadratic terms), allowed participation (linear term only), chronic pain intensity prior to surgery and phase of data collection. Fig. 3 shows examples. Directions of effects were consistent across most centers. The effect of pain relief received was U-shaped for some centers. In these centers, satisfaction scores were lower for patients with relief scores of around 40% than for patients with lower or higher

scores. The effect of allowed participation in pain treatment decisions was also U-shaped. Across centers, satisfaction scores were lowest for allowed participation scores of around 2-5. (Both U-shapes are also visible in univariable analysis, see Fig. O-1, online.)

After adding country group of clinical center, interaction with this covariate was only observed for the effects of pain relief received, allowed participation and chronic pain prior to surgery; the degree of heterogeneity between geographies appeared to be limited (Fig. 3).

Two-level normal response model based on the main analysis set, excluding IPO items

As the items of the IPO were anticipated to potentially mask influences occurring earlier in the perioperative period (e.g. choice of anesthesia), they were excluded in alternative analyses. Models excluding all IPO items did not achieve any relevant explanatory value. Models including only IPO items describing perception of pain treatment (allowed participation in pain treatment decisions and information on pain treatment options) but excluding those IPO items which could be regarded as direct correlates of postoperative pain experience and pain-related impairment (namely, worst pain, time spent in severe pain, pain interference with sleep, emotional impairment, treatment-related adverse event ratings, desire to have received more pain treatment and pain relief received) achieved a BIC of 51,737 compared to 53,937 for the corresponding random intercept-only model, indicating substantial explanatory value of the included covariates (Table 4, first column). The curved association with allowed participation remained the strongest. Satisfaction was again lowest at an allowed participation score of 3. In comparison with this reference point, allowed participation scores of 7 and 10, representing the observed median and the maximum, increased satisfaction by 0.70 (SE 0.05) and 2.19 (SE 0.10), respectively, on the 0-10 scale. (In complementary least squares regression, allowed participation alone achieved an R squared value of 0.14. Standardized regression coefficients in the full model were 0.28 for the linear term and 0.25 for the squared term.) The effects of the other retained covariates remained largely stable; however, the coefficients for chronic pain intensity prior to surgery and phase of data collection became non-significant. In contrast, body site of surgery was now significant and improved the fit of the model. Systemic opioid use (either alone or in combination with non-opioids or regional anesthesia drugs) in the recovery room and on the ward was significantly associated with lower satisfaction

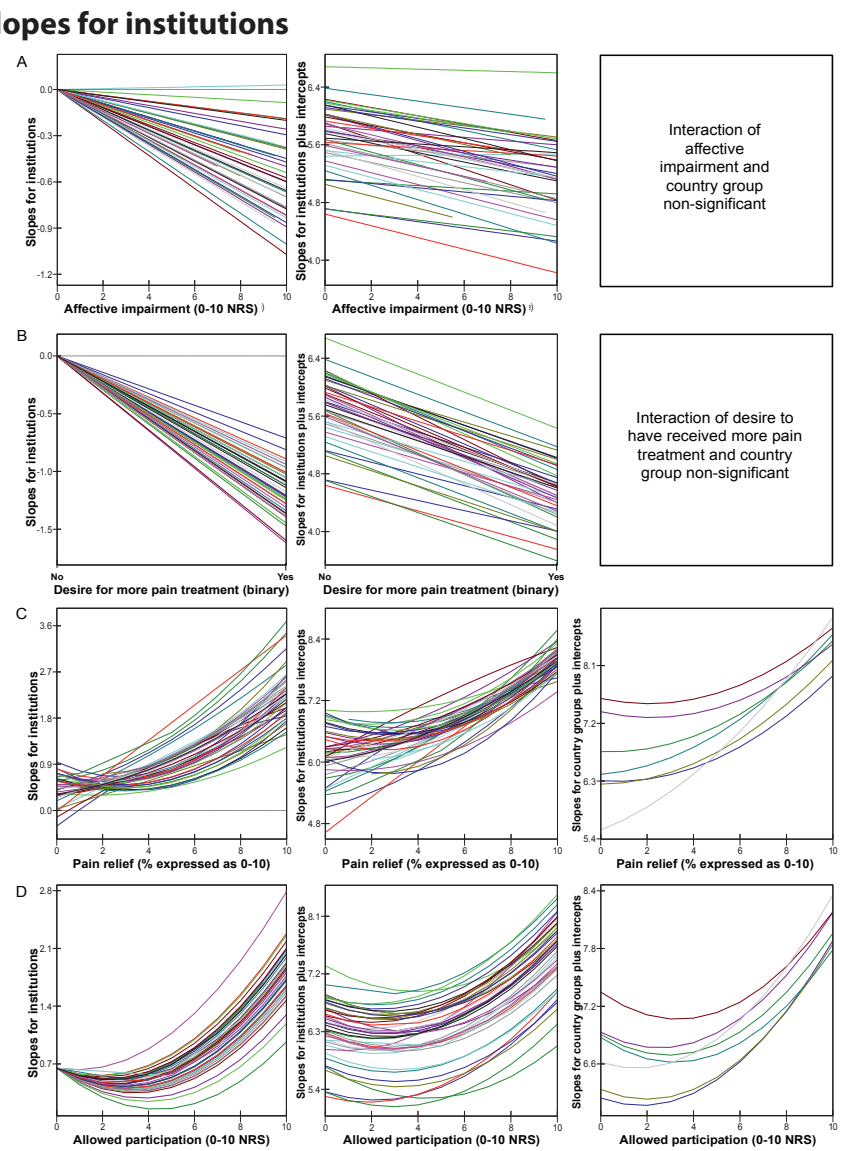

Figure 3. Impact of clinical centre (first and second columns; lines represent clinical centres) and country group (third column; lines represent country groups) on satisfaction with postoperative pain treatment (0 = extremely dissatisfied, 10 = extremely satisfied). The first column shows the variation of selected regression slopes (representing direction and strength of association) by clinical centre; the second column shows regression slopes and constant terms (base levels of satisfaction) by clinical centre; the third column shows corresponding estimates by country group. (Row A) Negative effect of emotional impairment (mean of 11-point [0–10] numeric rating scales representing anxiety and helplessness) on satisfaction ratings. (Row B) Negative effect of desire to have received more pain treatment. (Row C) Curved effect of pain relief received. (Row D) Curved effect of allowed participation in pain treatment decisions. In all cases, the association with satisfaction was quite consistent across clinical centres and country groups.

but only the indicator of use in the recovery room met criteria for inclusion in the final model. Other covariates representing types of pain treatment received in the recovery room or on the ward remained non-significant. The same was true for type of intraoperative anesthesia. (In complementary least regression, the full model achieved an R squared value of 0.18. Standardized regression coefficients for the additional covariates had absolute values of 0.08 or smaller.)

Significant random variation was seen for the effects of patient age, allowed participation (linear and squared terms) and information on pain treatment received. The directions of these effects were consistent across most clinical centers; the effect of allowed participation was again U-shaped.

Analyses based on the restricted analysis set and additional observations

Models estimated from the restricted analysis set were generally consistent with the models estimated from the main analysis set but some effects turned non-significant given much smaller sample size (Tables 3 and 4, second column). Body site of surgery and ICD-9-CM procedure code were of similar explanatory value in the models based on the restricted analysis set. An unplanned, ad hoc restriction of the analysis set to patients who underwent knee arthroscopy (ICD-9-CM 80.26), total knee replacement (81.54) or total hip replacement (81.51) (n = 1,680 to 1,725 depending on included model covariates) also showed surprisingly stable results (Table O-3 and Table O-4, on-line, third column).

A large number of interactions between patient-level covariates were significant and interpretable. For example, higher age appeared to weaken the effects of worst pain and time in severe pain. However, these interactions did not meet the criteria for inclusion in the final models and their additional explanatory value was minimal; they would not have altered the substance of the models. There were no influential observations with a relevant impact on the regression estimates. Although some covariates were substantially correlated, there was no indication of collinearity issues. In least squares regression models run in parallel to the multilevel normal response models, all variance inflation factors remained below or close to 2.

Additional models estimated for the purpose of validation produced consistent results. Examples of logistic (satisfaction score < 8 versus ≥ 8) and ordered logistic models are shown in Tables O-5 to O-8, on-line.

Table 4. Two-level normal response models of satisfaction with pain treatment based on the main and restricted analysis sets, without IPO items related to pain experience and pain-related impairment

	Main analysis set (n = 12,567)[a]		Restricted analysis set (n = 3,887)[b]	
	Coefficient (SE)	P Value[c]	Coefficient (SE)	P Value[c]
FIXED-EFFECTS PARAMETERS				
IPO items describing pain experience and pain-related impairment				
See Table 3	Excluded			
IPO items describing perception of pain treatment				
Allowed participation (linear term)[d]	0.174 (0.012)	< 0.001	0.155 (0.014)	< 0.001
Allowed participation (squared term)[d,e]	0.046 (0.003)	< 0.001	0.047 (0.003)	< 0.001
Information on pain treatment options received	0.338 (0.059)	< 0.001	0.318 (0.072)	< 0.001
Patient, procedure and site characteristics				
Age (decades)	0.073 (0.017)	< 0.001	0.082 (0.020)	< 0.001
Body site of surgery		< 0.001		< 0.001
Abdomen	Ref.		Ref.	
Limbs	-0.092 (0.044)	0.035	-0.217 (0.091)	0.018
Female reproductive organs and urinary tract	0.189 (0.092)	0.041	0.048 (0.214)	0.824
Thyroidal gland	0.164 (0.090)	0.068	0.128 (0.131)	0.329
Breast	0.405 (0.094)	< 0.001	0.388 (0.150)	0.010
Spine	-0.039 (0.114)	0.733		
Skin and subcutaneous tissue	-0.056 (0.110)	0.610		
Male reproductive organs and urinary tract	0.316 (0.129)	0.014		
Lymphatic system	0.462 (0.144)	0.001		
Cardiovascular system	0.469 (0.418)	0.262		
Duration of surgery (hours)	-0.089 (0.016)	< 0.001	-0.091 (0.017)	0.033
Systemic opioids in recovery room	-0.232 (0.041)	< 0.001	-0.198 (0.072)	0.006
Opioid use prior to surgery	-0.467 (0.073)	< 0.001	-0.378 (0.120)	0.002
Chronic pain intensity prior to surgery	Non-significant in models without IPO items related to pain experience and pain-related impairment			
Data collected in phase 2[f]				
Constant	6.036 (0.148)	< 0.001	6.145 (0.195)	< 0.001
RANDOM-EFFECTS PARAMETERS	See Table O-4, on-line			

The dependent variable is satisfaction with pain treatment, expressed on an 11-item (0-10) numeric rating scale forming part of the International Pain Outcomes Questionnaire (IPO). Only those independent variables are shown that met the inclusion criteria for one of the statistical models presented in Tables 3 and 4. Model statistics: Bayesian Information Criterion (BIC) = 51,737 (main analysis set) / 16,080 (restricted analysis set). ns = non-significant or no decrease in BIC. Ref. = reference category. SE = standard error. [a] All kinds of surgeries. [b] Fifteen frequently performed surgeries; see text. [c] Based on Wald tests of fixed effects parameters. [d] Expressed on an 11-item (0-10 or 0-100%) numeric rating scale forming part of the IPO. [e] Squared terms were centered around 5, i.e. the middle of the scale, to avoid collinearity effects. [f] Data collected in phase 2 of the PAIN OUT data collection.

DISCUSSION

The large, international PAIN OUT acute pain registry dataset provided a unique opportunity to study correlates of patient-reported satisfaction with pain treatment on postoperative day 1 and explore variation across clinical centers and countries. Three IPO items explained a third of the variability present in the satisfaction variable: pain relief received, perceived appropriateness of allowed participation in pain treatment decisions, and desire to have received more pain treatment since surgery. Patient factors and additional IPO items reflecting pain experience, pain-related impairment and information on pain treatment received achieved little additional explanatory value. This was partially due to correlations between covariates. In particular, worst pain intensity, time spent in severe pain, pain interference with sleep and emotional impairment were substantially correlated with relief received and desire to have received more pain treatment. Exclusion of some IPO items reduced the explanatory value of the models substantially but allowed us to identify surgery-related and pain treatment-related upstream effects (e.g. effects of site of surgery, systemic opioid use in the recovery room) that would have otherwise been masked. Although some patients gave seemingly paradoxical responses (i.e., high satisfaction ratings despite substantial pain, as reported previously), the majority of the associations identified were in line with expectations or at least intuitively understandable. Findings were strikingly consistent across centers from a large number of geographies, with the majority of variation occurring at the individual patient level.

Associations of satisfaction with relief received and allowed participation were reported previously but, to our knowledge, not their high impact and curved shapes: In some centers, patients with very low relief reported higher satisfaction than patients with some relief (Fig. 3, row C). This may be because these patients experienced only little pain or did not expect any relief [28]. Across all centers, patients with very low allowed participation reported higher satisfaction than patients with some allowed participation (Fig. 3, row D). These patients may not have considered participation as an option, or may not have been interested in participation. In both cases, the relative impact of expectations, actual experience and possibly other factors such as personality traits remains currently unknown.

Associations of higher satisfaction with lower worst pain intensity, less emotional impairment, less side effects of pain treatment, provision of information and higher age were reported previously.[4,5,14,17,18,20,21,25,27-29] We could not confirm a

reduced level of satisfaction in female patients as previously observed in a Swedish study,[27] although in both studies pain relief received was higher in male patients.

A number of the weaker associations identified were novel. Drowsiness may be a desirable effect in the early postoperative phase, for some patients, and a contribution to satisfaction may make intuitive sense. Higher satisfaction in patients with higher chronic pain levels prior to surgery may be explained by habituation or reduced expectations. A small negative impact of opioid use prior to surgery may be explained by less responsiveness to acute opioid treatment.

In the regression models that included direct descriptors of postoperative pain experience, types of anesthesia and pain treatment received were not associated with satisfaction. Even with these descriptors removed, type of intraoperative anesthesia had no discernible impact. Satisfaction was, in this case, lower in patients who received systemic opioids in the recovery room. This was consistently seen across analysis sets. Different pain levels during the wake-up phase (e.g. resulting from more or less painful surgery, use or non-use of regional anesthesia techniques, quality of intraoperative anesthesia) and uncontrolled-for characteristics co-influencing both satisfaction and opioid use (e.g. patient condition prior to surgery) may have played a role. Satisfaction was our sole focus; we did not study the impact of anesthesia and pain treatment techniques on the patients' pain experience. Our observation of a low overall degree of association between satisfaction and types of anesthesia and pain treatment received is compatible with an earlier systematic review.[17] The authors found that postoperative analgesic technique (e.g. use of regional analgesia compared with systemic opioids) led to statistically superior analgesia. However, the evidence available to them did not support subsequent improvements in patient-centered outcomes, inclusive of satisfaction.

Overall, our findings indicate that satisfaction with postoperative pain treatment is less associated with the patients' actual pain experience (which is determined to a relevant degree by somatosensory parameters) but rather with impressions of improvement and appropriateness of care (Tables 3 and O-3, on-line). The area of patient involvement in decision making and maintenance of control seems to be of high importance. This may, at least in part, explain the apparent paradox of high satisfaction ratings reported by patients experiencing substantial pain.

Based on theoretical constructs of satisfaction with medical services in general,[15,16] we can assume that satisfaction with postoperative pain treatment is an emotional reaction which results from the interplay of a patient's perioperative experience and expectations. Both experience and expectations are influenced by a wide range of

personal characteristics (including demographics, health status, personality traits and preferences). Whilst the PAIN OUT data collection included many it did not include all potentially relevant characteristics previously proposed in the literature. Notable exclusions were preoperative health status, acute pain level immediately before surgery and underlying diagnosis. More importantly, we did not measure patient expectations of pain [1,2,13,21] or participation. There was also no formal assessment of perceived staff effort or empathy which may be relevant factors on the side of the care environment.[3,17,29] In order to provide additional elements for a theory of satisfaction with pain treatment and its relationship with quality of perioperative care, future studies should consider these aspects. Research into the role of expectations for the three strongest effects observed in this study and into the exact nature of the U-shaped relationships observed would be of importance. For example, splitting the IPO participation item up into two, separately addressing desire for participation and actual allowed participation, could provide additional insights, as previously considered by others.[10,11] Additional studies should assess which elements patients from different geographical, cultural and ethnic backgrounds perceive as being particularly relevant to them, in the context of early postoperative pain treatment. This would shed further light on our observation of a very limited degree of inter-institutional and, seemingly, intercultural variation, which requires verification. Such research may require datasets with a stronger non-European representation. Ongoing recruitment of clinical centers from across the world into PAIN OUT may allow us to generate such data.

Our study has additional strengths and limitations. The IPO satisfaction item was deliberately phrased to focus patients on the results of their pain treatment, i.e. not the processes, techniques or other aspects. However, patients adopted a much broader perspective and took into account characteristics of the care process. We don't know how their responses would have changed if the satisfaction item had been phrased more generally. As our data collection was relatively early after surgery on postoperative day 1, patients could provide a "fresh" impression but for some patients, their early postoperative experience was still evolving. It would have been interesting to compare patient responses for at least two time points. Participation of clinical centers in PAIN OUT was self-selected. The data collection process was characterized by a high degree of consistency across centers. It may have given patients a feeling of being taken seriously and hence increased overall satisfaction ratings to a certain extent. However, we see no reasons to assume that this may have biased the relationships studied here or the observed degree of consistency

across centers and countries. Statistical methods were chosen such that center-level effects could be taken into account optimally. The use of normal response models despite a skew in the dependent variable enabled efficient multilevel modeling and was successfully validated by running other types of regression models for comparison. We accepted models with many covariates because we wanted to show all observable influences on satisfaction and thus provide material for theory development. As half of the countries involved were only represented by a single center, our ability to distinguish center-level from country-level effects was very limited. Therefore, we only performed a rudimentary, exploratory assessment of differences between country groups, at this stage.

In conclusion, this multilevel analysis of a large, international registry confirmed patient-reported satisfaction with pain treatment in the early postoperative phase to be influenced by pain experience, patient involvement and characteristics of the patient-caregiver relationship. Type of anesthesia and pain treatment techniques had little direct influence but may be linked to satisfaction via improved pain relief. Pain relief received, desire to have received more pain treatment and allowed participation in treatment decisions had the highest impact. Variability in satisfaction occurred mostly at the patient level, with little variability between centers from 15 countries. While further research is needed, we see a clear indication that the patient perspective should be assessed and valued in the care process. It would be inappropriate to focus on low pain intensity values as the sole driver and aim of postoperative pain management. To the degree they desire, patients should be provided with information and involved in pain treatment decisions.

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APPENDIX

Table O-1. International Pain Outcome Questionnaire final set of items

Item	Answer format
1. On this scale, please indicate the **worst pain** you had since your surgery:	NRS 0-10
2. On this scale, please indicate the **least pain** you had since your surgery:	NRS 0-10
3. How often were you in **severe pain** since your surgery? Please circle your best estimate of the percentage of time you experienced **severe pain**:	Percentage scale, 0-100%
4. Circle the one number below that best describes how much, since your surgery, **pain interfered with or prevented you from** ...	
a. doing **activities in bed** such as turning, sitting up, changing position	NRS 0-10
b. **breathing deeply** or **coughing**	NRS 0-10
c. **sleeping**	NRS 0-10
d. Have you been **out of bed** since your surgery?	yes/no
If yes, how much did **pain interfere or prevent you from doing activities out of bed** such as walking, sitting in a chair, standing at the sink:	NRS 0-10
5. Pain can affect our mood and emotions. On this scale, please circle the one number that best shows how much, since your surgery, **pain caused you to feel** ...	
a. **anxious**	NRS 0-10
b. **helpless**	NRS 0-10
6. Have you had any of the following **side effects** since your surgery? Please circle "0" if no; if yes, circle the one number that best shows the severity of each:	
a. **Nausea**	NRS 0-10
b. **Drowsiness**	NRS 0-10
c. **Itching**	NRS 0-10
d. **Dizziness**	NRS 0-10
7. Since your surgery, how much **pain relief** have you received? Please circle the one percentage that best shows how much relief you have received from all of your **pain treatments** combined (medicine and non-medicine treatments):	Percentage scale, 0-100%
8. Would you have liked **MORE pain treatment** than you received?	yes/no
9. Did you receive any **information** about your **pain treatment** options?	yes/no
10. Were you **allowed to participate in decisions** about your **pain treatment** as much as you wanted to?	NRS 0-10
11. Circle the one number that best shows how **satisfied** you are with the results of your **pain treatment** since your surgery:	NRS 0-10
12. Did you use or receive any **non-medicine methods** to relieve your **pain**?	yes/no
If yes, **check all** that apply: cold pack, meditation, deep breathing, heat, acupuncture, prayer, talking to medical staff, walking, massage, talking to friends or relatives, relaxation, imagery or visualization, TENS (Transcutaneous Electrical Nerve Stimulation), distraction (like watching TV, listening to music, reading), other (please describe)	

Table O-1. Continued

Item	Answer format
13. Did you have a **persistent painful condition for 3 months** or more before coming into hospital for this surgery?	yes/no
a. If yes, **how severe** was the **pain** most of the time? Please circle the number that indicates this.	NRS 0-10
b. If yes, **where** was this **persistent pain** located? Site of surgery, elsewhere, both (site of surgery and elsewhere)	

NRS = numeric rating scale. This set of items has previously been published, in a similar format, in Rothaug J et al. Patients' Perception of Postoperative Pain Management: Validation of the International Pain Outcomes (IPO) Questionnaire. J Pain 2013;14:1361-70.

Table O-2. International Classification of Diseases version 9 surgical procedure (ICD-9-CM) codes used to assign body site of surgery

Body site	Included ICD-9-CM codes or code ranges	Excluded ICD-9-CM codes or code ranges
Limbs	0.7, 0.8; 77.0-84.9	-- 81.0, 81.3, 81.6, 84.6, 84.8
Abdomen	17.0-17.9 42.0-55.9	17.4 --
Female reproductive organs and urinary tract	65.0-71.9	--
Thyroideal gland	06.0-06.9	--
Breast	85.0-85.9	--
Spine	03.0-03.9; 80.5; 81.0, 81.3, 81.6; 84.6; 84.8	-- -- -- --
Skin and subcutaneous tissue	86.0-86.9	--
Male reproductive organs and urinary tract	56.0-64.9	--
Lymphatic system	40.0-40.9	--
Cardiovascular system	35.0-37.9	--

Selection of ICD-9-CM codes focused on the codes present in the PAIN OUT dataset and may not necessarily lead to correct results with other PAIN OUT data cuts or data from other sources.

Table O-3. Two-level normal response models of satisfaction with pain treatment, with IPO items related to pain experience and pain-related impairment – extended version of Table 3 in the main publication document, including random effects parameters and an additional model (third column)

	Main analysis set (n = 14,086)[a]		Restricted analysis set (n = 3,915)[b]		Patients with knee or hip surgery (unplanned analysis; n = 1,725)[c]	
	Coefficient (SE)	P Value[d]	Coefficient (SE)	P Value[d]	Coefficient (SE)	P Value[d]
FIXED-EFFECTS PARAMETERS						
IPO items describing pain experience and pain-related impairment						
Worst pain intensity since surgery[e]	-0.023 (0.007)	0.001	-0.035 (0.013)	0.009	-0.038 (0.021)	0.068
Time in severe pain[e]	-0.048 (0.008)	< 0.001	-0.033 (0.015)	0.022	-0.017 (0.021)	0.428
Pain interference with sleep[e]	-0.036 (0.006)	< 0.001	-0.059 (0.011)	< 0.001	-0.063 (0.017)	< 0.001
Emotional impairment[e,f]	-0.057 (0.010)	< 0.001	-0.023 (0.013)	0.064	-0.032 (0.019)	0.088
Adverse event: drowsiness[e]	0.023 (0.006)	< 0.001	0.035 (0.010)	0.001	0.034 (0.016)	0.036
Adverse event: itching[e]	-0.020 (0.008)	0.019	-0.025 (0.018)	0.159	0.001 (0.024)	0.957
Adverse event: nausea[e]	-0.021 (0.009)	0.018	-0.022 (0.016)	0.163	-0.027 (0.015)	0.076
Desire to have received more pain treatment	-1.185 (0.068)	< 0.001	-1.244 (0.120)	< 0.001	-1.178 (0.122)	< 0.001
Pain relief (linear term)[e]	0.183 (0.014)	< 0.001	0.148 (0.021)	< 0.001	0.184 (0.032)	< 0.001
Pain relief (squared term)[e,g]	0.017 (0.003)	< 0.001	0.024 (0.006)	< 0.001	0.013 (0.006)	0.032
IPO items describing perception of pain treatment						
Allowed participation (linear term)[e]	0.118 (0.008)	< 0.001	0.108 (0.008)	< 0.001	0.098 (0.013)	< 0.001
Allowed participation (squared term)[e,g]	0.026 (0.002)	< 0.001	0.030 (0.003)	< 0.001	0.032 (0.005)	< 0.001
Information on pain treatment options received	0.222 (0.033)	< 0.001	0.128 (0.063)	0.041	0.229 (0.104)	0.028
Patient, procedure and site characteristics						
Age (decades)	0.018 (0.009)	0.045	0.016 (0.018)	0.377	-0.020 (0.031)	0.509
Body site of surgery	Non-significant in models with IPO items related to pain experience and pain-related impairment					
Duration of surgery (hours)						
Systemic opioids in recovery room						
Opioid use prior to surgery						
Chronic pain intensity prior to surgery	0.025 (0.006)	< 0.001	0.010 (0.008)	0.240	0.021 (0.014)	0.137
Data collected in phase 2[h]	-0.113 (0.049)	0.020	-0.094 (0.059)	0.112	-0.019 (0.094)	0.841
Constant	6.150 (0.139)	< 0.001	6.450 (0.218)	< 0.001	6.245 (0.366)	< 0.001

Table O-3 (Part 2)

	Main analysis set (n = 14,086)[a]		Restricted analysis set (n = 3,915)[b]		Patients with knee or hip surgery (unplanned analysis; n = 1,725)[c]	
	Coefficient (SE)	P Value[d]	Coefficient (SE)	P Value[d]	Coefficient (SE)	P Value[d]
RANDOM-EFFECTS PARAMETERS (level 2: institution)						
Variance of emotional impairment	0.002 (0.001)	< 0.001	--	ns	--	ns
Variance of adverse effect: nausea	0.001 (0.001)	< 0.001	0.004 (0.002)	0.018	--	ns
Variance of liked more pain treatment	0.082 (0.036)	< 0.001	0.203 (0.101)	0.045	--	ns
Variance of pain relief (linear term)	0.005 (0.002)	< 0.001	0.009 (0.003)	0.004	0.012 (0.006)	0.043
Variance of pain relief (squared term)	0.000 (0.000)	0.001	0.000 (0.000)	0.047	--	ns
Variance of allowed participation (linear term)	0.002 (0.001)	< 0.001	--	ns	--	ns
Variance of chronic pain intensity prior to surgery	0.000 (0.000)	0.012	--	ns	--	ns
Variance of data collected in phase 2	0.023 (0.014)	< 0.001	--	ns	--	ns
Variance of constant	0.402 (0.118)	< 0.001	0.634 (0.225)	0.005	0.965 (0.419)	0.021
Covariance of desire to have received more pain treatment, constant	-0.055 (0.031)	0.025	--	ns	--	ns
Covariance pain relief (linear term), constant	-0.034 (0.012)	< 0.001	-0.062 (0.024)	0.010	-0.104 (0.049)	0.032
Covariance pain relief, linear and squared terms	0.000 (0.000)	0.010	-0.001 (0.000)	0.039	--	ns
RANDOM-EFFECTS PARAMETERS (level 1: patient)						
Variance of constant	2.644 (0.032)	< 0.001	2.597 (0.060)	< 0.001	2.906 (0.100)	< 0.001

The dependent variable is satisfaction with pain treatment, expressed on an 11-item (0-10) numeric rating scale forming part of the International Pain Outcomes Questionnaire (IPO). Model statistics: Bayesian Information Criterion (BIC) = 54,201 / 15,166 / 6,920. ns = non-significant or no decrease in BIC. SE = standard error. [a] All kinds of surgeries. [b] Fifteen frequently performed surgeries; see main publication document. [c] Patients who underwent knee arthroscopy (ICD-9-CM 80.26), total knee replacement (81.54) or total hip replacement (81.51). [d] Based on Wald tests of fixed effects parameters and on likelihood ratio tests (in the model based on the main analysis set) or Wald tests (in the additional models, to contain computation time) of random effects parameters. [e] Expressed on an 11-item (0-10 or 0-100%) numeric rating scale forming part of the IPO. [f] Mean score of IPO questionnaire items representing anxiety and helplessness. Items were combined due to very similar behavior in the regression models. [g] Squared terms were centered around 5, i.e. the middle of the scale, to avoid collinearity effects. [h] Data collected in phase 2 of the PAIN OUT data collection.

Table O-5. Two-level logistic model of satisfaction with pain treatment (satisfaction score < 8 versus ≥ 8) based on the main analysis set, with IPO items related to pain experience and pain-related impairment

	Main analysis set (n = 14,086)[a]	
	Coefficient (SE)	P Value[b]
FIXED-EFFECTS PARAMETERS		
IPO items describing pain experience and pain-related impairment		
Worst pain intensity since surgery[c]	-0.045 (0.013)	< 0.001
Time in severe pain[c]	-0.054 (0.012)	< 0.001
Pain interference with sleep[c]	-0.044 (0.010)	< 0.001
Emotional impairment[c,d]	-0.083 (0.016)	< 0.001
Adverse event: drowsiness[c]	0.014 (0.010)	0.135
Adverse event: itching[c]	-0.037 (0.014)	0.006
Adverse event: nausea[c]	-0.019 (0.009)	0.040
Desire to have received more pain treatment	-1.150 (0.062)	< 0.001
Pain relief (linear term)[c]	0.232 (0.011)	< 0.001
Pain relief (squared term)[c,e]	0.075 (0.006)	< 0.001
IPO items describing perception of pain treatment		
Allowed participation (linear term)[c]	0.178 (0.012)	< 0.001
Allowed participation (squared term)[c,e]	0.043 (0.003)	< 0.001
Information on pain treatment options received	0.310 (0.054)	< 0.001
Patient, procedure and site characteristics		
Age (decades)	0.025 (0.015)	0.091
Body site of surgery	Non-significant in models with IPO items related to pain experience and pain-related impairment	
Duration of surgery (hours)		
Systemic opioids in recovery room		
Opioid use prior to surgery		
Chronic pain intensity prior to surgery	0.035 (0.008)	< 0.001
Data collected in phase 2[f]	-0.277 (0.056)	< 0.001
Constant	-1.587 (0.170)	< 0.001

Table O-5. Contunued

RANDOM-EFFECTS PARAMETERS (level 2: institution)		
Variance of emotional impairment	0.004 (0.002)	0.030
Variance of adverse effect: nausea	--	ns
Variance of liked more pain treatment	--	ns
Variance of pain relief (linear term)	--	ns
Variance of pain relief (squared term)	0.001 (0.000)	0.024
Variance of allowed participation (linear term)	0.002 (0.001)	0.045
Variance of chronic pain intensity prior to surgery	--	ns
Variance of data collected in phase 2	--	ns
Variance of constant	0.305 (0.091)	0.001
Covariance of desire to have received more pain treatment, constant	--	ns
Covariance pain relief (linear term), constant	--	ns
Covariance pain relief, linear and squared terms	--	ns
RANDOM-EFFECTS PARAMETERS (level 1: patient)		
Variance of constant	1 (fixed in logistic model)	

The dependent variable is satisfaction with pain treatment, expressed on an 11-item (0-10) numeric rating scale forming part of the International Pain Outcomes Questionnaire (IPO). ns = non-significant or no decrease in BIC. SE = standard error. [a] All kinds of surgeries. [b] Based on Wald tests. [c] Expressed on an 11-item (0-10 or 0-100%) numeric rating scale forming part of the IPO. [d] Mean score of IPO questionnaire items representing anxiety and helplessness. Items were combined due to very similar behavior in the regression models. [e] Squared terms were centered around 5, i.e. the middle of the scale, to avoid collinearity effects. [f] Data collected in phase 2 of the PAIN OUT data collection.

Table O-6. Ordered logistic model of satisfaction with pain treatment based on the main analysis set, with IPO items related to pain experience and pain-related impairment

	Main analysis set (n = 14,086)[a]	
	Coefficient (SE)	P Value[b]
IPO items describing pain experience and pain-related impairment		
Worst pain intensity since surgery[c]	-0.078 (0.010)	< 0.001
Time in severe pain[c]	-0.048 (0.008)	< 0.001
Pain interference with sleep[c]	-0.041 (0.007)	< 0.001
Emotional impairment[c,d]	-0.035 (0.008)	< 0.001
Adverse event: drowsiness[c]	0.045 (0.006)	< 0.001
Adverse event: itching[c]	-0.048 (0.009)	< 0.001
Adverse event: nausea[c]	-0.014 (0.006)	0.030
Desire to have received more pain treatment	-1.008 (0.046)	< 0.001
Pain relief (linear term)[c]	0.173 (0.007)	< 0.001
Pain relief (squared term)[c,e]	0.065 (0.002)	< 0.001
IPO items describing perception of pain treatment		
Allowed participation (linear term)[c]	0.154 (0.005)	< 0.001
Allowed participation (squared term)[c,e]	0.056 (0.002)	< 0.001
Information on pain treatment options received	0.230 (0.036)	< 0.001
Patient, procedure and site characteristics		
Age (decades)	0.019 (0.010)	0.046
Body site of surgery	Non-significant in models with IPO items related to pain experience and pain-related impairment	
Duration of surgery (hours)		
Systemic opioids in recovery room		
Opioid use prior to surgery		
Chronic pain intensity prior to surgery	0.032 (0.005)	< 0.001
Data collected in phase 2[f]	-0.150 (0.033)	< 0.001
Constant by cut-point		
Cut-point 1	-2.878 (0.121)	
Cut-point 2	-2.380 (0.110)	
Cut-point 3	-1.853 (0.102)	
Cut-point 4	-1.354 (0.098)	
Cut-point 5	-0.869 (0.095)	
Cut-point 6	0.037 (0.092)	
Cut-point 7	0.610 (0.092)	
Cut-point 8	1.458 (0.092)	
Cut-point 9	2.741 (0.094)	
Cut-point 10	3.905 (0.097)	

The dependent variable is satisfaction with pain treatment, expressed on an 11-item (0-10) numeric rating scale forming part of the International Pain Outcomes Questionnaire (IPO). SE = standard error. [a] All kinds of surgeries. [b] Based on Wald tests. [c] Expressed on an 11-item (0-10 or 0-100%) numeric rating scale forming part of the IPO. [d] Mean score of IPO questionnaire items representing anxiety and helplessness. Items were combined due to very similar behavior in the regression models. [e] Squared terms were centered around 5, i.e. the middle of the scale, to avoid collinearity effects. [f] Data collected in phase 2 of the PAIN OUT data collection.

Table O-7. Two-level logistic model of satisfaction with pain treatment (satisfaction score < 8 versus ≥ 8) based on the main analysis set, excluding IPO items related to pain experience and pain-related impairment

	Main analysis set (n = 12,567)[a]	
	Coefficient (SE)	P Value[b]
FIXED-EFFECTS PARAMETERS		
IPO items describing pain experience and pain-related impairment		
See Tables O-3, O-5, O-6	Excluded	
IPO items describing perception of pain treatment		
Allowed participation (linear term)[c]	0.204 (0.013)	< 0.001
Allowed participation (squared term)[c,d]	0.060 (0.004)	< 0.001
Information on pain treatment options received	0.393 (0.051)	< 0.001
Patient, procedure and site characteristics		
Age (decades)	0.083 (0.014)	< 0.001
Body site of surgery		< 0.001
Abdomen	Ref.	
Limbs	-0.112 (0.060)	0.061
Female reproductive organs and urinary tract	0.129 (0.120)	0.284
Thyroidal gland	0.110 (0.121)	0.361
Breast	0.390 (0.142)	0.006
Spine	-0.193 (0.147)	0.190
Skin and subcutaneous tissue	-0.083 (0.148)	0.573
Male reproductive organs and urinary tract	0.522 (0.171)	0.002
Lymphatic system	0.855 (0.269)	0.002
Cardiovascular system	1.107 (0.877)	0.207
Duration of surgery (hours)	-0.109 (0.021)	< 0.001
Systemic opioids in recovery room	-0.258 (0.055)	< 0.001
Opioid use prior to surgery	-0.363 (0.091)	< 0.001
Chronic pain intensity prior to surgery	Non-significant in models without IPO items related to pain experience and pain-related impairment	
Data collected in phase 2[e]		
Constant	-1.257 (0.137)	< 0.001
RANDOM-EFFECTS PARAMETERS (level 2: institution)		
Variance of allowed participation (linear term)	0.003 (0.001)	0.017
Variance of allowed participation (squared term)	0.000 (0.000)	0.044
Variance of information received	--	ns
Variance of age (decades)	--	ns
Variance of constant	0.233 (0.074)	0.002
Covariance participation (linear term), constant	--	ns
Covariance participation (squared term), constant	--	ns
Covariance participation, information received	--	ns
Covariance age (decades), constant	--	ns
RANDOM-EFFECTS PARAMETERS (level 1: patient)		
Variance of constant	1 (fixed in logistic model)	

The dependent variable is satisfaction with pain treatment, expressed on an 11-item (0-10) numeric rating scale forming part of the International Pain Outcomes Questionnaire (IPO). ns = non-significant or no decrease in BIC. Ref. = reference category. SE = standard error. [a] All kinds of surgeries. [b] Based on Wald tests. [c] Expressed on an 11-item (0-10 or 0-100%) numeric rating scale forming part of the IPO. [d] Squared terms were centered around 5, i.e. the middle of the scale, to avoid collinearity effects. [e] Data collected in phase 2 of the PAIN OUT data collection.

Table O-8. Ordered logistic model of satisfaction with pain treatment based on the main analysis set, excluding IPO items related to pain experience and pain-related impairment

	Main analysis set (n = 12,567)[a]	
	Coefficient (SE)	P Value[b]
IPO items describing pain experience and pain-related impairment		
See Tables O-3, O-5, O-6	Excluded	
IPO items describing perception of pain treatment		
Allowed participation (linear term)[c]	0.167 (0.005)	< 0.001
Allowed participation (squared term)[c,d]§	0.075 (0.002)	< 0.001
Information on pain treatment options received	0.334 (0.038)	< 0.001
Patient, procedure and site characteristics		
Age (decades)	0.095 (0.010)	< 0.001
Body site of surgery		< 0.001
Abdomen	Ref.	
Limbs	-0.237 (0.039)	< 0.001
Female reproductive organs and urinary tract	-0.224 (0.072)	0.002
Thyroidal gland	0.090 (0.084)	0.282
Breast	0.603 (0.089)	< 0.001
Spine	-0.173 (0.108)	0.108
Skin and subcutaneous tissue	-0.051 (0.108)	0.634
Male reproductive organs and urinary tract	-0.131 (0.118)	0.268
Lymphatic system	0.938 (0.158)	< 0.001
Cardiovascular system	0.770 (0.403)	0.056
Duration of surgery (hours)	-0.104 (0.015)	< 0.001
Systemic opioids in recovery room	-0.339 (0.036)	< 0.001
Opioid use prior to surgery	-0.531 (0.069)	< 0.001
Chronic pain intensity prior to surgery	Non-significant in models without IPO items related to pain experience and pain-related impairment	
Data collected in phase 2[e]		
Constant by cut-point		
Cut-point 1	-2.622 (0.112)	
Cut-point 2	-2.121 (0.098)	
Cut-point 3	-1.626 (0.088)	
Cut-point 4	-1.171 (0.082)	
Cut-point 5	-0.741 (0.079)	
Cut-point 6	0.061 (0.075)	
Cut-point 7	0.546 (0.074)	
Cut-point 8	1.208 (0.075)	
Cut-point 9	2.208 (0.076)	
Cut-point 10	3.139 (0.079)	

The dependent variable is satisfaction with pain treatment, expressed on an 11-item (0-10) numeric rating scale forming part of the International Pain Outcomes Questionnaire (IPO). Ref. = reference category. SE = standard error. [a] All kinds of surgeries. [b] Based on Wald tests. [c] Expressed on an 11-item (0-10 or 0-100%) numeric rating scale forming part of the IPO. [d] Squared terms were centered around 5, i.e. the middle of the scale, to avoid collinearity effects. [e] Data collected in phase 2 of the PAIN OUT data collection.

PART V

General discussion

CHAPTER 10

General Discussion

Increasingly more attention is being paid to the treatment of acute postoperative pain as it has become clear that it is not simply a short-lasting, unpleasant sensation, but can be associated with greater acute morbidity, longer hospital stays, and, in particular, can have long-term consequences such as chronic postoperative pain (CPSP).

Complications of severe acute postoperative pain: Pain chronification

Chronic postoperative pain is one of the most significant complications of acute postoperative pain, as highlighted in a review article published in 2000 by Macrae et al..[1] Despite a large number of subsequent studies on this topic, many questions still remain unanswered, particularly in regard to pathophysiology, risk factors, and prevention. The current state of knowledge is summarized in a review of the literature in **CHAPTER 2.**

Acute postoperative pain remains the most consistently observed risk factor for chronic postsurgical pain (CPSP). Thus, it seems logical to assume that prevention of severe acute pain could be an effective preventive approach to prevent CPSP. Numerous randomized controlled trials with different analgesic strategies (e.g., regional anesthesia, ketamine, gabapentin), however, have mostly shown negative results. Future studies must increasingly examine multimodal treatments, such as combinations of regional anesthesia, anti-hyperalgesic medications, wound infiltration, wound catheters, ketamine, and α-2-antagonists. In addition, other than in the case of inguinal herniorrhaphy, only a few types of different techniques for surgical procedures have been analyzed.

To date there is no universally accepted definition of CPSP chronic postoperative pain, and accordingly the incidence of CPSP varies markedly between studies. It is essential that CPSP be defined by means of an international consensus conference in order that it can be definitively examined. The majority of studies define CPSP as pain at the surgical site with an NRS score of more than 0. Such a low threshold may result in overestimation of the true prevalence of CPSP. Little is known to date, however, in regard to CPSP that limits activity and requires treatment: up to now, only pain-intensity cut-off points, such as NRS score greater than 4, have been employed. Future studies must examine more details about the pain disorder itself, for example, the frequency of pain attacks, their duration, radiation of the pain, classification as neuropathic and nociceptive

pain based on a clinical examination, rather than simply a neuropathic screening questionnaire, pain-related disability, pain triggers, and many more factors. Only then will it become clear which patients will actually need treatment, and whether these patients may have other risk factors than patients at low risk for CPSP who do not need treatment. Preoperative risk stratification would then be possible in subsequent trials, and only patients at greater risk could be included in order to avoid unnecessary side effects or complications from prophylactic treatment. For example, our study could demonstrate that in everyday clinical practice patients who underwent mastectomy (CPSP risk approx. 20%) have relatively mild acute pain **(CHAPTER 5)**. Routinely performing paravertebral blocks, as has repeatedly been recommended for acute pain therapy,[2]providing excellent pain relief and a reduced incidence of postoperative nausea and vomiting. The aim of the present study was to compare the use of a nerve-stimulator guided paravertebral nerve blockade technique to regular general anaesthesia for breast surgery.\nMETHODS: Sixty patients were prospectively randomized to receive either paravertebral nerve blockade or general anaesthesia for breast surgery. The primary end-point of the study was to assess postoperative analgesia (visual analogue scale and supplemental opioid requirements would thus appear to be overtreatment, especially when taking into account the associated risk of pneumothorax. By risk stratification, however, subgroups at high risk for CPSP could be identified in which paravertebral blocks could be employed. Due to insufficient numbers of patients, a Cochrane meta-analysis was unable to provide an appropriate recommendation for CPSP prevention.[3]

Classification of various kinds of surgery into pain-relevant surgical groups

In regard to acute postoperative pain, we know much about a few types of surgery and little or nothing about the majority of operative procedures. Numerous studies have published incidences of severe postoperative pain of 20%-40%.

Much effort has been made to improve pain treatment, but with only moderate success. It is not actually known how and where the available manpower and resources could be used most advantageously. Where do we already perform well, and where is there room for improvement? PROSPECT, a project to give evidence-based recommendations for procedure-specific pain treatment (www.postoppain.org), has provided data on ten types of surgery in the last few years, but surgeons and anesthesiologists are confronted with hundreds of different types of surgeries.

For this reason, the QUIPS (Quality Improvement in Postoperative Pain Treatment) project was initiated in 2004 to enable hospitals and surgical departments to anonymously compare themselves with others, as there were no comparative data available and departments had no way of assessing whether they were providing good or poor pain therapy. Participation in the QUIPS project is voluntary. The resulting benchmark data can be viewed online: in a diagram based on all outcome parameters, a hospital is anonymously ranked against the others. At present, more than 200 German hospitals are participating, and over 250,000 patients have been included. Due to widespread interest, the project was expanded under the name 'PainOut' to include all of Europe, and international participation in PainOut is now possible worldwide. The questionnaire is currently available in 23 languages.

In QUIPS, surgeries are documented using the German Surgical and Procedure Code, which includes more than 21,000 codes. The hierarchical assignment of surgical procedures to more and more specified types is described in **CHAPTER 5**. A total of 529 surgical groups were defined based on the extent of tissue lesions at the specific anatomic site as well as the surgical access route (e.g., laparoscopic, open, endoscopic). Minor differences in the extent of surgical lesions were assigned to one surgical group (e.g., partial thyroidectomy, hemithyroidectomy, total thyroidectomy). Many bone and joint surgeries are difficult to categorize in terms of associated pain due to the large number of different materials used, variability in incision length, and, particularly in trauma surgery, additional soft-tissue damage. However, this is the first basic grouping of surgical procedures related to postoperative pain that can be used in future studies. Due to the standardized perioperative pain assessment, comparison among large numbers of surgeries is possible.

A major problem in comparing international postoperative pain data in a simple manner is the great variety of national codes for operations. For example, The Netherlands, Germany, the United Kingdom, France, Spain, the Scandinavian countries, the United States, Canada, and Australia each have their own system of surgical documentation that includes between 7,000 and 21,000 operative codes. The WHO project for international standardization was abandoned many years ago due to individual national concerns. At the moment, PainOut employs the International Classification of Diseases (ICD-9) for surgical documentation, as it is free of charge and is available in the English language. However, this version is no longer being updated.

In order to achieve rapid automatic analysis of international data in the future, the surgical codes of the individual national systems would need to be grouped and then matched with our already existing classification. Matching of the codes from the different systems is, however, not always possible due to the differences in itemization, and is also highly complex because the codes are constantly being updated.

Risk factors for the development of severe postoperative pain

Many factors that are associated with severe postoperative pain have already been studied. Age, female gender, pre-existing pain, social factors, psychological factors such as anxiety, depression, or coping strategies have been described. For the clinician, however, it has so far been virtually impossible to assess the relevance of these factors and, in particular, their potential consequences for the therapeutic strategy. In addition, numerous studies have also yielded negative results and, for example in regard to age, to date only dichotomous comparisons between two age groups have been analyzed.

For the first time, analysis of the QUIPS and PainOut data has made it possible to perform procedure-specific comparisons**.** It appears that the risk factors age, gender, and preoperative chronic pain are independent of the type of surgical procedure.

This study is the first to demonstrate a nearly linear decrease in reported pain intensity with age. A further study based on the QUIPS data will analyze which factors may explain this phenomenon. It is not known whether simply increasing analgesic doses due to the higher metabolic rate in younger patients will be sufficient to provide better pain relief. Other possible causes might include fear, perhaps because younger patients have had less experience and contact with surgical suites and physicians.

Chronic preoperative pain is also significantly associated with postoperative pain. Here, too, we could demonstrate for the first time that a correlation exists between preoperative and postoperative pain intensity as well as the independence of the preoperative pain location from the surgical site. The QUIPS and PainOut data are currently being analyzed to determine whether chronic pain patients need more analgesics because of sensitization of the peripheral and central nervous systems, as described in **CHAPTER 2,** or whether they are already accustomed to pain and for this reason will not request more analgesia. In **CHAPTER 4,** chronic

preoperative pain was actually shown to be an independent parameter associated with greater satisfaction with postoperative pain therapy.

The relevance of the two factors age and chronic pain can be seen most clearly in the bar diagram showing selected operations with more than 1,000 patients **(CHAPTER 5)**: A pain score difference of approximately 30% higher is seen in the youngest patient group with chronic pain compared with the oldest group without chronic pain for the same surgical procedure.

The difference in pain scores between men and women is much less, 0.29 NRS points **(CHAPTER 5)**. The clinical relevance of gender as a risk factor was firstly analyzed **(CHAPTER 6)**. It is apparent here too that pain intensity is not the only relevant outcome variable. Although women reported somewhat higher pain scores in nearly all 20 types of operations surveyed, with equal opioid doses they did not express the wish to have had more analgesics. This finding indicates that in regard to pain medication there is no need to treat women differently than men. Non-medicinal treatment, however, in consideration of possibly higher expectations, coping strategies, or greater anxiety in women, could be a basis for improving preoperative preparation, for example, by providing more comprehensive information about postoperative pain therap.[4]

Although the duration of surgery **(CHAPTER 7)** is often mentioned as a risk factor in the literature, up to the present time there has never been a procedure-specific comparison. It is quite probable that longer-lasting procedures will cause more tissue damage, and thus, more pain than short procedures such as eye surgery or biopsies. Whether a longer operating time *within* a particular surgical group could produce more severe pain, perhaps due to a greater degree of inflammation, more irritation of nerve endings, longer stretching of the tissues by surgical retractors, or longer-lasting peritoneal irritation from a capnoperitoneum, has not previously been studied.

Our results indicate that there is a statistically significant overall association of increasing postoperative pain with increasing duration of surgery. However, the effect sizes are very small, and variation between different surgical procedures seems to be more important than differences in duration. For 34 procedures we looked in detail into this association and found no statistically significant relation between duration of surgery and postoperative pain. Only in three groups of surgeries (lumbar laminectomy, open and arthroscopic shoulder ligament repair) an increase in pain scores from the fastest to the slowest surgical group was seen which merits further investigation.

Therapeutic aims in acute postoperative pain therapy

As is true for CPSP, in acute postoperative pain the pain intensity is by far the most frequently used outcome parameter. In research, cut-off points (CP) are often used to define "sufficient" pain treatment, or opioid doses are titrated up to a specific CP. In clinical practice, patients are regularly asked about their pain intensity, and most pain-treatment protocols instruct the medical staff to strive for a CP on average of NRS 3 or 4. However, there is no evidence as to what is actually the optimal CP. There is also no general consensus regarding the optimal CP values representing mild and moderate or moderate and severe pain intensity. Likewise, no consensus exists on how to analyze the optimal CP. To maximize the validity of our analyses in **CHAPTER 8,** four methods were adopted to characterize the optimal CP for the NRS. These were: "preoperatively estimated tolerable pain intensity"; "differences in pain intensity among patients with and without the desire for more analgesics in the period from surgery to the first postoperative day"; "satisfaction with pain therapy"; and "pain-related interference with movement, sleep, mood, and deep breaths". Three of the four methods identified a CP of NRS 4 or greater as optimal.

However, the distribution of the CPs in single patients is so wide that using CPs in individual pain treatment should be discouraged. Repeated questioning of patients about their pain intensity in the postoperative setting is intended to identify trends in pain severity and to assess the effect of treatment. However, two other questions are more relevant for the individual patient than CPs: firstly, is the pain tolerable or not; and secondly, whether the patient wishes to receive more analgesics. When a patient reports intolerable pain or high pain scores but expresses a wish for no analgesics, this must raise concerns. It is important to inquire about the reason for those seemingly contradictory statements in order to uncover a possible fear of (more) side effects, fear of drug abuse, a general reluctance to take medication, the belief that further analgesics cannot further reduce the pain, or simply that this pain score is acceptable for this patient. A recent study underscores our results: only 30% of patients in the post-anesthesia care unit (PACU) with an NRS score of 6 and 50% of those with NRS 8 expressed the wish to receive more opioid medication. A cut-off value of NRS $\geq$ 5 would have had a positive predictive value of only 27% for predicting the wish for opioids. In 65% of cases where patients had NRS scores of 4-6 they had no wish for opioids because they perceived their pain as being tolerable.[5] In **CHAPTER 6**, the data on wish for more analgesics demonstrate this discrepancy. Among patients with the

worst possible pain intensity of NRS 10 reported 24 hours after surgery, only 40% expressed the wish to have had more analgesics. It is apparent that strict adherence to a pain intensity CP will lead to over- and undertreatment in large subgroups of patients.

Nevertheless, in most pain studies and also by health care regulating bodies such as the Dutch „Health Care Inspectorate ", patient-reported pain intensity is employed as a quality indicator for pain treatment. The problem in measuring the quality of pain therapy is, however, that this cannot be reduced to one or two outcome factors. Indeed, there is no global parameter or validated questionnaire that summarizes quality measurement in a single value. For patients, extremely variable factors can be decisive in judging whether their pain therapy is good or poor, whereas caregivers attempt to assess this information by using the general question: "Were you satisfied with your pain therapy?" Despite the multitude of satisfaction studies, however, this formulation remains difficult to understand. Some of the studies even demonstrated that satisfaction increased with more severe pain – the so-called satisfaction paradox.[6]

The results of our European multi-center study show that pain dynamics (more pain relief received) and how they are responded to (no desire to have received more pain treatment; and greater patient participation in pain-treatment decisions) play a much more important role in the patient's judgment **(CHAPTER 4)** than simply the actual value of the pain score. For the first time, our study has demonstrated a U-shaped association between satisfaction and "more pain relief received" as well as "greater patient participation in pain-treatment decisions". This is understandable, since patients who reported little or no pain either had only a minor, low-pain operation and did not expect to have much pain, or they had a more major procedure with pain that was treated well. Among our pain-ranking data are numerous minor to medium-sized procedures with moderate postoperative pain (e.g., cholecystectomy, appendectomy [30% wish for more analgesics]). It is possible that these patients represent the "valley" of the U, with higher than expected moderate pain and low satisfaction ratings.

An example of the satisfaction paradox could be a major abdominal procedure with and without an epidural catheter. A patient who is pain-free thanks to an epidural catheter following major abdominal surgery will be content. A patient who awakens after the same operation with severe pain that is treated promptly in the PACU with opioids until it reaches a tolerable level will be even more satisfied with his rapid and competent pain treatment, because he has actively experienced

both the pain situation and the therapeutic measure. In our study on satisfaction with pain treatment, regional anesthesia with or without a catheter also did not influence patient satisfaction; the example also shows, however, that the interpretation of an overall satisfaction value is difficult and does not necessarily indicate the quality of the pain treatment.

Poor pain treatment after medium-sized surgical procedures

The most remarkable result from the comparison of 179 operative procedures were high reported pain levels following medium-sized general surgery as well as orthopedic/trauma operations, **(CHAPTER 5)**. But how does it happen that a large number of surgical departments fail to apply good pain treatment after usual minor to medium-sized surgeries such as appendectomy or cholecystectomy?

There are several possible reasons for insufficient pain treatment in these type of surgeries, many of which are related to the quality of the process. For example, while most hospitals currently have written protocols for the treatment of postoperative pain, there are as yet no standards as to which elements the protocol has to include. Thus, it is not surprising that a survey of submitted postoperative pain protocols from 148 German hospitals identified incomplete instructions in pain treatment algorithms in 74% of these standard operating procedures.[7]

A further important cause for suboptimal treatment is lack of specific instructions for the use of rescue analgesics. If a PCA pump is not used, the first question that arises is whether intravenous (i.v.) or oral opioids should be administered. Both therapeutic strategies can be problematic, and there are almost no data in this regard in the literature. When i.v. opioids are titrated on the ward, there is a question as to whether a nurse is allowed to do this, or whether a physician must be summoned. Someone must actually stay at the bedside and wait for at least 5 minutes until the next i.v. dose may be injected. This cycle until adequate pain relief is achieved can be a time-consuming.

For oral treatment with rescue opioids, there is no information in the literature as to when the next rapid-acting dose may be administered. A rapidly acting oral opioid has reached its maximum effect after 1 hour; does this mean, however, that a tablet may be given every hour? Some pharmaceutical companies state in their package inserts that postoperative opioids are contraindicated because of possible bowel paralysis or reduced motility, as delayed-onset overdosing could occur when bowel activity normalizes.

Clear specifications must be provided to the nursing personnel as to how frequently and at what time intervals they may give a patient rescue medication and after how many repeat doses the responsible physician must be consulted. Thus, for example, a treatment path could stipulate that a physician must be notified after a rapid-acting opioid has been given two or three times with a 60-minute interval between doses. In any case, it is important to ask the patient about the effect of the treatment after 60 minutes, and not wait until the patient contacts the nursing staff. In addition to opioid rescue therapy, basal opioid treatment is also a common source of errors. A hospital should reach procedure-specific agreements on which operations should routinely have prolonged-action opioids ordered postoperatively in order that the patient can get through the night with good pain relief. He should not need to repeatedly ask for additional rescue medication because an adequate initial dose was never reached, as rapid-acting opioids have a duration of action of only 4 hours.

Most acute-pain protocols lack clear instructions on how to manage patients who are receiving postoperative opioids. The guideline that 1/6 to 1/10 of the basal opioid dose should be administered as a rescue dose is not widely known, which commonly leads to insufficient titration of opioids in this patient population. As demonstrated in **CHAPTER 8**, not a specific pain-intensity score should be the primary goal of acute pain therapy, but rather, the patient should determine when a tolerable level of pain has been reached and no additional analgesics are desired. Ambiguity in regard to the prescribing of NSAIDs occurs regularly. Without good documentation, it will remain unclear why an NSAID that was specified in the pain protocol was not actually ordered. Our results in **CHAPTER 6** showed that patients who underwent cesarean section with postoperative PCA received NSAIDs much less frequently than patients without PCA. This was most probably due to individual physicians deciding independently that PCA provides sufficient pain relief that would make an additional NSAID unnecessary. It seems unlikely that this reasoning would be documented in the standard operating procedures in the participating hospitals.

Insufficient pain treatment may not only be due to process related parameters, but also to skepticism from the medical staff towards the patient's reported pain intensity. The same pattern is seen in both older and current studies: medical personnel tend to underestimate pain intensity.[8–10] It has never been studied, however, what consequences this attitude actually has on pain treatment provided. If the in-house pain treatment protocol would always be followed, this effect should

be inconsequential. In our pain ranking, though, strikingly lower opioid doses are apparent, in particular, after minor and medium-sized operations in patients who had to ask for pain medication compared to patients who self-titrated opioids via i.v. PCA. If this were not the case, it would be difficult to understand why nearly 30% of patients reported the wish to have received more analgesics after cholecystectomy (mean for all operations in **CHAPTER 3**: 11%). Statements from physicians and nurses in everyday practice such as: "I have administered 18 mg of iv morphine already – I do not think that he is still in so much pain after this type of surgery". "The patient is quite anxious – that is the reason why he reports so much pain – actually it is a risk factor for pain perception and opioids will not help in such situations". "Look, he is calm and not groaning with pain, he has a normal blood pressure and normal pulse – I doubt that he needs more pain medication". This last statement has by now been refuted in several studies. The level of pain intensity has such a low correlation with sympathetic reactions such as plasma catecholamine levels, hemodynamic parameters, and cardiac autonomic control that the absence of these clinical signs can never exclude the presence of severe pain.[11] Similarly, pupil size also has no correlation with pain intensity.[12]

According to many RCTs, laparoscopic operations should be associated with much lower pain scores than open procedures. Our pain ranking, however, shows only minor differences, and at times similar or even higher pain intensities were discovered after laparoscopic interventions. Many laparoscopic procedures, such as appendectomies, show very low pain scores in RCTs, but it is not noted that on average 19 mg (SD 21) i.v. morphine were required via PCA after laparoscopic and 45 mg (SD 48) after open appendectomy. Morphine doses were substantially higher when the appendix had perforated, and there was no difference between the laparoscopic and open approach in these cases.[13] It is thus remarkable that, for example, the actual German guidelines for acute pain therapy recommend that "for minor surgery such as open and laparoscopic appendectomy or laparoscopic cholecystectomy treatment with non-opioids is generally sufficient."

To illustrate these problems in everyday clinical practice, we more closely analyzed pain in patients after cesarean section **(CHAPTER 4)**. This is a good example of a surgical procedure that is insufficiently treated in clinical practice despite good evidence from RCTs that sufficient pain-therapy methods are available (systemic pain therapy, TAP block, epidural and spinal anesthesia). The explanation for insufficient pain treatment is likely to be multifactorial, but it is apparent that the opioid doses administered were very low and the majority of the patients did not

receive any postoperative opioids at all on the ward. It seems probable that fear of opiate intoxication in the neonate via the mother's milk played an important role, as the guidelines only provide vague recommendations. It is surprising, however, that a hospital that decides to administer opioids restrictively would not increase the use of regional anesthesia procedures accordingly.

Conclusions and future directions

The results of our studies clearly indicate that pain treatment must be further tailored according to the surgical procedure and each particular patient's perception.

The individual patient's beliefs regarding tolerable pain intensity, the wish for more analgesics, or involvement in decision-making should be given a higher priority in future acute pain treatment. The origin and associations of known risk factors such as preoperative pain, age, or anxiety must be studied further to determine potential opportunities for improvement of pain treatment.

On a procedure-specific level, more RCTs are needed for surgeries that are not frequently performed. Additional analyses of procedure-specific pain outcomes in daily clinical practice, such as those from our cesarean-section patients, are important in order to reveal discrepancies between pain reported in clinical trials and pain in clinical practice.

The majority of surgeries performed – often designated as "minor" - in abdominal, orthopedic, and trauma surgery need particular attention. New approaches must be considered and implemented by hospitals to prevent undertreatment, especially in situations where PCA or regional anesthesia is not utilized.

We have studied pain during the first 24 hours after surgery, but little is known about the changes in pain in clinical practice during the following postoperative days. A recent study indicate that for a large proportion of surgical patients the assumption of a continuous decrease in pain intensity does not hold true.[14]

Long-term outcomes such as chronic postoperative pain will play an increasing role in decision-making to select the optimal surgical approach and analgesic treatment.

Finally, we do not know enough about feasibility and quality of postoperative pain treatment in low resource countries. A further spreading of the international PainOut project should serve to generate new insights for the improvement of pain treatment in these countries.

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PART VI

Summary

CHAPTER 11

Summary in English

Samenvatting in het Nederlands

Zusammenfassung auf Deutsch

SUMMARY IN ENGLISH

Adequate treatment of acute postoperative pain is still a major problem. Despite various approaches to improve postoperative pain treatment, such as conducting numerous randomized, controlled trials (RCTs), creating pain treatment guidelines, applying new regional analgesia techniques, as well as implementing acute pain services, no substantial decline in pain intensity scores has been observed in recent years. A major issue is the clinician's lack of knowledge of which surgical groups in his hospital are particularly at risk of developing severe pain, which would enable pain treatment to be adapted where necessary.
Many studies on risk factors for postoperative pain have been published. However, so far no consequences of this knowledge have been applied to risk factors in daily clinical practice. It is not known if the identified risk factors apply to all kind of surgery, or only to those subgroups studied. A further obstacle to providing good postoperative analgesia is the lack of knowledge about optimal treatment goals, weighing different outcomes such as pain intensity, side effects, and impairment of ambulation.

Acute postoperative pain is not only an uncomfortable sensation, but is also associated with acute complications such as increased cardiopulmonary problems, delayed ambulation, dissatisfaction, and longer hospital stays. In recent years, many studies have examined the influence of acute pain on the development of chronic postsurgical pain (CPSP) that persists for more than 3 months. **CHAPTER 2** gives an overview of the pathophysiology, risk factors, and prevention of CPSP. Pathophysiological mechanisms that are currently being studied include, in particular, peripheral and central sensitization. The primary goal is to prevent CPSP, as treating persistent pain is often challenging. Despite numerous RCTs, no definite prevention strategy has been identified. Acute postoperative pain is the most consistent risk factor, and a strong correlation has been found in CPSP-studies. Therefore, it appears to be even more important to treat acute postoperative pain sufficiently, as this practice might contribute to preventing CPSP.

CHAPTER 3 describes a comparison of pain for specific surgical procedures. Data from a total of 115,775 patients from 578 surgical wards in 105 hospitals were collected as a basis for this comparison. After strict exclusion of multiple-surgery cases and having defined a minimum number of 20 patients per surgical

group for comparison, 50,199 patients were assigned to 179 surgical groups. Pain ranking was based on worst pain intensity from the time of surgery to the first postoperative day.

The comparison demonstrates that orthopedic, trauma, and abdominal surgeries were grouped almost exclusively among the upper 50% of most painful surgeries. But for a number of open thoracic and abdominal types of surgeries, low NRS scores of 4 or less were reported. In those surgeries, the percentage of cases in which epidural analgesia (EA) was used was relatively high, often 50% or more. The average equivalent oral morphine use of patients without EA in most of these major surgical groups was greater than 35 mg/24h. It appears that the medical staff was aware of the painfulness of these surgeries, and accordingly good results in terms of pain management were achieved.

On the other hand, the results of pain treatment for several "minor" surgeries are alarming. For example, open appendectomy, open cholecystectomy, tonsillectomy, and hemorrhoidectomy ranked among the 25 most painful surgeries. Laparoscopic surgeries were often associated with similar pain scores compared to their open counterparts. Painfulness appears to be underestimated in laparoscopic surgery when the low opioid doses administered on the surgical ward are compared to the doses given in RCTs with patient-controlled analgesia (PCA).

Likewise, many patients suffered severe pain after "minor" orthopedic surgery such as ankle arthrodesis (rank 7), arthrodesis of metacarpophalangeal joints (rank 8), hand resection arthroplasty (rank 11), arthroscopic wrist revision (rank 39), and open metatarsal-bone reduction (rank, 49). In all of these surgeries the average oral morphine use on the ward was below 10 mg. Major spinal surgeries such as spinal fusion or scoliosis correction are among the most painful surgical interventions. Recent RCTs have indicated good pain control with intra-operatively placed epidural catheters. None of the patients included in the study so far had received this type of analgesia.

The results of this pain ranking illustrate that we are not a lways aware of the painfulness of a large number of surgeries; otherwise it is difficult to explain why no patient undergoing an open calcaneus osteotomy received a sciatic-nerve block, since this type of surgery was found to have the highest associated pain intensity. This is consistent, however, with the finding that peripheral nerve blocks were used in only 15% of cases in the 22 most painful orthopedic/trauma surgeries on the extremities.

Our comparison of 179 surgical procedures demonstrated a number of unexpected results, among them the high pain ranking of 811 cesarean-section (CS) patients with a mean worst pain intensity of NRS 6.1. Several RCTs have proven that mild to moderate pain scores can be achieved after CS. A number of pain-related outcome variables were analyzed to give a better insight into the pain perception of patients in our cohort. In **CHAPTER 4** it is demonstrated that CS patients, when compared to open, laparoscopic, and vaginal-laparoscopic assisted hysterectomy patients, reported higher pain intensities and pain-related interferences (moving, sleep, deep breathing, mood) and expressed the wish to have received more analgesics more often, whereas opioid use was significantly lower on the surgical ward.
Within the CS group, patients with i.v. PCA in combination with spinal or general anesthesia scored considerably better than patients without i.v. PCA after spinal or general anesthesia in terms of pain intensity, pain-related interference, and wish for more analgesics. Patients with PCA used comparable doses of opioids in relation to the patients in RCTs (30 mg i.v. morphine/24hours), whereas 62% of patients without PCA did not receive any opioids on the ward, although most national guidelines for postoperative pain treatment in breastfeeding mothers regard it as safe for the newborn as long as the mother is not significantly sedated by opioids. However, it is possible that medical staff are still uncertain about opioid use and prefer to follow the principle 'primum non nocere'. To improve this situation in hospitals with restrictive opioid administration, more regional anesthesia could be used such as transabdominal plane blocks, EA or spinal anesthesia with longer-lasting intrathecal morphine.

A large number of risk factors for the development of severe postoperative pain have been described in literature. The influence of age, preoperative pain, and gender has been studied with contradictory results**.** For the study described in **CHAPTER 5,** we selected the 30 most often performed surgeries for analysis, including nearly 23,000 patients. Preoperative chronic pain, younger age, and female gender were associated with more severe postoperative pain. Postoperative pain increased parallel to preoperative chronic pain intensity and with younger age. This relation was observed in all types of surgeries independent of the size, location, and painfulness of the procedure. Multi-level regression analysis indicated that for each 1.0-point increase in preoperative chronic pain intensity, postoperative pain increased by 0.14 NRS points (95% CI, 0.13 - 0.15). Similarly, postoperative pain decreased by 0.28 points (95% CI, 0.31 - 0.26) per decade older

age. Females reported slightly higher mean NRS points (0.29). The reasons for higher pain scores in younger patients are not yet understood; a greater need for analgesics, more anxiety (possibly due to less contact with health care and surgery), or other sociocultural factors may play a role. Higher postoperative pain intensity in chronic pain patients may be caused by peripheral and central sensitization of the pain-conduction neural system. Experimental and clinical studies have demonstrated higher pain perception in chronic pain patients, however, the implications for pain treatment in younger and chronic-pain patients have not yet been studied. It has not yet been clarified whether merely increasing the analgesic dose will lead to a successful outcome.

In the above-mentioned study, although chronic pain and younger age were found to be risk factors, the consequences for pain treatment strategies are not yet understood. Gender is one of the most widely examined risk factors in pain studies. Although numerous studies have identified female gender to be associated with more pain, many other studies found no difference compared to males. Our study in **CHAPTER 6** showed a small but consistent effect in 18 of 20 surgical groups, with female gender being associated with more intense pain. The multilevel analysis indicated a difference of 0.29 NRS points, which brings the clinical relevance of this statistically significant difference into question. However, no difference in the wish for more analgesics was reported on the first postoperative day. Moreover, females reported significantly higher pain-related interferences (movement, mood, sleep, and deep breathing). Although there appears to be a small gender difference in regard to postoperative pain intensity and pain-related interferences, the key clinical conclusion is that pain treatment need not be adapted in women because there were no differences in requests for more postoperative analgesics.

A procedure-specific analysis of the influence of duration of surgery on postoperative pain has been performed in all types of surgery including more than 150 patients (33 surgical procedures, n = 26,992) of the above mentioned cohort **CHAPTER 7**. In none of the 33 surgical groups a significant association of duration of surgery with pain intensity score was found. Results of a linear regression analysis (adjusted for age, preoperative chronic pain and used opioid dose) comprising all patients a ten-minute increase in duration of surgery was associated with 0.030 (95% CI 0.022; 0.037) increase on the NRS. This significant difference is that small that it is unlikely to have a clinical significant influence.

Pain intensity is by far the most frequently used outcome parameter for postoperative pain. In research, cut-off points (CP) are often used to define "sufficient" pain treatment, or opioid doses are titrated up to a specific CP. In clinical practice, patients are regularly asked about their pain intensity, and most pain treatment protocols instruct medical staff to strive for a CP on average of NRS 3 or 4. However, there is no evidence as to what is actually the optimal CP. There is also no general consensus regarding the optimal CP values representing mild and moderate or moderate and severe pain intensity. Likewise, no consensus exists on how to analyze the optimal CP. To maximize the validity of our analyses in **CHAPTER 8,** four methods were adopted to characterize the optimal NRS CP. These were: 'preoperatively estimated tolerable pain intensity'; 'differences in pain intensity among patients with and without the desire for more analgesics in the period from surgery to the first postoperative day'; 'satisfaction with pain therapy'; and 'pain-related interference with movement, sleep, mood, and deep breaths'. Three of the four methods identified a CP of NRS ≥ 4 as optimal. However, the distribution of the CPs in single patients is so wide that the use of CPs in individual pain treatment at all should be discouraged.

Many studies have demonstrated high satisfaction scores in patients with high pain scores, the so-called satisfaction paradox. Numerous influencing variables have been studied, but the framework of satisfaction with postoperative pain treatment is still poorly understood. In the multicenter cohort study in **CHAPTER 9**, over 24,000 patients from 51 centers in 14 countries were analyzed. Three variables could explain 35% of the variability of satisfaction with pain treatment: no desire to have received more pain treatment; more pain relief received; and greater patient participation in pain-treatment decisions. The latter two variables showed a U-shaped relation. Thus, patients with no or much pain relief were more satisfied than patients with some pain relief, possibly because these patients experienced only minor pain or did not expect to receive any relief. Likewise, very little and great patient participation in decision-making resulted in higher satisfaction scores than some degree of participation. Patients with little participation may not have considered participation to be an option, or may not have been interested in participating.

Adding further items that reflect pain experience (such as pain intensity or length of time with severe pain), pain-related interference (such as interference with movement or deep breathing), and age did not significantly contribute to

understanding the variability of the model. The results were consistent over the various hospitals, countries, and different types of surgery.
Our findings can at least partly explain the apparent satisfaction paradox. Patients' satisfaction is associated less with actual pain experience (and thus outcomes that are considered to be most important by the medical staff), but more with their impressions of improvement and appropriateness of care. New approaches to patient involvement in decision-making and maintenance of control may thus improve patients' perception of the quality of their pain treatment.

Altogether, our procedure-specific analyses have contributed to a better understanding after which types of surgeries pain treatment is insufficient in clinical practice. As after many minor surgeries high pain scores where reported which were often associated with low opioid use on the ward, new approaches can be developed by hospitals to improve their pain treatment. The high influence of younger age and preoperative chronic pain on postoperative pain intensity in all kinds of surgeries have been demonstrated and should be considered in pain treatment protocols. In future, quality of pain treatment and best pain treatment approaches should be analyzed in surgical procedures that have rarely been studied in terms of postoperative pain.

SAMENVATTING IN HET NEDERLANDS

Adequate postoperatieve pijnbestrijding is tot op heden een relevant probleem. Ondanks meerdere pogingen tot verbetering van de praktijk, zoals bijvoorbeeld het uitvoeren van meerdere gerandomiseerd gecontroleerde studies (RCT), het schrijven van richtlijnen voor pijnbestrijding, het toepassen van nieuwe regionale technieken en het implementeren van acute pijndiensten in de organisatie, kon er geen substantiële daling van de pijnintensiteit scores behaald worden. Een groot probleem is het gebrek aan klinische kennis welke chirurgische patiëntengroepen in het ziekenhuis een groter risico op ernstige postoperatieve pijn hebben en waarbij de clinicus dientengevolge zijn of haar pijntherapie op aan kan passen. Inmiddels zijn er veel studies over de risicofactoren van postoperatieve pijn verschenen. Er worden echter voor de alledaagse kliniek geen consequenties aan deze resultaten verbonden. Het is niet bekend of de geïdentificeerde risicofactoren gelden voor alle vormen van chirurgie of dat deze alleen gelden voor de onderzochte subgroepen. Een ander obstakel voor optimale pijnbestrijding is de onzekerheid van de behandeldoelen bij de postoperatieve pijnbestrijding, zoals het wegen van de pijnintensiteit, bijwerkingen en het mobiliseren van de patiënt.

Acute operatieve pijn is niet alleen een uiterst onaangename sensatie het is daarnaast geassocieerd met acute complicaties zoals een verhoogd cardiopulmonaal risico, verminderde mobiliteit, patiënt ontevredenheid en langere ziekenhuisopnames.
De laatste jaren zijn er meerdere studies verschenen die de invloed van acute pijn op de ontwikkeling van chronische postoperatieve pijn (CPSP), die langer aanhoudt dan drie maanden, hebben onderzocht. In **HOOFDSTUK 2** wordt een overzicht gegeven van de pathofysiologie, de risicofactoren en preventie van CPSP. Pathofysiologische mechanismen die momenteel in het bijzonder worden onderzocht zijn perifere en centrale sensitisatie. Het primaire doel is het voorkomen van CPSP, in de praktijk blijkt dit voor dit voor de behandelend arts vaak moeilijk. Ondanks meerdere RCT's kon er nog geen duidelijke strategieën ter preventie van CPSP worden ontwikkeld. Acute postoperatieve pijn is de belangrijkste risicofactor waarbij er een sterke correlatie is gevonden in CPSP studies. Met deze wetenschap is het van nog groter belang dat acute postoperatieve pijn adequaat wordt behandeld, aangezien dit mogelijk CPSP voorkomt.

In **HOOFDSTUK 3** wordt de pijnintensiteit van verschillende chirurgische procedures met elkaar vergeleken. In totaal werden van 115.775 patiënten de gegevens verzameld van 578 chirurgische afdelingen in 105 verschillende ziekenhuizen. Na strikte exclusie van patiënten die meerdere operaties hadden ondergaan en het stellen van een minimum van 20 patiënten per chirurgische groep werden 50.199 patiënten toegewezen aan 179 chirurgische operatie groepen. De vergelijking van de pijnscores waren gebaseerd op de hoogste pijnscore gerekend vanaf de operatie tot aan de eerste dag postoperatief. Uit de vergelijking van deze groepen blijkt dat orthopedische chirurgie, trauma chirurgie en abdominale chirurgie bijna uitsluitend gerekend worden tot de bovenste 50% van meest pijnlijke ingrepen. Voor een groot aantal operatieve ingrepen, zoals open thoracale chirurgie en verschillende types abdominale chirurgie, werden lagere pijnscores (NRS < 4) gerapporteerd. Het gebruik van epidurale analgesie in deze chirurgische subgroepen lag qua percentage, vaak 50% of meer, hoog. De gemiddelde equivalentsdosering orale morfine van patiënten zonder epidurale analgesie in de meeste chirurgische groepen lag hoger dan 35mg/24u. Het lijkt er hierbij op dat de medische staf zich bewust was van de pijnintensiteit van deze ingrepen waarbij dientengevolge qua pijnmanagement goede resultaten werden geboekt. Aan de andere kant waren de resultaten van de pijnbehandeling van verschillende zogenaamde kleine ingrepen alarmerend. De open appendectomie, open cholecystectomie, tonsillectomie en haemorrhoidectomie werden bijvoorbeeld gerekend tot de 25 meeste pijnlijke ingrepen. Laparoscopische ingrepen werden vaak vergelijkbaar gescoord qua pijnscore ten opzichte van hun equivalente open benaderingen. De pijn bij laparoscopische chirurgie lijkt te worden onderschat als men de lage dosering van morfine op de chirurgische afdeling vergelijkt met de doseringen gegeven in RCTs met patiënt gecontroleerde analgesie (PCA). Daarnaast lijden veel patiënten pijn na zogenaamde 'kleine' ingrepen zoals arthrodese van de enkel (plaats 7), arthrodese van metacarpophalageale gewrichten (plaats 8), resectie artroplastiek van de hand (plaats 11), revisie arthroscopie van de pols (plaats 39) en een open middenvoetsbeentje resectie (plaats 49). Bij al deze vormen chirurgie lag het gemiddelde morfine gebruik op de afdeling onder de 10 mg. Grote ingrepen aan het wervelkolom zoals een spondylodese of een scoliose correctie worden gerekend tot de meest pijnlijk chirurgische procedures. Recente RCTs hebben goede resultaten qua pijnbestrijding laten zien met peroperatief geplaatste epidurale katheters. In onze cohortstudies heeft geen enkele patiënt deze vorm van analgesie ontvangen. De resultaten van deze ranglijst van pijnscores

illustreert dat we ons niet altijd bewust zijn van de mate van pijn van een groot aantal ingrepen; anders valt het niet te verklaren waarom geen enkele patiënt die een open calcaneus osteosynthese onderging een nervus ischiadicus blokkade kreeg, aangezien deze ingreep is geassocieerd met de hoogste pijnintensiteit. Dit is echter consistent met de bevinding dat maar in 15% van de gevallen perifere zenuwblokkade werd gekozen als anesthesie vorm in 22 van de meest pijnlijke orthopedische/trauma ingrepen aan extremiteiten.

Tijdens de vergelijking van 179 chirurgische procedures vonden we een aantal onverwachte bevindingen, waaronder de hoogste gemiddelde pijnintensiteit score van NRS 6.1 bij 811 patiënten die een sectio caesarea (SC) ondergingen. Verschillende RCTs hebben aangetoond, dat na SC milde tot matige pijnscores mogelijk is. Om meer inzicht te verkrijgen in de pijnperceptie van de patiënten in ons cohort, werd een aantal pijngerelateerde uitkomsten geanalyseerd. In **HOOFDSTUK 4** wordt beschreven, dat SC-patiënten hogere pijnintensiteitscores aangeven. Daarnaast hebben deze patiënten meer pijngerelateerde problemen in de vorm van bewegen, slapen, doorademen of stemming in vergelijking met patiënten die een open, laparoscopische of vaginaal-laparoscopische hysterectomie ondergingen. Daarnaast hadden SC-patiënten vaker behoefte aan meer analgetica, hoewel het opiaatgebruik op de verpleegafdeling in deze groep significant lager lag.
Binnen de SC-groep scoorden patiënten met intraveneuze PCA in combinatie met spinale of algehele anesthesie aanmerkelijk beter dan patiënten zonder intraveneuze PCA na spinale of algehele anesthesie. Dit betreft pijnintensiteit, pijngerelateerde problemen en de wens voor meer analgetica. Patiënten met PCA gebruikten vergelijkbare hoeveelheden opiaten ten opzichte van de patiënten in RCTs (30 mg morfine i.v./24 uur). Van de patiënten zonder PCA kreeg 62% geen opiaten op de verpleegafdeling. Dit is opmerkelijk aangezien de meeste nationale richtlijnen voor postoperatieve pijnbehandeling bij moeders die borstvoeding geven, opiaatgebruik veilig voor de neonaat beschouwen voor zover de moeder niet volledig gesedeerd raakt door opiaten. Het is echter wel mogelijk dat de medische staf onzeker is over opiaatgebruik en daarom de voorkeur geeft aan het principe “primum non nocere”. Om de situatie in ziekenhuizen met restrictief opiaatbeleid te verbeteren, zouden meer regionale anesthesietechnieken, zoals transabdominale plane blocks, epidurale of spinale anesthesie met langwerkend intrathecaal morfine toegepast kunnen worden.

In de literatuur is een groot aantal risicofactoren beschreven voor de ontwikkeling van ernstige postoperatieve pijn. In deze studies zijn tegenstrijdige effecten van leeftijd, preoperatieve pijn en geslacht gerapporteerd. Voor het onderzoek in **HOOFDSTUK 5** hebben we bijna 23.000 patiënten geselecteerd die dertig van de meest uitgevoerde chirurgische procedures ondergingen. Preoperatieve chronische pijn, jonge leeftijd en het vrouwelijk geslacht zijn geassocieerd met ernstigere postoperatieve pijn. Postoperatieve pijn nam toe bij preoperatieve chronische pijn en bij jongere leeftijd. Deze relatie werd bij alle chirurgische procedures gevonden, onafhankelijk van de uitgebreidheid, de locatie en de pijnlijkheid van de procedure. De resultaten van de multilevel regressie analyse lieten zien dat voor elke toename van preoperatieve chronische pijnintensiteitscore met 1.0 punt, de postoperatieve pijn toenam met 0.14 NRS-punten (95% CI 0.13-0.15). Postoperatieve pijn nam daarentegen met 0.28 NRS-punten (95% CI 0.31-0.26) af per toename van de leeftijd met tien jaar. Bij vrouwen werd een hoger gemiddelde NRS gevonden (0.29) (95% CI 0.22-0.37). De oorzaken van hogere pijnscores bij jongere patiënten zijn niet goed begrepen. Grotere analgeticabehoefte, meer angst (mogelijk door minder voeling met de gezondheidszorg en chirurgie) of andere socioculturele factoren kunnen hierbij een rol spelen. Hogere postoperatieve pijnintensiteit bij chronische pijnpatiënten kan veroorzaakt worden door perifere en centrale sensitisatie van het neurale pijngeleidingssysteem. In experimentele en klinische onderzoeken is aangetoond dat chronische pijnpatiënten een hogere pijnperceptie hebben. De gevolgen van pijnbehandeling bij jongere patiënten en bij patiënten met chronische pijn zijn echter niet onderzocht. Daarnaast is niet bekend of alleen het ophogen van de analgeticadosering zal leiden tot een betere uitkomst.

Ondanks de bevinding dat chronische pijn en jonge leeftijd als risicofactoren werden gevonden in het hierboven beschreven onderzoek zijn de gevolgen van de pijnbehandelingsstrategieën in het hierboven beschreven onderzoek nog niet volledig opgehelderd.
Het geslacht is één van de meest bestudeerde risicofactoren in pijnonderzoeken. In talrijke onderzoeken werd het vrouwelijk geslacht geassocieerd met meer pijn, hoewel in vele andere onderzoeken geen verschil werd gevonden tussen mannen en vrouwen. In ons onderzoek (**HOOFDSTUK 6)** vonden we een klein, maar consistent effect in 18 van de 20 chirurgische operatiegroepen. Hierbij werd het vrouwelijk geslacht geassocieerd met ergere pijn. Het resultaat van de multilevel

analyse was een verschil van 0.29 NRS-punten (95% CI 0.22-0.37). Daarbij kan men zich afvragen wat de klinische relevantie is van dit statistisch significante verschil. Er werd echter geen verschil gevonden in de wens voor meer pijnstillers op de eerste postoperatieve dag. Daarnaast rapporteerden vrouwen significant hogere pijngerelateerde problemen betreffende bewegen, slapen, doorademen en stemming. Hoewel er kleine verschillen lijken te zijn voor wat betreft de postoperatieve pijnintensiteit en pijngerelateerde problemen, blijft de belangrijkste klinische conclusie dat het lijkt dat de pijnbehandeling niet aangepast hoeft te worden bij vrouwelijke patiënten, omdat er geen verschil was in postoperatieve opiaatbehoefte.

In het hierboven beschreven cohort werd een procedure-specifieke analyse gedaan voor het onderzoeken van de relatie tussen de duur van chirurgische procedure en postoperatieve pijn (**HOOFDSTUK 7**). In dit onderzoek werden alle chirurgische procedures bij meer dan 150 patiënten (33 procedures, n = 26.992) in de analyse meegenomen. In geen van de 33 chirurgische operatiegroepen werd een significante associatie gevonden tussen de duur van de procedure en pijnintensiteitscore.
De resultaten van de lineaire regressie analyse (gecorrigeerd voor leeftijd, preoperatieve chronische pijn en gebruikte opiaatdosering) toonde aan dat elke toename van de duur van de chirurgische procedure met tien minuten geassocieerd is met een toename van 0.030 NRS-punten (95% CI 0.022-0.037). Dit statistisch significante effect is echter dusdanig klein dat een klinisch relevant effect onwaarschijnlijk is.

Pijnintensiteit is de meest gebruikte uitkomstparameter voor de bestudering van postoperatieve pijn. In onderzoeken worden bepaalde grenswaarden (GW) bijvoorbeeld vaak gebruikt om "voldoende" pijnstilling te definiëren of opiaten worden tot een bepaalde GW getitreerd. In de klinische praktijk worden patiënten regelmatig gevraagd naar hun pijnintensiteit en in de meeste pijnbehandelingsprotocollen wordt gestreefd naar een gemiddelde GW van NRS 3 of 4. Er is echter geen enkel bewijs voor een definitie van de optimale GW. Daarnaast is er geen consensus over de GW die milde en matige of matige en ernstige pijnintensiteit representeren. Om de validiteit van onze analyses in **HOOFDSTUK 8** te maximaliseren, werden vier methodes toegepast om de optimale NRS GW te beschrijven. Deze methodes waren "preoperatief geschatte pijnintensiteit tolerantie", " verschillen in pijnintensiteit tussen patiënten met en

zonder aanvullende analgeticawens op de eerste postoperatieve dag", "tevredenheid pijnbehandeling" en "pijngerelateerde problemen betreffende bewegen, slapen, doorademen en stemming". Drie van de vier methodes toonden aan dat een GW van NRS ³ 4 optimaal is. De verdeling van GW bij individuele patiënten is echter dusdanig breed dat het gebruik van GW in individuele pijnbehandeling ontmoedigd dient te worden.

In veel onderzoeken is de zogeheten tevredenheidsparadox aangetoond, er werden namelijk hogere tevredenheidscores gevonden bij patiënten met hogere pijnscores. Talrijke variabelen zijn onderzocht, maar de achtergrond van deze tevredenheid bij postoperatieve pijnbehandeling is desondanks nog niet opgehelderd. In het cohort onderzoek in **HOOFDSTUK 9** werden 24.000 patiënten uit 51 ziekenhuizen in 14 landen geanalyseerd. Drie variabelen konden 35% van de tevredenheidsvariabiliteit verklaren, namelijk geen wens voor meer analgetica, meer pijnverlichting en een grotere patientparticipatie bij de besluitvorming. De laatste twee variabelen hadden een U-vormige relatie. Dus, patiënten met geen of veel pijnverlichting waren meer tevreden dan patiënten met enige pijnverlichting. Een verklaring hiervoor kan zijn dat de laatste genoemde groep patiënten al weinig pijn had of geen pijnverlichting verwachtte.
Erg weinig of juist veel patiëntparticipatie in de besluitvorming leidde tot hogere tevredenheidscores in vergelijking met enige vorm van participatie. Patiënten met weinig participatie kunnen participatie niet als optie hebben overwogen of zouden simpelweg niet geïnteresseerd in participatie kunnen zijn. Toevoeging van andere factoren, die pijnbeleving reflecteren (zoals pijnintensiteit of tijdsduur van ernstige pijn), pijngerelateerde problemen (bijvoorbeeld betreffende bewegen of doorademen) en leeftijd, droegen niet significant bij in het verklaren van de variabiliteit in het model. De resultaten waren consistent tussen verschillende ziekenhuizen, landen en chirurgische procedures. Onze bevindingen kunnen in ieder geval ten dele de tevredenheidsparadox verklaren. Patiënttevredenheid wordt minder geassocieerd met huidige pijnbeleving, maar meer met hun indruk van de geschiktheid en aanpassing van het zorgbeleid. Nieuwe benaderingen om patiënten meer te betrekken bij de besluitvorming zouden het oordeel van de patiënten over de kwaliteit van hun pijnbehandeling kunnen verbeteren.

Samenvattend.
Onze procedure-specifieke analyses dragen bij aan de kennis over onvoldoende pijnbehandeling na diverse chirurgische procedures in de klinische praktijk. Na diverse kleine chirurgische ingrepen werden vaak hoge pijnscores gerapporteerd met weinig opiaatgebruik op de afdeling. Dit biedt de mogelijkheid voor ziekenhuizen om nieuwe strategieën te ontwikkelen voor de verbetering van hun pijnbehandeling. De duidelijke effecten van jonge leeftijd en preoperatieve chronische pijn op postoperatieve pijnintensiteit na verschillende chirurgische procedures zijn aangetoond en de invloed van deze factoren zouden meegewogen kunnen worden bij het opstellen pijnbehandelingsprotocollen. In de toekomst zouden de kwaliteit van pijnbehandeling en de beste pijnbehandelingstrategieën geanalyseerd kunnen worden in chirurgische procedures waar postoperatieve pijn tot nu toe nog weinig onderzocht is.

ZUSAMMENFASSUNG AUF DEUTSCH

Eine adäquate postoperative Schmerztherapie stellt weiterhin ein relevantes Problem dar. Trotz verschiedener Lösungsansätze wie z.B. die Durchführung vieler randomisiert-kontrollierter Studien (RCT), Verfassen von Schmerztherapie Leitlinien, Anwendung neuer Regionalanästhesie-Verfahren oder Implementierung von Akutschmerzdiensten, konnte in den letzten Jahren keine wesentliche Schmerzintensitäts-Reduktion erzielt werden. Ein wesentliches Problem ist dabei, dass dem Kliniker keine Daten vorliegen welche operativen Eingriffe in seinem Krankenhaus besonders schmerzhaft sind, um auf diese Weise die Schmerztherapie besser anpassen zu können.

Mittlerweise wurden viele Studien über Risikofaktoren von postoperativen Schmerz publiziert. Jedoch wurden aus diesen Erkenntnissen keine Konsequenzen für den klinischen Alltag gezogen. Es ist nicht bekannt, ob die beschrieben Risikofaktoren nur für die bisher untersuchten operativen Eingriffe zutreffen oder ob sie für verschiedene Operationen Gültigkeit haben. Ein weiteres Hindernis für eine optimale Schmertherapie ist die Unklarheit von Therapiezielen in der postoperativen Schmerztherapie, wie z.B. das Abwägen von Schmerzintensität, Nebenwirkungen und Mobilisierung des Patienten.

Postoperative Schmerzen sind nicht nur ein unangenehmes Gefühl, sondern sind auch mit akuten Komplikationen wie erhöhtes kardiopulmonales Risiko, verzögerte Mobilisierung, Unzufriedenheit des Patienten und verlängerte Krankenhausaufenthalte assoziiert. In den letzten Jahren sind viele Studien über die Entwicklung von akuten zu chronischen postoperativen Schmerzen (CPSP), die länger als 3 Monate persistieren, publiziert worden. **KAPITEL 2** stellt einen Überblick über Pathophysiologie, Risikofaktoren und Prävention des CPSP dar. Pathophysiologische Mechanismen die zur Zeit besondere Aufmerksamkeit finden sind die periphere und die zentrale Sensibilisierung. Das primäre Ziel ist die Prävention des CPSP, da sich die Therapie der persistierenden Schmerzen häufig als schwierig erweist. Trotz zahlreicher RCTs konnte bisher keine klare Strategie zur Prävention des CPSP entwickelt werden. Daher ist die suffiziente Therapie des starken Akutschmerzes umso wichtiger, da dies der wichtigste Risikofaktor für CPSP ist und somit möglicherweise das Auftreten von CPSP reduziert werden kann.

In **KAPITEL 3** wird die Schmerzintensität von verschiedenen operativen Eingriffen miteinander verglichen. Insgesamt wurden Daten von 115.775

Patienten von 578 chirurgischen Stationen aus 105 Krankenhäusern erfasst. Für den Vergleich der chirurgischen Eingriffe wurden alle Patienten mit multiplen Operationen ausgeschlossen und eine Mindestanzahl von 20 Patienten pro Operationsgruppe festgelegt. Insgesamt wurden somit 50,199 Patienten zu 179 verschiedenen Operationsarten zugeordnet. Der Schmerzstärken-Vergleich basiert auf der Auswertung der stärksten Schmerzintensität von der Operation bis zum ersten postoperativen Tag.

Der Vergleich zeigt, dass unter den 50% der chirurgischen Eingriffe mit den höchsten postoperativen Schmerzen fast ausschließlich Patienten der Traumatologie, Orthopädie und Allgemeinchirurgie zu finden waren. Für einige große abdominale- sowie thoraxchirurgische Eingriffe waren die Schmerzintensitäten mit NRS-Werten < 4 relativ niedrig. In diesen Operationsgruppen war die Anzahl der verwendeten Epiduralkatheter mit zumeist mehr als 50% relativ hoch. Die durchschnittliche orale Morphin-Äquvivalenzdosis bei diesen Patienten ohne Epiduralanalgesie betrug zumeist mehr als 35 mg/24h. Es scheint, dass den behandelnden medizinischen Teams die Schmerzhaftigkeit dieser Operationen bewusst ist und dementsprechend gute Resultate bei den Schmerzintensitäten erreicht werden.

Andererseits sind die Schmerzintensitäten für eine Vielzahl von sogenannten kleinen operativen Eingriffen erschreckend hoch. So liegen z.B. die offene Appendektomie, die offene Cholezystektomie, die Tonsillektomie und die Hämorrhoidektomie unter den 25 schmerzhaftesten Eingriffen. Laparoskopische Eingriffe resultierten oftmals in ähnlich hohen Schmerzscores wie die offenen operativen Zugänge. Die Schmerzhaftigkeit von laparoskopischen Eingriffen scheint unterschätzt zu werden, wenn man die niedrig verabreichten Dosen von Opiaten in der Studienkohorte mit denen in RCTs bei gleichen Operationen vergleicht.

Ebenso litten viele Patienten nach kleinen orthopädischen Eingriffen unter starken Schmerzen, wie nach Sprunggelenks-Arthrodese (Rang 7), Arthrodese der metacarpophalagealen Gelenke (Rang 8), Resektionsarthroplastik der Hand (Rang 11), arthroskopische Revision des Handgelenks (Rang 39) und offene Metatarsal-Knochen Resektion (Rang 49). Bei allen diesen Operationen lag die durchschnittlich verabreichte orale Morphin-Äquivalenz auf der chirurgischen Station unter 10 mg. Große Wirbelsäulen-Operationen wie die Spondylodese oder die Skoliosen-Korrektur gehören zu den schmerzhaftesten chirurgischen Eingriffen. Aktuelle RCTs haben gute Schmerzlinderung mit intraoperativ durch

den Operateur gelegte Epiduralkatheter gezeigt. In unserer Kohorte hatte bisher kein Patient solch einen Schmerzkatheter erhalten.
Die Ergebnisse unseres Schmerzintensitäts-Vergleichs zeigen, dass wir uns der Schmerzhaftigkeit einer großen Anzahl von Operationen nicht bewusst sind – anders ist es nicht zu erklären warum keiner der Patienten mit offener Calcaneus Ostheosynthese einen Nervus ischiadicus Block erhalten hat, obwohl dieser Eingriffen mit der durchschnittlich höchsten Schmerzintensität angegeben wurde. Ebenso auffällig ist, dass lediglich 15% der Patienten der 22 Operationen mit den höchsten Schmerzintensitäten nach orthopädischen/traumatologischen Extremitäten-Eingriffen eine periphere Regionalanalgesie erhielten.
Unser Vergleich von 179 verschiedenen operativen Eingriffen bringt viele unerwartete Ergebnisse ans Licht, u.a. die hohe durchschnittliche Schmerzintensität von 811 Frauen nach Kaiserschnitt Entbindung (KS) mit einer durchschnittlichen stärksten Schmerzintensität von NRS 6,1. Eine Vielzahl von RCTs hat dargestellt, dass geringe bis moderate Schmerzen durchaus nach einem KS zu erreichen sind. Mehrere Schmerzrelevante Outcome Faktoren wurden analysiert, um eine bessere Einsicht in die Schmerz-Wahrnehmung der KS Patientinnen zu gewinnen. Im **KAPITEL 4** wird deutlich, dass Patienten nach KS im Vergleich zu Patientinnen nach offener, laparoskopischer und vaginal laparoskopisch-assistierter Hysterektomie höhere Schmerzintensitäten als auch höhere schmerzbedingte Beeinträchtigung angeben (Beeinträchtigung bei Bewegung, beim Schlaf, beim tiefen Durchatmen sowie auf die Stimmung). Zusätzlich äußerten KS-Patienten häufiger den Wunsch, gerne mehr Analgetika gehabt zu haben, wobei sie auch signifikant weniger Opiate auf der Normalstation erhalten haben im Vergleich zu den drei Hysterektomie-Gruppen.
Innerhalb der KS-Gruppe erzielten Patientinnen mit PCA Pumpe in Kombination mit Spinal- oder Allgemein-Anästhesie signifikant bessere Ergebnisse als Patientinnen ohne PCA Pumpe und Spinal- oder Allgemeinanästhesie in Bezug auf Schmerzintensität, schmerz-bedingter Beeinträchtigung und Wunsch nach mehr Analgetika. Patientinnen mit PCA Pumpe verabreichten sich mit RCTs vergleichbare Opiat-Dosen von 30 mg i.v. Morphin / 24 h, wohingegen 62% der Patientinnen ohne PCA überhaupt keine Opiate auf Normalstation verabreicht bekamen. Diese niedrigen Opiat-Dosen wurden gegeben, obwohl in den meisten nationalen Leitlinien eine Opiatbehandlung der Mutter als sicher, in Bezug auf das Stillen des Neugeborenen mit einer möglichen Opiat-Intoxikation, angesehen wird. Wahrscheinlich ist das medizinisch behandelnde Team weiterhin unsicher

über den Opiat Einsatz bei stillenden Müttern und folgt eher dem Leitsatz „primum non nocere". Um diese Situation in Krankenhäusern mit restriktivem Opiateinsatz zu verbessern, sollten mehr regionalanästhesiologische Verfahren verwendet werden, wie der transabdoninis plane block, die Epiduralanalgesie bzw. die Spinalanästhesie mit längerwirksamen intrathekalem Morphin, dass bis zu 24 Stunden suffiziente Analgesie erzielen kann.

Eine große Anzahl von Studien in Bezug auf Risikofaktoren auf die Entstehung starker postoperativer Schmerzen wurde bisher publiziert. Der Einfluss von Alter, präoperativem Schmerz und Geschlecht wurde in einigen Studien untersucht, jedoch mit widersprüchlichen Ergebnissen. Für die Studie in **KAPITEL 5** haben wir die 30 häufigsten Operationen des QUIPS Registers selektiert. Somit wurden fast 23.000 Patienten für diese Analyse eingeschlossen. Präoperativer chronischer Schmerz, jüngeres Alter und weibliches Geschlecht waren assoziiert mit stärkerer postoperativer Schmerzintensität. Postoperativer Schmerz stieg kontinuierlich mit präoperativer chronischer Schmerzintensität und mit jüngerem Alter an. Dieser Zusammenhang wurde in allen Operationsgruppen beobachtet, unabhängig vom Ausmaß, der Lokalisation und der Schmerzhaftigkeit des Eingriffes. Die Multiregressionsanalyse ergab, dass für jeden 1,0 Punkte-Anstieg an chronischer präoperativer Schmerzintensität, der postoperative Schmerz um NRS 0,14 anstieg (95% CI 0,13 – 0,15). Die postoperative Schmerzintensität sinkt mit jeder Lebensdekade um -0,28 (95% CI -0,31 bis -0,26) Punkte auf der NRS. Frauen berichten über geringfügig höhere Schmerzintensitäten (NRS 0,29). Die Ursache für stärkere Schmerzen bei jüngeren Patienten ist bisher nicht bekannt. Ein größerer Bedarf an Analgetika, mehr Angst (möglicherweise durch weniger Kontakt mit Ärzten, Krankenhaus und Erfahrung mit Operationen) oder andere soziale oder kulturelle Gründe, könnten eine Rolle spielen. Postoperative Schmerzen bei Patienten mit präoperativen chronischen Schmerzen könnten durch periphere bzw. zentrale Sensibilisierung des schmerzleitenden Nervensystems verstärkt werden. Experimentelle und klinische Studien haben ein höheres Schmerzempfinden bei Patienten mit chronischen Schmerzen nachgewiesen. Bisher ist es jedoch unklar, inwieweit diese Erkenntnisse Konsequenzen auf die Schmerztherapie bei jüngeren Patienten und bei denen mit chronischen Schmerzen haben muss. Bisher wurde nicht untersucht, ob lediglich eine höhere Analgetikadosis zu zufriedenstellenden Ergebnissen führen würde.

In der zuletzt beschriebenen Studie wurden chronischer Schmerz und jüngeres Alter als Risikofaktoren beschrieben, jedoch ist die Konsequenz dieses Wissens auf eine möglicherweise anzupassende Schmerztherapie nicht bekannt. Geschlecht ist einer der am umfangreichsten untersuchten Risikofaktoren für Schmerz. Obwohl eine große Anzahl von Studien das weibliche Geschlecht als Risikofaktor beschrieben haben, haben andere Studien keinen Unterschied feststellen können. Unsere Studie in **KAPITL 6** zeigt einen kleinen aber konsistenten Effekt in 18 der 20 untersuchten Operationsgruppen wobei Frauen stärkere Schmerzen angaben als Männer. Die Multilevel Regressionsanalyse ergab einen Unterschied von 0,29 NRS-Punkten. Ob dieser statistisch signifikante aber kleine Unterschied auch klinisch signifikant ist, ist fraglich. Frauen und Männer äußerten jedenfalls gleich häufig, dass sie gerne mehr Analgetika bekommen hätten. Zusätzlich berichteten Frauen über signifikant höhere schmerzbedingte Beeinträchtigung (Bewegung, tiefes Einatmen, Schlaf und Stimmung). Obwohl Frauen etwas höhere Schmerzwerte und schmerzbedingte Beeinträchtigung angaben, ist die wesentliche Schlussfolgerung dieser Studie, dass das Schmerztherapie-Management bei Frauen wahrscheinlich nicht angepasst werden muss, da kein Unterschied in dem Wunsch nach mehr postoperativen Analgetika bestand.

Eine Operationen-spezifische Analyse auf den Einfluss der Operations-Dauer auf den postoperativen Schmerz wurde in allen Operationsgruppen mit mehr als 150 Patienten durchgeführt (33 Operationsgruppen mit insgesamt 26,992 Patienten) der oben beschriebenen Kohorte **(KAPITEL 7)**. In keiner der 33 Operationsgruppen wurde ein signifikanter Zusammenhang zwischen der Dauer der Operation und den postoperativen Schmerzen gefunden. Eine lineare Regressionsanalyse mit allen Patienten der 33 Operationen eingeschlossen (adjustiert für Alter, Geschlecht, präoperative chronische Schmerzen und verabreichter Opiatdosis) ergab einen Anstieg der Schmerzintensität um 0,030 NRS Punkte (95% CI 0,022; 0,037) pro 10 Minuten längerer Operationszeit. Dieser statistische signifikante Unterschied ist so klein, dass es unwahrscheinlich ist, dass er einen klinisch signifikanten Einfluss hat.

Die Schmerzintensität ist bei Weitem der am häufigsten untersuchte Outcome-Faktor von postoperativen Schmerzstudien. In der Schmerzforschung wird ein Schmerzintensitäts-Grenzwert vor allem verwendet, um eine „suffiziente“ von einer „nicht suffizienten“ Schmerztherapie abzugrenzen oder um Opiate bis zu einem gewissen Grenzwert zu titrieren. In der klinischen Praxis wird

der Patient regelmäßig über seine Schmerzintensität befragt. In den meisten postoperativen Schmerztherapie-Protokollen wird eine Schmerzintensität von NRS 3 oder 4 angestrebt. Jedoch gibt es unzureichende Evidenz, was in der postoperativen Schmerzbehandlung ein anzustrebender Schmerzintensität-Grenzwert ist. Es gibt ebenfalls keinen allgemeinen Konsens darüber was der Grenzwert zwischen geringen und moderaten bzw. moderaten und starken Schmerzen ist. Demensprechend existiert auch kein Konsens wie Grenzwerte der Schmerzintensität analysiert werden müssen. Um die Validität der Analysen in **KAPITEL 8** zu maximieren, haben wir vier verschiedene Methoden angewendet, um den optimalen Schmerzgrenzwert festzulegen. Dies waren die vom Patienten „präoperativ eingeschätzte noch erträgliche Schmerzintensität", „Unterschied der Schmerzintensität zwischen Patienten mit ohne dem Wunsch nach mehr Analgetika in der Zeit seit der Operation bis zum ersten postoperativen Tag", „Zufriedenheit mit der Schmerztherapie", „schmerz-bedingte Beeinträchtigung bei Bewegung, beim tiefen Einatmen, beim Schlafen und auf die Stimmung". Drei der vier angewendeten Methoden resultierten in einem optimalen Schmerzgrenzwert zwischen geringem und moderatem Schmerz von NRS ≥ 4. Jedoch zeigte sich in dieser Studie, dass die Streuung der individuellen-Patienten Einschätzungen so groß waren, dass von der Anwendung von Schmerzintensitäts-Grenzwerten bei individuellen Patienten zur Festlegung eines Therapieziels nur abgeraten werden kann.

Viele Studien haben bei Patienten mit hohen Schmerzintensitäten auch hohe Zufriedenheits-Werte festgestellt, dass sogenannte Zufriedenheits-Paradox. Eine Vielzahl von Einflussfaktoren ist untersucht worden, trotzdem ist das Konstrukt „Zufriedenheit mit der Schmerztherapie" bisher nur unzureichend verstanden. In der Multicenter Studie in **KAPITEL 9** wurden mehr als 24.000 Patienten aus 51 Kliniken in 14 Ländern analysiert. Drei Variablen konnten mehr als 35% der Varianz von Zufriedenheit mit der Schmerztherapie erklären. 1) kein Wunsch nach mehr Schmerzmedikamenten 2) mehr erziele Schmerzreduktion 3) mehr Partizipation der Patienten bei Schmerztherapie Entscheidungen. Die beiden letzten Faktoren weisen eine U-förmige Assoziation auf. Demnach haben Patienten mit keiner oder viel Schmerzreduktion höhere Zufriedenheitswerte als Patienten mit nur etwas Schmerzreduktion; möglicherweise weil Patienten ohne Schmerzreduktion nur wenig Schmerzen hatten oder weil sie nicht viel Schmerzreduktion erwartet haben. Ähnliche Zusammenhänge findet man bei Patienten mit sehr wenig oder sehr

viel empfundener Partizipation bei schmerztherapeutischen Entscheidungen die zufriedener waren als Patienten mit nur etwas Mitentscheidungs-Möglichkeiten. Patienten mit keiner Mitentscheidung haben möglicherweise gar nicht erst in Erwägung gezogen, dass diese Option bestehen könnte oder waren nicht interessiert an einer Mitbeteiligung im Entscheidungsprozess.
Das Zufügen weiterer Items in das statistische Modell, die die Schmerzwahrnehmung abbilden (z.B. Schmerzintensität oder Dauer von starken Schmerzen), schmerzbedingte Beeinträchtigung (z.B. Beeinträchtigung der Bewegung oder des tiefen Durchatmens) sowie Alter des Patienten haben nicht signifikant zur Verbesserung der Varianz des Modells beigetragen. Die Ergebnisse waren konsistent über die verschiedenen Krankenhäuser, verschiedene Länder und zwischen verschiedenen operativen Eingriffen.
Unsere Ergebnisse können zumindest teilweise das Zufriedenheitsparadoxon erklären. Die Zufriedenheit des Patienten steht weniger im Zusammenhang mit der tatsächlich erfahrenen Schmerzstärke (also demnach Schmerz-Variablen von denen v.a. das medizinische Personal ausgeht, dass es eine entscheidende Rolle spielt) sondern mehr mit dem Eindruck der Verbesserung der Schmerzsituation sowie Richtigkeit und Angemessenheit der Schmerzbehandlung. Um die Patienten-Wahrnehmung der Qualität der Schmertherapie zu verbessern, sollten neue Wege gesucht werden auf welche Weise welche Patienten am Besten in den Entscheidungsprozess von Schmerzbehandlungen mit einbezogen werden können.

Schlussfolgernd, haben unsere prozeduren-spezifischen Analysen zum verbesserten Verständnis beigetragen welche Operationen im klinischen Alltag unzureichend schmerztherapeutisch versorgt werden. Nach vielen kleinen operativen Eingriffen wurden hohe Schmerzintensitäten berichtet, was häufig mit niedrigen Dosen verabreichter Opiate auf der Station im Zusammenhang stand. Diese Erkenntnisse können Krankenhäusern helfen ihre Behandlungsstrategien anzupassen und mehr auf Risikoeingriffe zu fokussieren. Der große Einfluss von jüngerem Alter und präoperativem Schmerz auf die postoperativen Schmerzen konnte in allen untersuchten Operationsarten gezeigt werden und sollte in Akutschmerz-Behandlungsprotokollen Beachtung finden. Zukünftig sollte die Qualität der Schmerztherapie sowie die optimalen Schmerztherapiekonzepte auch bei Operationen untersucht werden, die in Bezug auf postoperativen Schmerz bisher selten analysiert wurden,

CHAPTER 12

Publications

Scientific awards

Curriculum vitae

PUBLICATIONS

This thesis

1. **Gerbershagen HJ**
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SCIENTIFIC AWARDS

Scientific award of the German Society of Anesthesioloy and Intensive Care Medicine in 2011 ("Wissenschaftlicher Vortragswettbewerb") with the titel:

„Prozedure-specific quality comparison in postoperative pain treatment"

Scientific award of the German Pain Society in 2013 ("Förderpreis für Schmerzforschung") with the publication:

"Pain Intensity on the First Day after Surgery -
A Prospective Cohort Study Comparing 179 Surgical Procedures"

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CURRICULUM VITAE

Hans Jürgen Gerbershagen was born in Mainz, Germany. He studied medicine in Cologne, Manchester, and Cape Town and started his residency in anesthesiology and intensive care medicine at the University of Cologne. He finished his doctoral thesis at the Institute of Pathology at the University of Cologne. After a fellowship in chronic pain treatment at the Pain Clinic of the University of Cologne, he further specialized in palliative care medicine and graduated with a degree in health-care economics after a 2-year course. Following his board certification in Anesthesiology, he was certified as a Diplomate of the European Society of Anesthesiology (DESA). His research interest in perioperative pain was the topic of his doctoral thesis (habilitation) on chronic postoperative pain at the University of Cologne in 2011.

In 2009 he became a staff member and later senior attending physician of the department of anesthesiology at the University of Utrecht. To further develop his interest in clinical research, he followed a Master's program in epidemiology at the Julius Center for Health Sciences and Primary Care at the University of Utrecht. In addition to his interest in anesthesiology and pain management, he further specialized in intensive care medicine at the University of Utrecht.

At the beginning of 2015, he became head of the Department of Anesthesiology, Intensive Care, and Pain Medicine at the Marienhospital Gelsenkirchen in Germany.

Hans is married to Denise Gerbershagen and they have two children, Tobias and Felia.