Aspects of intrathecal morphine for postoperative pain relief in major orthopedic surgery.

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Aspects of intrathecal morphine for postoperative pain relief in major orthopedic surgery.

Aspecten van intrathecale toediening van morfine ter bestrijding van postoperatieve pijn bij orthopedische chirurgie aan heup en knie

(met een samenvatting in het Nederlands)**.**

Proefschrift

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The intrathecal route of morphine: why its clinical application in postoperative pain is still so limited

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Historical perspective

The isolation of morphine from opium by Seturner in 1803 and the introduction of the syringe and hollow needle to clinical practice by Wood in 1853 finally permitted opioids to be administered in carefully measured doses (Foldes 1964). Morphine was frequently used intramuscularly for preoperative medication as a supplement during ether and chloroform analgesia. In the late nineteenth century large amounts of morphine (1 to 2 mg/kg) were administered in divided doses intravenously, intramuscularly or both, as a complete anesthetic. Although initially popular, this technique was abandoned because of an alarming increase in operative morbidity and mortality. For the next 30 to 40 years, anesthesiologists rarely used narcotic analgesics intraoperatively. Introduction of ultra short-acting barbiturates as intravenous anesthetics and acceptance by anesthesiologists of the concept of balanced anesthesia renewed enthusiasm for the intraoperative use of opioids. In addition, opioids were used for postoperative analgesia by intramuscular or subcutaneous route (Miller 1986).

Systemically administered opioids: adverse effects

Presently, the most common method to bring about postoperative analgesia remains intramuscular or subcutaneous administration of opioids. However, these systemically, administered opioids cause a variety of adverse effects (table 1). Although a single effect - pain relief - is pursued, the incidence of adverse effects is high. Thus far, the ideal analgesic, powerful and devoid of adverse effects, remains to be found.

Table 1. The most common adverse effects of systemically administered opioids

Hypotension	Bradycardia	Respiratory depression
Nausea and vomiting	Constipation	Sedation
Drowsiness	Miosis	Physical dependence
Urinary retention	Dysphoria	

Opioid receptors

Over the last decades there has been a growing understanding of the mechanisms of action of opioids. The opioids receptors are found in the brain and spinal cord where they generate their analgesic effects. In 1973 three independent investigators described the presence of an opioid receptor in nervous tissue and hypothesized that endogenous substances probably stimulate this structure (Hughes 1973, Kosterlitz 1973, Terenius 1973). At this moment multiple types of opioid receptors are recognized. Specifically, the μ, κ, and δ types and their subtypes are recognized to mediate the analgesic effects of opioid drugs.

Alternative routes of administration of opioids, a peer review

The brain, the spinal cord and the spinal roots were considered as three potential major targets for pain control. When opioids are administered, the brain and spinal cord are the main site of action. For local anesthetics, the spinal cord and spinal roots are the target sites (table 2).

Table 2. The target site for analgesic action of opioids and local anesthetics.

	Brain	Spinal cord	Spinal roots
Intravenous opioids	+++	+	-
Intramuscular opioids	+++	+	-
Epidural opioids	++	++	-
Intrathecal opioids	+	+++	-
Intrathecal local anesthetics	-	++	+++
Epidural local anesthetics + opioids	++	++	+++
Intrathecal local anesthetics + opioids	+	+++	+++

For the opioids, the recognition of the importance of the sites of action resulted in the innovation of techniques and methods of administration: i.e. their regional application. Although opioid drugs can be administered in a selective fashion to the supraspinal structures selected, this approach is both difficult and hazardous. Moreover, the most frequent and dangerous adverse effects (see table 1) are caused by the supraspinal action of opioids. In contrast, the spinal cord is easily accessible by the conventional epidural

or intrathecal route. Likewise for local anesthetics these routes are customary and after such selective administration these drugs act at the nerves, nerve roots or spinal cord. Taken together, the epidural and intrathecal routes are logical for combined administration of opioids and local anesthetics.

The effects of perispinal opioids

In 1979, two reports acted as catalysts to promote further studies with spinal administered opioids. Wang et al. reported on the efficacy of intrathecal morphine to relieve unbearable malignant pain in 8 patients (Wang 1979). Behar et al. reported on the efficacy of morphine by epidural route in chronic pain patients (Behar 1979). Both authors pointed out that intrathecally-injected opioids are actually administered in close proximity to the opiate receptor site: i.e. at the place of effectiveness. After the first human administration of intrathecal morphine (Wang 1979), the effectiveness of opioids administered by the intrathecal route was studied for various painful conditions: i.e. malignant pain, chronic pain and postoperative pain. For treatment of malignant and chronic pain syndromes the use of intrathecal morphine gained rapid and general acceptance, particularly for patients who had used opioids by the oral route.

The aim of the intrathecal and epidural administration of opioids was to apply the drug as close as possible to the effector site in order to achieve maximal therapeutic effect with minimal adverse effects. The term "selective spinal analgesia" suggested by Cousins et al. (Cousins 1979) emphasizes the difference between analgesia obtained with relatively non-selective blockade of axonal conduction of local anesthetics and the highly selective actions of spinal opioids. Indeed, for intrathecal morphine the analgesic doses of morphine are only 1 – 2% of the systemic dose of morphine. Animal studies showed that intrathecal opioids are even effective after a dose of approximately 1/100 th. of the intravenous dose (Dirksen 1985). Thus, based on these data one may expect orthopedic surgical patients to be less drowsy, to recover faster and to be more co-operative after surgery. Moreover, the unique feature of intrathecally or epidurally administered opioids is the highly analgesic selective action with a nearly

complete lack of sensory (involving C and Aδ fibers), sympathetic, or motor block. This allows orthopedic surgical patients to ambulate without the risk of orthostatic hypotension or motor in-coordination that local anesthetics cause (intrathecal or epidural).

Unfortunately, the final result of selective administration by the perispinal route was not as ideal as expected. Specifically, a high incidence of nausea and vomiting, urinary retention, and itching was reported after intrathecal administration of opioids for postoperative pain relief (Carpenter 1992). Less common but extremely dangerous is the late respiratory depression that may occur 6 to 12 hours after intrathecal administration of opioids. It was recognized that the adverse effects following intrathecally-administered morphine (table 3) could be primarily explained by the action of opioids at supraspinal areas (Payne 1985). High doses of intrathecally-administered morphine are likely to progressively produce effects on systems other than the primary site of action. Thus regardless of the route, the administration of opioids may result in a dose-related manner adverse effects, including dangerous apnea.

Table 3. Adverse effects encountered after a single dose of intrathecal morphine for postoperative pain relief.

Postoperative nausea and vomiting
Urinary retention
Pruritus
Sedation
Respiratory depression
Constipation

Noteworthy, - and in addition to above mentioned adverse effects - there is no conclusive evidence that intrathecally injected opioids yield a higher quality of postoperative pain relief when compared to that produced by systemic opioids.

Taken together, the benefit of excellent postoperative pain relief after intrathecally administered morphine was observed in several clinical studies,

but the above mentioned adverse effects prove that the goal of a “selective spinal analgesia” has still not been achieved (optimal analgesic effect / minimal adverse effects).
In considering how to approach the goal “selective spinal analgesia” the physicochemical characteristics and dose of the selected opioids have to be considered.

Physicochemical characteristics

The distribution of intrathecally administered opioids between the water (cerebrospinal fluid) and fat (nervous structures, membranes) phase is determined by the hydro - / lipophilicity and the magnitude of the ionized fraction. Highly water-soluble drugs with large ionized fraction will linger in the water phase (CSF) and ascend rostrally. Therefore, the lipid solubility is an important property that contributes to the likelihood of respiratory depression. Moreover, lipophilic drugs with large unionized fraction will cross the lipid barriers fast and easily. Thereby, they will get access to the receptor sites and they will be eliminated fast, with little tendency to linger in the water phase.
Fentanyl and sufentanil are examples of the highly lipid-soluble opioids. It is in agreement with this property that these drugs show a rapid onset of action with minimal residual cerebrospinal fluid concentrations, which may ascend rostrally to the brain. In contrast, morphine is a typical water-soluble drug. Its slow onset of action after intrathecal injection coincides with a late peak concentration in cerebrospinal fluid. Its relative hydrophilicity results in slower efflux from the spinal cord and cerebrospinal fluid resulting in greater migration to the brain.
Although in apparent contradiction with the above, it is precisely the high degree of hydrophilicity that makes morphine the drug of choice for intrathecal administration. Its hydrophilicity underlies the long-term presence of the drug in the cerebrospinal fluid and thereby its long lasting analgesic effects up to 24 hours (Chauvin 1982) or more.

Optimal dose

Since the first human administration of intrathecal morphine in man in 1979 we are still looking for the optimal dose: the dose that will cause the best analgesia and the least adverse effects. This technique has been applied widely in anesthesia but the optimal dose of morphine to cause excellent analgesia with minimal adverse effects has still not been established. Noteworthy, it was soon recognized that the doses initially administered were indeed far too high, and gradually lower dosages were introduced.

Fig 1a. History of intrathecal morphine dose in total hip surgery (highest dose).

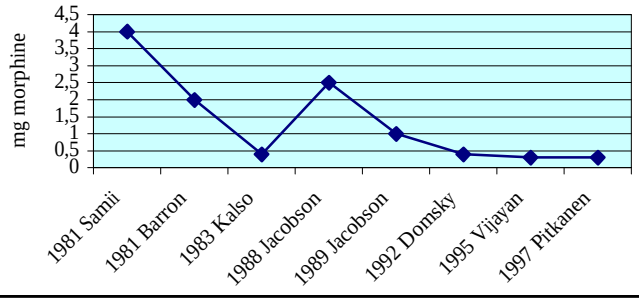
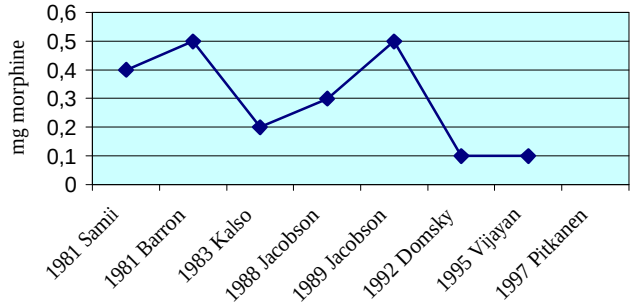


Fig 1b. History of intrathecal morphine dose in total hip surgery (lowest dose)



Dosages for intrathecal morphine found in literature range from 0.1 to 4 mg for total hip surgery (see figure 1a and 1b).

The goal is to achieve maximum analgesic effect with as little adverse effect as possible. This goal can be achieved by using the intrathecal route of

administration but not the oral, subcutaneous or intravenous route. Further improvement of the analgesic effect and minimizing the incidence of adverse effects can be pursued by: 1. studies that define the optimal dose of morphine in different types of surgery and 2. developing endorphino mimetic drugs, specifically tailored for perispinal use.

Chapter 2

Aim of the study

Aim of the study

Surgery and anesthesia are associated with postoperative sequelae such as pain, nausea and vomiting, drowsiness, sleep disturbances, respiratory and circulatory complications, hypothermia, urinary retention and other unfavorable experiences. The incidence of these sequelae is different in various surgical procedures. Orthopedic surgery is characterized by a high incidence of severe postoperative pain, urinary retention, and nausea and vomiting in the postoperative period (Carpenter 1992). Severe postoperative pain is known to adversely affect patient outcome after a variety of surgical procedures. (Jamison 1993, Ready 1996). Under treatment of pain may impede short-term recovery and may even have a detrimental long-term effect on health (Liebeskind 1991, Jänig 1994). Excessive analgesic drug administration may cause a high incidence of the above-mentioned adverse effects in the postoperative period. Therefore, appropriate pain management for postoperative patients may contribute to improved recovery and in orthopedic surgical cases to earlier mobilization, optimal early rehabilitation, a short postoperative hospital stay and a reduction in costs (ASA report 1995).

The Sint Maartenskliniek, Nijmegen is a 333 bed categorical hospital in the eastern part of the Netherlands and has traditionally specialized in Orthopedic Surgery. The operating room department has four operating rooms available. In 1996, when one anesthetist and a number of nurse anesthetists were available for clinical work in the operating rooms only, 3300 orthopedic surgical procedures were performed annually. From 1996 to 1999 there was an increase in orthopedic operations of 20 %. Nowadays, four anesthesiologists are working in the hospital, not only for clinical work in the operating rooms, but also involved in: the preoperative evaluation of patients in an out patient clinic; postoperative critical care and pain management; pain service for patients suffering from chronic pain; and, scientific research. This increase in activities has contributed to an improved quality of clinical care.

The postoperative pain management in the Sint Maartenskliniek has changed considerably in the last few years. In this thesis several clinical aspects of the change in postoperative pain management of major orthopedic surgery of the lower limb is described. In 1996 it was considered necessary to improve the postoperative management of pain, in order to reduce suffering of patients and to avoid of suboptimal conditions for rehabilitation of patients following orthopedic surgery. In view of the considerations given in the first chapter of this thesis, we considered whether to use the intrathecal or the epidural route of administration of opioids and local anesthetics. Several aspects were taken into consideration before a final conclusion was made. Two alternatives were specifically considered: the use of a continuous epidural catheter or the intrathecal administration of analgesics using a single shot technique (table 1).

Table 1. Differences of epidural catheter and intrathecal single shot technique

Properties of drugs	Epidural catheter	Intrathecal single shot
Onset of local anesthetics	Slow	Fast
Onset of morphine	Slow	Slow
Dosage of morphine	High	Low
Dosage of local anesthetics	High	Low
Technique		
Catheter	Necessary	Not necessary
Infusion pumps	Necessary	Not necessary
Technique failures	Possible	Rare

Table 1. continued.

Financial costs	Epidural catheter	Intrathecal single shot
Drugs	High	Low
Materials	High	Low
Manpower	High	Low
Education level	High	Low

Technique related side effects	Epidural catheter	Intrathecal single shot
Post spinal puncture headache	No	Yes
Late respiratory depression	Dependent on dose	Possible at low doses
Motor dysfunction after 24 hours	Yes	No
Problems 12 hours after induction	Technique failures	Respiratory depression
Perforation of dura	0.5% by catheter	100%
Unnoticed high block	Possible	No

Finally we have chosen the intrathecal single shot technique with bupivacaine and morphine. The main considerations that made us to select this technique were:

1. Fast onset to surgical anesthesia;
2. Adequate postoperative pain relief in the first hours following surgery;
3. Minimal need for extra additional manpower to assist in technical problems with continuous catheter techniques in the first 24 hours postoperatively;
4. Limited need for training of ward nurses with a new technique (epidural);
5. Cost/effectiveness.

Following our hypothesis that the intrathecal route – from the theoretical point of view – would be the optimal one for administration of morphine to achieve adequate post postoperative pain relief after major orthopedic surgery of the lower limb with a low incidence of adverse effects. Indeed analgesia was judged to be improved when compared to the pain relief regime in the past, using intramuscular opioids. Our ward nurses noticed an

unexpectedly high incidence of adverse effects. Especially nausea and vomiting, urinary retention, and itching were observed to be important drawbacks of the intrathecal opioid technique.

In considering this outcome we hypothesized that a reduced dose intrathecal morphine still produce similar pain relief scores but with minimization of the incidence of adverse effects.

To answer this question, a randomized, double-blind trial was undertaken to establish the optimum dose of intrathecal morphine in terms of adequate pain relief after total hip surgery and to evaluate whether the lowest effective dose indeed was associated with a reduction of adverse effects (Chapter 3). Two relevant practical aspects were specifically highlighted.
First, a major problem in the practical study design was that the pharmaceutical companies do not provide mixtures of local anesthetics and opioids for intrathecal application in man. We recognized that precisely defined dosing was necessary for this study. Therefore, we to designed and described the method of preparation of a morphine/bupivacaine mixture for intrathecal administration (Addendum).
Second, studies in experimental animals had suggested that pre-emptive analgesia might improve the quality of postoperative pain management (Brennan 1997). That's why we examined whether the severity of preoperative pain was related to postoperative pain levels and morphine intake in patients undergoing first hip replacement (Chapter 4).

Next to the evaluation of analgesic effectiveness, the aim of our studies was to study in detail the incidence of adverse effects and to evaluate which factors might contribute. Therefore, specific attention was paid to the most prominent adverse effects following orthopedic surgery and anesthesia: post operative nausea and vomiting (PONV), itching, and urinary retention.
One of the most distressing side effects related to the use of intrathecal morphine is postoperative nausea and vomiting (PONV). However, several factors affect the incidence and severity of this complication. Actually it is not known to which extent low doses of intrathecal opiates cause or

contribute to PONV? Therefore, we investigated the relationship of PONV and intrathecal opiate by comparing the incidence of PONV in patients who received intrathecal bupivacaine for surgery and postoperative pain relief to the incidence of PONV in patients who were given bupivacaine plus morphine. Since metoclopramide was found to be the best drug to reduce PONV after intrathecal anesthesia in orthopedic patients (Spelina 1984) we investigate the potential usefulness of this anti-emetic in the treatment of PONV in orthopedic patients who received intrathecal morphine (Chapter 5).

Another very disturbing adverse effect induced by intrathecal morphine is itching. This adverse effect was evaluated in Chapter 6.
In this study we addressed the following questions:

1) Is itching a dose dependent phenomenon following intrathecal morphine administration and is itching reduced following the lower doses of (0.025 – 0.2 mg) intrathecal morphine?
2) Does systemically administered morphine contribute to the problem of itching; and,
3) How well can itching, caused by low doses of intrathecal morphine, be managed by applying a standardized treatment using promethazine and - for intractable itch – naloxon (Chapter 6).

Another frequently observed adverse effect associated with surgery and anesthesia is urinary retention. Kamphuis et al. observed that the function of the lower urinary tract following intrathecal anesthesia remains disturbed long after the intrathecal regional blockade has worn off (Kamphuis 1998). This contributes to postoperative urinary retention and to postoperative discomfort. Evaluation of the filling of the urinary bladder in postoperative period by physical examination has always been an inaccurate method. Recent development allow for assessment of the volume of the bladder non-invasively and with reasonable accuracy by ultrasound (Coombes 1994). We considered that this measurement could be applied for a more logical approach to the decision whether to pass a urinary catheter in patients after

intrathecal anesthesia or not. This topic was investigated in a study using the BladderScan® in Chapter 7.

Chapter 3

Optimization of the dose of intrathecal morphine in total hip surgery: a dose finding study

This study has been published:

Optimization of the dose of intrathecal morphine in total hip surgery: a dose finding study. R. Slappendel, E.W.G. Weber, R. Dirksen, M.J.M. Gielen, J. van Limbeek. Anesth. Analg. 1999; 88 (4): 822-6.

Optimization of the dose of intrathecal morphine in total hip surgery: a dose finding study

Introduction

Many studies (Domsky 1992, Kalso 1983, Grace 1996, Reat 1989) have shown that intrathecal administration of morphine provides excellent postoperative pain relief in major orthopedic surgery. However use of spinal morphine was often associated with unpleasant side effects such as urinary retention, pruritus and postoperative nausea and vomiting (PONV) (Cousins 1984). Moreover, early studies reported late respiratory depression in some cases, but intrathecal doses of morphine as high as 2.5 mg were used (Reay 1989, Jacobson 1988, Gustafsson 1982).

The water-soluble nature of morphine contributes to the longevity of its analgesic effect, and allows the rostral ascent (Max 1985, Payne 1985) that underlies the risk of late respiratory depression. The cerebrospinal fluid opioid concentration is dose dependent (Nordberg 1984), as are both analgesia and respiratory depression (Bailey 1993). Profound and prolonged respiratory depression was reported by Bailey et al. (Bailey 1993). after an intrathecal dose of 0.6 mg, and minimal, yet statistically significant, respiratory depression occurred even after 0.15 mg morphine (Yamaguchi 1990).

We hypothesized that even lower doses might further minimize side effects, but were unclear whether these doses would offer the desired analgesic effect. For these reasons, a randomized, double-blind trial was undertaken to establish the optimum dose of intrathecal morphine that effectively relieves pain after total hip surgery and to evaluate whether the lowest effective dose indeed coincides with minimized side effects.

Methods

The study was approved by the ethical committee of our hospital and written informed consent was obtained from all patients. One hundred forty-three consecutive patients (ASA 1-3) scheduled for total hip surgery

during intrathecal anesthesia were included in the study in a prospective, randomized, double-blind manner.

All patients were premedicated with 5, 7.5, or 10 mg midazolam (0.1 mg/kg) orally one h before spinal anesthesia. Intrathecal anesthesia (27 gauge quincke needle) was produced by administering 20 mg bupivacaine plus morphine dissolved in 4 mL. Patients were allocated to four groups: Group I, 0.025 mg, Group II, 0.05 mg, Group III, 0.1 mg and Group IV, 0.2 mg morphine. The delivered morphine dose was known to the pharmacist in case of an adverse event.

The anesthesiologist administered 1 mg midazolam at the minimum interval of 5 min until the patient indicated that the desired sedation was achieved. Non-invasive blood pressure, heart rate (electrocardiogram), oxygen saturation (SpO_2), and respiratory frequency were continuously monitored during anesthesia and in the intensive care unit during the first 24 h after surgery.

In the post-operative period, all patients were treated with the nonsteroidal anti-inflammatory drug nabumeton 1500 or 2000 mg orally (first dose: one h before surgery), 1 dose a day (30 mg/kg). If nabumeton was contraindicated, oral paracetamol was given (70 mg/kg, 6 times a day). Pain was evaluated using visual analog scores (VAS. VAS ranges from 0 - 10; with 0 = no pain and 10 = most severe pain). For each individual patient we assessed the highest VAS score in the 24 h period and total pain VAS scores [area under the curve (AUC) of VAS scores in the 24 h period]. If pain was present morphine was administered intravenously by patient controlled analgesia (PCA) pump. The settings of the PCA pump (BRAUN®, Melsungen, Germany) were: baseline 0.0 mg/h, bolus dose 1.0 mg, bolus interval 5 min, maximum 30 mg dose per 4h.

PONV were treated according to the standard protocol. The first step was 10 mg metoclopramide intramuscularly, followed by 10 mg metoclopramide intramuscularly after one h when necessary. If symptoms persisted 1.25 mg droperidol was given, and finally 5 mg tropisetron both intravenously. Each step was initiated by patient request. The minimum interval between each step was one h. PONV was evaluated from the following data: 1) the

patient's subjective feeling (the presence or absence of subjective nausea); 2) the patient's request to be treated with an antiemetic; and, 3) the actual consumption of antiemetics.

Other side effects scored in the postoperative period included: respiratory depression (defined as breathing frequency below 10 per min and arterial blood gas showing acidosis and hypercarbia); itching (by specific inquiry and recording of the antipruritic medication (promethazine)); urinary retention (defined as absence of spontaneous voiding at 7 h after surgery and volume at catheterization of > 400 mL); hypotension (> 25% reduction of preoperative mean arterial blood pressure); and bradycardia (heart rate below 40 bpm). The presence or absence of any of these side effects was noted at 3 h intervals during the 24 h observation period. Also, the medication for treatment of any of these side effects was registered at the same intervals during the 24 h observation period.

Analysis of interval scored data as performed using analysis of variance techniques or t-tests (paired or unpaired respectively depending on data structure). Non-parametric techniques (Kruskall Wallis) were used when necessary. Post-hoc analysis was done by using the Duncan test with significance level of $p = 0.05$. Proportions were analyzed with Chi-square statistics and Fischer's Exact test. The alpha level for all analysis was set on $p=0.05$. Data are reported as means (SD).

Results

Demographic data and intraoperative factors are given in Table I. The four groups did not differ in age, height, weight or gender. Also, the patient groups were not different in any other characteristics; e.g.: the preoperative use of beta blockers; the magnitude of blood loss during surgery; the percentage of patients who got sedation during surgery; use of cementation and concurrent blood pressure drop.

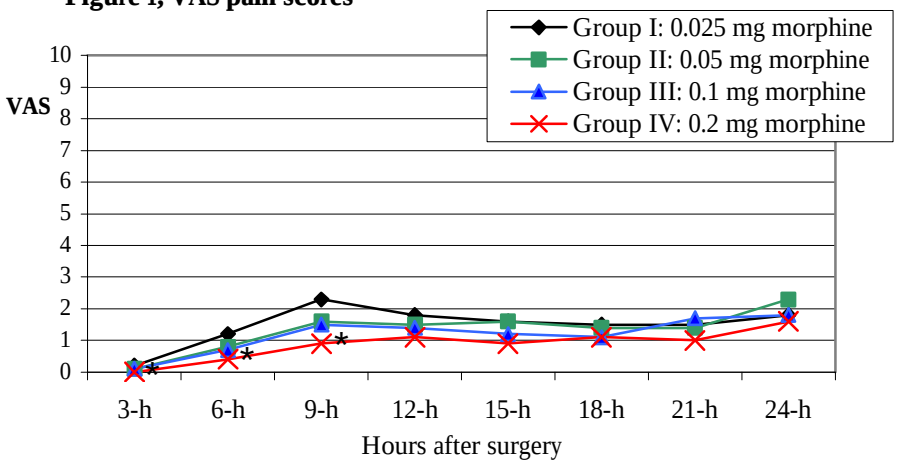
Table I. Demographic data and intraoperative factors.

Group	I	II	III	IV
Intrathecal morphine (mg)	0.025	0.05	0.1	0.2
N	35	37	37	34
Age (years)	63 (13)	66 (9)	62 (15)	63 (11)
Height (cm)	168 (8)	170 (8)	170 (7)	168 (9)
Weight (kg)	70 (11)	74 (14)	75 (11)	74 (14)
Gender (m.f)	12, 23	10 , 27	10 , 27	7 , 27
Sedation during surgery (%)	77.1%	86.5%	83.8%	85.3%
Beta blocker use preoperatively (%)	20.0%	18.9%	13.5%	14.7%
Intra operative blood loss (mL)	614 (290)	559 (305)	595 (261)	526 (260)
Cementation	77.1%	64.9%	56.8%	50.0%
Blood pressure drop following cementation	5.7%	8.1%	5.4%	5.9%

Age, height, and weight are given as mean (SD) values. n = number of patients, m = male, f =female. Blood pressure drop = > 25% reduction from preoperative mean arterial blood pressure within 5 min of the hip cementation.

As can be depicted from figure 1, VAS pain scores were below 3 in the postoperative period in all patients in all four groups.

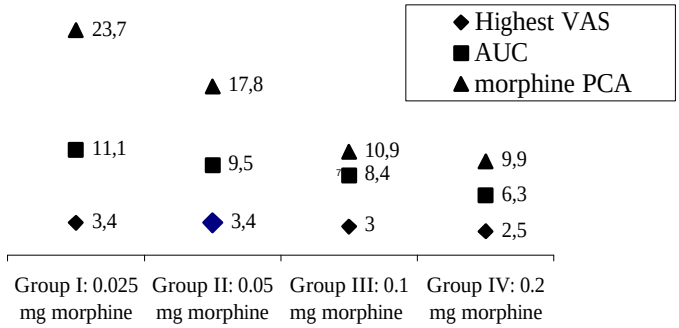
Figure 1, VAS pain scores



VAS pain scores during 24 h after surgery given as mean. VAS pain scores = visual analog scale 0 - 10; with 0 = no pain and 10 = most severe pain. *p<0.01, Fisher test.

The highest VAS score of each individual patient in the 24 h period and total pain VAS scores [area under the curve (=AUC) of VAS scores in the 24 h period] were highest for group I (figure 2).

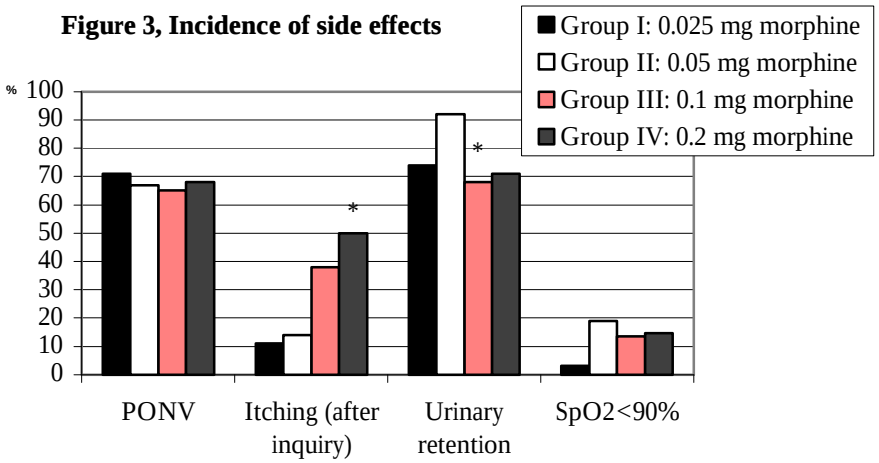
Figure 2, Pain scores and morphine use



Pain scores and morphine use. Highest VAS = highest individual VAS pain score during 24 h postoperative. AUC = area under the curve represents total VAS pain scores in the 24 h postoperative period. ** = statistical difference between group IV versus other group I and II, $p<0.0001$. Morphine PCA = dose of morphine in mg used in 24 hours after surgery by PCA pump.

These higher VAS scores were associated with a significantly higher consumption of systemic morphine in group I. The mean use of systemic morphine administered by the PCA infusion pump was in group I to IV, respectively: 23.7 mg, 17.8 mg, 10.9 mg and 9.9 mg (group I different from III and IV: $p<0.01$). Figure 3 shows the incidences of side effects in group I, II, III, and IV respectively. The incidences of PONV and urinary retention were not different among groups I, II, III and IV, nor was the consumption of antiemetics. The mean number of antiemetics used in all patients was 1.2 (1.1) , 1.2 (1.3) , 1.1 (1.2) and 1.3 (1.2) in groups I to IV, respectively. PONV occurred at a higher overall incidence during the first 24 h after surgery in women than men (incidence in women vs. men 77 and 44%, respectively; $p < 0.05$).

Figure 3, Incidence of side effects



Incidence of side effects during the first 24 h after surgery. PONV = postoperative nausea and vomiting. SpO_2 = transcutaneous oxygen saturation. *=$p<0.05$.

A respiratory rate below 10 breaths per min did not occur in any patient. Arterial oxygen saturation was monitored continuously. The incidence of desaturations below 90% is summarized in figure 3. The SpO_2 of all these patients increased when oxygen was administered (3 liter per minute by nasal catheter). Arterial blood gases sampled at such desaturations below 90 % did not show acidosis.

The incidence of itching was dose related as was the incidence of request for antipruritic medication.

Heart rates decreased 6 to 16 % in all groups after anesthesia, returning to baseline levels 12 h postoperatively. The incidence of hypotension was 48.6%, 56.8%, 54.0% and 73.5% of the patients ($p<0.05$, between group III and IV) in groups I to IV respectively.

Discussion

The major finding of this study is that the optimum dose of intrathecal morphine after total hip surgery is as low as 0.1 mg (group III). This dose resulted in excellent pain relief and a low demand for systemic morphine in the first 24 h after surgery. The higher dose of 0.2 mg intrathecal morphine

did not produce better analgesia, and the incidence of itching was higher and the degree of hypotension more profound and longer lasting. Intrathecal morphine doses below 0.1 mg were less effective.

Many studies have evaluated effects of intrathecal morphine for postoperative pain relief after surgery (Domsky 1992, Kalso 1983, Grace 1996, Reat 1989). These studies (Grace 1996, Reat 1989, Jacobson 1988) used higher doses of morphine (up to 2.5 mg) or included patients undergoing different types surgery (Jacobson 1988). In our study the site and type of surgery was restricted to total hip replacement surgery. Adequacy of morphine is reflected by VAS scores and systemic morphine demand from a PCA pump. After the 0.1 mg intrathecal morphine dose postoperative pain was effectively relieved during the first 24 h.

PONV showed similar overall incidences in all groups. In this study we confirm the high incidence of PONV after orthopedic surgery (Weber 1998, Carpenter 1992). Again PONV was not induced by these low doses of intrathecal morphine as found in our earlier study (Carpenter 1992).

A major concern with intrathecal morphine is respiratory depression. Intrathecal morphine has been shown to cause significant dose-related decreases in SpO_2 in human volunteers after doses of 0.2 – 0.6 mg (Bailey 1993). The time to depression of the slope of the ventilatory response to carbon dioxide curve show peak respiratory depressant effects following lumbar intrathecal morphine administration that concur with the moment of highest cervical cerebrospinal fluid concentrations found in another study (Max 1985, Payne 1985): i.e. at approximately four to five h after injection. After the lowest dose evaluated in this study (0.2 mg) mild respiratory depression effects were found in laboratory conditions (Bailey 1993). Whether similar changes in respiration were present in our clinical study is unclear. Likewise, others have failed to identify signs of respiratory depression in clinical conditions, provided that the intrathecal dose of morphine is restricted to doses less than 0.15 mg (Yamaguchi 1990). The inability to correlate such mild respiratory depressant effects with low intrathecal doses of morphine may well relate to the fact that a decrease in SpO_2 is a common phenomenon in elderly patients following both general and intrathecal anesthesia (Brown 1994). Also, not only intrathecal

morphine but a whole array of anesthetic drugs can contribute to respiratory depression. In a recent study eight cases of serious respiratory depression were detected from the charts of approximately 1600 patients who received systemic morphine by PCA (Etches 1994). Our elderly patients were premedicated and sedated with midazolam, intravenous morphine was administered by PCA pump and systemic antiemetic drugs (droperidol and/or metoclopramide) were used in the postoperative period. Yet, the magnitude and incidence of decreases in oxygen saturation were similar to those reported in another postoperative study in elderly patients not exposed to intrathecal morphine (Brown 1994). The key question is whether respiration after a total hip procedure is affected to a greater extent when intrathecal morphine is used than when it is left out. We point out that the mild respiratory depressant effects after 0.2 mg morphine intrathecally, represent an effect at a dose twice as large as the one that we defined as the optimum one. Also, any anesthesia technique affects respiration, and you can always argue that very large numbers of patients need to be studied to be sure that no respiratory depression after an intrathecal dose of 0.1 mg morphine. In our view monitoring in intensive care units is not required because of the administration of 0.1 mg intrathecal morphine, even in the opiate naive, elderly patient.

Another dose related intrathecal morphine side effect is itching, but it is easy to manage with a single dose of promethazine when necessary.

Patients in all groups showed, as expected, a decrease of heart rate and blood pressure after intrathecal anesthesia with bupivacaine and morphine use (Carpenter 1992). Only one patient in group I (the lowest dose of intrathecal morphine) had bradycardia. The blood pressure drop after 0.2 mg intrathecal morphine was more profound and longer lasting. In our earlier study (Weber 1998) we found that 16% of the patients developed bradycardia when the effect of intrathecal bupivacaine without morphine subsided in the postoperative period.

In summary, the intrathecal dose of 0.1 mg morphine added to bupivacaine gives excellent post-operative analgesia for total hip surgery. The earlier used higher doses of intrathecal morphine (Kalso 1983, Reay 1989, Jacobson 1988) (> 0.2 mg up to 2.5 mg) were more effective and can cause

unnecessary and dangerous side effects. In our view 0.1 mg intrathecal morphine added to bupivacaine provides excellent postoperative analgesia in the first 24-h, assists in hemodynamic stability, and will not cause significant respiratory depression. Finally, after this intrathecal morphine dose, there appears to be no need for routine intensive care-based recovery, even in elderly patients.

Chapter 4

The intensity of preoperative pain is directly correlated with the amount of morphine needed for postoperative analgesia

This study has been published:

The intensity of preoperative pain is directly correlated with the amount of morphine needed for postoperative analgesia. R. Slappendel, E.W.G. Weber, M.L.T. Bugter, R. Dirksen. Anesth. Analg. 1999; 88 (1): 146-8.

The intensity of preoperative pain is directly correlated with the amount of morphine needed for postoperative analgesia

Introduction

Studies have shown that severe postoperative pain can influence patient outcome after surgery (Jamison 1993, Ready 1996). Undertreatment of pain may impede short-term recovery and may even have a detrimental long-term effect on health (Liebeskind 1991, Jänig 1994). Appropriate pain management for postoperative patients contributes to earlier mobilization, shortened hospital stay, and reduced costs (ASA 1995). Preclinical studies in experimental animals suggest that preemptive analgesia might improve the quality of postoperative pain management (Brennan 1997). Although the beneficial effects of preemptive analgesia are less evident clinically (Collis 1995), severe pain syndromes, such as phantom limb pain may be reduced or even prevented by preemptive epidural blockade (Wall 1988). Thus, we may consider that preoperative pain can give rise to postoperative problems. The aim of this study was to examine whether the severity of preoperative pain is related to postoperative pain levels and morphine intake in patients undergoing first hip replacement.

Methods

The ethical committee of our hospital approved the study. Sixty consecutive patients suffering from osteoarthritis of the hip scheduled for first total hip surgery were included. Preoperative Visual Analog Scale (VAS) scores and analgesics were assessed one day before surgery. Three groups of patients were recognized: patients with mild pain (VAS score between 0 to 4), moderate pain (VAS score from 4 to 7), or severe pain (VAS score from 7 to 10).

All patients started a non-steroid antiinflammatory drug, nabumetone 2000 mg on the day of surgery, and continued this dosage for at least three postoperative days. All patients were premedicated with midazolam 5, 7.5,

or 10 mg (i.e. ± 0.1 mg/kg) orally one h before spinal anesthesia. All patients received intrathecal anesthesia with bupivacaine 20 mg and 0.1 mg morphine dissolved in 4 mL. At the patient's request further sedation was given using midazolam: 1 mg every 5 min until the desired level of sedation was achieved. In the postoperative period pain was treated with oral nabumeton 2000 mg once a day, starting on the day of surgery. A patient controlled analgesia (PCA) pump was connected immediately after surgery and set at the baseline infusion rate of 0.5 mg morphine/h, with bolus dosage 1 mg morphine at a minimum interval of 5 min.

Non-invasive blood pressure, electrocardiogram, transcutaneous oxygen saturation, and respiratory frequency were continuously monitored during anesthesia and in the intensive care unit during the first 24 h after surgery. All postoperative side effects; pain (VAS scores), postoperative nausea and vomiting, itching, urinary retention (> 400 mL), hypotension (decrease of mean arterial blood pressure to below 80% of its preoperative value) were registered during 3-h observation periods, as was the amount of morphine consumption by PCA pump.

Statistical analysis was performed using ANOVA, followed by Newman-Keuls post-hoc analysis when appropriate. P value less than 0.05 was considered as significant. Data are expressed as mean ± SD.

Results

Two patients were excluded from the study because their postoperative records were not complete. The group with pre-operative mild pain consisted of 12 patients, the group with moderate pain 18 patients, and the group with severe pain 28 patients.

Age, weight, height and preoperative intake of non-steroid anti-inflammatory drugs were not different among the three groups (Table 1). None of the patients used narcotics preoperatively. The incidence of postoperative side effects, nausea and vomiting, urinary retention, and itching showed no differences between groups. Respiratory depression did not occur in any patient.

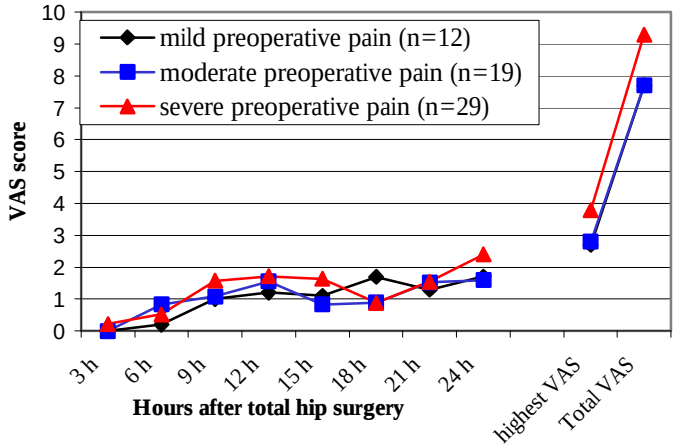
Table 1. Demographic data

	Mild preoperative pain (n=12)	Moderate preoperative pain (n=18)	Severe preoperative pain (n=28)
Gender M/F	1 / 11	2 / 16	7 / 21
Age (years)	62 (±10)	67 (±8)	62 (±11)
Height (cm)	168 (±8)	168 (±7)	168 (±7)
Weight (kg)	76 (±13)	69 (±12)	74 (±12)
NSAID use	40%	39%	40%

n = number of patients, M = male, F = female. Standard deviation between parentheses. No differences between groups.

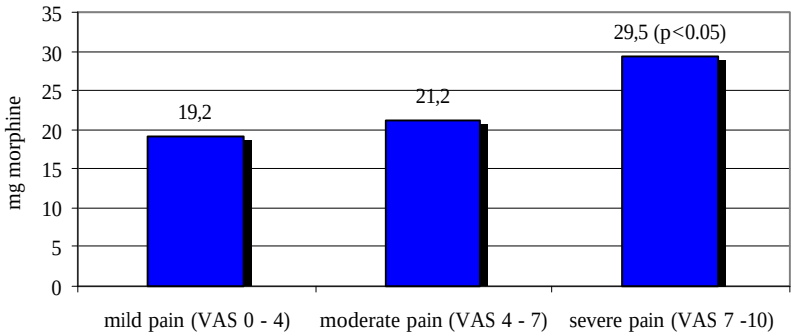
Excellent pain relief in the postoperative period was achieved in all groups (Figure 1). There were no differences between groups in VAS scores in any of the 3-h observation periods. Likewise the total VAS scores were not different. The morphine intake during the first 24 hours was different among three groups (ANOVA: $F(2.55) = 4.54$, $p=0.015$), and post hoc analysis showed the highest intake by patients in the severe pain group. The mean morphine intake was 19.2 mg (SD ± 8.3) in the mild pain group, 21.2 mg (SD ± 12.1) in the moderate pain group, and 29.5 mg morphine (SD ± 12.6) in the severe pain group in the first 24 h postoperatively (figure 2).

Figure 1. Post-operative pain scores



Pain VAS scores in relation with time after surgery. VAS = Visual Analoque Scale, 0 = no pain and 10 = most severe pain. Highest VAS = highest VAS score during 24 hours after surgery. Total VAS = The sum of the VAS scores at each of the eight times indicated. No statistical differences between groups.

Figure 2. Morphine by PCA pump



The mean amount of morphine intake by patient controlled analgesia (PCA) pump in the first 24 h postoperatively. VAS = Visual Analoque Scale, 0 = no pain and 10 = most severe pain. Severe pain group is significantly different from the mild and moderate pain group.

Discussion

This study shows, that patients with severe preoperative pain need an approximately 50 % higher morphine intake by PCA pump to attain the same level of postoperative analgesia in first 24 h after total hip surgery, than patients with mild or moderate preoperative pain. It also shows that patients want to lower their pain scores to the same range regardless of where these scores started from preoperatively.

Pain is an extremely complex process that involves the interaction of an array of neurotransmitters and neuromodulators at all levels of the neuraxis (Siddall 1997, Dirksen 1991, Willis 1991). A long duration of severe pain may change the processing of pain, for instance by involving pain memory and/or neuroplastic changes (Dirksen 1991, Neugebauer 1990). Identification of various receptors and processes that are involved in the transmission of pain at the spinal level, has led to the use of new agents and techniques in pain management (Siddal 1997). These include the use of preemptive analgesia and techniques such as intrathecal drug administration and epidural spinal cord stimulation (Siddall 1997, Coli 1993, Katz 1992). For example, the preoperative administration of sodium naproxen or intravenous morphine significantly reduces the analgesic requirements in the postoperative period (Coli 1993). Preemptive epidural morphine was found to be superior to epidural morphine given postoperatively for pain relief after lumbar laminectomy (Kundra 1997). Pre- or post incision administration of either intrathecal morphine or bupivacaine reduced hyperalgesia on the day of surgery (Brennan 1997). In our study all of these measures were included to minimize postoperative pain and postoperative morphine requirements: i.e. administration of nabumeton preoperatively, and presurgical intrathecal administration of bupivacaine and morphine. The relationship between preoperative pain level and postoperative morphine intake indicates that preoperative assessment of pain in an individual patient allows anticipation of the patient's needs; this can lead to better postoperative pain relief.

Our data contrast with those of a recent study on major joint surgery, where no such relationship was found (Jamison 1997). However, in their study five types of orthopedic surgery were included (total hip arthoplasty, total knee

arthroplasty, total hip revision, total knee revision and total knee bilateral), and as well as various preoperative diagnoses (osteoarthritis, rheumatoid arthritis, degenerative joint disease, avascular necrosis, juvenile rheumatoid arthritis and “other”). It is clear that differences in type of surgery and underlying diagnosis could affect the degree of postoperative pain. Further, their analysis consisted only of a questionnaire dealing with patient satisfaction filled in on the day of discharge.

In our view, severe chronic pain syndromes need specific attention by the anesthesiologist and other medical attendants. Preemptive analgesia in patients with severe chronic pain was found effective to avoid the postoperative pain problem of phantom limb (Wall 1988). Our study shows that perseverance of pain occurs in cases of the more common pain syndromes like osteoarthritis of the hip as well. To improve the quality of postoperative pain control, one may consider starting analgesic treatment in the preoperative period. We consider whether such improvement can be achieved by simple measures, e.g.: by doing total hip surgery in an earlier phase when pain is not yet severe; by extended pretreatment with non steroidal anti-inflammatory drugs, or by administration of a higher preoperative dose of intrathecal morphine. Perhaps specific attention to this aspect of the total hip procedure may improve the outcome.

Chapter 5

Intrathecal addition of morphine to bupivacaine is not the cause of postoperative nausea or vomiting

This study has been published:

Bijeffecten van intrathecaal morfine. R. Slappendel, E.W.G. Weber, R. Dirksen, M.J.M. Gielen. Nederlands tijdschrift voor Anesthesiologie. 1997; 10: 1-6.

and:

Intrathecal addition of morphine to bupivacaine is not the cause of postoperative nausea or vomiting. Weber EWG, Slappendel R, Gielen MJM, Dirksen R. Reg Anesth Pain Med 1998; 23 (1): 81-86.

and:

Intrathecal addition of morphine to bupivacaine. Letter to the editor. Weber EWG, Slappendel R, Gielen MJM, Dirksen R. Reg. Anesth. Pain Med. 1999; 24 (1): 94-95.

Intrathecal addition of morphine to bupivacaine is not the cause of postoperative nausea or vomiting

Introduction

Spinal opiates are frequently used for postoperative pain control in major orthopedic surgery of the lower limb (Törn 1994, Knudsen 1994, Kalso 1983). In our clinic, the intrathecal combination of a local anesthetic plus an opiate serves as an easy and cheap anesthetic technique which produces both excellent surgical conditions and excellent post operative pain relief. Moreover, the patients can ambulate quickly after surgery once the effect of the local anesthetic has worn off, as opiates do not impair motor function.

Despite the advantages of spinal opiates, bothersome side effects were described and these include respiratory depression, urinary retention, postoperative nausea and vomiting (PONV) and pruritis. The (late) respiratory depression causes concern, because it is hazardeous. However, it is extremely rare when small doses of intrathecal morphine are used (< 0.3 mg). In contrast, nausea and vomiting occur far more frequently in the postoperative period. These two bothersome side effects are attributed to the intrathecal use of opiates and not to local anesthetics (Morgan 1989, Yaksh 1981, Quinn 1994), although either symptom does occur in the absence of intrathecal opiates as well.

We had two questions. First, to which extent do intrathecal opiates cause or contribute to PONV? Therefore, we investigated the relationship of PONV and intrathecal opiate by comparing the incidence of PONV after intrathecal bupivacaine to the incidence of PONV after bupivacaine plus morphine. Metoclopramide was found to reduce PONV after intrathecal anesthesia in orthopedic patients (Spelina 1984). The second question relates to the use of metoclopramide for treatment of PONV: how effectively can the drug reduce the incidence of PONV after intrathecal morphine.

Methods

The study was approved by the ethical committee of our hospital and informed consent was obtained from all patients. Four hundred consecutive patients scheduled for major orthopedic surgery of the lower limb by intrathecal anesthesia were included in the study after an informed consent. All patients were premedicated with approximately 0.1 mg/kg midazolam (that is 5, 7.5, or 10 mg) orally one hour before spinal anesthesia. Patients were allocated to three groups. Group I consisted of the first 200 consecutive patients. Spinal anesthesia was produced in each of these patients by administering 20 mg bupivacaine plus 0.2 mg morphine solved in 4 mL, intrathecally. Group II consisted of the next 100 patients and spinal anesthesia was produced in the same way: by administering 20 mg bupivacaine and 0.2 mg morphine solved in 4 mL. In addition, each of patient of group II was treated with metoclopramide 20 mg intramuscularly after settlement of anesthesia and a second dose of 20 mg metoclopramide was administered intramuscularly after arrival at the recovery room. Finally, group III consisted of the next 100 patients. Spinal anesthesia was produced by the intrathecal administration of 20 mg bupivacaine only.

Adequate sedation was provided to each patient during the procedure: the anesthesiologist administered 1 mg midazolam at the minimum interval of 5 minutes untill the patient indicated that the desired sedation was settled. Non-invasive blood pressure, heart frequency (ECG), SpO_2, and respiratory frequency were continuously monitored during anesthesia and at the intensive care unit during the first 24 hours after surgery.

Pain: In the post-operative period, all patients were treated with the analgetic diclofenac 2 mg/kg orally, 3 doses a day. If diclofenac was contra-indicated oral paracetamol was given (50 mg/kg, 4 times a day). Pain was scored using VAS scores (0 - 10; with 0 = no pain). If pain was present (VAS score>3) morphine 0.14 mg/ kg was administered intramuscularly to a maximum of 6 times 10 mg per day.

Postoperative nausea and vomiting (PONV) was treated according to the standard scheme (figure 1). Each sequential step was adapted at the interval of 1 hour. Step 1 was the administration of 10 mg metoclopramide intramuscularly. When PONV persisted or recurred, the same dose of metoclopramide was administered i.m.. If PONV still persisted, 1.25 mg droperidol was given intravenously. Finally, if step 1 through 3 had not reduced PONV satisfactory then 5 mg tropisetron was given intravenously (step 4; figure I). Postoperative nausea and vomiting was evaluated from: 1. the patient's subjective feeling (the presence or absence of subjective nausea or actual vomiting was noted at the interval of 3 hours during 24 hours postoperatively); 2. the patient's request to be treated with an anti-emetic; and, 3. the actual consumption of antiemetics used.

Figure 1. Standardized treatment of postoperative nausea and vomiting with antiemetics during 24 hours after surgery.

first step:	10 mg metoclopramide intramuscular
second step:	10 mg metoclopramide intramuscular
third step:	1.25 mg droperidol intravenous
fourth (final) step:	5 mg tropisetron intravenous

Each step was started by patient's request. The minimum interval between each step was one hour.

Other side effects scored in the postoperative period included itching, urinary retention (defined as absence of spontaneous voidance of urine at 7 hours after surgery and the bladder content at catheterisation of > 400 mL), hypotension (> 20% reduction of preoperative mean arterial blood pressures), and bradycardia (heart rate below 40 beats per minute). The presence or absence of these side effects was noted at a 3 hourly interval during the 24 hour observation period. Also, the medication for treatment of these side effects was registered at the same interval during the 24 hour observation period.

Statistical analysis

Pain scores were analyzed using a one way ANOVA followed by Scheffé 's post hoc analysis. The incidence of PONV was analyzed by Fisher's exact test. P value less than 0.05 was considered as significant.

Results

Demographic data and the incidence of side effects are given in table I. The three groups did not differ for age, gender, and peroperative blood loss. Type and duration of the surgical procedures at the lower limb were similar for the three groups.

Table 1. Demographic data and side effects

	Group I	Group II	Group III
n	200	100	100
intrathecal bupivacaine	20 mg	20 mg	20 mg
intrathecal morphine	0.2 mg	0.2 mg	-
intramuscular metoclopramide	-	40 mg	-
mean age (SD) in years	64.5 (11.1)	65.5 (12.5)	66.6 (10.9)
site of operation (knee/hip %)	24.5% / 75.5%	30% / 70%	17%/83%
Itching %	51.5%	53%	3%*
Urinary retention % (> 400 mL)	63.8%	64.3%	78.6%
Hypotension	42%	40%	35%
Bradycardia	0%	0%	16%*

n = number of patients *=P<0.001. Further explanation see text.

Pain

As can be depicted from the VAS scores given in table 2 excellent pain relief was present in the post operative period for all patients in group I and II. Highest pain VAS scores (i.e. comparing the highest VAS score of each individual patient in the 24 hour period) and total pain VAS scores (area under the curve (=AUC) of VAS scores in the 24 hour period) were highest for group III. Highest VAS scores: $F(2.396) = 32.92$, $p < 0.001$; Scheffé's post hoc: group III different from group I and II, and AUC VAS scores: $F(2.396) = 54.14$, $p < 0.001$; Scheffé's post hoc: group III different from group I and II (see Table 2).

Table 2. Mean VAS pain scores during 24 hours after surgery

hours after surgery	3	6	9	12	15	18	21	24	HV	AUC
Group I	0.05	0.31	0.73	0.81	0.66	0.72	0.66	0.71	1.8	11.5
	(0.35)	(1,32)	(1,63)	(1.54)	(1.53)	(1.62)	(1.39)	(1.39)	(0.2)	(1.2)
Group II	0.05	0.38	0.77	0.82	0.80	0.40	0.66	0.51	1.6	11.7
	(0.29)	(1.13)	(1.51)	(1.54)	(1.65)	(1.21)	(1.52)	(1.17)	(0.2)	(2.0)
Group III	0.49**	2.14**	2.52**	2.27**	1.95**	0.86	1.03**	1.61**	3.8*	35.5*
	(1.24)	(2.27)	(2.19)	(1.98)	(1.84)	(1.21)	(1.27)	(1.74)	(0.2)	(2.4)

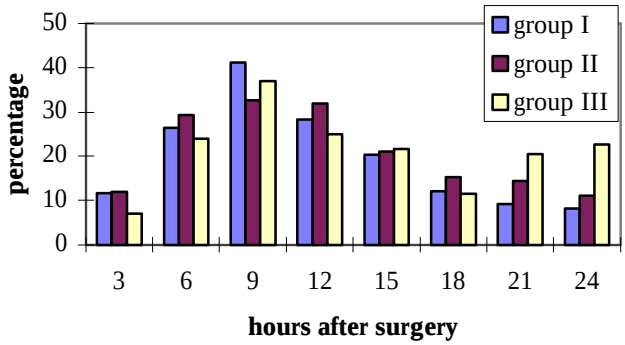
Standard deviation between arrows. HV = mean of highest individual VAS scores during 24 hours postoperative. AUC = area under the curve of VAS scores in the 24 hour period postoperative. * = statistical difference between group III versus group I, and II, $p<0.0001$. ** = statistical difference between group III versus group I, and II, $p<0.001$. Further explanation see text.

These higher VAS scores occurred even though a relevantly and significantly higher consumption of systemic morphine was noted for patients treated with bupivacaine alone (group III) compared to those of group I and II (bupivacaine plus morphine).

Postoperative nausea and vomiting (PONV)

Patients subjective feeling every 3 hours postoperatively showed no statistical differences between groups. The maximum PONV percentages were 41.1%, 32.7% and 37% respectively, which all were reached 9 hours after surgery (Figure 2, Table 3). The consumption of antiemetics was similar in all groups. The number of patients who needed one or more antiemetics during the first 24 hours after surgery was 112 (56.6%), 57 (58%) and 60 (60%) in group I, II and III respectively. The mean number of antiemetics used in all patients was 1.1 (SD 0.97) , 1.1 (SD 0.86) , and 1.2 (SD 1.06) , in group I, II, and III respectively. The mean number of antiemetics used in patients with PONV was 1.9, 1.9, and 2.0 respectively.

Figure 2. PONV percentage



PONV = postoperative nausea and vomiting

Table 3. PONV percentages during 24 hours after surgery

hours after surgery	3	6	9	12	15	18	21	24
Group I	11.7%	26.4%	41.1%	28.3%	20.4%	12.1%	9.2%	8.2%
Group II	12.0%	29.3%	32.7%	32.0%	21.1%	15.2%	14.5%	11.1%
Group III	7.0%	24.0%	37.0%	25.0%	21.6%	11.6%	20.5%	22.6%

Patient's subjective feeling of PONV every 3 hours postoperatively

Other side effects:

Itching mainly occurred in patients treated with intrathecal morphine: the incidence was 51.5% (group I) and 53% (group II), in contrast to only 3% in group III ($p<0.001$). The incidence of urinary retention (defined as absence of spontaneous voidance of urine at 7 hours after surgery and the bladder content at catheterisation of > 400 mL) was 63.8%, 64.3% and 78.6% in group I,II and III respectively. Hypotension (defined as decrease > 20% from base line level) was present in 42%, 40% and 35% in groups I,II and III respectively. As can be depicted from table I, bradycardia (heart rate below 40 bpm) presented in group III only, and had the incidence of 16%, which seemed statistically different ($p<0.001$). Typically, bradycardia presented in the very same period that motor function recovered.

Discussion

The main finding of this study is that the incidence of postoperative nausea and vomiting was not different for the three groups of patients. This means that the notion that intrathecal morphine is a main cause for postoperative nausea and vomiting is not valid. Also, the present mode for treatment of PONV is without effect. These findings and outcome of three modes of anesthetic treatment of patients subjected to major orthopedic surgery of the lower limb are discussed further.

This study confirms the combined administration of intrathecal morphine and bupivacaine that results in excellent surgical conditions, also produces excellent postoperative pain relief during at least 24 hours. However the only side effect definitely caused by intrathecal morphine is itching which is easy to treat.

In earlier studies (Törn 1994, Knudsen 1994, Kalso 1983, Morgan 1989) the incidence of PONV after intrathecal morphine in major orthopedic surgery was between 50% and 65%. We confirm the generally high incidence of PONV that proved especially high after orthopedic surgery (Quinn 1994) in all our groups. In their reports, the various authors seemed to imply that it is the intrathecal morphine that caused PONV. Our study shows no relationship between the use of intrathecal morphine and the hight of the incidence of PONV, even though postoperative nausea and vomiting occurred in high frequencies in all our groups and the incidence was equal to above mentioned studies. Therefore, we propose that intrathecal morphine did not attribute to PONV.

In a study of Carpenter (Carpenter 1992) a lot of possible variables were able to influence the development of PONV. The variables gender, height, hypertension, history of carsickness, base line heart rate, position for spinal puncture, type of local anesthetic, dose of anesthetic, were able to influence PONV, but were kept all constant in our study. The highest frequency PONV occurred 9 hours after surgery, which can be an argument that intrathecal medicaments caused PONV. Regarding our results PONV was not induced by intrathecal morphine, and was more likely due to type and dose of local anesthetic.

Low dosages of metoclopramide are ineffective to reduce PONV after intrathecal anesthesia in orthopedic patients (Spelina 1984). In the higher dosages we used metoclopramide it was not effective to treat PONV, in contrast to the study of Knudsen et al (Knudsen 1994). They found a reduction in the incidence of PONV from 58% to 17% after 40 mg metoclopramide intramuscularly. However the presence of PONV was recorded up to five hours after surgery. The anti-emetic properties of metoclopramide result centrally from its blockade of dopamine receptors of the chemoreceptor trigger zone, in higher doses antagonism of the central 5-HT_3 -receptors and peripherally from its stimulation of gastric and small bowel motility, thereby preventing the gastric stasis and dilation that are part of the vomiting reflex (Schulze-Delrieu 1981). However, it is not expected that intrathecal morphine or bupivacaine cause a decrease in gastric or small bowel motility. So it can be concluded that central action of metoclopramide (antagonism of dopamine and 5-HT_3 -receptor) did not reduce PONV after intrathecal morphine or bupivacaine. Besides dopamine and 5 HT_3 -receptors, muscarinic cholinergic and histamine receptors play a role in mediating the emetic response Watch 1992). Recently one study (Moscovici 1995) and one correspondence (Ramaioli 1996) suggested that central administration of anticholinergic drugs indeed reduce PONV, after epidural or intrathecal anesthesia with bupivacaine and morphine. Thus, we consider whether another type of local anesthetic, a lower dose of intrathecal local anesthetic, lower peak block heights, or centrally administered cholinergic drugs can help to produce the lower incidence of PONV.

In conclusion, intrathecal morphine added to bupivacaine is superior to intrathecal bupivacaine alone for major orthopedic surgery. It is a cost effective technique that minimizes the use of analgesics and disposables in the per- and postoperative period. Also, there is no need for catheters, infusion pumps or PCA pumps. Moreover, the excellent post-operative analgesia and hemodynamic stability are arguments to choose this anesthetic technique. Despite these benefits, one has to cope with some at times bothersome side effects. This study focussed the side effect postoperative nausea and vomiting. There is ample reason to relate PONV and 0.2 mg

intrathecal morphine. Also, present treatment of PONV proved unsatisfactory and difficult.

Chapter 6

Itching after intrathecal morphine
Incidence and treatment

This study has been submitted to the European Journal of Anesthesiology.
Robert Slappendel , Eric W.G. Weber, Bart Benraad, Jacques van Limbeek, Ris Dirksen.

Itching after intrathecal morphine
Incidence and treatment

Introduction

Intrathecal opiates are often used for postoperative pain control in major orthopedic surgery of the lower limb (Domsky 1992, Kalso 1983, Grace 1996, Reay 1989). In our clinic, the intrathecal combination of a local anaesthetic and an opiate serves as an easy and cheap anaesthetic technique which produces both excellent surgical conditions and excellent post operative pain relief. Moreover, the patients can ambulate quickly after surgery once the effect of the local anaesthetic has worn off, as opiates do not impair motor function.

Earlier studies used intrathecal morphine in doses up to 2.5 mg morphine, and many side effects were reported, including the dangerous late respiratory depression (Reay 1989, Jacobson 1988) and the more harmless but at times extremely bothersome side effects of postoperative nausea and vomiting, urinary retention and itching. The incidence of post operative nausea and vomiting, or urinary retention were unrelated to intrathecal morphine when doses of 0.2 mg are used (Weber 1998). In this study we evaluated whether the incidence and severity of itching can be minimised by adapting the low dose range of intrathecal morphine. Our questions were: 1) is itching a dose dependent phenomenon and is its incidence less after the lower doses of the range of 0.025 – 0.2 mg morphine intrathecally; 2) does systemically administered morphine contribute to the problem of itching; and, 3) how well can we control itching caused by low doses of intrathecal morphine by applying a standardised treatment using promethazine and - for intractable itch - naloxon.

Methods

The study was approved by the ethical committee of our hospital and written informed consent was obtained from all patients. Finally hundred forty three consecutive patients scheduled for total hip surgery by intrathecal anesthesia were included in the study after an informed consent.

All patients were premedicated with 5, 7.5, or 10 mg midazolam (approximately 0.1 mg/kg) orally one hour before intrathecal anesthesia. Intrathecal anesthesia was produced in each of these patients by administering 20 mg bupivacaine plus morphine solved in 4 mL, intrathecally. Intrathecal puncture was performed in a sitting position. Patients were allocated and randomized to four groups in a double blind manner: Group I, 0.025 mg (0.00625 mg/mL), Group II, 0.05 mg (0.0125 mg/mL), Group III, 0.1 mg (0.025 mg/mL) and Group IV, 0.2 mg (0.05 mg/mL) morphine. The morphine dose was only known to the pharmacist. Adequate sedation was provided at patient request during the procedure: the anaesthesiologist administered 1 mg midazolam at the minimum interval of 5 minutes until the patient indicated that the desired sedation was settled. Non-invasive blood pressure, heart frequency (ECG), SpO_2, and respiratory frequency were continuously monitored during anesthesia and at the intensive care unit during the first 24 h after surgery.

Itching In the postoperative period the presence of itching, and treatment for itching were noted every 3 hours by nurses at the intensive care ward. Itching was treated by a standardised protocol. In brief, the need for relief of itching was indicated by the patient. Thus, only on request of the patient, treatment of itching was initiated with a first dose of 25 mg promethazine intramuscularly. If itching had not diminished within 1 hour after this intramuscular injection, 0.12 mg naloxon was given subcutaneously. If itching diminished but returned after a period longer than one hour, intramuscular injection with promethazine was repeated once. If itching did not diminish after an subcutanous injection of naloxon an continuous intravenous drip with naloxon was started at 5 μg/kg/h. The severity of itching was estimated from the requirement of treatment, and we recognised three categories: mild = only present after inquiry, moderate = need for promethazine, severe = need for naloxon.

Pain: In the post-operative period, all patients were treated with the analgesic nabumeton 30 mg/kg orally, 1 dose a day (1000 mg, 1500 mg or 2000 mg). Pain was evaluated using VAS scores (0 - 10; with 0 = no pain). If

pain was present morphine was administered intravenously in a patient controlled manner. The settings of the PCA (patient controlled analgesia) pump (BRAUN®, Melsungen, Germany): baseline 0.0 mg/hour, bolus dose 1.0 mg, bolus interval 5 minutes, maximum 30.0 mg per 4 hours.

Other side effects. The presence or absence of other side effects (post operative nausea and vomiting (= PONV), urinary retention, sedation) was noted at a 3 h interval during the 24 h observation period. Also, medication to treat these side effects were registered at the same interval during the 24 h observation period.

Statistical analysis Pain scores were analysed using a one way ANOVA followed by Scheffé 's post hoc analysis. The incidence of PONV was analysed by Fisher's exact test. P value less than 0.05 was considered significant. Incidences of and the severity of itching was analysed by chi-sqaure tests. The adjusted standardized residuals indicate the contribution of each cell of the table to the significance of the purposed differences. The duration of itching was calculated and analyzed by means of an anova with a Scheffé 's post hoc test.

Results

Demographic data are given in table 1. The four groups did not differ for age, length, weight or gender. Likewise other variables, e.g. preoperative use of beta blockers, peroperative blood loss, percentages of patient's which got sedation during surgery, use of cementation, and blood pressure drop (> 25% decrease in MAP after cementation) showed no differences among the groups.

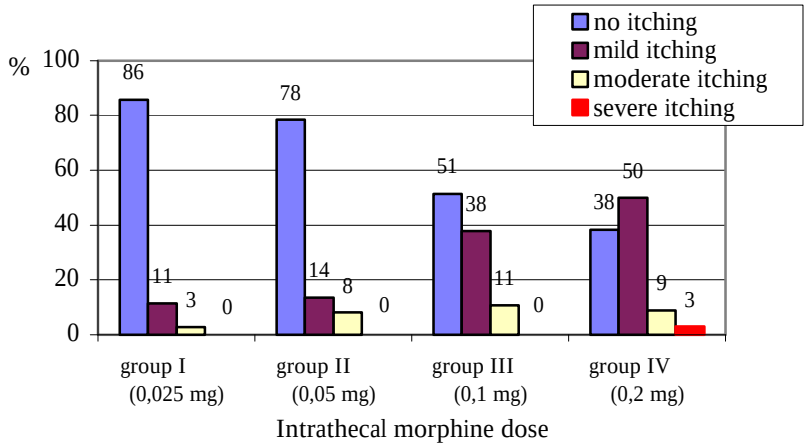
Itching Itching occurred in all groups. The overall incidence of itching was related to intrathecal morphine dose (figure 3) and time after surgery (figure 4). The overall incidences of itching were: 14.3%, 21.6% , 48.6% and 61.7% in group I, II, III, and IV respectively.

Table 1. Demographic data and intraoperative factors.

Group	I	II	III	IV
Intrathecal morphine	0.025	0.05	0.1	0.2
n	35	37	37	34
Age in years	62.6 (12.8)	65.9 (8.9)	61.9 (15.2)	62.9 (11.3)
Length in cm	167.6 (7.8)	169.5 (8.2)	169.7 (7.4)	167.9 (8.6)
Weight in kg	69.5 (11.4)	73.5 (14.1)	74.9 (10.9)	74.2 (13.6)
Gender (m/f)	12/23	10/27	10/27	7/27

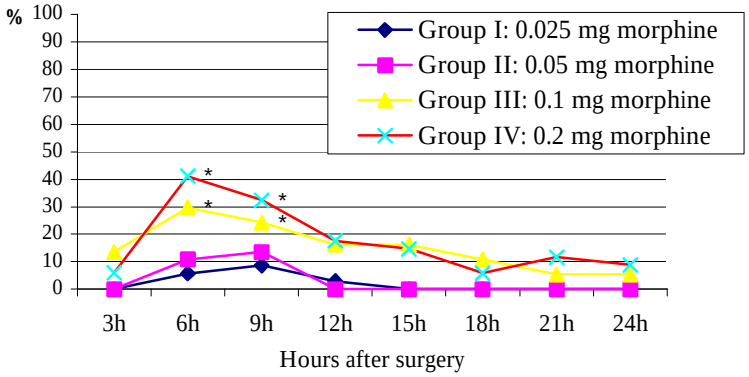
Age, length, and weight are given as mean values, standard deviation in parentheses. n = number of patients, m = number of men, f = number of female. Standard deviation in parentheses.

Figure 3. Incidence and severity of itching



Incidence and severity of itching in four groups. Mild itching = only present after inquiry, moderate itching = need for promethazine, severe itching = need for naloxon). * indicates statistical differences between group III and IV versus group I and II. For details see text.

Figure 4. Incidence of itching



Incidence of itching related to time after surgery. * indicates statistical differences between group III and IV versus group I and II. For details see text.

The adjusted standardized residuals indicate a trend over group I to IV respectivly varying from -3.1, -2.2, 1.8 to 3.3 in favor of itching (chi-square = 22.74; df = 3; p = 0.00005). The incidence of itching was related to time after surgery. Highest (time related) incidences of itching were found 6 to 9 hours after surgery (figure 4). The mean duration (hours) of itching in patients who itched was: 3.6, 3.4, 7.5, and 6.7 in group I, II, III, and IV respectively. A post hoc comparison between groups revealed that the duration of itching only differed between group I and II versus group III and IV respectively (F = 11.27; df (3,142); p = 0.0000). Both the need for treatment (figure 3) and the mean hours of itching (table 2) increased with the intrathecal morphine dose.

Table 2. Mean hours of itching

	Group (n)	Itching (n)	Mean hours of itching	Total hours of itching
Group I: 0.025 mg morphine	35	5	3.6	18
Group II: 0.05 mg morphine	37	8	3.4	27
Group III: 0.1 mg morphine	37	18	7.5	135
Group IV: 0.2 mg morphine	34	21	6.7	141

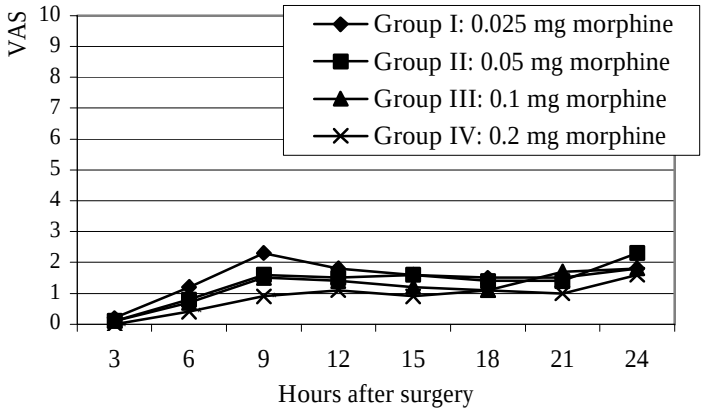
n = number of patients.

Patients who experienced itching used significantly less systemic morphine (n = 52; 11.7 (± 11.7) mg morphine) then those patients who did not have itching at all (n=91; 18.0 mg (± 14.3) morphine, t = 2.71; df = 139; p = 0.008). In our population of patients we found no relation between age, gender, weight and the incidence of itching.

Pain

As can be depicted from the VAS scores given in figure 5, excellent pain relief was present in the post operative period for all patients in all groups. The mean use of systemic morphine administered by PCA infusion pump was in group I to IV respectively: 23.7 mg; 17.8 mg; 10.9 mg; and, 9.9 mg. A statistical difference is present between group III and IV versus group I, $p<0.01$. No correlation was found between VAS scores and itching.

Figure 5. VAS pain scores



Other side effects

Respiratory depression (defined as breathing frequency below 10 per min and arterial blood gas showing acidosis and hypercarbia) did not occur in all groups. Incidences of PONV were 34.3%, 45.9%, 37.8% and 41.2% in group I, II, III, and IV respectively. The incidence of urinary retention (defined as absence of spontaneous voidance of urine at 7 hours after surgery and the bladder content at catheterisation of > 400 mL) was 74.2%, 92.0%, 67.6% and 70.6% in group I, II, III and IV respectively. There were no differences among the four groups for these two side effects and there was no correlation between PONV, incidence and degree of sedation or urinary retention with itching.

Discussion

This study shows clearly, that intrathecal injection of morphine in human beings results in itching and the incidence of this effect increased in a dose dependent fashion in the dose range of 0.025 – 0.2 mg intrathecal morphine. Itching responded well to the antihistaminic drug promethazine in the dose of 25 mg intramuscularly.

In our study the incidence of itching is found to increase in a dose related fashion. The incidence of itching after intrathecal morphine in our study

(14.7 to 61.3%) was similar to that earlier reported in the elderly orthopedic patient (Jacobson 1988, Weber 1998). The incidence of itching after intrathecal bupivacaine alone (without added morphine) was 1% in an earlier study in 100 patients (Weber 1998). Even higher incidences and a greater intensity of itching were found in young women after elective caesarean section (Alhashemi 1997, Cardosos 1998, Milner 1996). However, we have not found a relation between gender or age to the incidence of itching in the population studied. The incidence of itching was not found to relate to the dose in the study of Milner who compared 0.1 and 0.2 mg intrathecal morphine after elective caesarean section (Milner 1996). Yet, our findings are based on inquiry every three hours, which seems to be the best way to establish the incidence of itching (Pinckaers 1980, Dirksen 1980).

Highest incidences of itching were found 6 to 9 hours after surgery (figure IV), i.e. 7.5 to 10.5 hours after intrathecal injection. The kinetics of the liquor flow (Partain 1978) and the delay between moment of injection and itch are consistent, which suggests that supraspinal centrally located morphine receptors mediate itching. In accordance with this notion are data of animal studies (Thomas 1993, Tohda 1997) which implied opioid receptors in the medullary dorsal horn in an itch-like phenomenon. Noteworthy, centrally induced itch is always sensed in the skin, and thereby itch is caused by systemic administration of morphine. Here, itching has an incidence of approximately 1% (Weber 1998), and it may relate to morphine's ability to cause release of histamine (Hermens 1985).

We do not expect that the administration of an antihistaminic drug is causal therapy for centrally induced itching. Nevertheless, it was highly successful in most patients. Only in one patient in group IV 25 mg promethazine was insufficient on its own and naloxon was needed. Several drugs (e.g. droperidol, propofol, diphenhydramine) have been used without success in clinical studies (Alhashemi 1997, Horta 1996, Warwick 1997). Nalbuphine (Alhashemi 1997) effectively relieved itching by intrathecal morphine, but resulted in higher pain VAS scores. Ondansetron is only used in case reports to treat itching (Larijani 1996).

We conclude that even after low doses of intrathecal morphine the incidence of itching is high and typically dose related to intrathecal

morphine. When necessary it is easy to treat by administration of promethazine 25 mg intramuscularly.

Figure 1. Standard operating procedure for the evaluation of itch.

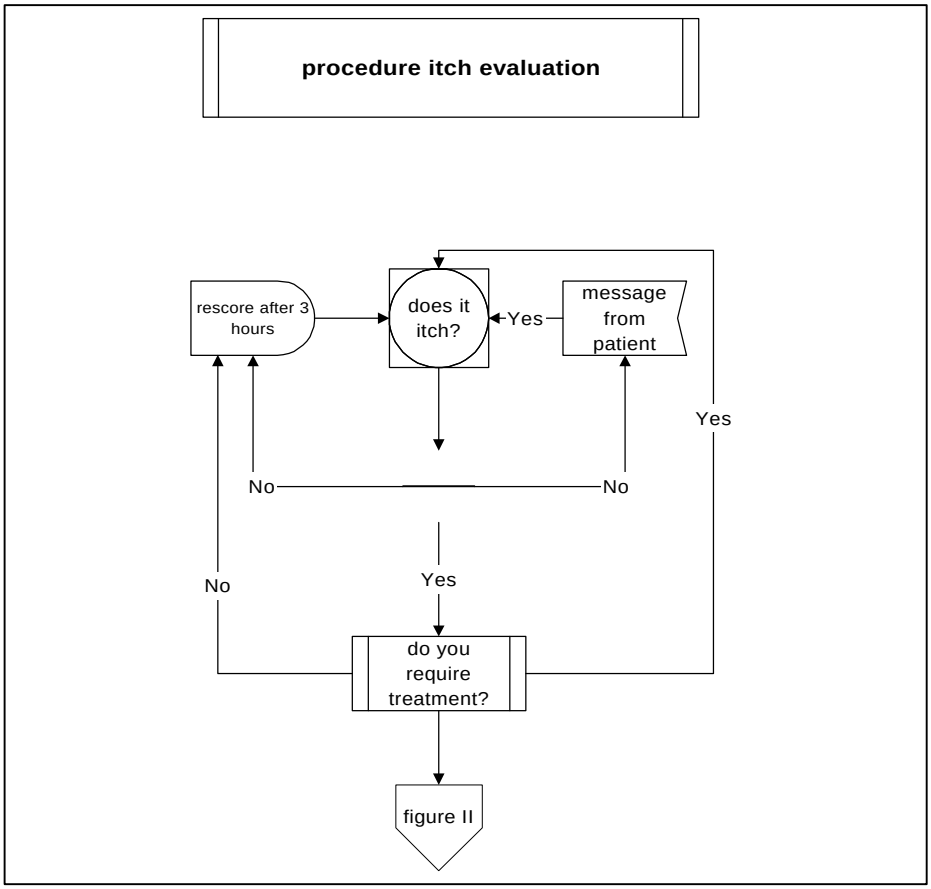
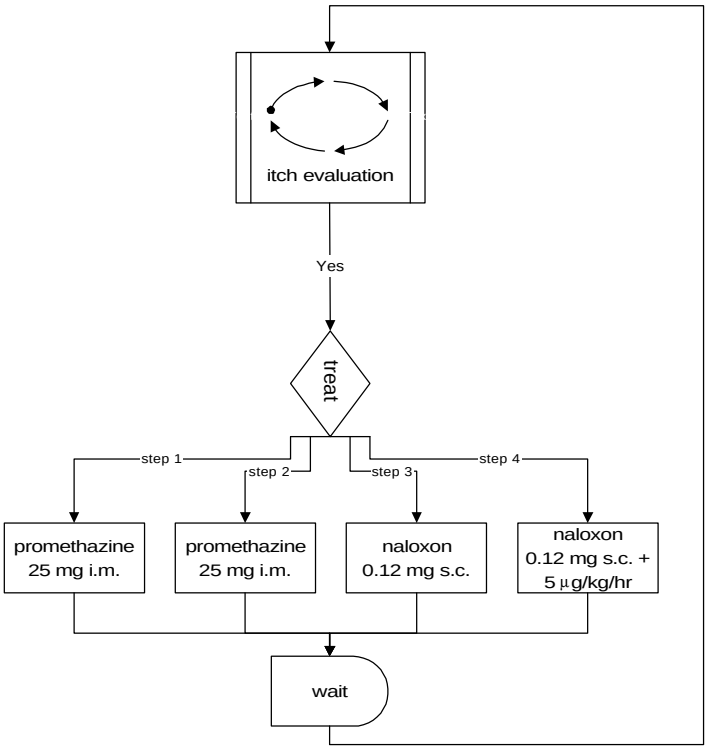


Figure 2. Flowchart for itch evaluation and the four steps of treatment.



Chapter 7

Non-invasive measurement of bladder volume as an indication for bladder catheterization after orthopedic surgery and its effect on urinary tract infections

This study has been published:

Non-invasive measurement of bladder volume as an indication for bladder catheterization after orthopedic surgery and its effect on urinary tract infections. R. Slappendel, E.W.G. Weber. European Journal of Anaesthesiology 1999; 16: 503-506.

Non-invasive measurement of bladder volume as an indication for bladder catheterization after orthopedic surgery and its effect on urinary tract infections

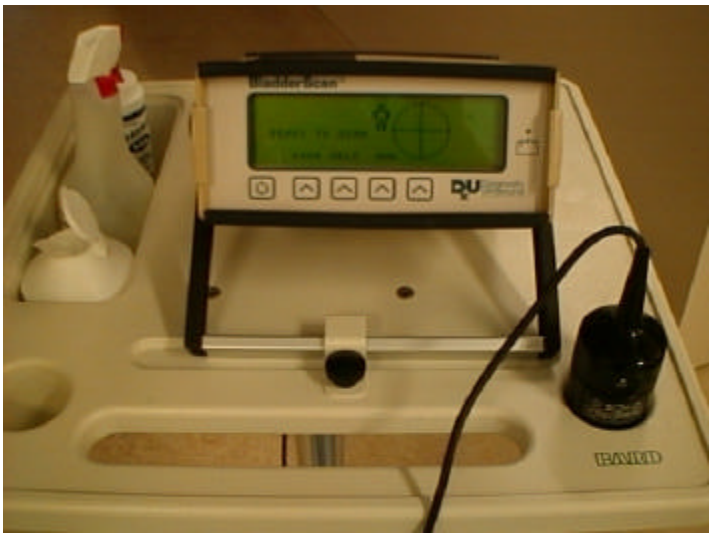
Introduction

Our hospital specializes in elective orthopedic surgery. In our experience, the two most common short-term complications are nausea and vomiting and urinary retention, both of which occur in about 10% of patients. Now that the volume of the bladder can be measured non-invasively and with reasonable accuracy by ultrasound (Coombes 1994), we wondered if this measurement could be used for a more logical approach to the decision to pass a urinary catheter. We studied the number of urinary catheters used and number of urinary tract infections in two periods, one before and one after the introduction of ultrasonic measurement by the BladderScan®.

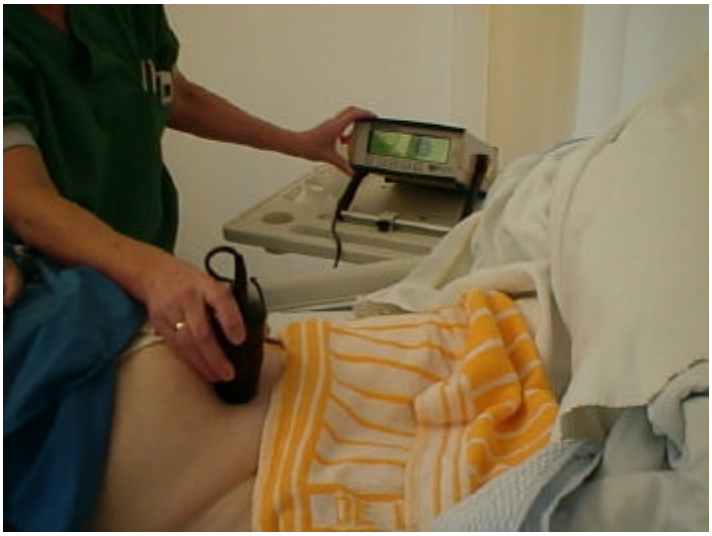
Materials and Methods

The BladderScan® (Diagnostic Ultrasound Europe B.V., Lage Dijk 14, 3401 RG IJsselstein, The Netherlands) is a small portable instrument (fig. 1), which measures the bladder volume accurately (Coombes, Fuse 1996). Low energy ultrasound is reflected from the bladder wall and an algorithm calculates the bladder volume. The BladderScan® is approved by the Food and Drug Administration (USA) (FDA) and is available clinically in the USA. A company representative instructed the nurses in the recovery and intensive care wards on the instruments use (Fig. 2). The instructions required less than 1 h. Patients were catheterized by nurses in the recovery and intensive care wards, and by doctors on the general wards. Before the BladderScan® became available, guidelines for catheterization were pre-operative incontinence of urine, post-operative incontinence of urine after spinal or epidural anesthesia, blood loss during surgery of more than 1 liter, a medical history of prostatic enlargement, abdominal approach for surgery to the lumbar spine, long-term use of an epidural catheter, no spontaneous diuresis by 8 h after surgery, or unexplained restlessness. After the

BladderScan® became available, the guideline about spontaneous diuresis was modified to no spontaneous diuresis 8 h after surgery combined with a bladder volume estimated at more than 800 mL.



The BladderScan® is a small portable instrument of 2.5 kg



The BladderScan® in use, which measures the bladder volume by ultrasound.

Bladder volume was measured every 6 h, unless there had been spontaneous diuresis, if the patient had unexplained restlessness, or there had been no spontaneous diuresis 8 h after surgery. The benefits of measuring bladder volume were judged by the quantity of disposables used for catheterization (sterile gloves, local anaesthetic gel, sterile swabs, urine bags and trays, disposable syringes, saline solution and sterile drapes) and the incidence of urinary tract infections. Our supplies department audited the use of disposables and urinary infections were monitored by the microbiology laboratory. Neither department was aware of our study. The Wilcoxon signed rank test ($p < 0.05$ considered significant) was used to test for statistical differences between use of catheters and incidence of infections before and after the introduction of the BladderScan®.

Results

The details of the patients for the two periods under review are shown in Tables 1 and 2: there were 1920 patients between 1 January 1997 and 30 April 1997,and 2196 patients between 1 May 1997 until 30 September 1997.

Table 1. Patient characteristics

	Period before ultrasonic bladder volume measurement	Period with ultrasonic bladder volume measurement
Number of patients	1920	2196
Male/Female	38.2%/61.8%	38.0%/62.0%
Age (years)	45.7 (SD ± 17.8)	45.2 (SD ± 19.7)
Anesthesia	62.3%	79.1%
General anesthesia	57%	53.8%
Spinal anesthesia	38.7%	41.2%
Plexus anesthesia	3.8%	5.0%

Table 2. Type of surgery

Type of surgery %	Period before ultrasonic bladder volume measurement	Period with ultrasonic bladder volume measurement
Cervical spine	2.8	3.6
Thoracic spine	1.5	2.4
Lumbar spine	16.5	16.0
Shoulder/upper arm	6.7	7.8
Elbow/forearm	2.1	2.2
Hand/wrist	5.1	4.3
Pelvis/hip	28.3	27.1
Upper leg	1.3	1.3
Knee/lower leg	22.7	23.4
Ankle/foot	13.0	11.9
Total	100	100

No statistical differences.

There were no important differences between the two groups of patients who gave their consent to participate in the study, which had the approval of the hospital ethics committee. The nursing staff easily understood the guidelines for catheterizing the bladder and the BladderScan®, was easy to use. The need for disposables was halved in the period in which the BladderScan® was used, and there were fewer urinary tract infections (Table 3).

Table 3. Results

	Period without bladder volume measurement	Period with bladder volume measurement
Number of patients	1920	2196
Number of catheters used	602	349
Percentage of patients who were catheterized	31.4%	15.9%*
Number of urinary tract infections	18	5*

*= $p<0.05$.

Discussion

The likelihood of post-operative urinary retention depends on the type and duration of surgery, and the type of anesthesia. Longer operations are more likely to lead to urinary retention, and surgery to the pelvis or lumbar spine obtunds the micturition reflexes because of the proximity of the peritoneum (Tetzlaff 1995). Neuraxial blockade (Caudal, epidural or intrathecal anesthesia) reduces the urge for micturition (Torda 1984). In other studies, urinary retention increased after major hip and knee surgery, and retention makes urinary tract infections more likely (Mitchell 1991, McQueen 1992).

In our study, patients in the two study periods were similar. Slightly fewer patients in the second period underwent surgery without anesthesia, which might have decreased the risk of urinary retention by a small amount, but not enough to affect our overall finding. There has been a previous report suggesting the urinary infection rate can be reduced by using the BladderScan® (Moore 1997), and in our study there was a statistically significant decrease in disposables and urinary tract infections after introducing the BladderScan®. This decrease was not simply because of better attention to aseptic technique during the second period the risk of urinary retention has always been a concern in our daily practice. However, our study cannot answer definitively whether using the BladderScan® reduces the infection rate, as there are many factors that we have not studied. These include antibiotic usage, and single in-and-out, catheterization, neither of which we used. The marked reduction in the use of disposables necessary for bladder catheterization means that the purchase costs of a BladderScan® will be recouped within 2 years. This calculation does not include the price of antibiotics and prolonged hospital stay due to urinary tract infections. In addition to the cost effectiveness of the BladderScan®, there was also a reduction in the nurse's workload and less inconvenience and discomfort for the patients. We now use the BladderScan® routinely in the recovery and intensive care wards. We realize that our study was sequential and not randomized, but we believe there is a clear benefit from measuring the bladder volume.

Chapter 8

General discussion

General discussion

In clinical care for surgical patients, the provision of optimal postoperative pain relief to patients with minimal adverse effects remains one of the most challenging and difficult tasks for anesthetic teams.
In 1996 we decided that a major effort to improve the quality of postoperative care was needed, in order to achieve superior patient comfort; and, to reduce postoperative complications, related to inadequate pain relief. After reviewing the literature extensively, we selected on practical and theoretical grounds the method of intrathecal application of opioids plus local anesthetics.

Choice for single shot intrathecal anesthesia

Practical grounds	Theoretical grounds
Fast onset to surgical anesthesia	Opioids have their effect at the opiate receptor site, which is located in the spinal cord.
No additional manpower is needed to assist in techniqual problems during 24 hours	
No need for extensive education of nurses with a new technique	
Low financial costs	

From data in the literature we were aware of the risk of adverse effects by intrathecal opioids such as postoperative nausea and vomiting, urinary retention, pruritus, sedation, respiratory depression. We hypothesized that the use of very low doses of intrathecal morphine might result in minimal adverse effects, but we were uncertain whether such low doses would still offer the desired analgesic effect. In the 5 studies (Chapter 3 to 7) several aspects related to this analgesic policy were investigated.

Postoperative pain

Recently a European task group on postoperative pain (Europain 1998) set the VAS score of 3 (ranging from zero to ten) or higher in resting patients as a threshold to start active pain control. In our dose finding study (Chapter 3) we found that an intrathecal dose of 0.1 mg morphine added to 20 mg bupivacaine provide acceptable postoperative pain relief after total hip replacement surgery according to these standards of the task force. After this single intrathecal dose injection pain VAS scores were below 3 during 24 hours after surgery (Chapter 3), with only a minimum amount of supplement systemic morphine (mean 10.9 mg, SD ± 10.4) during the 24 hours period was needed to achieve this effect. In a subsequent study we demonstrated that the intensity of preoperative joint pain was significantly correlated with postoperative pain and the postoperative morphine intake for postoperative analgesia (Chapter 4). The relationship between preoperative pain level and postoperative morphine intake indicates that preoperative assessment of pain in an individual patient allows one to anticipate the patient's needs. This can lead to better postoperative pain relief. To improve the quality of postoperative pain control, one may consider whether it helps to start analgesic treatment in the preoperative period. Perhaps such improvement can be achieved by some simple measures, e.g.: by doing total hip surgery in an earlier phase when pain is not yet severe; by extended pre-treatment with non steroidal anti-inflammatory drugs, pre-treatment with opioids, or by administration of a higher preoperative dose of intrathecal morphine. Perhaps specific attention to this aspect of the total hip procedure may improve the outcome.

Postoperative nausea and vomiting

In the literature the incidence of postoperative nausea and vomiting is reported to be high following anesthetic techniques using intrathecal local anesthetics and opioids. Disappointingly in contrast to our hypothesis this happened to be the case in all our studies in orthopedic patients with intrathecal morphine (Chapter 3, 4, 5 and 6). More than 60% of the patients experienced a period of postoperative nausea and vomiting in the first 24 hours after total hip surgery. However the incidence of postoperative

nausea and vomiting was not related to different dosages of intrathecal morphine (Chapter 3). Surprisingly, the incidence of postoperative nausea and vomiting was similar to patients who did not receive intrathecal morphine at all! (Chapter 5). This implies that a low dose of intrathecal morphine, which provides excellent pain relief, is not a main cause for postoperative nausea and vomiting. Unfortunately, the present protocol for treatment of postoperative nausea and vomiting using metoclopramide was ineffective and we need studies to improve the treatment of this nasty complication (Chapter 5).

Itching

Another side effect associated with intrathecal morphine in our orthopedic patients is itching. In our study itching was found to be a dose dependent phenomenon. Unfortunately, itching occurs even after low doses (0.025 – 0.2 mg) of intrathecal morphine, which were effective in terms of pain relief (Chapter 6). After the optimal dose of 0.1 mg intrathecal morphine only 11% of the patients reported mild itching. Severe itching for which treatment with naloxon was required was not present in our patients who received 0.1 mg intrathecal morphine for postoperative pain relief (Chapter 6).

Urinary retention

Urinary retention occurs frequently after surgery and anesthesia and was unfortunately also found it to be a frequently occurring complication in the patients who received intrathecal morphine for pain relief. After total hip surgery, the incidence of urinary retention was found to be 60% and more. The main finding of our two studies was that the incidence of urinary retention for patients who received intrathecal bupivacaine with or without low doses of intrathecal morphine was similar (Chapter 3 and 5). This implies that a low dose of intrathecal morphine, which provides excellent pain relief, is not a main cause for urinary retention. In the detection of urinary retention was causes annoying discomfort and may lead to morbidity in patients following surgery and intrathecal anesthesia the BladderScan® was introduced and evaluated in a study. The need for urinary tract catheterization was reduced by half in the period in which the

BladderScan® was used, and significantly fewer urinary tract infections were observed (Chapter 7).

Respiratory depression

It is a major concern that the application of intrathecal morphine can result in late respiratory depression. Intrathecal morphine has been shown to cause significant dose-related decreases in SpO_2 and alveolar ventilation in human volunteers after doses of 0.2 – 0.6 mg (Bailey 1993). After the lowest dose evaluated in this study under laboratory conditions (0.2 mg) mild respiratory depressant effects were seen (Bailey 1993). In all our clinical studies performed with low doses of intrathecal morphine 0.025 – 0.2 mg late respiratory depression was actively met for but it was not observed. (Chapter 3 to 6). In total the total of 2400 patients that we investigated in our clinic from 1996 until the end of 1999. In retrospect, no cases of clinically relevant respiratory depression were detected in any of these patients who received systemic morphine by PCA at our recovery or intensive care ward. In our view, routine instrumental monitoring for postoperative respiratory depression even in the opioid naive elderly patient is not necessary provided that the intrathecal dose is of 0.1 mg of morphine or less.

Cardiovascular adverse effects

We did not study cardiovascular adverse effects following intrathecal morphine extensively. A common experience was that the heart rate might decrease with 6 to 16 % after anesthesia, returning to baseline levels 12 h postoperatively. The incidence of hypotension was 48.6% to 73.5% (Chapter 3). These cardiovascular changes were considered to be insignificant with respect to outcome. Surprisingly, bradycardia (heart rate below 40 bpm) presented in patients (incidence 16%) who did not receive intrathecal morphine (Chapter 5). Typically, this bradycardia presented in the very same period that motor function recovered and did not occur in patients who receive intrathecal morphine. It can be explained as a vagal reaction to postoperative pain when the effect of the spinal blockade ceases.

Final conclusion

The simplicity of the intrathecal analgesic technique, the resulting excellent post-operative analgesia and hemodynamic stability were important arguments to select this anesthetic technique for per- and postoperative pain relief in our population of orthopedic surgical patients. A dose of 0.1 mg morphine intrathecally applied was found to result in optimal pain relief. Despite these benefits, one has to cope at times bothersome adverse effects. The main - and surprising - finding of our studies was that the incidence of the most frequently occurring adverse effects: postoperative nausea and vomiting, and urinary retention was not related to the addition of intrathecal morphine. Itching was found to be related to the dose of intrathecal morphine. Itching was mild low after low doses of intrathecal morphine and late respiratory depression did not occur at the doses studied. We hypothesized that lowering the dose of intrathecal morphine would lead to an optimal pain relieving effect with a reduction of adverse effects to an acceptable level. To a certain extent this was confirmed in our studies, but further benefit from optimization of dose schemes is not expected. Therefore, further improvement of the quality of care in pain relief in orthopedic surgical patients should be sought at in other pain relief modalities and/or the development of analgesic drugs with better pharmacodynamic properties for intrathecal application.

Chapter 9

Summary

Summary

Chapter 1

Although intrathecal morphine is used to achieve postoperative pain relief for more than 20 years the primary goal to realize: "selective spinal analgesia" without adverse effects is still behind the horizon. The optimal site to administer opioids e.g. morphine is as close as possible to the opiate receptor site (spinal cord) by the intrathecal route, as it is the place of effectiveness. To improve the clinical effectiveness of intrathecal morphine two strategies are proposed: 1. to lower the intrathecal dose of morphine and thereby reduce the supraspinal adverse effects while maintaining the analgesic effects; 2. further research to synthesize highly selective endorphin mimetic drugs with a minimum of side effects.

Chapter 2

In Chapter 2 the aims of the study are formulated. Following our hypothesis that the intrathecal route – from the theoretical point of view – would be the optimal one for administration of morphine to achieve adequate post postoperative pain relief after major orthopedic surgery of the lower limb with a low incidence of adverse effects. We hypothesized that low doses of intrathecal morphine might probably result in similar pain relief scores but might minimize the incidence of adverse effects.

Chapter 3

This study was designed to determine the optimal intrathecal dose of morphine in total hip surgery. The optimal intrathecal dose was defined as the dose, which provides effective analgesia with minimal side effects during 24 h after total hip surgery. Patients (n=143) scheduled for total hip surgery were randomized to four double-blinded groups with a standardized bupivacaine dose but different doses of intrathecal morphine: group I, 0.025 mg; group II, 0.05 mg; group III, 0.1 mg; and, group IV, 0.2 mg. Pain scores, intravenous morphine intake {patient controlled analgesia (PCA)} and morphine related side effects (respiratory depression, postoperative nausea and vomiting, itching, urinary retention) were recorded for 24 h after surgery. Excellent postoperative pain relief was present in all groups. The

highest pain scores were found in group I. The mean use of systemic morphine administered by PCA infusion pump was: 23.7 mg, 17.8 mg, 10.9 mg and 9.9 mg, in group I, II, III, and IV, respectively ($p<0.01$, group III and IV versus group I). We conclude that 0.1 mg intrathecal morphine is the optimal dose for pain relief after hip surgery with minimal side effects.

Chapter 4

The aim of this study was to examine whether severity of preoperative pain intensity is predictive for postoperative pain and morphine consumption. Sixty consecutive patients scheduled for total hip surgery during intrathecal anesthesia were studied. Preoperative Visual Analogue Scale (VAS) scores and analgesic intake was assessed one day before surgery. Three groups of patients were identified: those with mild pain (n=12, VAS score between 0 to 4), moderate pain (n=18, VAS score from 4 to 7) and severe pain (n=28, VAS score from 7 to 10). Postoperative pain scores were recorded in the first 24 h, as well as the amount of morphine delivered by patient controlled analgesia (PCA) pump. There were no differences between groups in VAS scores at any time. Severe preoperative pain levels correlated with significantly higher postoperative morphine intake. The mean morphine intake during the first 24 h postoperatively was: 19.2 mg in the mild pain group; 21.2 mg in the moderate pain group, and 29.5 mg in the severe pain group ($p < 0.05$ compared to both other groups). We conclude that patients with severe preoperative pain: a) self medicate to achieve postoperative pain scores equivalent to those of patients with mild and moderate pain, and b) require a higher postoperative morphine intake for adequate analgesia than patients with mild or moderate preoperative pain.

Chapter 5

This study evaluated the questions: firstly, to what extent do spinal opiates contribute to PONV (post operative nausea and vomiting); and, secondly, how effectively can metoclopramide reduce the incidence of PONV after intrathecal administration of morphine. All patients were scheduled to undergo major joint surgery of the lower limb. The patients were allocated to three groups. Group I (n=200): intrathecal anesthesia was induced by

administration of 20 mg bupivacaine and 0.2 mg morphine. Group II (n=100): intrathecal anesthesia was induced using the same dosages and drugs for intrathecal anesthesia, but in addition systemic metoclopramide was injected in two doses of 20 mg. Finally, for patients in group III (n=100) intrathecal anesthesia was induced by the administration of 20 mg bupivacaine only.
The maximum PONV percentages were 41.1%, 32.7% and 37% in group I, II and III respectively. The consumption of antiemetics was similar in all groups. The number of patients who needed one or more additional antiemetics during the first 24 hours after surgery was 112 (56.6%), 57 (58%) and 60 (60%) in group I, II and III, respectively.
Administration of metoclopramide did not reduce the overall incidence of PONV. Our study shows no relationship between the use of 0.2 mg intrathecal morphine and the incidence of PONV during 24 hours postoperatively.

Chapter 6
This study was designed to determine whether low doses of intrathecal morphine still result in itching and it evaluates the outcome of using standardized treatment with promethazine and - for intractable itch - naloxon.
Patients (n=143) scheduled for total hip surgery were randomized to four double-blinded groups with a standardized bupivacaine dose but different doses of intrathecal morphine: group I, 0.025 mg; group II, 0.05 mg; group III, 0.1 mg; and, group IV, 0.2 mg (same patients as Chapter 3). The presence or absence of itching was noted every three hours for a twenty-four hour period. When requested by the patient, the standard procedure for treatment was initiated.
The incidence of itching was: Group I: 14.3%; Group II: 21.6%; Group III: 48.6%; and, Group IV: 61.7%. Itch was treated by administering promethazine intramuscularly in 2,9% (Group I); 8,1% (Group II); 10.8% (Group III); and, 8.9% (Group IV) respectively. Only in group IV there was 1 patient who needed naloxon to treat itching. The incidence and severity of itching is a dose related side effect in the dose range of 0.025 – 0.2 mg of

intrathecal morphine. Itching even occurs after the low doses of intrathecal morphine, but symptoms vanish after promethazine 25 mg intramuscularly.

Chapter 7

A non-invasive ultrasound imaging technique (BladderScan®) was used prospectively in an attempt to reduce the need for catheterization of the urinary bladder and the incidence of urinary tract infections after orthopedic surgery. Over a 4-month period, in which 1920 patients were included, catheterization was performed if there was no spontaneous voidance of urine by 8 h after surgery. A total of 31% of these patients were catheterized, and 18 patients developed urinary tract infections. In a 4-month period, there were 2196 patients, catherization was performed only if the bladder volume was more than 800 mL 8 h after surgery. The incidence of catheterization decreased to 16%, and 5 patients developed urinary tract infections. In our patients, measuring bladder volume reduced the need for an urinary catheter and thereby the risk of urinary infection.

Samenvatting

Hoofdstuk 1

Alhoewel er al meer dan twintig jaar morfine wordt toegediend in de intrathecale ruimte om een optimale postoperatieve pijnstilling te bereiken is ons uitgangspunt nog steeds niet bereikt: “selectieve spinale analgesie”. De optimale plaats van toediening van opiaten is zo dicht mogelijk bij de receptorplaats (het ruggenmerg), omdat dit de plaats is waar het effect gegenereerd wordt. Om de klinisch effectiviteit van intrathecale opiaten te verbeteren worden 2 mogelijkheden voorgesteld: 1. verlagen van de intrathecale dosis van morfine en daarmee de ongewenste supraspinale effecten verminderen of 2. verder onderzoek naar de ontwikkeling van zeer selectieve endorfine mimetische stoffen.

Hoofdstuk 2

In hoofdstuk 2 zijn de doelstellingen van dit proefschrift geformuleerd. Vanuit theoretisch oogpunt lijkt de intrathecale toedieningsweg de meest optimale om een goede postoperatieve pijnstilling te bereiken. De hypothese was dat een lage dosis intrathecaal morfine een goede pijnstilling kan geven terwijl de incidentie van bijeffecten gering behoeft te zijn.

Hoofdstuk 3

Deze studie is opgezet om de optimale dosis intrathecaal morfine voor heupchirurgie vast te stellen. Deze optimale intrathecale dosis is gedefinieerd als die dosis waarbij er een effectieve pijnstilling na de operatie wordt verkregen welke vergezeld gaat met minimale bijwerkingen gedurende 24 uur na de heup vervangende operatie. Patiënten (n=143) welke een heupvervangende operatie ondergingen werden gerandomiseerd naar 4 dubbelblinde groepen met een vaste bupivacaïne dosis maar verschillende doseringen intrathecaal morfine: Groep I, 0,025 mg; Groep II, 0,05 mg; Groep III, 0,1 mg; en Groep IV, 0,2 mg. Pijnscores, intraveneuze morfine behoefte, op een patiënt gecontroleerde manier, en de aan morfine gerelateerde bijwerkingen (ademhalingsdepressie, postoperatieve misselijkheid en braken, jeuk en urineretentie) werden geregistreerd

gedurende 24 uur na de operatie. Uitstekende postoperatieve pijnstilling was aanwezig in alle groepen. De hoogste pijnscores werden gevonden in Groep I. De gemiddelde hoeveelheid intraveneus toegediende morfine was: 23,7 mg, 17,8 mg, 10,9 mg and 9,9 mg, in respectievelijk Groep I, II, III, en IV ($p<0.01$, Groep III en IV versus Groep I). Wij concludeerden dat 0,1 mg intrathecaal toegediende morfine de optimale dosis is voor pijnstilling na een heupvervangende operatie hetgeen gepaard gaat met de minste bijwerkingen.

Hoofdstuk 4

De vraagstelling van deze studie was of de Ernst van de preoperatieve pijn gerelateerd is aan de postoperatieve pijn en morfine consumptie. Zestig patiënten welke een heupvervangende operatie ondergingen werden bestudeerd. De preoperatieve pijnscore (Visual Analogue Scale = VAS) en het analgetica gebruik werden 1 dag voor de operatie in kaart gebracht. Er werden 3 groepen vastgesteld: die met geringe pijn (n=12, VAS score tussen 0 en 4), gematigde pijn (n=18, VAS score van 4 en 7) en ernstige pijn (n=28, VAS score tussen 7 en 10). De postoperatieve pijnscores werden geregistreerd in de eerste 24 uur na de operatie, evenals de hoeveelheid morfine via de PCA pomp (PCA = patiënt gecontroleerde analgesie). Er waren geen verschillen in de pijnscores op welk moment dan ook. Ernstige preoperatieve pijn correleerde met een significant hoger morfine gebruik postoperatief. De gemiddelde morfine opname gedurende de eerste 24 uur postoperatief was: 19,2 mg in de groep met geringe preoperatieve pijn; 21,2 mg in de groep met gematigde preoperatieve pijn, en 29.5 mg in de groep met ernstige preoperatieve pijn ($p < 0.05$ vergeleken met de beide andere groepen). We concludeerden dat patiënten met een ernstige preoperatieve pijn: a) zichzelf medicatie toedienen tot er gelijke postoperatieve pijn scores ontstaan als patiënten met een geringe of gematigde preoperatieve pijn; en, b) een grotere postoperatieve morfine behoefte hebben voor adequate pijnstilling dan patiënten met geringe of gematigde preoperatieve pijn.

Hoofdstuk 5

Deze studie richtte zich op de vraag in hoeverre spinale opiaten bijdragen aan postoperatieve misselijkheid en braken en vervolgens hoe effectief metoclopramide de incidentie van postoperatieve misselijkheid en braken na intrathecale toediening van morfine kan verminderen. Patiënten werden toegewezen aan drie groepen die allen een heup- of knievervangende operatie ondergingen. Groep I (n=200) kreeg een intrathecale anesthesie door toediening van 20 mg bupivacaïne en 0,2 mg morfine, in groep II (n=100) werd dezelfde intrathecale anesthesie toegediend met de toevoeging van metocloramide 20 mg intramusculair na toediening van de anesthesie en een tweede dosis van 20 mg metoclopramide intramusculair bij aankomst op de verkoeverkamer. Tenslotte, groep III (n=100) kreeg een intrathecale anesthesie toegediend met alleen 20 mg bupivacaïne.

De maximum PONV percentages waren 41,1%, 32,7% en 37% in respectievelijk groep I, II en III. Het gebruik van anti-emetica was gelijk in alle groepen. Het aantal patiënten dat een of meer extra antibiotica nodig had in de eerste 24 uur na de operatie was 112 (56%), 57 (58%) en 60 (60%) in respectievelijk groep I, II and III.

Toediening van metoclopramide gaf geen vermindering van de incidentie van postoperatieve misselijkheid en braken. Deze studie liet geen relatie zien tussen het gebruik van 0,2 mg intrathecaal toegediend morfine en de incidentie van postoperatieve misselijkheid en braken gedurende de eerste 24 uur na de operatie.

Hoofdstuk 6

Het in dit hoofdstuk beschreven onderzoek werd verricht om vast te stellen of ook lage doseringen intrathecaal morfine nog steeds jeuk veroorzaakt. Tevens werd de standaard behandeling van jeuk met promethazine, en voor onhoudbare jeuk, naloxon beoordeeld.

Patiënten (n=143) welke een heupvervangende operatie ondergingen (dezelfde patiënten als die in hoofdstuk 3) werden gerandomiseerd naar 4 dubbelblinde groepen met een vaste bupivacaïne dosis maar verschillende doseringen intrathecaal morfine: Groep I, 0,025 mg, Groep II, 0,05 mg, Groep III, 0,1 mg en Groep IV, 0,2 mg. De aan- of afwezigheid van jeuk

werd iedere 3 uur geregistreerd gedurende de eerste 24 uur postoperatief. Indien nodig werd een standaard behandeling voor jeuk ingesteld.
De incidentie van jeuk was: groep I: 14,3%; groep II: 21,6%; Groep III: 48,6%; en, Groep IV: 61,7%. Jeuk werd behandeld met toediening van 25 mg promethazine intramusculair in respectievelijk 2,9% (groep I); 8,1% (groep II); 10,8% (groep III), en 8.9% (groep IV). Alleen in groep IV was er 1 patiënt welke naloxon nodig had om jeuk te behandelen. De incidentie en Ernst van jeuk is dosis gerelateerd aan intrathecaal morfine in de range van 0,025 – 0,2 mg. Jeuk komt nog steeds voor bij lage doseringen morfine, maar de symptomen verdwijnen na 25 mg promethazine intramusculair.

Hoofdstuk 7

Een niet invasieve ultrageluid techniek (Bladderscan®) werd op een prospectieve wijze gebruikt om het blaasvolume te meten om daarmee het aantal onnodige blaascatheterisaties en blaasinfecties na orthopedische operaties te verminderen. In een periode van 4 maanden werden 1920 patiënten geincludeerd, waarbij blaascatheterisatie werd toegepast indien er geen spontane diurese was 8 uur na operatie. Totaal werd er 31% van deze patiënten de blaas gecatheteriseerd, en 18 patiënten ontwikkelde een urineweginfectie. In de volgende periode van 4 maanden werden 2196 patiënten geincludeerd. Hierbij werd blaascatheterisatie alleen toegepast indien het blaasvolume meer was dan 800 ml eveneens 8 uur na operatie. Het aantal benodigde blaascatheterisaties daalde naar 18%, terwijl 5 patiënten een urineweginfectie ontwikkelde. Bij onze patiënten populatie was er door de niet invasieve blaasvolume meting een verminderde noodzaak voor blaascatheterisatie waarschijnlijk ook minder urineweginfecties.

Chapter 10

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Addendum

The preparation of 0.1 mg morphine in 4 mL bupivacaine 0.5%.

This addendum has been published:

The preparation of 0.1 mg morphine in 4 mL bupivacaine 0.5%.
R. Slappendel, B. Benraad, E.W.G. Weber, M.L.T. Bugter, R. Dirksen.
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which was a reply to: One drop of morphine added to local anaesthetics by means of a 23 –gauge injection needle can relieve postoperative pain under spinal anesthesia. Hirokatsu Toyoyama, Koh Mizutani, Yoshiro Toyoda. Anesth Analg 2000; 90(4):1000

Addendum

The preparation of 0.1 mg morphine in 4 mL bupivacaine.

A reply to: One drop of morphine added to local anesthetics by means of a 23 –gauge injection needle can relieve postoperative pain under spinal anesthesia. Hirokatsu Toyoyama, Koh Mizutani, Yoshiro Toyoda.

We thank our Dr Toyoyama et al. for their response dealing with the preparation of drugs in our article. However we do not support their proposal that the anesthesiologists dilutes or adds the morphine themselves to the bupivacaine. To guarantee the best quality of all mixtures which are not purchased from the pharmaceutical industry we have these prepared by our hospital pharmacy department. For all routes of administration of drugs in our anesthesiology practice we must be certain that the exact concentration of the drug is present and that a sterile method of preparation has been used.

The actual method for preparation of the drug mixtures in our study (1), bupivacaine 0.5% solution plus morphine 0.1 mg per 4 mL is given below.
A dry 2 L bottle is filled with 770 mL sterile water for injection. Five grams bupivacaine hydrochloride 1.00 H2O PhEur (Pharmacopae European) and 7.70 grams Sodium chloride H2O PhEur are weighed and added to the water and mixed by a magnetic spatula. With a 10 mL pipette 25 mL morphine (10mL=10mg) is added to the solution. Diluted hydrochloric acid is added to a pH of 4.0. Sterile water is added up to 1 kg. When the sterile water has been added the fluid is mixed during another 10 minutes by the magnetic spatula until a homogeneous fluid exists. Next, nitrogen is led through the solution for fifteen minutes. The bottle is closed with a paraffin film.

In an ampulla's filling machine the ampulla's are filled up to 5.3 mL. Nitrogen needles are placed in the gas holders just before and after the filing holders. The ampulla's are sterilized in a steam autoclave for 16 min and 121 centigrade. The ampulla's are labeled and numbered. A list of the labels is kept in the pharmacy. For each batch of 70 ampulla's, 60 ampulla's are used in clinical practice. The remaining ten ampulla's are used for quality check. The concentrations of morphine and bupivacaine are measured using high pressure liquid chromatography (HPLC). The pH is measured by a glass electrode. The osmolality is measured (norm 271 - 301). Finally the germ number is determined before filtration and must be below 10 germs per mL. In all, we strongly recommend to refrain from less methods. The safety range of intrathecal morphine is just one drop.

Curriculum vitae

Robert Slappendel werd geboren op 15 februari 1960 te Gouda. De lagere school werd in Reeuwijk doorlopen. Het eindexamen Atheneum B werd 1978 afgelegd aan de rijksscholengemeenschap te Brielle. In datzelfde jaar werd gestart met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Het arts examen werd behaald in mei 1985. Aansluitend volgde hij de in 1985 en 1986 de B-opleiding Cardiologie in het Zuiderziekenhuis te Rotterdam (opleider: Dr X.H. Krauss). In oktober 1986 werd aangevangen met de opleiding anesthesiologie in het Academisch ziekenhuis Nijmegen (opleiders: Prof. Dr. J.F. Crul, Prof. Dr. H. Beneken Kolmer en Prof. Dr. L.H.D.J. Booij). Inschrijving als anesthesioloog in het specialistenregister vond plaats op 1 januari 1991. Na zijn opleiding bleef hij nog 5 jaar werkzaam als staflid in het Academisch ziekenhuis Nijmegen. In deze periode maakte hij deel uit van het pijnteam (hoofd: Prof. Dr. B.J.P. Crul). Hier ontstond de interesse voor de behandeling van patiënten met chronische pijn.

Sedert december 1995 startte hij samen met zijn collega E.W.G. Weber in de St. Maartenskliniek te Nijmegen. Alhier werd een moderne afdeling anesthesiologie met al zijn facetten afgebouwd: orthopedische anesthesie met een accent op locoregionaal anesthesie, PACU afdeling, een preoperatieve assessment poli, diagnostiek en behandeling van pijnklachten uitgaande van het bewegingsapparaat. Medio 1996 werd gestart met het onderzoek naar de optimale dosis en effecten van toediening van intrathecale opiaten voor de behandeling van postoperatieve pijn.

Robert Slappendel is getrouwd met Gerdien van den Hurk. Hij heeft vier kinderen Anne (1990), Liza (1992), Emiel (1993) en Laura (1995).

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