Research in trauma surgery: from design to execution

The construction of an RCT and methodological considerations

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The construction of an RCT and methodological considerations
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Research in trauma surgery: from design to execution

The construction of an RCT and methodological considerations

Onderzoek in trauma chirurgie: van ontwerp naar uitvoering
De constructie van een RCT en methodologische overwegingen
(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER ONE

General introduction and outline of the thesis

Epidemiology of ankle fractures

Ankle fractures are the most common lower extremity fractures.(1). The incidence of ankle fractures varies between 100 and 150 per 100,000 person-years and is rising (2-4). Ankle fractures occur most in young men or older women (1;3;4). Most ankle injuries are caused by twisting injuries or simple falls, often during sport activities (2). They are associated with high costs for both the affected individual and society. These costs are a sum of the surgical procedures, subsequent hospitalization, but also the duration of occupational disabilities (5-8). Therefore, ankle fractures lead to a great societal burden and hence require adequate medical treatment. Various classification systems are used to categorize and describe the range of ankle fractures (9-11). However, indications for surgical or conservative therapy are mainly based on the congruity of the ankle and joint stability. Operative treatment is performed when the congruity of the ankle needs to be restored (10). Furthermore, operative treatment is initiated to prevent arthrosis on the long-term. Although indications for surgical fixation are widely accepted, controversy exists regarding the postoperative treatment of ankle fractures (12). A wide range of postoperative treatment regimens have been used, ranging from immobilization in a plaster cast without weight-bearing for multiple weeks to immediate post-operative protected mobilization (12-15). The different postoperative treatments cause differences in functional outcome, the rate to return to activities and the rate of complications (12-15). However, many studies use diverse in- and exclusion criteria, creating heterogeneous patient populations (16-19), impairing direct comparison between (and across) studies. In addition, studies include a diversity of types of ankle fractures (20-22), which might affect the observed effects of operative treatment. Therefore, patient selection and fracture identification need to be accounted for, in the investigation for the best suitable postoperative treatment regimen of ankle fractures. This thesis tries to identify the most optimal postoperative treatment regimen of ankle fractures.

Research in trauma surgery

The number of published studies in biomedical research has dramatically increased over the past years. In January 2017, there were more than 24 million citations in MEDLINE (23). The studies are used to guide physicians in clinical decision making as physicians are expected to

apply evidence based medicine. However, studies differ in their design, methodological quality, reporting quality, studied patient population, and other conditions. The differences in studies cause a challenge in providing the most optimal treatment for an individual patient. Systematic reviews and meta-analyses can navigate physicians in clinical decision-making as they summarize the current evidence on a particular topic or for a specific situation (24). Systematic reviews and meta-analyses of the effects of medical interventions often focus on RCTs (12), which are still considered the gold standard for generating evidence. For that reason, the RCT design occupies the top of the evidence pyramid in the classic construction of scientific research. However, it can be questioned whether RCTs always provide the best evidence in surgery (25;26). A secondary objective of this thesis is to identify the position of observational studies in trauma surgery research, with a focus on trauma surgery for ankle fractures.

Outline of this thesis

The aim of this thesis was to identify the most optimal postoperative treatment of ankle fractures. The secondary objective was to evaluate the value of observational studies in trauma surgery research. First, the current practice in the Netherlands is evaluated. **Chapter 2** encompasses the most frequently used classification systems and the consensus concerning classification, treatment and post-operative treatment in daily practice in the Netherlands. Next, a systematic review and meta-analysis was performed on the postoperative treatment of ankle fractures in the worldwide literature (**chapter 3**). This study included both randomised controlled trials (RCTs) and cohort studies, in order not to limit the generalizability of its results. The diversity on the postoperative treatment of ankle fractures might be explained by the diversity in patient demographics or the heterogeneity in the type of ankle fracture. It is long time suggested that different trauma mechanisms cause different types of ankle fractures. A rare type of ankle fracture, an isolated posterior malleolar fracture, is discussed in **chapter 4**, including a review of the literature, giving insight in the relation between classification, intrinsic stability and how this dictates treatment strategy. Besides fracture type, patient characteristics may be a factor that influence outcomes, both in functional recovery as well as complications. The association between these factors and complications following surgical treatment of ankle

fractures is described in **chapter 5**. In addition, this chapter studied complications with regard to their relation with the postoperative treatment regime. It is suggested that trauma mechanisms are largely different in mono- and polytrauma patients, ranging from low- to high energy impact. The differences in classification of ankle fractures in these different types of patients with different trauma energy impact are encountered in a retrospective cohort study in **chapter 6**. The differences in classification, treatment and outcome of ankle fractures show that different types of ankle fractures require a different treatment. From all different types of ankle fractures, supination eversion is the most common type of injury in low energy monotrauma patients and therefore causes most ankle fractures. However, the best suitable postoperative treatment for these fractures in patients without severe comorbidities, as discussed before, is unknown. The WOW! Study, Weight bearing Or non-Weight bearing after surgically fixed ankle fractures, addressed this lack of knowledge. **Chapter 7** describes the protocol of this multicentre randomised controlled trial. In this study early weight-bearing as tolerated is compared to the two traditional treatment methods: weight-bearing in a cast or non-weight bearing mobilization. Strict patient and fracture selection has been applied in this study. The promising results of the multicenter randomized controlled trial are shown in **chapter 8**.
A critical view on clinical research on postoperative trauma care and the position of observational studies is analyzed in **chapter 9**. The value of observational studies in trauma surgery is further analysed in **chapter 10** and **chapter 11**.

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CHAPTER TWO

Post-operative care for surgically treated ankle fractures: current status in the Netherlands

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Abstract

Aim

To make an inventory of the current situation with regard to the aftercare of a defined operatively treated ankle fracture in the Netherlands.

Methods

During a national trauma convention in 2012, Amsterdam, a survey was held among the (trauma and orthopedic) surgeons. The questions related to the current method of after-treatment of operatively treated ankle fractures indaily practice or possible existing consensus.

Results

A response rate of 64% was achieved. The Weber classification is most used in daily practice (70%). The treatment methods after an operatively treated ankle fracture, Lauge-Hansen supination-eversion type 4, vary widely. Mobilisation without weight-bearing is being preferred (60%). The majority of the respondents believes that there is no consensus on the after-treatment of operatively treated ankle fractures (91%).

Conclusion

The results have shown no consensus intreatment methods of operatively treated ankle fractures. The majority of the respondents preferred nonweightbearing as primary after-treatment.

Ankle fractures are common after falls from height and sports accidents1.

Commonly used classifications for ankle fractures are the 1) Danis-Weber, 2) Lauge Hansen and 3) AO classification (2-4). The surgical indication and surgical technique are based on this classification and the degree of displacement of the ankle joint. Nevertheless, there is currently no consensus regarding post-operative care of ankle fractures. Based on a survey with an attached case study, we identified the most frequently used classification system and type of post-operative care in daily practice in the Netherlands.

During the *Traumadagen* (national traumatology conference) in 2012 in Amsterdam, (orthopaedic) trauma surgeons and orthopaedic surgeons who were present at the conference were invited to participate in a survey. The total response rate was 64% (206 respondents) of the congress visitors. The survey consisted of a case study concerning an ankle fracture and corresponding questions regarding fracture classification, initial treatment and post-operative care.

Question 1
How would you treat the fracture in figure 1?
1) surgical treatment or 2) conservative treatment.
Background: A widely accepted indication for surgical treatment of ankle fractures is the presence of tibiotalar displacement more than 2 mm, dislocation of the medial malleolus, or a malleolus tertius fragment if more than 25% of the total tibia joint surface is involved.
Answer: The fracture shown in figure 1 has tibiotalar displacement of more than 2 mm; as a result, surgical treatment according to current standards is indicated.
Response: More than 99% of the respondents would offer the patient a surgical reduction and internal fixation (table). Less than 1% of the respondents chose a conservative treatment, which can be explained by the absence of information about the age and comorbidities of the patient in question. These are factors that certainly affect such a decision.

Figure 1 Ankle fracture belonging to question 1

Question 2:

Which classification system do you use for assessing ankle fractures? 1) Lauge Hansen classification; 2) Danis-Weber classification or 3) AO classification2-4.

Background: Commonly used classifications for ankle fractures are the 1) Danis-Weber, 2) Lauge Hansen, and 3) AO classifications (2-4). All classification systems have specific advantages and disadvantages.

The *Danis-Weber classification* describes the level of the fibula fracture relative to the syndesmosis. The assessment resulting from this classification does not take the number of malleolar fractures or the ligamentous stability into account. The advantages of this classification are a rapid overview and a simple derivation of the treatment consequences related to surgical technique (3).

The *Lauge Hansen classification* describes both the trauma mechanism and the foot position at the time of the traumatic event. Although the accuracy of this classification is debated in the literature, it is considered to provide

the most accurate description of both osseous injury and ligamentous injury (4).
The *AO classification* is based on the standard AO principles of fracture classification. All fractures are classified according to segment and then ranked into three types (A-C), followed by classification into three subgroups. The advantage of this approach is that all fractures are classified according to the well-known AO system (2).
Response: The Danis-Weber classification was the most frequently (70%) used classification in daily practice (table). The responses of the consultants (orthopaedic surgeons and (orthopaedic) trauma surgeons) and residents in training were virtually the same. Of the total number of respondents, 22% reported that they use the Lauge Hansen classification and 8% the AO classification.

Question 3
How would you classify the fracture in figure 2?
1) Supination-Eversion type 3; 2) Supination-Eversion type 4; 3) Pronation-Eversion type 3; 4) Weber B or 5) Weber C.
Background: In the description according to Lauge Hansen, Supination-Eversion type 3 involves a disruption of the anterior tibiofibular ligament with or without a small avulsion fracture of the front of the tibia (Tillaux-Chaput fracture) or fibula (Le Fort-Wagstaffe fracture), spiral fracture of the lateral malleolus and rupture of the posterior tibiofibular ligament and/or fracture of the malleolus tertius. Supination-Eversion type 4, in addition to the injuries for type 3, involves disruption of the deltoid ligament or fracture of the medial malleolus. A distinction between Weber classification B and C is based on the level of the fibula fracture in relation to the syndesmosis.
Answer: A ligamentous disruption is of course not visible on an X-ray, when dislocation is not present. The contours resulting from soft tissue swelling of the medial malleolus and lateral displacement of the talus may indicate disruption of the deltoid ligament. This indicates Supination-Eversion type 4. According to the Weber classification, this is a Weber B fracture, because the fibula fracture is at the level of the syndesmosis.
Response: In total, 70% of the respondents reported that they would assess the fracture according to the Danis-Weber classification (table), of which 88% classified the fracture as a Weber B fracture. The remaining respondents in this group (12%) classified the fracture as a Weber C

Figure 2 Ankle fracture belonging to question 3

fracture. Fracture assessment according to the Lauge Hansen classification was almost evenly divided between Supination-Eversion type 3 (48%) and type 4 (46%).

Question 4

If surgically treated, which type of postoperative care would you use for this fracture?
1) six weeks of non-weightbearing mobilisation; 2) six weeks of mobilisation with a walking cast; 3) immediate weight-bearing mobilisation without a cast or 4) other.

Background: At the time internal fixation for ankle fractures became more frequently the treatment of choice, the standard type of postoperative care was non-weightbearing immobilisation with a cast (5). However, non-weightbearing immobilisation has disadvantages, such as muscle atrophy and reduced range of motion of the ankle. During the same period, a second trend emerged, which promoted active, non-weightbearing

exercise for the ankle (6). Three randomised trials compared these types of postoperative care, but showed no differences between them (7-9). Improvements in technique and osteosynthesis materials, along with the societal demand for faster recovery, led to the development of orthoses. The combination of active ankle exercises with rigidity created the possibility for weight-bearing mobilisation. Full weight-bearing mobilisation, with use of an orthosis, is deemed possible as soon as two weeks after surgery (10). However, when a higher risk of wound infections was observed with these orthoses, their popularity declined (11;12).
Response: The majority of respondents (60%) had a preference for non-weightbearing active mobilisation as post-operative treatment, which is especially explicit with the consultants (table). In total, 14% of the respondents would use a post-operative treatment other than weight-bearing mobilisation, a walking cast or immediate weight-bearing mobilisation without a cast.

Question 5
In your opinion, is there a consensus in the Netherlands about postoperative care for ankle fractures?
1) yes or 2) no.
Background: In the literature, various types of postoperative care are described and compared, ranging from non-weightbearing mobilisation to immediate weight-bearing mobilisation. Based on the results, all of these authors suggested that larger, prospective, randomised studies are required to provide clarity about the best type of post-operative care (12-15). Due to insufficient numbers of patients in the studies conducted so far, no definitive conclusions could be drawn.
Response: A large majority of respondents (91%) stated that there was no consensus in the Netherlands about post-operative care for surgically treated ankle fractures (table). Of the respondents who believe that there was consensus (9%), the opinions were divided about the best type of postoperative care: 47% of this group chose non-weight-bearing mobilisation and 42% chose weight-bearing mobilisation with a walking cast. The described survey taken during the "*Traumadagen*" proved to be an effective method to determine the opinions on a general issue concerning a commonly occurring fracture; within 12 hours, responses were obtained from more than 200 consultants (orthopaedic surgeons and (orthopaedic) trauma surgeons) and residents in training (surgery and

orthopaedics). No differences in results were found between orthopaedic surgeons and (orthopaedic) trauma surgeons.
In daily practice, the Danis-Weber classification is most frequently used. With respect to the best type of postoperative care, there appears to be no consensus in the Netherlands. These results illustrate the current situation in our country. The aim for the future is to work towards a national consensus on postoperative care for ankle fractures. To this end, a large, prospective, randomised, multi-centre study has been initiated.

Table 1 Results survey

Question	Consultants	Residents	Total
1. treatment fracture			
surgical treatment	143 (99%)	63 (98%)	206 (99%)
conservative treatment	2 (1%)	1 (2%)	3 (1%)
total	145	64	209
2. classification system			
Lauge-Hansen	24 (22%)	11 (23%)	35 (22%)
Danis-Weber	79 (71%)	33 (67%)	112 (70%)
AO	8 (7%)	5 (10%)	13 (8%)
total	111	39	160
3. Fracture classification			
supination-Eversion type 3	18 (12%)	12 (19%)	30 (14%)
supination-Eversion type 4	20 (14%)	9 (14%)	29 (14%)
pronation-Eversion type 3	3 (2%)	1 (1%)	4 (2%)
weber B	89 (62%)	38 (60%)	127 (61%)
weber C	14 (10%)	4 (6%)	18 (9%)
total	144	64	208
4. postoperative care			
six weeks of non-weightbearing mobilisation	87 (60%)	38 (59%)	125 (60%)
six weeks of mobilisation with a walking cast	35 (24%)	14 (22%)	49 (23%)
immediate weight-bearing mobilisation without a cast	3 (2%)	2 (3%)	5 (2%)
other	20 (14%)	10 (16%)	30 (15%)
total	145	64	209
5. consensus			
yes	19 (13%)	0 (0%)	19 (9%)
no	124 (87%)	63 (100%)	187 (91%)
total	143	63	206

The Weightbearing Or non-Weightbearing (WOW) study will determine the best postoperative care for a specific type of surgically treated ankle fracture (Supination-Eversion type 2-4). Participants in the study will be randomised between three postoperative care strategies: 1) primary exercise-stable fixation, six weeks of non-weight-bearing mobilisation, 2) six weeks of weight-bearing mobilisation with a walking cast 3) primary exercise-stable fixation with full weight-bearing mobilisation (to the permissible weight).

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CHAPTER THREE

Weight-bearing and mobilization in the postoperative care of ankle fractures: a systematic review and meta-analysis of randomized controlled trials and cohort studies

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Abstract

Aim

To determine the effectiveness and safety of interventions used for rehabilitation after open reduction and internal fixation of ankle fractures.

Methods

A systematic review and meta-analysis was performed using both randomized trials and cohort studies. The effect of mobilization, weight-bearing, and unprotected weight-bearing as tolerated on postoperative recovery was compared using the Olerud Molander score, return to work/ daily activities, and the rate of complications.

Results

A total of 25 articles were included. Ankle exercises resulted in earlier return to work and/or daily activities compared to immobilization (mean difference (MD) -20.76 days; 95% confidence interval (CI) -40.02 to -1.50). There was no difference in the rate of complications between exercises and immobilization (risk ratio (RR) 1.22; 95% CI 0.60 to 2.45) or between early and late weight-bearing (RR 1.26; 95%CI 0.56 to 2.85).

Conclusion

Results of this meta-analysis show that following ankle surgery, 1) active exercises accelerate return to work and daily activities compared to immobilization, 2) early weight-bearing tends to accelerate return to work and daily activities compared to late weight-bearing. Active exercises in combination with immediate weight-bearing may be a safe option.

Introduction

Ankle fractures are the most common type of lower extremity fracture and among the most common types of fractures worldwide.(1) The incidence of ankle fractures is between 100 and 150 per 100,000 person-years and rising.(2,3) More than half of ankle fractures occur during sports activities, which is indicative of a healthy patient population.(4)

Ankle fractures are associated with high costs for both the affected individual and society. These costs are related not only to the operation and subsequent hospitalization, but also to the duration of occupational disability.(5–8) To reduce these latter costs, early functional return is crucial.(9)

While various classification systems exist to describe ankle fractures, the indication for surgery depends on the congruency of the ankle joint.(10–12) When an incongruent joint is present, fractures are often treated by open reduction and internal fixation to stabilize the ankle joint. The postoperative care regimens vary widely, e.g. from immobilization in a plaster cast without weight-bearing for multiple weeks to immediate post-operative protected mobilization. Even direct post-operative unprotected weight-bearing as tolerated has been suggested.(13)

Several systematic reviews have been published on various aspects of postoperative care regimens.(14–17) However, none of these reviews could provide clear advice for the postoperative care of ankle fractures since the regimens differ in terms of protection, ankle movements, and weight-bearing. In this systematic review and meta-analysis, non-randomized studies were included to potentially assist in showing effectiveness. Furthermore, specific aspects of the post-operative care regimen were compared.

The aim of this study was to determine the effectiveness and safety of interventions that are used for rehabilitation after open reduction and internal fixation of ankle fractures.

Methods

A published review protocol does not exist.

Search strategy and selection criteria

Randomized controlled trials (RCT's) and cohort studies evaluating postoperative care regimen of ankle fractures were included in this systematic review and meta-analysis (Weber, AO or Lauge Hansen classifications).(10,11) Two reviewers (DS and FH) independently searched the MEDLINE and EMBASE electronic databases in January 2014. No language or publication restrictions were applied to the search, and disagreements were resolved by discussion (DS, FH and RH). The search was conducted using the following specific broad search string: (ankle fracture OR Lauge Hansen OR Weber) AND (cast OR orthosis OR weight-bearing) AND (Olerud Molander OR follow-up).

Quality assessment

The methodological quality of all included studies was assessed by three reviewers (DS, FH and RH) using the 'risk of bias' assessment tool provided by The Cochrane Collaboration.(18)

Outcome measures

The effectiveness and safety of the postoperative care regimens were evaluated using the following outcome measures: the Olerud Molander score for functional objective outcome (short-term and long-term),(19) return to work and/or daily activities in days for functional subjective outcome, and rate of complications, which is a direct result of the postoperative care regimen, for safety outcome.

Data extraction

Two reviewers (DS and FH) independently extracted the following data: authors, year of publication, study design, treatment groups, outcome, results between 6 and 12 weeks (short-term), results after 6 months (long-term), confidence interval (CI) or P value, and complications. The complications were defined as reported in the studies. Author contact was attempted for studies with missing data.

Data analysis

Studies were included in the short-term analysis for the Olerud Molander score if results between 6 and 12 weeks were reported. If more short-term results were reported, the results closest to 6 weeks were used.

Studies were included in the long-term analysis if results after 6 months were reported. If more results were reported on the long-term, the Olerud Molander scores from the final survey were used.
Review Manager (RevMan©) software version 5.2 was used for the meta-analysis. A mean difference (MD) was calculated for continuous outcomes. The Inverse Variance (IV) with fixed effect (Fixed) or with random effect (Random) method was used to construct a 95%CI. If a study did not report standard deviation (SD), the value was not estimated. Available case analysis was performed with missing data. A risk ratio (RR) was calculated for complications, which was the only dichotomous outcome. The Mantel-Haenszel (M-H) with fixed effect (Fixed) or random effect (Random) method was used to compute a 95%CI for the dichotomous outcome. The assessment of statistical heterogeneity was done by visual inspection of the forest plots, the Tau^2 test, the Chi^2 test, the degrees of freedom (df), the I^2 value and the overall effect Z-test. If the I^2 value was below 25%, fixed effects were used. If the I^2 value was 25% or greater, random effects were used. After the primary analyses, sensitivity analyses were performed. In the sensitivity analyses on bias, all studies with less than 5 high risk factors for bias were included. Studies with 5 or more high risk factors for bias were excluded. In the sensitivity analysis on study design, only RCT's were included. In the sensitivity analyses on time, all studies published after 2000 were included.

Results

Search

The MEDLINE and EMBASE search identified 259 and 87 studies, respectively. The 14 relevant studies from the initial search were checked for related citations, resulting in 28 relevant studies.
In Kimmel et al. mobilization started with a difference of one day between the two groups and in Starkweather et al. with a difference of seven days.(20,21) Partenheimer et al. only analysed one group of patients. (22) Therefore, these studies were not included. Ultimately, a total of 25 studies met the inclusion criteria (Figure 1).(13,23–46)

Baseline characteristics

Of the 25 included studies, 12 were RCT's, 7 were prospective studies, 1 was a retrospective study, and 5 were partly prospective and partly retrospective studies. A total of 1376 participants were included. Studies

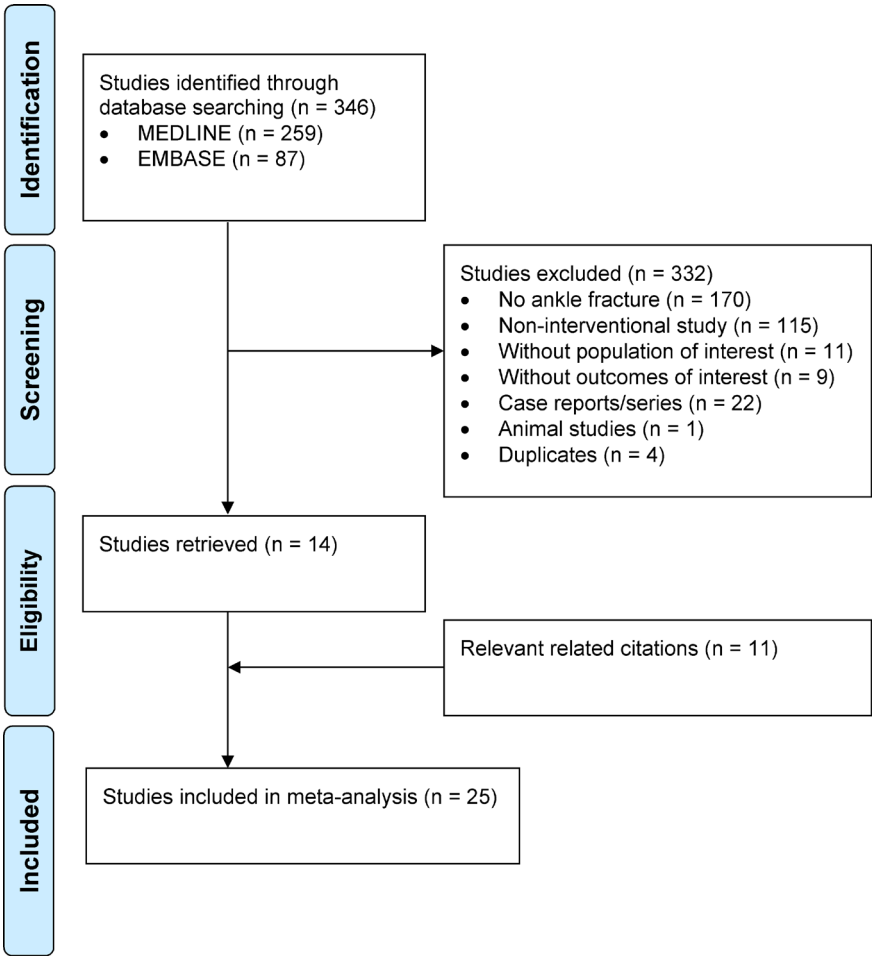

Figure 1 A flowchart following the PRISMA guidelines of the search strategy.

included in this meta-analysis did not describe the classification of ankle fractures (AO, Weber or Lauge Hansen), age, or medical co-morbidities in relation to the different outcomes (Appendix 1).

Bias

Nearly all studies had a high risk of bias, both cohort studies and RCT's (Figure 2). More than half of the studies had a high risk on random sequence generation (52%), on allocation concealment (80%), and on blinding of outcome assessment (80%). Since treatment was visible, the participants and personnel of all studies, cohort studies and RCT's, were not blinded.

In 11 (44%) studies, a high risk of other bias was found. In 7 of these studies, patients with a Weber A fracture who had undergone surgery were included.(13,27,33,36,38,39,43) However, further specifications of these fractures were not presented.

Effect of mobilization

A total of 19 studies investigated the effect of mobilization (ankle exercises) on recovery.(13,27–33,35–38,40–46) Honigmann et al. and Laarhoven van et al. only reported the median results and Wetzler et al. did not describe enough data for analysis. (36,37,46) Therefore, these three studies were excluded from the analysis. Tropp et al. used a modified Olerud Molander score.(44) Finsen et al. compared 3 groups with each other; only groups A and B with a non-weight-bearing treatment were analysed.(32)

The Olerud Molander score was reported in 9 studies. No statistically significant results were found with the short-term (MD -6.88; 95%CI -17.66 to 3.91) or long-term Olerud Molander score (MD -1.05; 95%CI -4.11 to 2.00). The return to work and/or daily activities was reported in 7 of the active mobilization studies. (Figure 3). The total mean difference was -20.76 days in favour of the ankle exercises group (95%CI -40.02 to -1.50).

Complications were reported entirely (and attributed to a group) in 12 studies. The nature and definition of the complications differed, but they were comparable in terms of severity. No statistically significant difference was found in the occurrence of complications (RR 1.22; 95%CI 0.60 to 2.45). Lehtonen's data skewed the results.(38)

Unprotected mobilization was described in 7 studies.(13,32,36,37,39,41,43) With the exception of Gul et al., these studies used unprotected mobilization in combination with late weight-bearing (3-6 weeks post-operatively).(13) Finsen et al. and Lund-Kristensen et al. did not report the groups in which complications occurred.(32,39) Siddique et al. did not report the complications.(41) No statistically significant difference was found in the occurrence of complications (RR 1.03; 95%CI 0.42 to 2.50).

Effect of weight-bearing

The effect of weight-bearing on postoperative recovery was reported in 11 studies that compared early versus late weight-bearing.(13,23–26,32,34,36,37,42,46) Honigmann et al. and Laarhoven van et al. reported only the median scores, and Wetzler et al. did not describe enough data for analysis. Therefore, these three studies were excluded from analyses. (36,37,46)

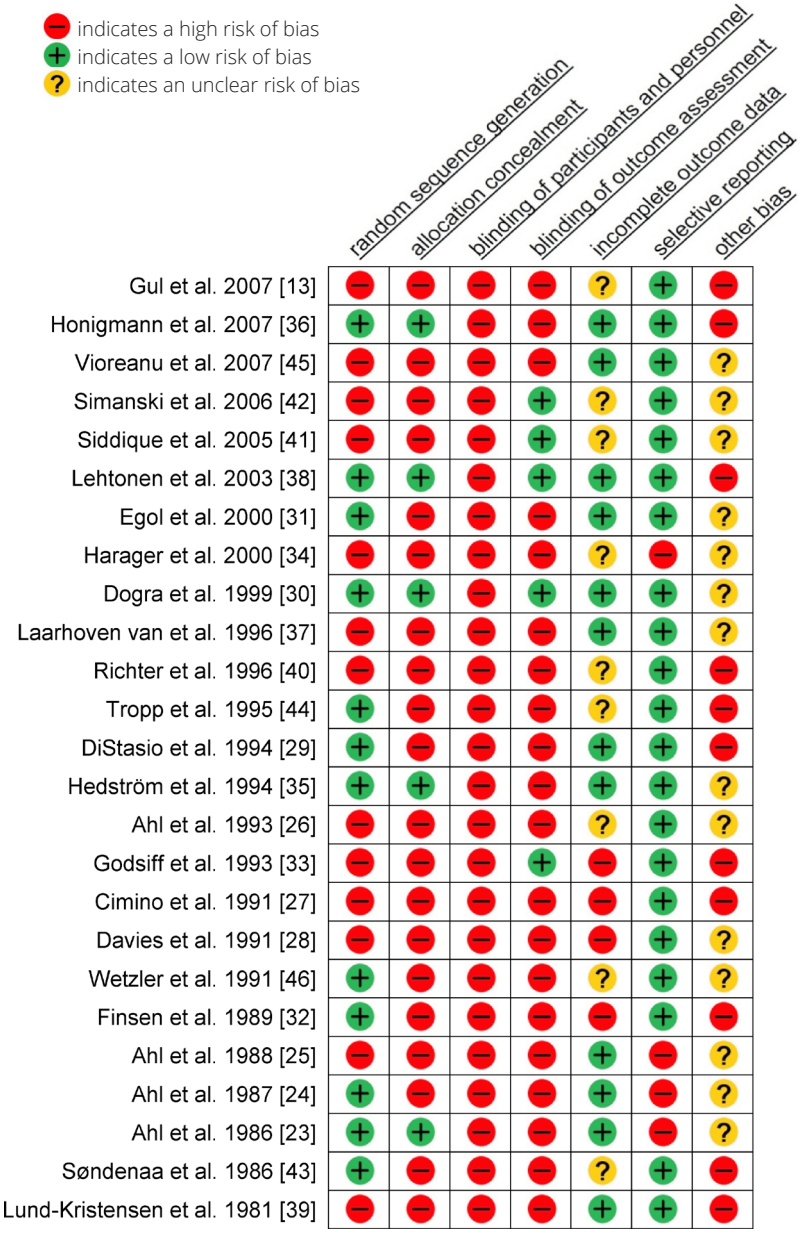

Figure 2 Risk of bias assessment

Study or Subgroup	ankle exercises Mean	SD	Total	immobilization Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Davies et al. 1991	133	0	21	203	0	20		Not estimable
Egol et al. 2000	53.8	0	27	106.5	0	28		Not estimable
Finsen et al. 1989	66.5	28	18	96.6	36.4	19	18.1%	-30.10 [-50.96, -9.24]
Gul et al. 2007	54.6	15.5	25	91.3	20.2	25	21.7%	-36.70 [-46.68, -26.72]
Lehtonen et al. 2003	65	19	50	63	13	50	22.4%	2.00 [-4.38, 8.38]
Simanski et al. 2006	64.4	38.5	23	75.6	49	23	16.4%	-11.20 [-36.67, 14.27]
Vioreanu et al. 2007	67	18.7	33	94.9	24.4	29	21.4%	-27.90 [-38.83, -16.97]
Total (95% CI)			**197**			**194**	**100.0%**	**-20.76 [-40.02, -1.50]**

Heterogeneity: Tau² = 419.80; Chi² = 52.54, df = 4 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.11 (P = 0.03)

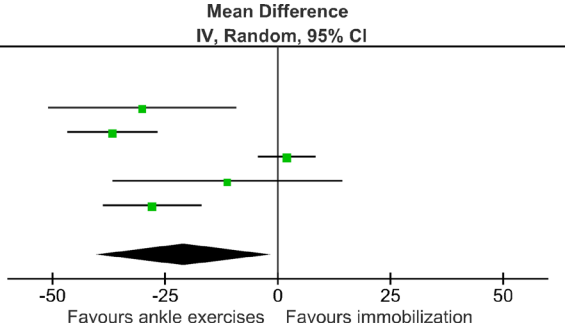

Figure 3 Effect of mobilization; return to work/daily activities
The mean difference (SD) on the return to work/daily activities is shown between the ankle exercises groups and the immobilization groups.

Study or Subgroup	early weight-bearing Mean	SD	Total	late weight-bearing Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Finsen et al. 1989	90.3	42	19	96.6	36.4	19	29.0%	-6.30 [-31.29, 18.69]
Gul et al. 2007	54.6	15.5	25	91.3	20.2	25	42.5%	-36.70 [-46.68, -26.72]
Simanski et al. 2006	64.4	38.5	23	75.6	49	23	28.5%	-11.20 [-36.67, 14.27]
Total (95% CI)			**67**			**67**	**100.0%**	**-20.62 [-42.46, 1.22]**

Heterogeneity: Tau² = 266.25; Chi² = 7.28, df = 2 (P = 0.03); I² = 73%
Test for overall effect: Z = 1.85 (P = 0.06)

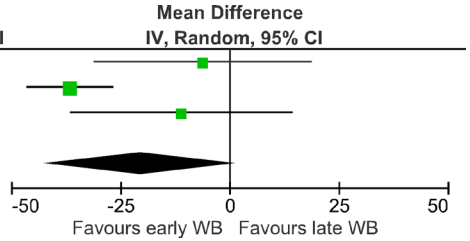

Figure 4 Effect of weight-bearing; return to work/daily activities
The mean difference (SD) on the return to work/daily activites is shown between the early weight-bearing groups and the late weight-bearing groups.

Analysis of the short-term Olerud Molander score was not possible. Although the long-term Olerud Molander score was reported in three studies, only Simanski et al. reported the SD values, so analysis of the long-term score also was not possible.(42)

Of the 11 studies, only 3 reported the mean results of return to work and/or daily activities (Figure 4). In Finsen et al., the two groups without ankle exercises (groups B and C) were used in the analysis.(32) The total mean difference was -20.62 days in favour of the early weight-bearing group (95%CI -42.46 to 1.22). For analysis of complications, 8 of the 11 studies were used. No statistically significant difference was found (RR 1.26; 95%CI 0.56 to 2.85). Weight-bearing as tolerated began immediately after surgery in 3 studies.(13,27,34) Harager et al. only reported the complications of one group.(34) Therefore, only 2 of the 3 studies were analyzable. There was no statistically significant difference in the occurrence of complications (RR 0.69; 95%CI 0.28 to 1.73).

Unprotected weight-bearing as tolerated immediately after surgery

Gul et al. was the only study to report unprotected immediate weight-bearing as tolerated.(13) No significant differences were found between the groups in the Olerud Molander score, postoperative pain intensity, and length of hospital stay. Analysis of return to work/daily activities resulted in a statistically significant mean difference of 36.7 days in favour of the unprotected immediate weight-bearing as tolerated group.

Sensitivity analyses

In the sensitivity analyses on bias, 9 studies with 5 or more high risk factors for bias were excluded.(13,25,27,28,32–34,39,40) All analyses were repeated without these studies. The results remained in favour of the same group but lost their statistical significance, indicating insufficient power to demonstrate effectiveness if only high quality studies are used (Table 1). In the sensitivity analyses on study design about the effect of mobilization on the occurrence of complications, the result became significant (RR = 3.38; 95%CI = 1.82 to 6.28). The other analyses on study design showed no significant differences. In the sensitivity analyses on time, the results remained in favour of the same group and the effect of weight-bearing on the return to work/daily activities became significant (MD -26.75; 95%CI -51.13 to -2.37).

Table 1 Results of sensitivity analyses

Outcome	Results	Sensitivity analysis on bias	Sensitivity analysis on study design	Sensitivity analysis on time
Effect of mobilization				
Olerud Molander Score on short-term*	-6.88 (-17.66; 3.91)	-6.88 (-17.66; 3.91)	0.06 (-7.18; 7.31)	-6.84 (-19.87; 6.19)
Olerud Molander Score on long-term*	-1.05 (-4.11; 2.00)	-1.05 (-4.11; 2.00)	-0.28 (-3.50; 2.94)	-2.67 (-10.06; 4.72)
Return to work/daily activities in days*	**-20.76 (-40.02; -1.50)**	-12.18 (-34.89; 10.53)	-12.45 (-43.75; 18.85)	-18.68 (-40.70; 3.33)
Complications**	1.22 (0.60; 2.45)	2.09 (0.93; 4.70)	**3.38 (1.82; 6.28)**	1.71 (0.67; 4.37)
Complications; unprotected treatment**	1.03 (0.42; 2.50)	1.05 (0.30; 3.66)	3.43 (0.15; 79.74)	***
Effect of weight-bearing				
Return to work/daily activities in days*	-20.62 (-42.46; 1.22)	***	***	**-26.75 (-51.13; -2.37)**
Complications**	1.26 (0.56; 2.85)	1.41 (0.46; 4.36)	1.05 (0.06; 17.81)	1.00 (0.41; 2.45)
Complications; weight-bearing as tolerated immediately after surgery**	0.69 (0.28; 1.73)	***	***	***

* = results are presented as mean difference (95%CI)
** = results are presented as risk ratio (95%CI)
*** = ≤ one study can be included, therefore analysis cannot be performed

Discussion

Results of this systematic review and meta-analysis on a combination of cohort studies and randomized controlled trials show that after ankle surgery, 1) active exercises accelerate return to work and daily activities compared to immobilization, 2) early weight-bearing tends to accelerate return to work and daily activities compared to late weight-bearing. Furthermore, active exercises in combination with immediate weight-bearing may be a safe option that needs to be further explored.

These conclusions are based on 25 studies, 18 of which are quasi-randomized trials used in the recently published Cochrane meta-analysis of Lin et al.(47) The Cochrane meta-analysis found limited evidence supporting early commencement of ankle exercises and weight-bearing, as it resulted in a reduced activity limitation score and an improved range of motion. However, there was also an increase in complication rates. A limitation of the Cochrane meta-analysis is that only randomized and quasi-randomized controlled trials were included, and as a result, most analyses were performed on 1-3 studies. This leads to a reduced possibility to show effectiveness. In contrast, this meta-analysis also included other study designs, which has been suggested by previous surgical and orthopaedic literature.(48,49) The randomization process in surgical trials is cumbersome and creates an artificial situation that may deviate from "normal" clinical practice substantially.(50) Therefore, results of this meta-analysis are more likely to correspond to "standard" clinical practice, despite all the drawbacks of non-randomized clinical research. This concept has been initiated in the field of surgery and we extrapolated this in the postoperative treatment. The patients cannot be blinded for their treatment regime and return to work or daily activities is a patient subjective outcome measure. Sensitivity analyses, which do not show a change in direction of the results after correcting for study quality, support this phenomenon. The sensitivity analysis according to study design for complications changed into statistical significance in favour of immobilization. These results are heavily influenced by the study of Lehtonen et al.(38)

This study provides data about return to work, which is becoming increasingly important for health care providers in current practice. We found that active mobilization results in earlier return to work and/or daily activities of 21 days. This result might lead to a cost reduction in social security payments and lost wages.(5,7,51)

Other reviews have been published on various aspects of postoperative care regimens.(14–17) Nash et al. concluded that immobilization provides no benefit, and Thomas et al. concluded that it is difficult to determine whether early motion is overall better or worse than cast immobilization.(15,17) Black et al. suggested that early weight-bearing might allow for faster rehabilitation and earlier return to work.(14) Smith et al. concluded that because of the little difference in outcome, the optimum time to

commence weight-bearing cannot be determined.(16) These reviews focused on whole postoperative care regimens rather than specific aspects of postoperative care and could not give a differentiated clinical advice. In this review, we analyzed separate aspects of the postoperative care regimen: effect of ankle exercises, weight-bearing, and unprotected treatment in order to tailor clinical advice accordingly.

Nilsson et al. suggested that a difference of 4.4 points in the Olerud Molander score is of clinical interest for a group of patients.(52) This meta-analysis shows an even greater difference in the Olerud Molander score of 6.88 points on short-term in favour of active mobilization and 8.00 points on long-term in favour of early weight-bearing. Both outcomes fail to reach statistical significance but are in concordance with previous analyses.(15,17,47)

Due to the inclusion of all relevant study designs without language restrictions, a large number of studies were evaluated in this meta-analysis. Three independent reviewers systematically evaluated the studies for risk of bias. In this quality assessment, a great deal of bias was found in the published studies, which rendered the results of these studies less reliable. The different variables used in this meta-analysis could cause heterogeneity because of poor definitions of these variables in some of the included studies. This meta-analysis describes the complications as defined in the studies, which allowed the severity of complications to be compared. However, definitions vary and thus may result in bias.

Direct active mobilization after surgery is advantageous compared to immobilization, and weight-bearing shows a similar trend. This meta-analysis shows no increased risk for complications with active mobilization after early weight-bearing. Therefore, the combination of active mobilization and early weight-bearing might be a promising strategy. Gul et al. published encouraging results on direct unprotected weight-bearing as tolerated in a retrospective study design.(13) Currently, there are two trials being conducted on the postoperative care of ankle fractures (NCT01196338 and NTR3727).

Conclusion

Active mobilization results in an earlier return to work. Both active mobilization and immediate protected weight-bearing may be safe postoperative care strategies after ankle surgery, so the regimen choice should be based on patient demands with an emphasis on active mobilization. Unprotected weight-bearing as tolerated after ankle surgery may also be a safe and promising choice. As such, future research should address this option.

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Appendix 1 Characteristics of included studies

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Ahl et al. 1986 (23) Randomized controlled trial	(A) Late weight-bearing (starting from the fourth postoperative week) in a below-knee cast (n = 22)	-	-	+	-	-	Olerud Molander score	Not reported	Not reported	Not reported	Group A: 2 older patients with osteoporosis revealed a redislocation of the lateral malleolus on radiograms	The Olerud Molander score is mentioned in the methods but the results are not reported (high risk on selective reporting).
	vs											
	(B) Early weight-bearing (starting from the first post-operative day) in a below-knee cast (n = 24)	+	-	+	-	-						
Ahl et al. 1987 (24) Randomized controlled trial	(A) Late weight-bearing (starting from the fourth postoperative week) in a below-knee cast (n = 28)	-	-	+	-	-	Olerud Molander score	Not reported	Not reported	Not reported	Group A (2) and Group B (6) cases of superficial wound infection or skin irritation The difference between the 8 cases was not significant Group B: 1 case redislocation (caused by a new trauma)	The Olerud Molander score is mentioned in the methods but the results are not reported (high risk on selective reporting).
	vs											
	(B) Immediate weight-bearing (starting from the first post-operative day) in a below-knee cast (n = 25)	+	-	+	-	-						

Results which are not used in analyses are written in italics. Complications that are not directly related to the post-operative treatment regimen and the complications with an unknown group are also written in italics.
+ = yes / present; - = no / not present

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Ahl et al. 1988 (25) Randomized controlled trial and retrospective comparisons to Ahl et al. 1986	(A) Ankle exercises without weight-bearing in a dorsal splint (n=25) vs (B) Ankle exercises with weight-bearing in an orthosis (n=26) Both groups were initially treated with a plaster cast without weight-bearing during the first postoperative week	- +	+ +	+ -	- +	- -	Olerud Molander score	Not reported	Not reported	Not reported	No complications	The Olerud Molander score is mentioned in the methods but the results are not reported (high risk on selective reporting).
Ahl et al. 1993 (26) Randomized controlled trial and retrospective comparisons to Ahl et al. 1987	(A) Ankle exercises without weight-bearing in a dorsal splint (n=19) vs (B) Ankle exercises with weight-bearing in an orthosis (n=21) Both groups were initially treated with a plaster cast without weight-bearing during the first postoperative week	- +	+ +	+ -	- +	- -	Olerud Molander score	Group A = 53 Group B = 66 (at 3 months)	Group A = 76 Group B = 82 (at 6 months) Group A = 86 Group B = 90 (at 18 months)	Not reported Not reported Not reported	Group B: 3 cases with superficial wound infection, 1 case with local wound necrosis and 1 case with skin irritation, caused by the orthosis	

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Cimino et al. 1991 (27) Partly prospective study (63/71), partly retrospective study (8/71)	(A) Immobilization in a cast (immediate full weight-bearing) (n=19)	+	-	+	-	-	---	---	---	---	Group A: 2 cases with wound complication 1 case with painful bursa (reoperation) 1 case with hardware loosening (reoperation) Group B: 2 cases with wound complication 1 case with widening of the malleoli due to syndesmosis injury Group B: 1 case with a femoral-neck fracture and a pulmonary embolism	Eight patients are previously reported (high risk on other bias). Weber A fractures are included (high risk on other bias). Three patients are mistakenly assigned to group B (high risk on other bias).
	vs											
	(B) Ankle-foot orthosis (immediate full weight-bearing) with ankle exercises (n=32)	+	+	-	+	-						

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Davies et al. 1991 (28) Prospective study	(A) Immobilization in a below-knee plaster of Paris (n = 20)	-	-	+	-	-	Return to work (in days)	Group A = 203 Group B = 133	---	p = 0.084	Group A:3 cases with a wound infection Group B:2 cases with a wound infection Group A:2 cases with an early removal of metal 1 case with osteoporosis Group B: 6 cases with an early removal of metal 2 cases with osteoporosis 1 case with a combination of above described complications	
	vs	-	+	-	-	+						
	(B) Ankle exercises and continuous passive movements (after 24 hours in a below-knee plaster of Paris backslab) (n = 21)											
	Both groups were non-weight-bearing											
DiStasio et al. 1994 (29) Randomized controlled trial	(A) Immobilization in a below-knee short-leg cast (n = not reported)	-	-	+	-	-	Return to work (in days)	Group A = 186 Group B = 174	---	Reported as not significant	Group A:2 cases with a superficial wound infection Group B:1 case with a superficial wound infection Group unknown:5 cases with a removal of internal fixation hardware for local symptomatology	The results are reported for only 34% of the patients (high risk on other bias). The total number of patients is reported, but not how many of these patients are assigned to the different treatment groups (high risk on other bias).
	vs	-	+	-	+	-						
	(B) Physical therapy immediately after surgery in a removable short-leg orthosis (n = not reported)											
	Both groups were non-weight-bearing for 6 weeks (total n = 61)											

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Dogra et al. 1999 (30) Randomized controlled trial	(A) Non-weight-bearing in a plaster cast in the first two weeks postoperatively without ankle exercises (n=26)	-	-	+	-	-	Olerud Molander score	Group A = 43.4 (30 - 65) Group B = 46.2 (35 - 60) (at 12 weeks)	---	Reported as not significant	Group unknown: 1 case of superficial wound infection	
	vs	-	+	+	-	-						
	(B) Non-weight-bearing with ankle exercises in the first two weeks postoperatively. The ankle was resting in a plaster slab at all other times. (n=26) In both groups a below-knee plaster cast was applied after two weeks, graduated weight-bearing was instructed.											

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Egol et al. 2000 (31) Randomized controlled trial	(A) Non-weight-bearing fibre-glass short-leg cast without ankle exercises After 6 weeks patients started physiotherapy (n=28)	-	-	+	-	-	Return to work (in days) (35 out of 55 patients)	Group A = 106.5 Group B = 53.8	---	p = 0.007	Group A: 1 case with pulmonary embolus	
	vs											
	(B) Non-weight-bearing in a removable functional brace (aircast) with active and passive exercises of the ankle and subtalar joint by a physiotherapist Patients continued the ankle exercises at home (n=27)	-	+	-	+	-						
	Both groups were initially treated for the first 2 or 3 days with a plaster A-O splint Both groups started weight-bearing at 6 weeks											

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Finsen et al. 1989 (32) Randomized controlled trial	(A) Non-weight-bearing in a light-weight plaster-of-Paris cast (n=19)	-	-	+	-	-	Return to work (in days)	Group A = 96.6 (SD = 36.4) Group B = 66.5 (SD = 28) Group C = 90.3 (SD = 42)	---	reported as not significant	Group C: 1 case with readmission because of swelling, irritation of the skin and blistering Group unknown:2 cases with a superficial wound infection 1 case with a deep wound infection 3 cases with a superficial infection or a small area of necrosis of the skin after removal of the plate and screw.	The total loss to follow-up is reported, but not how the loss to follow-up is divided between the different treatment groups (high risk on other bias).
	vs											
	(B) Non-weight-bearing without a plaster cast (first three days in a plaster-of-Paris splint) with ankle exercises (n=18)	-	+	-	-	+						
	vs											
	(C) Weight-bearing in a below-knee cast with a rubber walker (n=19)	+	-	+	-	-						
Godsiff et al. 1993 (33) Prospective study	(A) No early ankle exercises in a non-weight-bearing cast for 6 weeks (n = 20)	-	-	+	-	-	---	---	---	---	Not reported	Weber A fractures are included (high risk on other bias).
	vs											
	(B) Early active and passive ankle exercises in a non-weight-bearing cast for 6 weeks (n = 27)	-	+	+	-	-						

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Gul et al. 2007 (13) Retrospective study	(A) Immobilization and non-weight-bearing in a plaster cast (n=25)	-	-	+	-	-	Olerud Molander score	---	Group A = 84 Group B = 82 (at an average 37,5 months)	p = 0.858	Group A: 1 case with superficial wound infection 1 case with a pulmonary embolism 1 case with loss of internal fixation at one week which was re-operated 1 case with non-union who refused re-operation Group B: 3 cases with superficial wound infection who were put in an ankle brace to limit dorsal and plantar flexion for 1-2 weeks but were allowed to continue with full weight-bearing 1 case of posttraumatic arthritis Group B: 2 cases of syndesmotic screw breakage	Weber A fractures are included (high risk on other bias).
	vs											
	(B) Immediate functional and full weight-bearing mobilization without a plaster cast (n=25)	+	+	-	-	+	Return to work (in days)	Group A = 91.3 (SD = 20.2) Group B = 54.6 (SD = 15.5)	---	p < 0.001		

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Harager et al. 2000 (34) **Partly prospective and partly retrospective study**	(A) Non-weight-bearing for 3 weeks followed by 3 weeks of weight-bearing (n = 73)	-	-	+	-	-	---	---	---	---	Group A: Not reported Group B: 5 cases with a superficial wound infection 1 case with a slightly dislocated fracture 2 cases with a deep venous thrombosis	The hospital stay is mentioned in the methods but the quantitative results are not reported (high risk on selective reporting). The complications of group A are also not reported (high risk on selective reporting).
	vs											
	(B) Immediate full weight-bearing in a below-knee walking cast (n = 62)	+	-	+	-	-						
Hedström et al. 1994 (35) **Randomized controlled trial**	(A) Weight-bearing in a walking cast without ankle exercises (n=25)	+	-	+	-	-	Olerud Molander score	Group A = 70 Group B = 80 (at 3 months)		Reported as not significant	Group A: 1 case with superficial wound infection	
	vs								Group A = 85 Group B = 85 (at 6 months)	Reported as not significant	Group B: 2 cases with superficial wound infection	
	(B) Weight-bearing in an orthosis with ankle exercises (n=28)	+	+	-	+	-				Reported as not significant	Group B: 4 cases with arthrosis	
									Group A = 88 Group B = 100 (at 18 months)			

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Honigmann et al. 2007 (36) Randomized controlled trial	(A) Functional postoperative treatment without external stabilization (full weight-bearing after 6 weeks) (a plaster of Paris splint was applied for 2-4 days) (n=22) vs (B) Weight-bearing in a vacuum orthosis (vacoped) (full weight-bearing is allowed after 14 days) (n=23) Both groups had 15kg weight-bearing starting between 2nd and 4th postoperative day. Both groups had free ankle movements	-	+	-	-	+	Olerud Molander score (median)	Group A = 42.5 Group B = 42 (at 6 weeks)	---	p = 0.46	No complications	Weber A fractures are included (high risk on other bias).
								Group A = 72 Group B = 69 (at 10 weeks)	---	p = 0.55		
		+	+	-	+	-	Return to work (in days) (median)	Group A = 53 Group B = 37	---	p = 0.79		

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Laarhoven van et al. 1996 (37) Prospective study	(A) Non-weight-bearing functional unprotected mobilization and crutches (n=40)	-	+	-	-	+	Olerud Molander score (median)	Group A = 40 Group B = 45 (at 10 days)	---	p = 0.47	Group A: 2 cases with a superficial wound infection 1 case with osteitis	
								Group A = 50 Group B = 65 (at 6 weeks)		p = 0.02	Group B: 4 cases with a superficial wound infection	
	vs	+	-	+	-	-						
	(B) Early weight-bearing in a below-knee walking plaster (n=41)							Group A = 80 Group B = 85 (at 3 months)		p = 0.84	Group unknown: 3 cases with secondary dislocation after operation	
	Both groups were initially treated for two to five days with a plaster cast postoperatively								Group A = 95 Group B = 95 (at 1 year)	p = 0.90	1 case with delayed union 2 cases with Sudeck's dystrophy	
							Return to work (in days) (median)	Group A = 79 Group B = 78	---	p = 0.54		

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Lehtonen et al. 2003 (38) Randomized controlled trial	(A) Below-knee plaster cast; after 2 weeks partial weight-bearing in a fibreglass short leg walking cast and full weight-bearing at 4 weeks (n=50) vs (B) Functional Air-Stirrup ankle brace (Aircast); after 2 weeks partial weight-bearing and full weight-bearing at 4 weeks (n=50)	+	-	+	-	-	Olerud Molander score	Group A = 54 (SD = 13) Group B = 52 (SD = 14) (at 6 weeks)		Reported as not significant	Group A: 4 cases with a superficial wound infection 2 cases with a deep-vein thrombosis	Weber A fractures are included (high risk on other bias).
		+	+	-	+	-		Group A = 75 (SD = 14) Group B = 75 (SD = 13) (at 12 weeks)		Reported as not significant	1 case with chronic dysesthesia of the skin Group B: 16 cases with a superficial wound infection	
									Group A = 89 (SD = 8) Group B = 88 (SD = 9) (at 52 weeks)	Reported as not significant	4 cases with a deep wound infection 3 cases with dehiscence of the wound	
									Group A = 87 (SD = 8) Group B = 87 (SD = 9) (at 2 years)	Reported as not significant	3 cases with chronic dysesthesia 1 case with local skin necrosis 1 case with chronic allodynia 1 case with loss of internal fixation	
							Return to work (in days)	Group A = 63 (SD = 13) Group B = 65 (SD = 19)	---		1 case with refracture of the lateral malleolus Group A: 1 case with chronic skin irritation Group B: 2 cases with chronic skin irritation 1 case with postspinal headache	

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Lund-Kristensen et al. 1981 (39) **Prospective study**	(A) Dorsal plaster-of-Paris splint for 2 to 10 days (average 3 days) with ankle exercises after removal of the dorsal splint (n=10)	-	-	+	-	-	---	---	---	---	Group unknown: 1 case with a small abscess over a loose screw 1 case with pes equines	Weber A fractures are included (high risk on other bias). Very low number of patients (n=28) are included (high risk on other bias).
	vs (B) Plaster-of-Paris cast (for 4 to 6 weeks postoperative); as soon as possible the patients were mobilized using crutches (n=3)	-	+	+	-	-						
	vs (C) Without any external fixation with ankle exercises (n=15) All groups became weight-bearing on average at 9 weeks.	-	+	-	-	+						
Richter et al. 1996 (40) **Prospective study**	(A) Plaster immobilization (non-weight-bearing) (n=19)	-	-	+	-	-	Olerud Molander score	---	Group A = 85.0 Group B = 92.4 (on average at 17,3 months)	Not reported	No complications	Children are included (high risk on other bias).
	vs (B) Early mobilization (n=42)	-	+	-	-	-						

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Siddique et al. 2005 (41) **Prospective study**	(A) Immobilization in a below-knee plaster cast (n=22)	-	-	+	-	-	Olerud Molander score	Group A = 33.0 (SD = 19.0) Group B = 39.2 (SD = 19.5) (at 6 weeks)	---	p = 0.29	Not reported	
	vs (B) Mobilization without a cast (n=22) Both groups were treated with partial weight-bearing at 4 weeks and gradually progressed to full weight-bearing	-	+	-	-	+		Group A = 67.5 (SD = 21.9) Group B = 69.5 (SD = 22.5) (at 12 weeks)	---	p = 0.76		
Simanski et al. 2006 (42) **Partly prospective and partly retrospective study**	(A) Immobilization (no functional treatment) in a below-knee plaster cast without weight-bearing (starting in a below-knee splint until ankle swelling was reduced) (n=23)	-	-	+	-	-	Olerud Molander score	---	Group A = 79 (SD = 19) Group B = 87 (SD = 14) (at least at 12 months)	p = 0.25	Group A: 1 case with pseudarthrosis of the fibula 2 cases with superficial wound infection 1 case with reflex sympathetic dystrophy (p = 0.66) Group B: 1 case with reflex sympathetic dystrophy 1 case with an allergic reaction to the chrome-nickel plate	
	vs (B) Early functional (active and passive ankle exercises) treatment in a brace (aircast) with immediate partial weight-bearing; full weight-bearing after 3 weeks (n=23)	+	+	-	+	-	Return to work (in days)	Group A = 75.6 (SD = 49.0) Group B = 64.4 (SD = 38.5)		p = 0.63		

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Søndenaa et al. 1986 (43) Randomized controlled trial	(A) Non-weight-bearing immobilization in a plaster cast (n=23)	-	-	+	-	-	---	---	---	---	Group B: 1 case with a superficial wound infection	Weber A fractures are included (high risk on other bias).
	vs	-	+	-	-	+						
	(B) Unprotected non-weight-bearing with active ankle exercises (after 3 days of pain immobilization in a plaster slab) (n=20) Both groups were allowed full weight-bearing after 6 weeks											
Tropp et al. 1995 (44) Randomized controlled trial	(A) Immobilization in a plaster cast (n = 15)	+	-	+	-	-	Modified Olerud Molander score	Group A = 70 (SD = 21) Group B = 77 (SD = 19) (at 10 weeks)		Reported as not significant	Group A: no complications Group B: 1 case with a wound with slight secretion	Very low number of patients (n=30) are included (high risk on other bias). The total number of patients is reported, but not how many of these patients are assigned to the different treatment groups (high risk on other bias).
	vs											
	(B) Early mobilization in an ankle brace (n = 15) In both groups weight-bearing was allowed	+	+	-	+	-			Group A = 88 (SD = 22) Group B = 92 (SD = 10) (at 12 months)	Reported as not significant		

Publication and study design	Groups (n = number of patients)	Protection					Outcome	Results 6-12 weeks	Results ≥ 6 months	P value	Complications	Details bias assessment
		Weight-bearing	Mobili-zation	Cast	Orthosis	Unpro-tected						
Vioreanu et al. 2007 (45) Prospective study	(A) Immobilization in a below-knee nonremovable fibreglass cast (non-weight-bearing) (n=29)	-	-	+	-	-	Olerud Molander score	Group A = 63.75 (SD = 9.19) Group B = 79.92 (SD = 11.32) (at 9 weeks)	---	p < 0.05	Group A: 2 cases with deep vein thrombosis of popliteal vein Group B: 1 case with a superficial wound infection	
	vs											
	(B) Early mobilization in a removable fibreglass cast with active and passive ankle exercises (non-weight-bearing) (n=33)	-	+	+	-	-		Group A = 81.07 (SD = 9.56) Group B = 93.17 (SD = 8.76) (at 12 weeks)	---	Reported as not significant	1 case with break down and subsequent infection of the wound which needed removal of hardware	
	Both groups were initially treated for 10 to 14 days in a dorsal plaster of Paris splint						Return to work (in days)	Group A = 94.9 (SD = 24.4) Group B = 67 (SD = 18.7)	---	p < 0.05	1 case with a deep wound infection which needed removal of hardware	
Wetzler et al. 1991 (46) (abstract only) Randomized controlled trial	(A) Short leg cast for 6 weeks (n = 25)	-	-	+	-	-	Return to work (in days)	No difference between both groups	---	Reported as not significant	Number of complications in both groups are not significantly different	
	vs											
	(B) Pneumatic walker for 1 to 2 weeks and then a pneumatic ankle brace (n = 20)	+	+	-	+	-						

CHAPTER FOUR

The isolated posterior malleolar fracture and syndesmotic instability: a case report and review of the literature

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Abstract

Background

Ankle fractures are among the most common type of fractures in the lower extremity. A posterior malleolar fracture is frequently part of a more complex ankle fracture and only in rare cases it occurs as isolated injury. Posterior malleolar fractures often occur with associated injuries, such as a Maisonneuve fracture or with bi- or trimalleolar ligamentous injuries. Knowledge about these associated injuries is essential to prevent missed diagnoses. The aim of this article is to describe the isolated posterior malleolar fracture, the possible associated injuries, the diagnostic work-up and therapeutic consequences.

Case report

We present a case of a 26-year-old male patient who sustained an isolated posterior malleolar fracture with 4.5 years follow-up.

Discussion

Isolated fractures of the posterior malleolus are uncommon injuries. Diagnosis, treatment and outcome can seldom be extracted from large series. However, several cases have been described in literature, which we have summarized.

Conclusion

This case report and literature review shows that isolated posterior malleolar fractures might occur as part of a more complex ankle injury, in combination with a fracture of the lower leg or after high energy trauma. Physicians should be aware of these associated injuries. Diagnostic work-up should include X-rays of the knee and lower leg and a CT scan of the ankle. If diagnosed and treated properly, isolated posterior malleolar fractures have a good long-term functional outcome.

Background

Ankle fractures are among the most common type of fractures in lower extremity injuries (1). A fracture of the posterior malleolus is frequently present in combination with other injuries such as pilon tibiale fracture, spiral tibial shaft fracture, or as part of bi- or trimalleolar ankle fracture (2;3). Posterior malleolar fractures and their treatment are frequently discussed (2;4). However, an isolated posterior malleolar fracture is an uncommon injury as it occurs in about 1-4% of all ankle fractures (5;6). Nonetheless, case reports of isolated posterior fractures have been published since 1828 (7). An isolated posterior malleolar fracture is also known as a Volkmann's fracture or an Earle's fracture (7;8). This injury is easily missed on plain radiographs and requires awareness of the treating physician (9). In the present study, we describe a patient with an isolated posterior malleolar fracture including the long-term follow-up, which has been reported in line with the SCARE statement (10).

The aim of this article is to describe the isolated posterior malleolar fracture, possible associated injuries, diagnostic work-up and therapeutic consequences by presenting a case and summarizing current literature.

Case Report

A 26-year-old male patient attended the emergency department in October 2010 because of pain in his left ankle. The pain had occurred after a backward fall while his left foot stayed fixed to the ground, while playing tennis. The ankle was immediately painful, swollen and the patient was unable to bear weight. He did not have any other complaints or signs of injury.

His medical history was limited to stomach pains for which he used omeprazole 40 milligram capsules and he had hay fever. He smoked and had a body mass index of 29.1.

On physical examination swelling and tenderness was present at the left medial malleolus. Significant tenderness was present over the posterior aspect of the lateral malleolus. In addition, dorsiflexion was impossible because of pain. Further range of motion was not limited, but was subjected to pain. There were no neurovascular injuries and there was no pain at the proximal fibula. There were no wounds, no bruising, no deformity or any other signs of injuries present.

According the Ottawa rules an ankle x-ray was made which showed an isolated posterior malleolar fracture with subtle lateralization of the talus as indicated by medial widening (11). There were no signs of a previous ankle luxation (figure 1). To exclude other fractures, x-rays of the knee and lower leg were made. These x-rays did not show any other fractures. Therefore, a Computed Tomography (CT) was performed, which confirmed an isolated posterior malleolar fracture with minimal displacement (figure 2). Lateralization of the talus was present in the coronal and transversal planes indicating syndesmotic instability (figure 3).

The patient was treated by operative fixation by an (orthopaedic) trauma surgeon, in which the talus was reduced and the syndesmosis stabilized with two syndesmotic screws (see supplementary . The posterior malleolar fracture was treated conservatively. After a day in hospital the patient was treated in a circular weight bearing cast for 6 weeks. The syndesmosis screws were removed 12 weeks after the initial trauma.

The patient had an uneventful recovery. Follow-up after 4.5 years showed a good functional outcome with an Olerud Molander score of 100 out of 100 points (12). The patient only complained about a slightly decreased mobility in his ankle during ice-skating.

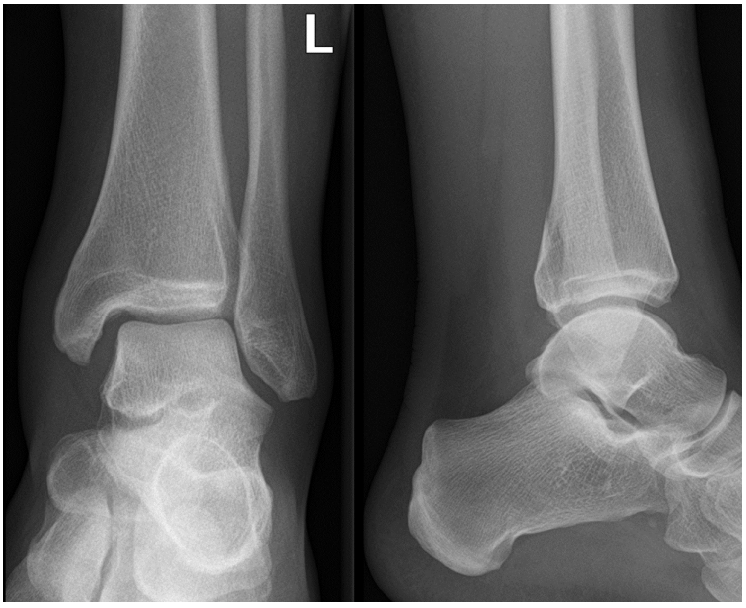

Figure 1 Mortise and Lateral View X-ray of Left Ankle
Mortise and lateral view X-ray of left ankle on the day of trauma showing an isolated posterior malleolar fracture which could be easily missed.

Figure 2 Sagital Computed Tomography Scan of Left Ankle
Sagital Computed Tomography Scan of left ankle one day after trauma showing an isolated posterior malleolar fracture with minimal displacement.

Figure 3 Transversal and Coronal View Computed Tomography Scan of Left Ankle.
Transversal and coronal view Computed Tomography scan of left ankle one day after trauma showing lateralization of the talus.

Discussion

Isolated fractures of the posterior malleolus are uncommon injuries and no large case series are available in current literature. We performed a literature serach and identified 75 cases (5;6;9;13-19). The mean age was 31.6 (±5.7) years, with men being more often affected than women (total of 45 males and 30 females). Most of them had no or small displacement and 85% were treated conservatively. Nearly all patients had an uneventful recovery and no fracture healing disorders were described (table 1).

Posterior malleolar fractures regularly occur in combination with other malleolar fractures in supination external rotation or pronation eversion injuries. An isolated fracture of the posterior malleolus should therefore be regarded as a sign of a more complex injury of the ankle joint, until proven otherwise. It can also occur in combination with a fracture of the lower leg caused by rotational force (20). Furthermore, these fractures are known injuries in parachute landings or as part of a pilon tibiale fracture (16). They result from impression of the talus on the posterior edge of the distal tibia (20). Besides other fractures, it should also be noted that ligamentous injuries can exist (5). Obviously, the tibiofibular syndesmosis injury should be suspected and the medial malleolus should be inspected for hematoma and tenderness. Therefore, knowledge of the Lauge Hansen classification, and injury pattern is important to understand the fracture type.

Initially, an isolated posterior malleolar fracture can easily be missed on plain radiographs and diagnosed as ankle sprain (9). Delayed diagnosis has shown to be associated with longer incapacity and more severe physical sequelae (cracking, pain and stiffness) (16). These findings indicate that a fracture of the posterior malleolus should be actively searched for. An x-ray of the lower leg, including the knee, should always be made to exclude a Maisonneuve fracture as in pronation eversion stage 4 injuries. A CT scan should be performed to confirm lateralization of the talus. Another advantage of the CT scan is the possibility to evaluate the size of the fragment and the congruency of the joint surface. In our opinion, stress radiographs or magnetic resonance imaging (MRI) should not be part of the standard diagnostic work-up for posterior malleolar fractures. As the diagnostic accuracy of X-rays of the ankle for undisplaced fractures is disputable, a MRI scan might be considered in patients with persistent ankle complaints without a clear diagnosis (4;21). The advantage of MRI in

this subset of patients is the ability to diagnose ligamentous injuries and osteochondral lesions.

When an isolated posterior malleolar fracture has been diagnosed, both non-operative and operative treatment are described (table). The indication for surgical treatment is still under debate (22). Size of the fracture fragment and joint congruency are often used to determine the indication for operative treatment. However, most of these discussions concern posterior malleolar fractures as part of more complex ankle injury. Surgical treatment should be considered if the fragment is larger than 5% to prevent radiographic osteoarthritis. However, the influence of fragment size and joint congruency on osteoarthritis on the long-term has only been demonstrated radiographically but not clinically (23). Several surgical techniques are used for fixation of the posterior malleolus. Good functional outcomes are described after leg screw fixation, buttress plating of the posterior fragment or screw fixation of syndesmotic injuries (24).

This case report and literature review shows that an isolated posterior malleolar fracture might occur as part of a more complex ankle injury, in combination with a fracture of the lower leg or after high-energy trauma. Physicians should be aware of these associated injuries. Diagnostic work-up should include X-rays of the knee and lower leg and a CT scan of the ankle. If diagnosed and treated properly, an isolated posterior malleolar fracture has a good long-term functional outcome.

Table 1 Previously Reported Cases of Isolated Posterior Malleolar Fractures (n = 10 prior publications)

Author	Year of publication	Number of patients	Age (y[a])	Sex (Male/ Female)	Mechanism of injury
Nugent et al. (18)	1962	2	32	F[b]	twisted ankle while stepping in a hole
			25	M[c]	motor vehicle accident with inversion of the ankle
Buschmeyer et al. (15)	1984	4	41	F	plantar flexion
			59	M	unknown
			21	F	supination
			17	M	supination eversion
Boggs (13)	1986	3	27	F	falling down the stairs
			13	F	unknown mechanism while sliding into a base
			41	F	jump from slowly moving truck
Neumaier et al. (6)	1997	25	32	13 F 12 M	11 were caused by slipping on ice or snow. Second most common cause was sporting accidents. 3 cases had a peculiar mechanism.
Bourdon et al. (14)	2008	1	56	F	unspecified
Donken et al. (5)	2011	20	31	6 F 13 M	1 traffic; 9 sports; 6 domestic 1 work; 2 other
Miller et al. (17)	2012	1	19	F	10 foot high fall
Comat et al. (16)	2014	12	30.6 (R 20-40)	12 M	parachute jump

Displaced	Size posterior malleolar fragment	Treatment	Outcome
no	10% to 15% involvement of the distal tibial articular surface	conservative	radiographic healing
NR[d]	NR	conservative	radiographic healing and pain free
no	2x0.5cm	conservative	all without restriction of movement and radiographic healing without signs of arthrosis
yes	3x1cm	operative	
no	2.5x1cm	conservative	
no	3x0.5cm	conservative	
no	unknown but without involvement of the articular surface	conservative	uneventful recovery
3 mm	25% of the articular surface	operative	radiographic healing
no	a third of the articular surface	conservative	without sequelae
21 out 24 had small displaced fragments	the articular surface was involved in all cases between 1/10 and 4/10	22 conservative 3 operative	13 out of 22 were symptom free 8 out of 22 reported swelling and pain in the ankle following extreme overload 2 out of 22 reported decreased professional capacity
NR	NR	NR	NR
median of 4mm displacement	median of 12% joint contact area	conservative	median Olerud Molander score was 100 points (median of 20 years of follow-up)
no	less than 25%	conservative	radiographic healing, return to full activity without limitations in 20 weeks
no	8 intra-articular involving less than one-third of the joint surface	conservative	6 out of 8 with late diagnosis and treatment had sequelae 0 out of 4 with early diagnosis and treatment had sequelae

Table 1 Continued

Author	Year of publication	Number of patients	Age (y[a])	Sex (Male/ Female)	Mechanism of injury
Ozler et al. (9)	2014	7	32 (R[e] 23-40)	2 F 5 M	forced plantar flexion alone or combined with axial compression in all patients (2 during sports, 4 staggered while walking and 1 was unable to describe the mechanism)
Serbest et al. (19)	2015	1	37	F	pushing brake pedal during a traffic accident while wearing high heels

[a] y = years; [b] F = Female; [c] M = Male; [d] NR = not reported; [e] R = range; [f] AOFAS = American Orthopaedic Foot & Ankle Society.
If more than 5 patients were reported, mean numbers with standard deviation in parentheses were supplied if available.

Displaced	Size posterior malleolar fragment	Treatment	Outcome
no	mean of 17% to the articular surface	conservative	AOFAS[f] ankle hindfoot mean score of 86 at 3 month follow-up 1 non-union at 6 months. no instability or degenerative changes at 1 year follow-up in all patients
yes	involving more than 25% of the articular surface	operative	AOFAS score of 96

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CHAPTER FIVE

Factors associated with wound- and implant related complications following surgical treatment of ankle fractures

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Abstract

Aim

The aim of this study was 1) to describe epidemiology of complications following surgical treatment of ankle fractures, and 2) to assess which factors are associated with the most frequent complications.

Methods

A retrospective cohort study was conducted in two level 2 and one level 1 trauma center in a single trauma region in the Netherlands. Study variables were collected from electronic patient records, all ankle fractures were classified according to the Lauge Hansen classification and complications were recorded.

Results

A total of 989 patients were included from 3 hospitals. 173 complications were observed in 156 patients (15.8%). The most frequent complication was a wound related complication, which occurred in 101 (10.2%) patients. Implant related complications occurred in 44 (4.4%) patients. Other complications such as cast pressure spots, post-traumatic dystrophy, nonunion, impingement and pneumonia occurred in 28 patients (2.8%).
The 2 most important complications were further analyzed for risk factors. Multivariate analysis showed that risk factors for wound related complications were advanced age, increased ASA classification, smoking, right as symptomatic side, open fracture and initial external fixation. Most implant related complications were caused by malreduction (n=22) or untreated syndesmotic injury (n=19). Malreduction was associated with supination eversion fractures (p=0.059) whereas untreated syndesmotic injury occurred more often after pronation external rotation fractures (p<0.001).

Conclusion

The most frequent complications after ankle fracture surgery were wound- and implant related complications. Postoperative wound related complications were multifactorial and depended on a combination of trauma-, patient- and treatment related factors. Contrary, implant related complications occurred due to the interaction between the type of fracture and subsequent surgical treatment.

Introduction

Ankle fractures are among the most common type of fractures worldwide (1). More than half of the ankle fractures occur in young men during sports activities and in older women (2;3). The diverse trauma mechanisms cause different types of ankle fractures, which can be classified using several fracture classification systems (4;5). Over the years, many systems have been developed to classify ankle fractures. The three systems most used in clinical practice and research are the 1) Lauge Hansen classification, 2) Danis-Weber classification, and 3) AO classification (4-6). The AO and Danis-Weber system only describe the bone-specific injuries of an ankle fracture, whereas the Lauge Hansen classification is more complex, but also describes the extent of ligamentous injury and thereby ankle stability (4-6). In general, stable ankle fractures are treated nonoperatively. When incongruity of the ankle mortise is present or the stability of the ankle joint is compromised, surgical treatment is indicated (7). After surgery, an accelerated functional recovery is crucial for early return to daily activities, work and sports. However, certain complications may occur following surgical treatment, resulting in delayed functional recovery or long-term disability and considerable associated costs (8-11). Several studies assessed complication rates following surgical treatment of ankle fractures, showing that wound related complications are the most frequently occurring complications (12-17). Wound related complications have been related to patient factors (i.e., age, diabetes). However, the generalizability of these studies is limited as only selected groups of patients were included in small numbers, or only a few variables were assessed. The epidemiology of complications after ankle surgery is still unclear and could be influenced by trauma-, patient- and treatment related factors. Interaction between variables is only scarcely explored. By identifying “high-risk” patients, measures can be taken to reduce or even prevent complications in these patients. The aim of this study was 1) to describe epidemiology of complications following surgical treatment of ankle fractures, and 2) to assess which factors and their interactions are associated with the most frequent complications.

Patients/Materials and Methods

A retrospective cohort study was conducted in two level 2 trauma centers (St Antonius Hospital Nieuwegein and Diakonessenhuis Utrecht) and one level 1 trauma center (University Medical Center Utrecht) in the Netherlands. Using the hospitals surgical registration database all patients with a surgically treated ankle fracture between January 2008 and January 2013 were identified using International Classification of Diseases (ICD) codes. Patients who had reached the age of 18 years or older with both pre- and postoperative radiographs (pre-operative radiographs were without a cast) of the injured ankle were included. All patients who returned for post-operative outpatient department visits were included in this study. Data were extracted from the electronic patient records. To assess fracture classification, mortise and lateral view radiographs from admission at the Emergency Room were used. Two investigators (DS and JB) classified all fractures. In case of a dispute, consensus was reached with two senior investigators (MH and FH). In addition, all fractures with implant failure were classified in a consensus meeting to classify the type of failure. Ankle fractures were assessed as being uni-, bi- or trimalleolar, complex, and were classified according to the Lauge Hansen, AO and the Weber classification (4-6).

Study Variables

Data regarding patient demographics (sex, age, body mass index, the American Association of Anesthesiologists (ASA) classification, preoperative mobility, diabetes, immunological compromise by medication or infection, peripheral arterial disease, smoking or psychiatric diseases which were present during hospital admission), trauma and fracture variables (trauma mechanism, symptomatic side, open fracture, ankle luxation fracture, fracture classification as measured by Lauge Hansen, Weber and AO classification, uni/bi/trimalleolar fracture, complex fracture), surgical variables (interval between trauma and surgery in days, whether surgery was during day or night, surgical treatment with open reduction and internal fixation or initial external fixation), postoperative variables (postoperative treatment protocol: cast immobilization and weight-bearing regime) and complications were collected. The postoperative treatment protocol was classified as weight-bearing if weight-bearing started within three weeks after surgery. Pre-operative mobility was assessed as immobile if patient used a wheelchair or crutches before the occurrence of the fracture.

Smoking was defined as a dichotomous outcome: yes or no (patients who quitted smoking were considered non-smokers). A fracture was classified as complex if a fracture consisted out of more than 2 parts.
If variables were not mentioned in the electronic patient file it was assumed that what was not recorded, was absent in the patient. This means that, e.g. peripheral arterial disease was assumed absent if not mentioned in the file, and the patient was not under supervision of a vascular surgeon nor used any medication for peripheral arterial disease. All variables were established before data extraction was performed.

Outcome Variables

All complications were noted. The used outcome variables and their definitions are described in table 1. Wound related complications included all wound healing disorders, superficial and deep wound infections. Implant related complications which required revision surgery were categorized as: 1) malreduction, 2) inadequate fixation, 3) implant breakage, 4) untreated syndesmotic injury or 5) primary failure of external fixation. All the above-mentioned outcomes were defined before data extraction was performed. Interaction was analyzed for patient related, trauma related and treatment related (surgical and post-operative) factors. All complications were analyzed for interaction between the Lauge Hansen classification and an additional factor.

Data and Statistical Analysis

Continuous parametric data were presented as means with standard deviations; dichotomous data as frequencies with percentages. Uni- and multivariate analyses were performed using univariate and multivariate logistic regression analysis in order to identify independent predictors for occurrence of postoperative wound related complications. Univariate analyses were carried out between wound related outcome and each covariate. Variables showing a p-value <0.15 in the univariate analysis were included in the multivariate analysis. Multivariate logistic regression with simultaneous entry was performed. After multivariate analyses, interaction analyses was performed. As no other variables were significantly different between those with and without implant failure, we did not carry out multivariate regression. To compare characteristics of the patients with and without implant failure, the independent samples Student's t-test was used for continuous data, and the Pearson's Chi-square was used for

Table 1 Outcomes variables and definitions used

Outcome variables	Definition used
Wound related complications	
Wound healing disorders	Any deviation in the postoperative course, but without the need for additional pharmacological or surgical intervention.
Superficial wound infection	A clinical suspicion of a wound infection based on redness and pus and/or fever in combination with the necessity of antibiotic treatment.
Deep wound infection	All characteristics of a superficial wound infection with additional surgical debridement.
Deep venous thrombosis	A deep vein thrombosis proven by ultrasound (which was only performed in case of clinical signs of a deep venous thrombosis) and treated with an anticoagulant.
Pulmonary embolisms	Emboli in the lungs proven by radiological imaging and treated with an anticoagulant.
Implant related complications	Revision surgery after the primary surgical intervention due to an unsatisfactory result, loss of reduction or a broken implant (implant failure). Broken cortical screws were considered implant failures if the fracture was not healed and/or the ankle mortise was incongruent.
Malreduction	Misalignment of medial or lateral malleolus, regardless of accompanying syndesmotic injuries.
Inadequate fixation	Malpositioned implant.
Implant breakage	Broken implant material or implant bent to the extent that it affected the congruence of the ankle mortise.
Untreated syndesmotic injury	The lack of placement of syndesmotic screw resulting in an incongruent ankle mortise.

dichotomous and categorical data. To test the interaction of the Lauge Hansen classification and the type of implant related complication a Fisher-Freeman-Halton test was performed. Missing data were excluded from analyses. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Approval

In accordance with the legal departments of the participating hospitals and their local Ethics Commission, individual patient approval was not required due to full anonymity of the included patients and the retrospective study design.

Results

Baseline Demographics

A total of 989 patients treated between January 2008 and January 2013 were included, ranging from 18 to 96 years old. Patient, trauma and fracture characteristics are summarized in Table 2. The majority of patients were considered healthy (ASA 1 or ASA 2 in 89%) and history of smoking was present in 27% of patients. The major causes were traffic, falls and sports (55% of population). Almost half (46%) were unimalleolar fractures, and Weber B fractures (68%) were the most common. Only 1% of all surgically treated ankle fractures occurred as part of multiple injuries in polytrauma patients. The BMI and ASA classification was missing in 193 and 66 patients respectively and were therefore excluded from in the multivariate analyses. For all other (surgical) variables 10 cases in total had missing data.

Characteristics of surgery and postoperative care are summarized in Table 3. Patients had surgical treatment on average 5 days after trauma. The majority were surgically treated during day hours (87%). Early weight-bearing (within 3 weeks, with or without cast) was applied in 20% of the cases with a mean start at 2.0±1.0 weeks. Late weight-bearing (after 3 weeks) was applied in 79% of the cases with a mean start at 5.7±1.3 weeks.

Complications

Complications occurred in 156 (16%) patients, of which 13 patients had multiple complications, resulting in 173 complications (Table 4). Of all complications 58% were wound related. A total of 101 (10% of the study population) patients had a postoperative wound related complication of which 28 (3%) were wound healing disorders, 46 (5%) superficial wound infections and 27 (3%) deep wound infections. Implant related complications accounted for 25% (n=44; 4% of the study population) of all complications.

Table 2 Patient demographics of all included patients with an ankle fracture

Characteristics	Study population (n = 989)	percentage
Patient demographics and medical history		
Age (mean±SD)	48.1±17.9	n/a
Gender male	423	42.8%
BMI (mean±SD)	27.1±4.9	n/a
ASA classification		
I	553	55.9%
II	322	32.6%
III	47	4.8%
IV	1	0.1%
Pre-operative immobility	34	3.4%
Diabetes	67	6.8%
Immunologically compromised	24	2.4%
Peripheral arterial disease	9	0.9%
Smoking	270	27.3%
Psychiatric disease (in the past)	109	11.0%
Trauma and fracture demographics		
Trauma mechanism		
Simple inversion trauma	359	36.3%
Fall < 3 meters	165	16.7%
Fall > 3 meters	9	0.9%
Traffic	199	20.1%
Car accident	16	1.6%
Motor accident	13	1.3%
Scooter accident	23	2.3%
Bicycle accident	135	13.7%
Pedestrian accident	12	1.2%
Sport	168	17.0%
Suicide attempt	2	0.2%
Other	39	3.9%
Unknown	48	4.9%
Symptomatic side left	457	46.2%
Open fracture	44	4.4%
Ankle luxation fracture	150	15.2%
Complex fracture	210	21.2%
Polytrauma	12	1.2%

Table 2 Continued

Characteristics	Study population (n = 989)	percentage
Fracture classification		
Uni/bi/trimalleolar		
Unimalleolar	458	46.3%
Bimalleolar	296	29.9%
Trimalleolar	235	23.8%
Weber classification		
Weber A	4	0.4%
Weber B	675	68.3%
Weber C	251	25.4%
No fibular fracture	59	6.0%
Lauge Hansen		
Supination Adduction	24	2.4%
Supination External Rotation	652	65.9%
Pronation Abduction	24	2.4%
Pronation External Rotation	280	28.3%
Pronation Dorsiflexion	2	0.2%
Not classifiable	7	0.7%
AO-classification		
44-A1	1	0.1%
44-A2	2	0.2%
44-A3	1	0.1%
44-B1	268	27.1%
44-B2	186	18.8%
44-B3	173	17.5%
44-C1	99	10.0%
44-C2	111	11.2%
44-C3	38	3.8%
Only medial fracture	47	4.8%
Medial and posterior fracture	6	0.6%
Fibular and posterior fracture	55	5.6%
Only posterior fracture	2	0.2%

SD = Standard Deviation; BMI = Body Mass Index (weight / (weight in kilograms)^2); n/a = not applicable; BMI had a total of 193 missings, ASA classification 66 and the other variables had none

Table 3 Surgery demographics of all included patients with an ankle fracture

Characteristics	Study population (n = 989)	percentage
Surgery and postoperative care		
Interval between trauma and surgery in days (mean±SD)	5.36±8.4	n/a
Time of surgery		
Day (8:00 – 18:00 hours)	862	87.2%
Overnight (18:00 – 8:00 hours)	126	12.8%
External fixation	20	2.0%
Postoperative care		
Weight-bearing starting before 3 weeks post-surgery	205	20.8%
Cast immobilization	469	47.6%
Type of internal fixation		
Lateral fracture		
2x screw fixation	111	11.2%
Screw fixation and neutralization plate	314	31.7%
Compression plate or bridging plate	364	36.8%
No fixation	61	6.2%
Other	74	7.5%
Not applicable	65	6.6%
Medial fracture		
1x screw fixation	35	3.5%
1x screw fixation and Kirschner-wire	85	8.6%
2x screw fixation	138	14.0%
Zuggertung fixation	122	12.3%
No fixation	72	7.3%
Other	46	4.7%
Not applicable	491	49.6%
Posterior fracture		
1x screw fixation	41	4.1%
2x screw fixation	25	2.5%
No fixation	227	23.0%
Other	14	1.4%
Not applicable	682	69.0%
Syndesmosis screw	184	18.6%

SD = Standard Deviation; n/a = not applicable; in the surgery and postoperative care section there were a total of 10 missings and the other variables had none

Table 4 Complications after ankle fracture surgery

Complication	frequency	percentage
Wound related complications	101	10.2%
Wound healing disorders	28	2.8%
Superficial wound infection	46	4.7%
Deep wound infection	27	2.7%
Implant related complications	44	4.4%
Deep venous thrombosis	5	0.5%
Pulmonary embolism	2	0.2%
Other	21	2.1%

Other complications such as deep venous thrombosis, pulmonary embolisms, cast pressure spots, post-traumatic dystrophy, malunion, nonunion, impingement, pneumonia and urinary tract infection occurred in 28 patients (3%). The rate of complications did not differ between the level 1 and level 2 trauma centers (p=0.739).

The two most frequent complications (wound related complications and implant related complications) were further analyzed as the combination of these encompassed 84% of all postoperative complications.

Univariate analysis of wound related complications demonstrated that an older age, an ASA 3/4 classification as compared to 1/2, preoperative immobility, smoking, (history of) psychiatric disease, right as symptomatic side, open fracture, bimalleolar or trimalleolar fractures and initial external fixation impart a significant higher risk of wound related complications (Table 5). Multivariate analysis showed that age, smoking, right as symptomatic side, open fracture and initial external fixation are independent variables that have a significant higher risk on wound related complications (Table 5). Interaction analyses did not result in relevant or significant results, indicating the remaining factors were unique parameters.

A total of 44 patients (4%) had implant related complications of which some occurred for multiple reasons (Table 6). Most implant related complications were caused by malreduction (n=22) or had an untreated syndesmotic injury (n=19) (Table 6). Only 5 patients (1%) had implant breakage after surgery. Patients with implant related complications had a shorter interval between time of injury and subsequent surgery (3.3±3.9 days) compared to patients without implant failure (5.5±8.5 days) (p=0.031).

Table 5 Factors associated with wound related complications, univariate and multivariate analyses

Characteristics	No wound complications (n=888)	Wound complications (n=101)	Univariate analysis	Multivariate analysis
			Odds Ratio (95%CI)	Odds Ratio (95%CI)
Patient demographics and medical history				
Age (mean±SD)	**47.2±17.7**	**55.3±18.2**	**1.03* (1.01-1.04)**	1.03* (1.01-1.04)
Gender male	379 (42.7%)	44 (43.6%)	1.04 (0.68-1.57)	
BMI (mean±SD)	27.1±5.0	26.9±4.6	0.99 (0.95-1.04)	
ASA classification				
I	509 (61.5%)	44 (46.3%)	RC	
II	285 (34.4%)	37 (38.9%)	0.67 (0.42-1.06)	
III	33 (4.0%)	14 (14.7%)	3.17* (1.56-6.45)‡	
IV	1 (0.1%)	0 (0%)		
Pre-operative immobility	27 (3.0%)	7 (6.9)	2.38* (1.01-5.60)	0.87 (0.30-2.55)
Diabetes	56 (6.3%)	11 (10.9%)	1.82 (0.92-3.59)	0.99 (0.44-2.21)
Immunologically compromised	21 (2.4%)	3 (3.0%)	1.26 (0.37-4.31)	
Peripheral arterial disease	8 (0.9%)	1 (1.0%)	1.10 (0.14-8.89)	
Smoking	**234 (26.4%)**	**36 (35.6%)**	**1.55* (1.00-2.39)**	2.04* (1.26-3.32)
Psychiatric disease (in the past)	89 (10.0%)	20 (19.8%)	2.22* (1.30-3.79)	1.83 (0.96-3.48)
Fracture demo-graphics				
Symptomatic side right	**467 (52.6%)**	**65 (64.4%)**	**1.63* (1.06-2.50)**	2.07* (1.28-3.34)
Open fracture	**30 (3.4%)**	**14 (13.9%)**	**4.60* (2.35-9.01)**	3.06* (1.27-7.37)
Ankle luxation fracture	129 (14.5%)	21 (20.8%)	1.54 (0.92-2.59)	0.91 (0.49-1.70)
Comminuted fracture	184 (20.7%)	26 (25.7%)	1.33 (0.83-2.13)	
Polytrauma	12 (1.4%)	0 (0%)	NC	

Table 5 Continued

Characteristics	No wound complications (n=888)	Wound complications (n=101)	Univariate analysis	Multivariate analysis
			Odds Ratio (95%CI)	Odds Ratio (95%CI)
Uni/bi/tri-malleolar				
Unimalleolar	428 (48.2%)	30 (29.7%)	RC	RC
Bimalleolar	257 (28.9%)	39 (38.6%)	2.17* (1.31-3.57)	1.64 (0.93-2.90)
Trimalleolar	203 (22.9%)	32 (31.7%)	2.25* (1.33-3.80)	1.84 (0.99-3.39)
Surgery and postoperative care				
Interval between trauma and surgery in days (mean±SD)	5.3±8.5	5.9±6.7	1.01 (0.99-1.03)	
Time of surgery				
Overnight surgery (18:00 – 8:00 hours)	110 (12.4%)	16 (15.8%)	1.33 (0.75-2.35)	
Day (8:00 – 18:00 hours)	777 (87.6%)	85 (84.2%)		
Initial external fixation	**11 (1.2%)**	**9 (8.9%)**	**7.80* (3.15-19.31)**	4.39* (1.43-13.49)
Postoperative care				
Start weight-bearing within first three weeks post-operatively	183 (20.7%)	22 (22.0%)	1.08 (0.66-1.78)	
Immobilization	413 (46.7%)	56 (55.4%)	1.42 (0.94-2.15)	0.88 (0.55-1.43)

CI = Confidence Interval; RC = Reference Category; NC = Not Calculable; ‡ = because ASA 4 was classified to one patient, this patient was included in the group with ASA 3 patients for analysis; * = A p-value less than 0.05 was considered statistically significant

Table 6 Type of implant related complication and ankle fracture classification using Lauge Hansen

Type of implant related complication	Supination adduction (24)	Supination external rotation (652)	Pronation abduction (24)	Pronation external rotation (280)	p-value^
Malreduction (n=22)	1	15	0	6	0.059
Inadequate fixation (n=9)	0	5	0	4	1.000
Untreated syndesmotic injury (n=19)	0	5	0	14	<0.001*
Implant breakage (n=3)	0	2	1	0	0.130
Primary failure of external fixation (n=2)	0	1	1	0	0.130
Total (n=55)	1	28	2	24	

* = A p-value less than 0.05 was considered statistically significant;
^A Fisher-Freeman-Halton exact test was performed because for every type of implant failure the expected count was less than 5 in more than 20%.

Univariate analysis and subsequent multivariate analysis demonstrated that all other characteristics were not statistically different between patients with implant failure and patients without implant failure. Bivariable interaction analysis of fracture classification and type of implant related complication showed a significant correlation between pronation exorotation injuries and untreated syndesmotic injuries ($p<0.001$). Malreduction was associated with supination eversion fractures ($p=0.059$).

Discussion

The most frequent complications after ankle fracture surgery were wound- and implant related complications. Wound related complications were multifactorial and depended on a combination of patient related, trauma related and treatment related factors but not on postoperative treatment protocols. The type of implant related complication was dependent on the interaction between the type of fracture and subsequent surgical treatment, but the occurrence was not related to patient, or trauma related factors.

After ankle fracture surgery, more than half of all unplanned readmission are due to causes unrelated to the surgery or surgical site (18). This affirms, that apart from fracture related factors, patient related factors are important in the selection of patients for surgical treatment of ankle fractures. We demonstrated that age was one of the significant risk factors for wound related complications, which was earlier demonstrated by Miller et al. and Louie et al (8;19). Geriatric patients (70 years or older) had an odds ratio of 2.395 (95%CI 1.450 to 3.955; results not shown) for wound related complications compared to patients younger than 70 years. As the incidence of geriatric ankle fractures is rising, this will be an increasing problem and efforts should be made to face the challenges in these mostly osteoporotic fractures (20;21). More minimal invasive surgical techniques are currently under investigation, however, these techniques are to be positioned in their adequate indication area (22-24). An older age is frequently accompanied by diabetes, but also in the younger population the prevalence of diabetes has increased. Diabetes influences the microcirculation and therefore might influence wound healing. Surprisingly, diabetes was only suggestive for an increased complication risk in the present study ($p=0.086$). Earlier studies demonstrated that an elevated HbA1c level increased the risk of complications (25;26). Although

it is beyond the scope of this study, in the Netherlands most patients with diabetes are closely monitored and it is tempting to speculate that adequately controlled diabetes should not be considered a risk factor.
Another factor that is usually associated with wound complications due to vascular compromise is smoking. In the present study smoking was confirmed to be a risk factor for the development of wound complication (27;28). However, this study was not designed to determine the impact of continued smoking after surgery versus quitting smoking prior to surgery. There is compelling literature that quitting preoperatively has a positive impact on the complication rate and therefore the operating surgeon should encourage the cessation of smoking (29).
Patient related factors are frequently interrelated with fracture characteristics. An open fracture is more prone to wound related complications. In elderly patients, this will most likely be caused by soft tissue damage resulting in a worse environment for wound healing. In younger patients, an open fracture is most likely due to high energy impact resulting in more soft-tissue injury (30). However, high quality evidence concerning the treatment of open ankle fractures is lacking (31). In open fractures, external fixation might be a suitable treatment option. Furthermore external fixation is used in polytrauma patients as damage control orthopedics or in patients with severe co-morbidity (32). The present study showed an increased risk of wound related complication after initial external fixation. Therefore, if not part of a polytrauma patient, immediate internal fixation for ankle fractures might be preferable.
Furthermore, postoperative treatment protocols might influence outcome. Previous studies showed that early mobilization did not increase wound related complications and might even shorten hospital stay (33;34). In the present study, early weight-bearing did not show a higher complication rate compared to late weight-bearing. It should be noted that most “weight-bearing” patients in the present study used a walking cast. Other studies suggest that patients with normal protective sensation can safely bear weight sooner than most protocols permit, even in the elderly patients (34;35).
In contrast to the earlier mentioned combination of factors leading to wound related complications, the type of fracture and subsequent surgical treatment were parameters associated with the type of implant related complications. This interaction has scarcely been studied and has only been examined without the use of the Lauge Hansen classification

(36). Ovaska et al. showed that patients were more often re-operated due to implant related complications if the posterior or medial malleolus was involved in the fracture. Implant related complications were most common (59%) at the syndesmosis (36). This was confirmed in our study in which malreduction and untreated syndesmotic injury were the most common reasons for implant related complications. Both were associated with specific types of fractures according to the Lauge Hansen classification. Anatomical reduction and fixation in "simple" supination eversion fractures should be achieved whereas syndesmotic injury must be suspected in pronation external rotation fractures. A malreduced syndesmotic injury results in significantly worse functional outcomes and even increases the risk on wound complications (17;37). Therefore, knowledge of fracture patterns is essential to prevent complications. The subsequent treatment requires a well thought-out plan. This might give a reason for the significantly shorter interval between time of injury and subsequent surgery in patients with implant failure compared to patients without implant failure.

This study might be limited by using the Lauge Hansen classification, which is known for its large intra- and inter-observer variability (38;39). By using a consensus meeting to classify fractures, this effect might be restricted. Furthermore, there was no specific fixed time frame for the outcomes to occur. In addition, the retrospective nature of this study leads to a possible higher amount of missing data. Missing data might result in underestimation of the prevalence of a variable. However, this study is based on data from 3 hospitals including 14 surgeons, which increases generalizability in contrast to other studies (8).

To our knowledge this is one of the largest studies on risk factors for complications after surgical treatment of ankle fractures including a large number of variables covering patient related, fracture related and treatment related factors. By analysis of this large cohort, it can be demonstrated that patient-, fracture- and treatment related factors are independently associated with development of postoperative wound related complications in ankle fractures, making it a multifactorial problem which should be addressed accordingly. Contrary, the type of implant related complication occurred solely due to the interaction between the type of fracture and subsequent surgical treatment, making it an easy item for quality improvement.

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CHAPTER SIX

Differences in classification between mono- and polytrauma and low- and high-energy trauma patients with an ankle fracture: a retrospective cohort study

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Abstract

Background

Although fracture type and treatment options for ankle fractures are well defined, the differences between mono- and polytrauma patients and low- and high energy trauma have not been addressed. The aim of this study was to compare fracture type and trauma mechanism between mono- and polytrauma and low- and high-energy trauma patients with an ankle fracture.

Methods

This was a single center retrospective cohort study. Fractures were classified according to the Lauge Hansen classification and a descriptive classification. High energy trauma (HET) was defined by triage criteria. All other patients were classified as low energy trauma (LET). Patients were divided into two groups based on the injury severity score (ISS). Monotrauma patients were defined as patients with an ISS of 4-11 with an isolated ankle fracture or an ankle fracture with a minor contusion or laceration. Polytrauma patients were defined as patients with an ISS ≥ 16 with at least 2 body regions involved. Patients with an ISS from 12-15 were excluded.

Results

A total of 96 patients were eligible for analysis. Sixty-two patients were monotrauma and thirty-four patients experienced polytrauma. There was a significant difference between mono- and polytrauma patients in Lauge Hansen classification ($p<0.001$). Monotrauma patients had a high incidence of an isolated supination external rotation injury. Supination adduction and pronation abduction injuries were more often observed in polytrauma patients. The same pattern was observed for ankle fractures after HET compared to LET ($p<0.001$), as all pronation abduction and supination adduction injuries were observed after a high energy trauma mechanism.

Conclusion

This study indicates that polytrauma patients sustain different types of ankle fractures compared to patients with an isolated ankle fracture. This difference is likely due to the high energy transfer associated with polytrauma, as pronation abduction and supination adduction injuries were only observed due to high energy.

Introduction

The incidence of ankle fractures in adults is approximately 100-180 fractures per 100,000 people each year (1-3). Most fractures are treated non-operatively with a splint or a cast (4, 5). Indications for surgery are well defined: surgery is indicated when the congruency of the ankle joint in Mortise view or the stability of the ankle is compromised (6, 7). Since the ankle is prone to osteoarthritis caused by posttraumatic malunion and cartilage damage, preservation of a congruent ankle is of utmost importance (8, 9).

Ankle stability after a fracture is frequently described by the Lauge Hansen classification, as it incorporates both trauma mechanism and the stability based on bony and ligamentous injuries (10). The Lauge Hansen classification helps determine whether and what kind of surgical intervention is necessary (10-12). In the general trauma population, approximately 60% of ankle fractures are classified as a Lauge Hansen supination external rotation (SE) injury. Pronation external rotation (PE) injuries account for about a quarter of all ankle fractures. Supination adduction (SA) and pronation abduction (PA) are relatively uncommon injuries (1, 3). The target population of these observational studies most often consists of patients with low energy trauma (LET) injuries, such as sports-related and twisting injuries.

It is generally thought that high energy trauma results in different fracture patterns, although robust data on this subject is lacking (6). Whereas polytrauma is frequently (but not always) the result of high energy trauma (HET), which is usually a more direct trauma, monotrauma is frequently the result of inversion, twisting, and sport-related injuries from low impact trauma. The aim of this study was to determine differences in classification and trauma mechanism between mono- and polytrauma patients with an ankle fracture.

Material and Methods

Our Institutional Review Board (IRB) approved this single center retrospective cohort study. Data were retrieved from the Dutch National Trauma Registry (DNTR) for central Netherlands and the hospital's electronic patient database. The DNTR contains prospectively collected documentation of sustained injuries in admitted trauma patients from arrival in the emergency department until discharge. All injuries recorded during the hospital visit at the University Medical Center Utrecht, a level 1 trauma center, were collected and registered. Patients were identified using ICD-10 codes for ankle fracture from January 2007 until December 2012. All patients 16 years and older with an ankle fracture were eligible for inclusion. Adequate x-rays at admission consisting of mortise and lateral views were required. Patients were excluded when initial treatment was done elsewhere or not available.

For all patients, general demographic information, trauma mechanism, open fracture (yes/no), injury severity score (ISS) and trauma intensity (LET or HET) were retrieved from the database. HET was defined according to the triage criteria defined by the Dutch National Ambulance Protocol (version 7.2, table 1) (13, 14). All other patients were classified as LET. All participating investigators (including (orthopaedic) trauma surgeons) classified the fractures according to the Lauge Hansen classification in a consensus meeting. In addition, the fractures were classified in a descriptive manner. This included the Danis-Weber classification, number of fractured malleoli, type of fracture of the lateral and medial malleolus, and congruity of the ankle joint (15).

To differentiate between mono- and polytrauma patients, the injury severity score was used. The ISS is a scoring system used to assess trauma severity and is a predictor for morbidity and mortality (16). The ISS is based upon the Abbreviated Injury Scale (AIS). To calculate an ISS for an injured person, the body is divided into six body regions: head /neck, face, chest, abdomen/ pelvis, extremities and external. Patients were divided in two groups based on the ISS. Monotrauma patients were defined as patients with an ISS of 4-11 with an isolated ankle fracture or an ankle fracture with a minor contusion or laceration. Monotrauma patients with multiple fractures in one extremity were excluded. Polytrauma patients were defined as patients with an ISS ≥ 16 with at least 2 involved body regions. Patients with an ISS from 12-15 were excluded from analysis (Table 2).

Table 1 Dutch National Triage Protocol

Fall from height ≥3m
Motor vehicle accident > 65 Km/h
Motor vehicle
Vehicle deformity > 50 cm
Passenger compartment intrusion > 30 cm
Vehicle rollover
Passenger ejection from vehicle
Fatality in same vehicle
Car–pedestrian or car–bicycle impact > 10 km/h

Table 2 Injury Severity Score (ISS)

Body region	Injury description	AIS	Square of AIS
Head/neck	subarachnoid bleeding	3	9
Face		0	
Chest	pneumothorax	3	9
Abdomen		0	
Extremity	Distal fibula fracture	2	4
	Metatarsal fracture	2	
External	excoritiation of forefoot	1	1
			Sum of top 3
Total ISS			9+9+4= 22

Statistical analyses

Descriptive statistics (means with standard deviations (SD) or frequencies with percentages) were applied to baseline characteristics. Differences between mono- and polytrauma patients were assessed with the two-group Student's t-test for continuous variables and with the Pearson Chi-square test or, in case of zero cell counts, with Fisher's exact tests for categorical variables. P-values of < 0.05 were considered statistically significant.

Results

Using the database, 346 admitted patients with an ankle fracture were identified using ICD codes (Figure 1). A total of 250 patients were excluded due to other fractures or multiple fractures of the lower leg (in the monotrauma group) or missing x rays prior to treatment, leaving 96 patients for analysis. Sixty-two patients were defined as monotrauma and 34 patients as polytrauma (Figure 1).

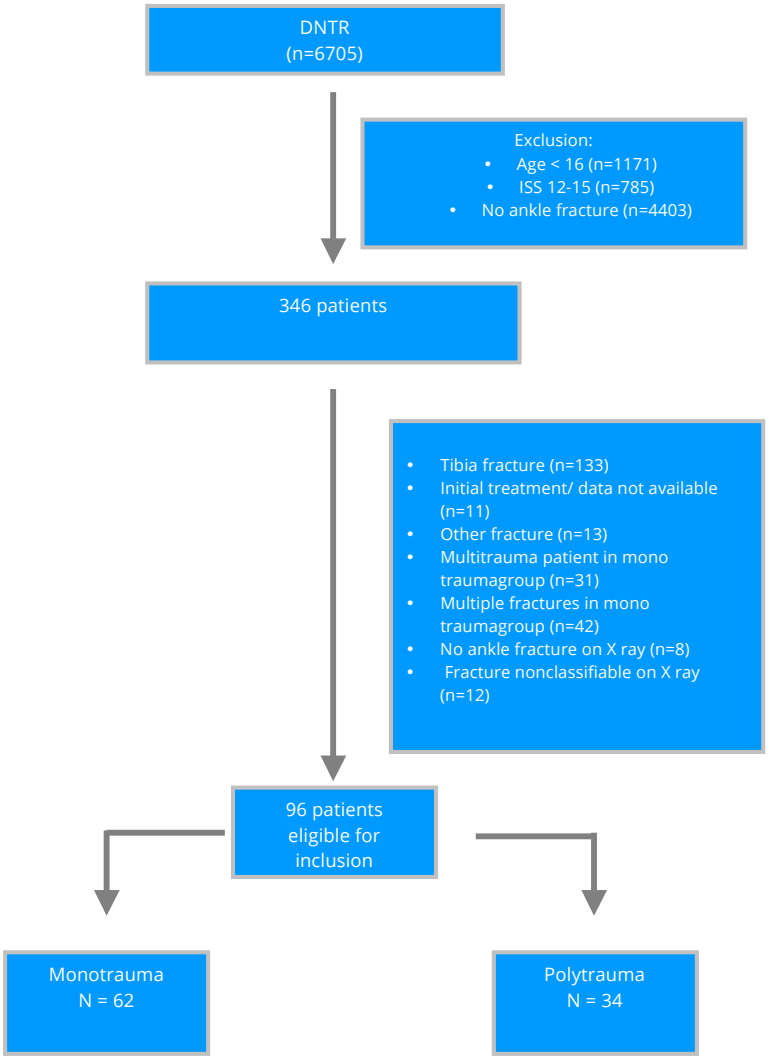

Figure 1 Inclusion Flowchart.

Baseline characteristics are described in table 3. The polytrauma group is male dominated and younger compared to the monotrauma group. There was a significant difference in trauma mechanism, trauma intensity and the number of open fractures between mono- and polytrauma patients. Most monotrauma patients experienced LET while all polytrauma patients experienced HET.

There was a significant difference between mono- and polytrauma patients in Lauge Hansen classification (p<0.001, Table 4). Monotrauma patients had a high incidence of supination external rotation injuries as isolated injury. Supination adduction and pronation abduction injuries were relatively more common in polytrauma patients. Pronation external rotation injuries were equally divided between mono- and polytrauma patients.

Table 3 Basic demographic information

	Monotrauma		**Polytrauma**		**p-value (n=96)**
ISS, mean	6,7	SD: 2.5	27	SD: 8.4	
Age (years), mean	51	SD: 21	44	SD:16	0.086^
Sex	n	%	n	%	
Male	31	50	24	71	0.051*
Female	31	50	10	29	
Injured side					
Left	26	42	18	50	0.45*
Right	36	58	16	50	
Trauma mechanism					
Traffic	17	27	27	79	<0.001~
Sports	12	19	0	0	
Fall from height	6	10	4	12	
Other	27	44	3	9	
Open fracture					
Yes	18	28	3	9	0.026*
No	44	72	31	91	
Trauma intensity					
Low energy trauma	45	73	0	0	<0.001~
High energy trauma	17	27	34	100	

ISS: Injury Severity Score. * assessed with Pearson Chi-Square test. ^ Assessed with T-test. ~assessed with Fishers exact test.

Table 4 Bivariable analysis

	Supination adduction		Supination exorotation		Pronation abduction		Pronation eversion		p-value n=96
	n	%	n	%	n	%	n	%	
Patient									
Monotrauma	3	21	38	86	2	33	19	59	<0.001*
Polytrauma	11	79	6	14	4	67	13	41	
Trauma mechanism									
Traffic	11	79	17	39	3	50	13	41	0.004~
Sports	1	7	5	11	0	0	6	19	
Fall from height	2	14	1	2	1	17	6	19	
Other	0	0	21	48	2	33	7	22	
Trauma intensity									
Low energy trauma	0	0	33	75	0	0	12	37	<0.001~
High energy trauma	14	100	11	25	6	100	20	63	

* assessed with Pearson Chi-Square test. ~assessed with Fishers exact test.

Table 5 Descriptive classification of the fracture

	Monotrauma		Polytrauma		p-value	LET		HET		p-value
	N	%	N	%	(n=96)	N	%	N	%	
Weber classification										
A	2	3	6	18	<0.001~	0	0	8	16	<0.001~
B	35	56	4	12		30	67	9	18	
C	22	35	11	32		13	29	20	39	
No lateral fracture	3	5	13	38		2	4	14	27	
Number of fractured malleoli										
1	17	27	21	62	0.001~	11	25	27	53	0.001*
2	34	55	13	38		24	53	23	45	
3	11	18	0	0		10	22	1	2	
Lateral malleolus fracture										
No fracture	3	5	13	38	<0.001~	2	4	14	28	0.002*
Oblique	39	63	14	41		32	71	21	41	
Comminuted	20	32	7	21		11	24	16	31	
Medial malleolus fracture										
No fracture	20	32	10	29	0.059~	13	29	17	33	0.001~
Horizontal	22	35	6	18		21	47	7	14	
Oblique	19	31	14	41		11	24	22	43	
Vertical	1	2	4	12		0	0	5	10	
Congruent ankle mortise										
Yes	16	26	26	76	<0.001~	33	73	21	41	0.002*
No	46	74	8	24		12	27	30	59	

~Assessed with Fisher's Exact Test, * asessed with Chi-Square test

An even more pronounced pattern was observed for ankle fractures from HET compared to LET ($p<0.001$), as all pronation abduction and supination adduction injuries were in patients who suffered a high energy trauma mechanism.
There were significant differences between mono- and polytrauma patients when the fractures were classified descriptively. Most monotrauma patients had a Weber B fracture (56%), whereas relatively more polytrauma patients had no fracture of the lateral malleolus ($p<0.001$). This also resulted in a significant difference between mono- and polytrauma patients with respect to type of fracture of the lateral malleolus and the number of fractured malleoli ($p<0.001$ and $p=0.001$, Table 5). Most low energy trauma patients had a Weber B fracture (69%) with a congruent ankle joint (73%), whereas most high energy trauma patients had a Weber C fracture (39%, $p<0.001$) and a incongruent ankle joint on Mortise view (59%, $p=0.002$, Table 5). Furthermore, there was a significant difference between the energy mechanism (LET or HET) and location and type of fracture of the malleoli (Table 5).

Discussion

To our knowledge, this is the first study that relates the classification of ankle fractures to trauma mechanism and energy transfer. Furthermore, classification was related to polytrauma. Results of this study indicate that monotrauma patients had a high incidence of external rotation injuries. In contrast, polytrauma patients sustained more supination adduction and pronation abduction injuries, most likely due to high energy trauma mechanism, as all SA and PA injuries were caused by high energy impact. Distribution of ankle fractures in monotrauma patients in this study is comparable to the common distribution pattern described in literature (1, 3). However, polytrauma patients are a different entity, probably due to the differences in trauma mechanism and energy transfer from trauma intensity. Low energy trauma and sports-related injuries might result in rotational forces causing external rotation injuries, which were more frequently observed in the monotrauma group. In contrast, supination adduction and pronation abduction injuries are the result of high energy impact and direct forces, which were more frequently observed in the polytrauma group.

With respect to the differences in trauma intensity, a recent study in triage demonstrated that only a limited number of patients who suffered an HET resulted in polytrauma. On the other hand, the majority of polytrauma patients suffered their injuries from high energy impact (13). Thus, polytrauma is most frequently the result of high energy transfer, and this is reflected in table 4 as the type of ankle fracture according to Lauge Hansen. Supination adduction and pronation abduction injuries were solely seen after HET. This hypothesis is further supported by the differences in descriptive classification in this study.

Functional outcome was not reported in this study. Prior studies showed that polytrauma patients suffered moderate functional disability both short and long-term, especially when lower extremity injuries were present (7, 17-21). Ankle fractures were not a separate entity in these studies. Evidence on outcomes after ankle fractures is primarily based on results of monotrauma ankle fractures (22-24). Our study showed a clear difference in fracture type and trauma mechanism between mono- and polytrauma patients, emphasizing the need to distinguish between these groups in future studies.

Lauge Hansen is an ankle fracture classification that is based on the extent of injury to various ligamentous and osseous structures and also describes the fracture mechanism (10-12, 25). One of the limitations of this classification is its large inter- and intra-observer variability (26, 27). The ideal method to recognize these ligamentous injuries in order to appropriately classify the fracture is a preoperative Magnetic Resonance Imaging (MRI)(28). MRI is not standard preoperative protocol in our hospital, therefore, results of MRI were not available for this study. To minimize the inter-observer variability, two orthopaedic trauma surgeons experienced with the Lauge Hansen classification participated in a consensus meeting to classify the fractures. When the Lauge Hansen classification was not sufficient to classify the fracture the most appropriate Lauge Hansen classification was used. However, it is known that more complex injury patterns are not captured in the Lauge Hansen classification (29-31). Observers were blinded to patient and trauma characteristics.

This study is limited by its retrospective nature and lack of outcome data in both groups. The DNTR only registers admitted patients, which may result in an underrepresentation of monotrauma patients. However, data from the DNTR were prospectively collected, and two database managers

and a trauma surgeon constantly evaluated the data's accuracy. All of the data were collected in one level 1 trauma center, thereby excluding institution preference influence.

Conclusion

This study indicates that polytrauma patients sustain different types of ankle fractures compared to patients with an isolated ankle fracture. This difference is likely due to the high energy transfer associated with polytrauma, as pronation abduction and supination adduction injuries were only observed in patients who suffered a HET. As current follow-up studies of ankle fractures are largely based on isolated injuries, follow-up studies of polytrauma patients with ankle fractures are needed.

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CHAPTER SEVEN

Weight bearing or non-weight bearing after surgically fixed ankle fractures, the WOW! Study: study protocol for a randomized controlled trial

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Abstract

Background

The optimal post-operative care regimen after surgically fixed Lauge Hansen supination exorotation injuries remains to be established. This study compares whether unprotected weight bearing as tolerated is superior to protected weight bearing and unprotected non-weight-bearing in terms of functional outcome and safety.

Methods

The WOW! Study is a prospective multicenter clinical trial. Patients between 18 and 65 years of age with a Lauge Hansen supination exorotation type 2,3 or 4 requiring surgical treatment are eligible for inclusion. An expert panel validates the classification and inclusion eligibility. After surgery, patients are randomized to either the 1) unprotected non-weight bearing, 2) protected weight bearing or 3) unprotected weight bearing group.

The primary outcome measure is ankle-specific disability measured by the Olerud-Molander ankle score. Secondary outcomes are 1) quality of life (e.g. return to work and resumption of sport), 2) complications, 3) range of motion, 4) calf wasting and 5) maximum pressure load after 3 months and 1 year.

Discussion

This trial is designed to compare the effectiveness and safety of unprotected weight bearing with two commonly used post-operative treatment regimens after internal fixation of specified intrinsically stable but displaced ankle fractures. An expert panel has been established to evaluate every potential subject, which ensures that every patient is strictly screened according to the inclusion and exclusion criteria and that there is a clear indication for surgical fixation.

Trial registration: The WOW! Study is registered in the Dutch Trial Register (NTR3727). Date of registration: 28-11-2012.

Background and rationale

Ankle fractures in adults occur frequently with an annual incidence of approximately 100 to 180 fractures per 100,000 people each year (1-3). Most ankle fractures occur after inversion or eversion twisting trauma and sports injuries. For stable non-displaced ankle fractures, a conservative treatment with a splint or cast is indicated (4, 5). However, when the congruity of the ankle fork or the joint stability is compromised, open reduction and internal fixation is required to attain full function of the ankle joint (6, 7).

While indications for surgical treatment are rather well defined, controversy exists with regard to the optimal postoperative care regimen (8). Post-operative care regimens vary widely from plaster casts and functional bracing to unprotected non-weight bearing and weight bearing (9-15). Prior studies show a possible advantage of (protected) weight bearing over (protected) non-weight bearing and of functional mobilization over non-functional mobilization with crutches (11, 16). Some recent, small retrospective and matched control studies even suggested that early (unprotected) weight bearing results in faster recovery and better ankle function (11-13).

The objective of this trial is to compare functional outcome and safety after three different post-operative care regimens: 1) unprotected non-weight bearing, 2) protected weight bearing, and 3) unprotected weight bearing.

Methods and Design

Study design

This is a prospective multicenter randomized controlled trial involving six hospitals in the Netherlands. The study has been approved by the local Institutional Review Board (IRB) under protocol number WOW-01/NL40835.100.12. This study compares three different post-operative care regimens after ankle surgery; all patients with a Lauge Hansen supination exorotation type 2,3 or 4 requiring surgical treatment are eligible for inclusion.

After registration of the patient, an anonymous X-ray is sent to an expert panel. This panel consists of six experienced orthopaedic trauma surgeons. The fracture is classified according to the Lauge Hansen classification and advice on whether or not operative fixation is indicated is provided within

24 hours. A patient is eligible for inclusion when a majority of the expert panel agrees that operative fixation is necessary and the fracture type meets the inclusion criteria. When votes are split equally, the chairman (LL) is the tiebreaker. A flow chart of the study is shown in figure 1.

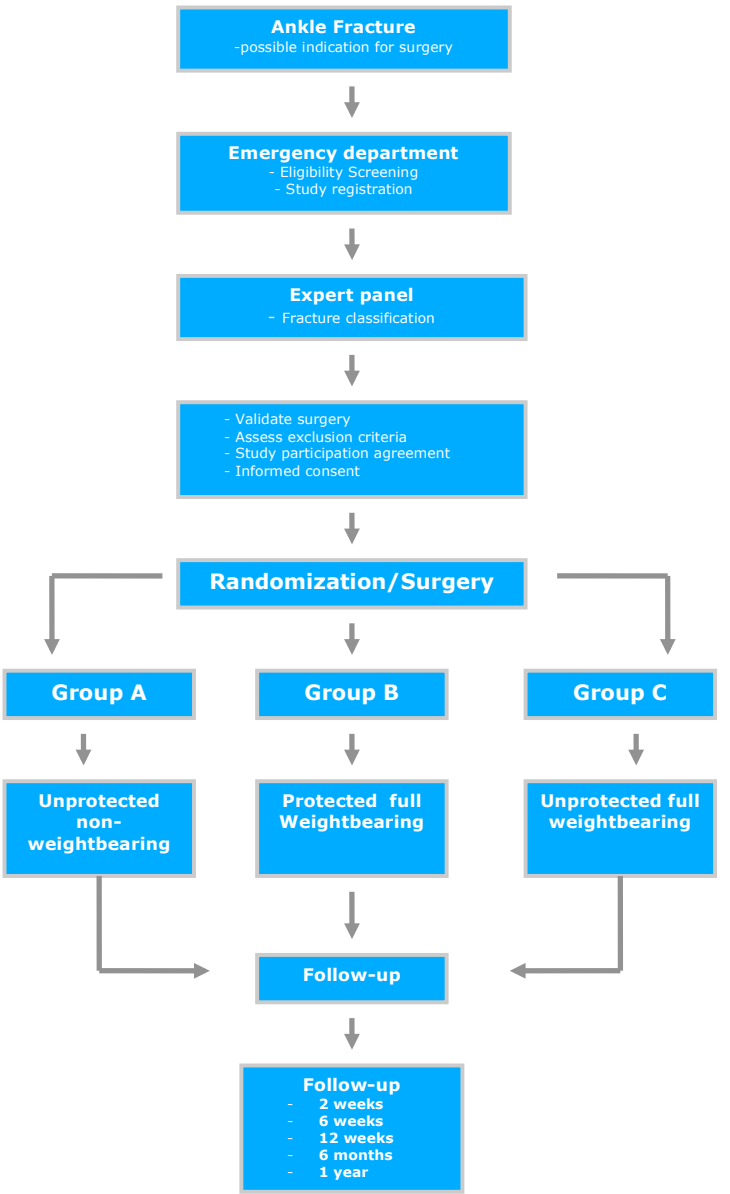

Figure 1 Flowchart WOW! Study

Patient population

All non-pregnant, Dutch speaking patients are being recruited from the participating hospitals in the emergency room or pre-operatively during an outpatient department visit. Patients are screened for eligibility according to the inclusion and exclusion criteria (table 1). The treating physician or study staff explains the study and informed consent is obtained from each patient. Retrospective data of the participating hospitals shows that approximately 395 patients per year undergo surgery for ankle fractures. Approximately 20% of these patients would be eligible for enrollment according to our inclusion criteria. If this trend continues, we anticipate enrollment of 79 patients per year (table 1).

Table 1 Inclusion and exclusion criteria.

Inclusion	Exclusion
Patients aged 18-65	Pre-existent impaired mobility
Lauge Hansen supination-eversion 2-3-4	Pre-existent cognitive disability
Articular discongruity > 2mm on X ray	Expected insufficient stable fracture fixation.
	Necessity for a syndesmosis screw
	Tertius fragment which requires operative treatment.
	BMI> 30
	Diabetes Mellitus
	Polytrauma patients (ISS>16 or >2 AIS regions)
	Gustillo 2 and 3 open fractures
	Inability to comply with non weight bearing regimen
	Inability to comply follow up.

BMI: body mass index; ISS: Injury Severity Score; AIS: Abbreviated Injury Scale

Inclusion and exclusion criteria

All patients between 18 and 65 years with a Lauge Hansen supination exorotation type 2, 3 and 4 are eligible for inclusion (figure 2). Exclusion criteria include pre-existent impaired morbidity, cognitive disability, body mass index >30, and Diabetes Mellitus. All inclusion and exclusion criteria are listed in table 1.

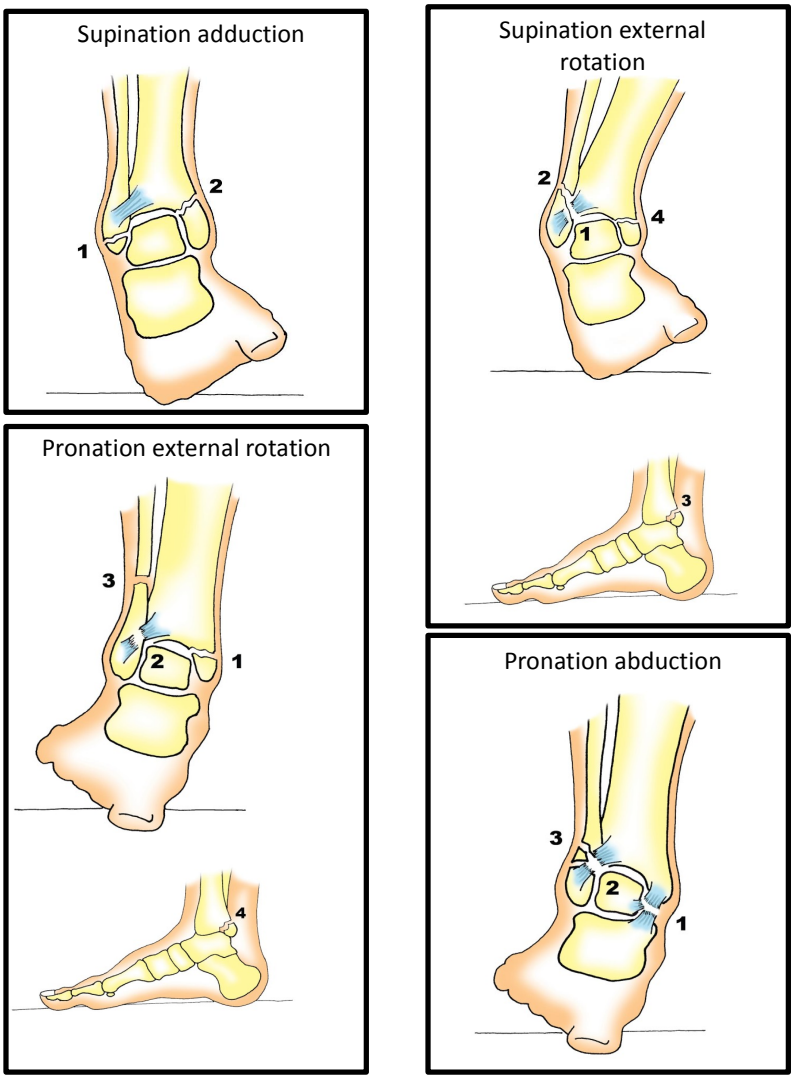

Figure 2 The Lauge Hansen classification
Trauma mechanism of ankle fractures. Supination abduction: 1 talofibularligament sprain or fibular avulsion, 2 vertical medial malleolus fracture. Supination external rotation: 1 anterior tibiofibular ligament sprain, 2, lateral oblique fibular fracture, 3 avulsion of posterior malleolus or ligament rupture, 4 transverse medial malleolus fracture or disruption of deltoid ligament. Pronation abduction: 1 transverse medial malleolus fracture or deltoid ligament, 2 anterior tibiofibular ligament sprain, 3 transverse comminuted fracture of the fibula. Pronation external rotation: 1. transverse medial malleolus fracture or deltoid ligament disruption, 2 anterior tibiofibular ligament disruption, 3 oblique or spiral fracture of the fibula, 4 avulsion of posterior malleolus of posterior tibiofibular ligament.

Interventions

After enrollment, patients are scheduled for surgery. The ankle fixation technique is ultimately determined by the treating physician; however, advice is provided by the expert panel based on the X-ray. After surgery, all patients are randomized to one of three post-operative care regimens: 1) Unprotected non-weight bearing group– functional weight bearing as tolerated –, 2) protected weight bearing group – weight bearing as tolerated with a below knee cast for 6 weeks –, 3) unprotected weight bearing group– mobilization with crutches, active ankle exercises. All patients see a physiotherapist post-operatively or after cast removal to learn exercises and receive advice on how to start mobilizing according to their specific post-operative care regimen. The physiotherapists have been instructed by the investigators. Patients in the protected weight bearing group receive Low Molecular Weight Heparin (LMWH) as thrombosis prophylaxis for the entire duration of immobilization. For the unprotected non-weight bearing and unprotected weight-bearing groups, anti-thrombotic treatment is not indicated.

Randomization process

Patients are randomized using computerized block randomization to either protected weight bearing, unprotected non-weight bearing or unprotected weight bearing. The randomization is stratified by the participating hospitals. The blocks for randomization consist of 21 patients with the three post-operative care regimens equally represented in each block. Follow up is by the intention-to-treat (ITT) principle. Following surgical fixation, the treating surgeon logs into the private website where the patient is randomized to one of three post-operative care regimens.

Postoperative management and follow up

Patients are treated during same day admission if possible. According to their post-operative care regimen, patients receive a cast, exercise instructions and a physiotherapist referral letter. All patients are reviewed in the outpatient clinic by the treating surgeon and/or investigator at 2 weeks, 6 weeks, 3 months, 6 months and 1 year after surgery. At all post-operative outpatient visits, a standardized clinical exam is conducted including three standardized patient reported outcome questionnaires; the Olerud Molander Ankle Score (OMAS), the Short Form-36 (SF-36) and the Visual Analogue Scale (VAS) (table 2).

Table 2 Study assessments by timepoint

timepoint	Intake	2 weeks	6 weeks	12 weeks	6 months	1 year
OMAS*	X		X	X	X	X
SF-36^	X		X	X		X
Wound inspection		X	X			
Calf circumference			X	X	X	X
Range of motion			X	X	X	X
Demographics	X					

* Olerud Molander Ankle Score, ^ Short Form 36

Primary outcome measures

The Olerud Molander Score (OMAS) is a scoring scale for symptom evaluation in patients with an ankle fracture and in patients with other acute ankle injuries (17). This score ranges from 0 to 100%, with 100% representing normal ankle function (17). It was developed specifically as a comparative research measure to improve consistency and uniformity in ankle injury reporting (17). A difference of 5 to 10 points between two groups on the OMAS is defined as a clinically relevant result.

Secondary outcome measures

The Short-Form Health Survey (SF-36) is one of the most widely used generic health questionnaires. It was developed as a medical outcome score to measure the functional health status of a patient (18, 19). It has been translated into Dutch and validated as a useful questionnaire to assess a broad array of health-related quality-of-life issues (19).

Other secondary measures of function include Range Of Motion (ROM) (plantar and dorso-flexion), weight-bearing pressure load, and calf wasting (difference in calf circumference at enrollment and at 12 weeks post-operative) of the injured ankle. Pain is measured by the Visual Analogue Scale (VAS) on an 11-point Likert scale. Return to work and sports is also recorded. The pressure load of the injured and non-injured ankle is measured by a scale at every visit, starting at 6 weeks.

Post-operative complications are defined as 1) wound healing problems (no interventions required), 2) superficial wound infections (requiring oral antibiotic treatment based on a wound culture), 3) infection near hardware (requiring surgical debridement and intravenous antibiotic treatment based on a deep tissue culture) 4) hardware failure (requiring re-

operation) and 5) mal-union or non-union (clinically and radiographically confirmed) and 6) deep venous thrombosis (confirmed by ultrasound).

Sample size and Power

Our hypothesis is that ankle specific disability assessed with the Olerud Molander Ankle Score (OMAS) is less for unprotected weight bearing when compared to protected weight bearing and unprotected non-weight-bearing. An a priori power analysis for superiority of treatment with unprotected weight bearing has been conducted for this hypothesis. To detect a clinically significant 7 point difference on the OMAS at 12 weeks follow-up between unprotected non weight-bearing and unprotected weight-bearing with a standard deviation of 10, α=0.05, β=0.90, two-sided test (based on superiority of unprotected weight-bearing), and a maximum loss to follow-up of 20%, a sample size of 75 patients per group is necessary. Therefore, a total of 225 patients are needed for this study.

Statistical analysis

Analysis will be conducted according to the intention-to-treat principle. In bivariable analysis, Pearson's correlation will be used for continuous variables, Student's t-test for dichotomous variables such as gender, and ANOVA for categorical variables such as the post-operative care regimen. Multivariate analyses will only be performed post hoc and are considered hypothesis-inducing as opposed to hypothesis-testing and will be ascribed as such.

Data and safety monitoring board (DSMB) and interim analysis

Participation in this trial does not elicit additional risks besides the standard complications of ankle surgery, such as wound infections, deep venous thrombosis and hardware failure (12, 13). Although all three post-operative care regimens are independently investigated, unprotected weight bearing by unrestricted mobilization as tolerated has not yet been investigated in a randomized trial. Therefore, strict criteria for premature termination are implemented.

A Data Safety Monitoring Board (DSMB) has been established. An interim analysis will be conducted after every serious adverse event and after half of the target enrollement is reached. The DSMB consists of two independent physicians and one clinical epidemiologist. The members are not committed to this trial. The DSMB will provide advice that will be disclosed to the Institutional Review Board. The steering committee

may terminate the study prematurely if advised by the DSMB. In addition, statistically significant, sufficiently powered and clinically relevant results during interim analysis may be compelling to terminate the trial prematurely. For this trial, the following termination criteria have been established:

- 10% Hardware failure percentage in any of the treatment groups (20, 21)
- Wound infection percentage exceeding 20% in any of the treatment groups (14, 21)

Ethical approval

This study will be conducted according to the principles of the Declaration of Helsinki (version 9, October 2008, Seoul) and in accordance with the Medical Research Involving Human Subjects Act. The Verenigde Commissie Mensgebonden Onderzoek (VCMO) approved the study in the St. Antonius hospital and Diakonessenhuis. The Centrale Commissie Mensgebonden Onderzoek approved the study in Medisch Centrum Haaglanden. The Medisch Ethische Toetsingscommissie approved the study in the St. Elisabeth hospital. Ethical Approval from the Twee Steden hospital was obtained from the board of directors based on VCMO approval.

Discussion

This trial is designed to compare the effectiveness and safety of unprotected weight bearing with two commonly used post-operative treatment regimens after internal fixation of specified intrinsically stable but displaced ankle fractures. An expert panel has been established to evaluate every potential subject, which ensures that every patient is strictly screened according to the inclusion and exclusion criteria and that there is a clear indication for surgical fixation.

Prior research reports high patient satisfaction scores and no disadvantage for early weight bearing (12, 13, 22). The combination of functional treatment and early weight bearing may reduce soft tissue atrophy and development of osteoporosis and better preserve ankle ROM (13). Therefore, direct postoperative weight-bearing and early mobilization has the potential benefit of earlier functional recovery (8-14, 16, 23, 24).

Ankle fractures in this trial are described by the Lauge Hansen classification. This classification describes the intrinsic stability, demonstrates the trauma mechanism, and incorporates ligament injuries (25). This trial aims to provide evidence for the optimal post-operative care regimen

after surgical repair, solely for Lauge Hansen supination exorotation 2-3 and 4 ankle fractures. In contrast to the majority of studies that include patients with all types of ankle fractures requiring operative fixation, this study describes a relatively stable fracture, which may be more suitable for immediate unprotected weight-bearing (11-13). A limitation of the Lauge Hansen classification is its low inter-observer kappa value (26). The expert panel has been implemented to address this and minimize inter-observer variability.

There are limitations to this study. Not all available post-operative care regimens, such as functional bracing, are studied in this trial, as it has been suggested that functional bracing is associated with an increased risk of post-operative wound healing problems (21).

The termination criteria of this trial exceed the percentages mentioned in literature; the majority of these studies are retrospective studies and small prospective trials (11, 20, 21). However, the use of strict termination criteria is important to ensure the safety of the patient.

This prospective randomized controlled trial compares three different post-operative care regimens after open reduction and internal fixation of ankle fractures. By analyzing ankle disability, pain, quality of life, ROM, weight bearing and resumption of daily activities, this trial assesses the optimal post-operative care regimen for a specific ankle fracture.

Trial status

The institutional Review Board has approved the study, and patient enrollment has begun in five of the six participating centers. Approval is still pending in one hospital. Recruitment commenced in February 2013, and 73 patients are currently enrolled in this study. Inclusion rates are expected to increase now that most participating centers have received approval. Based on our power analysis and expected yearly inclusion of 79 patients, enrollment of the 225th patient is expected in October 2016. Analysis will be conducted one year later once follow-up is completed.

Acknowledgements

Alice C. Meijer: Digital graphic design of Lauge Hansen figures

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CHAPTER EIGHT

Weight-bearing or non-weight-bearing after surgical treatment of ankle fractures: a multicenter randomized controlled trial

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SUBMITTED

Abstract

Background

Postoperative care regimens of ankle fractures vary widely, and it remains unclear which postoperative treatment is preferable. The objective of this trial was to provide evidence for the optimal post-operative treatment regimen after surgical fixation of Lauge Hansen supination external rotation stage 2-4 ankle fractures. The goal of this study was to assess if unprotected weight-bearing as tolerated is superior to protected weight-bearing and unprotected non-weight-bearing in terms of functional outcome and complications.

Methods

A randomized controlled trial was performed from January 2013 until October 2016. A multicenter trial was conducted in four teaching hospitals in the Netherlands, both Level I and II trauma centers. Patients, ranging from 18 to 65 years of age without severe comorbidities, with a supination external rotation type 2-4 ankle fracture, which was confirmed by an expert panel of orthopedic trauma surgeons. Patients were randomized to unprotected non-weight-bearing, protected weight-bearing, and unprotected weight-bearing as tolerated.The primary endpoint of the study was the Olerud Molander Ankle Score (OMAS) twelve weeks after randomization. The secondary endpoints were health-related quality of life using the SF-36v2, time to return to work, time to return to sports, and the number of complications.

The WOW study was registered in the Dutch Trial Register (NTR3727) under protocol number WOW-01/NL40835.100.12. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3727

Results

The trial was terminated early as advised by the Data and Safety Monitoring Board at interim analysis. A total of 115 patients were randomized. The O'Brien-Fleming threshold for statistical significance for this interim analysis was 0.008 at 12 weeks. The OMAS was higher in the unprotected weight-bearing group after 6 weeks (61.2±19.0) compared to the protected weight-bearing (51.8±20.4) and unprotected non-weight-bearing groups (45.8±22.4) (p=0.011). All other follow-up time points did not show significant differences between the groups. Unprotected weight-bearing showed a significant earlier return to work (p=0.028) and

earlier return to sports (p=0.005). There were no differences in the quality of life scores or number of complications.

Conclusions
Unprotected weight-bearing and mobilization as tolerated as postoperative care regimen improved short-term functional outcomes and led to earlier return to work and sports, yet did not result in an increase of complications in adult patients without comorbidities.

Background

Ankle fractures are the most common type of lower extremity injury and the incidence is rising (1;2). In addition, ankle fractures are the most commonly operated lower extremity injury worldwide. Ankle fractures can be classified according to the Lauge Hansen classification (3). More than half of ankle fractures are supination external rotation fractures, caused by minor trauma (4). For a good functional recovery and prevention of osteoarthritis, fractures with incongruency of the tibiotalar joint are treated operatively (5). Subsequently, a wide variety of postoperative care regimens are used, ranging from immobilization in a cast without weight-bearing to immediate weight-bearing without a cast (6-8). Various studies have shown good functional outcomes one year after surgery for the different postoperative protocols (8-10). However, immobilization in a cast can result in stiffness of the ankle and non-weight-bearing can result in delayed functional recovery (8;9;11). Protective devices such as a brace have shown high rates of postoperative wound complications, with a potentially decreased functional outcome (12;13).

Even more, post-operative treatment regimens might influence the efficacy of functional recovery, as differences in the time to return to work between the various treatment regimens are suggested. Therefore these regimes have direct impact on societal costs (14). However, due to heterogeneity of studies, it remains unclear which postoperative treatment regimen is preferable and whether specific types of patients or fractures might benefit from a more progressive regimen. Recently, unprotected weight-bearing was described in a small cohort study, which revealed a significant earlier return to work without a higher rate of complications compared to protected non-weight-bearing (6). Biomechanical analysis has shown no implant failure or loss of reduction after early weight-bearing of surgically treated ankle fractures (15). However, the functional outcome and the safety of unprotected early weight-bearing and mobilization remain unclear, as the combination of both early weight-bearing and mobilization has not been studied in a randomized trial (9;16).

Prior studies included a wide range of ankle fractures, including those with syndesmotic injuries (12;17;18). This poses a challenge, as different types of ankle fractures may require a different operative and postoperative approach. In addition, most studies did not employ strict patient selection with respect to comorbidities that may affect rehabilitation (12;18).

The objective of this multicenter randomized controlled trial was to

provide evidence for the optimal post-operative treatment regimen after surgical fixation of Lauge Hansen supination external rotation stage 2-4 ankle fractures (19). The goal of this study was to assess if unprotected weight-bearing as tolerated is superior to protected weight-bearing and unprotected non-weight-bearing in terms of functional outcome and complications.

Materials and methods

Trial Design and Population

The WOW study, registered in the Dutch Trial Register (NTR3727), was performed in accordance with the Declaration of Helsinki and approved by the local Institutional Review Board under protocol number WOW-01/NL40835.100.12 (20). The rationale and methods are described in more detail in the published study protocol (19). No changes to the protocol occurred after trial commencement.

Patients with a supination external rotation type 2-4 ankle fracture were included between January 2013 and October 2016 (3). In- and exclusion criteria are shown in Figure 1. Patients were recruited and enrolled at the emergency departments or outpatient clinics of the participating hospitals in an urban environment. Indication for surgery was stated at the discretion of the treating surgeon. The study was conducted in four teaching hospitals in the Netherlands: Diakonessenhuis (level 2 trauma center), St. Antonius Hospital (level 2 trauma center), Haaglanden Medisch Centrum (level 1 trauma center) and the Elisabeth-TweeSteden hospital (level 1 trauma center).

In order for a participant to be included in the trial, he or she had to fulfill all inclusion and exclusion criteria, informed consent had to be obtained, the fracture had to be classified by at least 3 out of 6 orthopaedic trauma surgeons as a supination external rotation injury (19). The expert panel consisted of 6 experienced orthopedic trauma surgeons. The expert panel was notified about a potential participant by an email that included an anonymous x-ray for classification on a web-based database. A patient was eligible for inclusion when the majority of the panel agreed on the Lauge Hansen fracture type and all other inclusion criteria were met. When votes were split equally, the chairman's (LL) vote was decisive. The operative technique and implants used were dictated by surgeon preference and the surgeon had a final decision in participant enrollment after testing the syndesmosis intra-operatively.

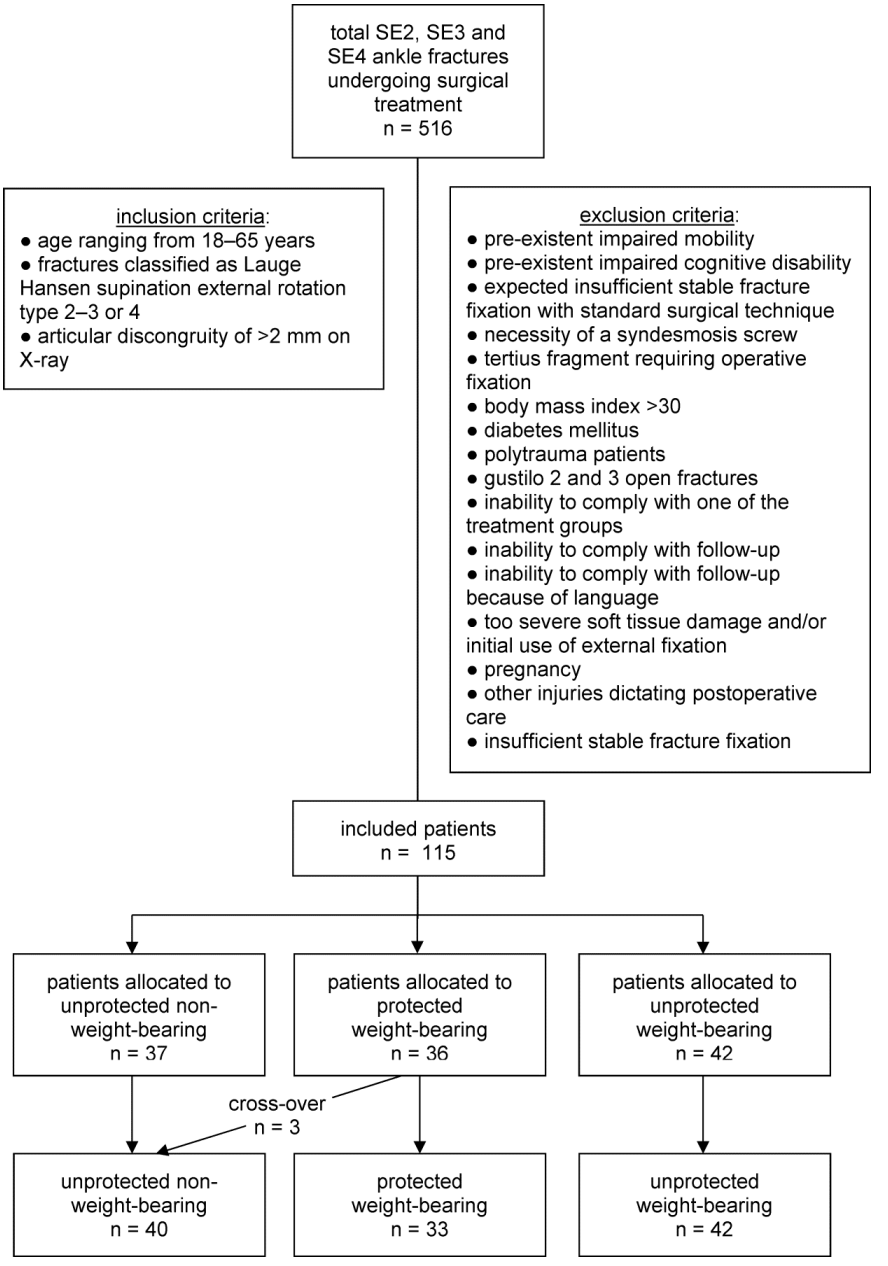

Figure 1 Flowchart of patient selection in the WOW! Study
Flowchart indicating patient selection. Three patients crossed over due to cast irritation.
SE = supination external rotation

Randomization and Postoperative Treatment

Patients were randomized using a computerized random number generator with an allocation ratio of 1:1:1 in blocks of 21 patients. The three postoperative care regimens were: 1) unprotected non-weight-bearing – mobilization with crutches, active ankle exercises without cast or brace, 2) protected weight-bearing – weight-bearing as tolerated with a below knee cast for 6 weeks, or 3) unprotected weight-bearing – functional weight-bearing as tolerated. Unprotected non-weight-bearing included a pressure dressing in the first 24 hours postoperatively. After six weeks, weight-bearing was allowed and gradually increased to full-weight-bearing in another six weeks. Protected weight-bearing included a ten-day back slab plaster splint. After ten days, the patient received a weight-bearing cast for the remaining first six weeks. Patients in the protected weight-bearing group received low molecular weight heparin as thromboembolic prophylaxis for the entire duration of immobilization. Unprotected weight-bearing included a pressure dressing in the first 24 hours postoperatively. After the first 24 hours, weight-bearing was allowed as tolerated by the patient. All patients consulted a physical therapist post-operatively or after cast removal to learn exercises and received advice on how to start mobilizing according to their specific post-operative care regimen. Physical therapists received a letter with study information and instructions for the different treatment arms.

End points and Follow-up

The primary endpoint of the study was the functional outcome using the Olerud Molander Ankle Score (OMAS), which was filled out at 6 weeks, 12 weeks, 6 months and 1 year after randomization (21). The OMAS is a patient reported outcome measure for evaluating symptoms after ankle injuries. The OMAS ranges from 0 to 100. A higher score indicates a better functional outcome (21). The secondary endpoints were health related quality of life using the SF-36v2 (which was filled out at twelve weeks and one year after randomization), time to return to work in weeks, time to the return to sports in weeks, and the number of complications (22). A higher score of the SF-36v2 indicates less disability (range from 0 to 100). A coordinating researcher was in charge of all follow-up visits in order to prevent inconsistency of data.

Sample size calculations

A sample size calculation was performed for a superiority trial of treatment with unprotected weight-bearing vs. protected weight-bearing vs. unprotected non-weight-bearing, based on a previous report covering protected weight-bearing or ankle exercises (14). To detect a clinically significant 7-point difference (SD 10) on the Olerud Molander Ankle Score (OMAS) at 12 weeks, with two-sided $\alpha = 0.05$ and power of 0.90, a sample size of 60 subjects per treatment arm was required (i.e., 180 subjects in total). We anticipated a maximum loss to follow-up of 20%, leading to a sample size of 75 patients per group and a total of 225 patients needed for this study (19).

Statistical Analysis and interim analysis

Patients were analyzed in accordance with the intention-to-treat principal. Continuous data were presented as means with standard deviations; dichotomous data as frequencies with percentages. Continuous outcome data (OMAS, time to return to work, time to return to sports, and the SF-36) were compared by means of ANOVA; dichotomous outcome data (complications) were compared by means of Pearson's Chi-square test. At 3 months and 1 year, follow-up information was available for 88% and 86% of the subjects, respectively, for all outcomes. We performed an available case analysis, and no corrections for loss-to-follow-up were applied. No subgroup or other additional analyses were performed. All statistical analysis were performed using Statistical Package for the Social Sciences (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

An interim analysis was planned after every serious adverse event and after half of the target enrollment was reached. A data and safety monitoring board (DSMB), consisting of two independent physicians and one epidemiologist, was established to advise the steering committee. The study would be terminated early if 1) 10% hardware failure occurred in any of the treatment groups, 2) wound infection percentages exceeded 20% in any of the treatment groups, or 3) statistically significant, sufficiently powered, and clinically relevant results were reached at interim analysis (19). Post-hoc the O'Brien-Fleming (OBF) alpha spending function was used, to determine the statistical significance level based on the proportion of subjects included in the interim analysis to the required sample size in the absence of loss to follow-up.

Results

Patient selection and baseline characteristics

A total of 115 consecutive patients were included at interim analysis. The OBF threshold for statistical significance of the primary outcome for this interim analysis was 0.008. Figure 1 shows a flowchart of the selection of patients, including the number of excluded patients. Appendix 1 shows the number of patients who were not considered eligible for participation with the reasons for exclusion. The baseline characteristics of the patients who were included in the trial are shown in Table 1. The study also included patients with (SE-4) fracture dislocations. The mean age of the included patients was 39.0 (±14.4) years, ranging from 18 to 65 years, of which 61 (53.0%) were men. All surgeries were performed or supervised by consultant orthopedic trauma surgeons. Implants used are shown in Table 1. A total of 3 patients switched from the protected weight-bearing group to the unprotected non-weight-bearing group because of cast irritation. Follow-up rates of the participating hospitals are described in Appendix 2.

Primary outcome: functional outcome scores

The OMAS was higher in the unprotected weight-bearing group after 6 weeks (61.2±19.0) compared to the protected weight-bearing (51.8±20.4) and unprotected weight-bearing groups (45.8±22.4) (p=0.011) (Table 2 and Figure 2). All other follow-up time points did not show significant differences in terms of OMAS between the groups. The functional outcome results at interim analysis contributed to an early termination of the trial. Appendix 3 provides details about the pair-wise comparisons of the functional outcomes between the three groups.

Secondary outcomes: time to return to work, time to return to sports, quality of life and complications

Unprotected weight-bearing showed a significantly earlier return to work with a mean of 4.1 weeks compared to 5.7 and 7.0 weeks (p=0.028). The patients in the unprotected weight-bearing group also showed an earlier return to sports with a mean of 8.9 weeks compared to 12.7 and 14.1 weeks (p=0.005). There were no significant differences in quality of life scores between the different groups after both 12 weeks and 1 year (Table 3).

Table 1 Baseline characteristics of included patients with ankle fracture

	Unprotected non-weight-bearing (n=37)	Protected weight-bearing (n=36)	Unprotected weight-bearing (n=42)
Mean age in years (±SD)	37.8 (±13.7)	41.5 (±14.2)	37.8 (±15.1)
Age range in years	18-65	18-62	18-65
Number of males (%)	23 (62.2%)	16 (44.4%)	22 (52.4%)
Symptomatic side right	21 (56.8%)	23 (63.9%)	18 (42.9%)
Smoking	7 (28.0%) (12 missing)	5 (22.7%) (14 missing)	9 (36.0%) (17 missing)
Cause of fracture			
Fall < 3 meter	0 (%)	2 (5.6%)	4 (9.5%)
Fall from scooter	0 (%)	0	2 (4.8%)
Fall from bicycle	8 (21.6%)	8 (22.2%)	8 (19.0%)
Sport	9 (24.3%)	3 (8.3%)	13 (31.0%)
Winter sports	1 (2.7%)	2 (5.6%)	1 (2.4%)
Simple inversion	17 (45.9%)	20 (55.6%)	12 (28.6%)
Other	2 (5.4%)	1 (2.8%)	2 (4.8%)
Lauge Hansen classification			
Supination external rotation type 2	14 (37.8%)	9 (25.0%)	14 (33.3%)
Supination external rotation type 3	2 (5.4%)	4 (11.1%)	0
Supination external rotation type 4	21 (56.8%)	23 (63.9%)	28 (66.7%)
Type of fixation lateral malleolus			
2x screw fixation	3 (8.1%)	4 (11.1%)	7 (16.7%)
Screw fixation and neutralization plate	19 (51.4%)	22 (61.1%)	23 (54.8%)
Neutralization plate	7 (18.9%)	7 (19.4%)	6 (14.3%)
Dorsolateral buttress plate	8 (21.6%)	3 (8.3%)	6 (14.3%)
Type of fixation medial malleolus			
1x screw fixation	1 (2.7%)	2 (5.6%)	1 (2.4%)
1x screw fixation and Kirschner-wire	2 (5.4%)	0	4 (9.5%)
2x screw fixation	2 (5.4%)	1 (2.8%)	1 (2.4%)
Zuggertung	2 (5.4%)	1 (2.8%)	6 (14.3%)
Other	0	1 (2.8%)	0
Not applicable / no fractured medial malleolus / no fixation required	30 (81.1%)	31 (86.1%)	30 (71.4%)

No statistically significant differences were found in baseline characteristics between the 3 treatment groups after randomization. SD = Standard Deviation

Table 2 Results and differences in Olerud Molander Ankle Score, time to return to work and sports

	Unprotected non-weight-bearing (n=37)	**Protected weight-bearing (n=36)**	**Unprotected weight-bearing (n=42)**	**p-value**
Olerud Molander score 6 weeks	45.8 (±22.4)	51.8 (±20.4)	61.2 (±19.0)	0.011*
Olerud Molander score 12 weeks	67.9 (±19.8)	68.6 (±14.6)	72.2 (±19.4)	0.566*
Olerud Molander score 6 months	80.9 (±18.0)	86.0 (±13.9)	85.5 (±19.2)	0.496*
Olerud Molander score 1 year	88.7 (±11.4)	89.1 (±15.0)	86.8 (±16.0)	0.773*
Time to return to work in weeks×	7.0 (±5.3) (n=32)	5.7 (±4.9) (n=34)	4.1 (±3.3) (n=39)	0.028*
Time to return to sports in weeks×	14.1 (±5.7) (n=26)	12.7 (±8.4) (n=25)	8.9 (±4.7) (n=35)	0.005*
Complications	Total: 5 (13,5%) - 3x low grade infection - 1x dystrophy - 1x deep venous thrombosis	Total: 1 (2,7%) - 1x low grade infection	Total: 3 (7,1%) - 3x low grade infection	0.228†

This table shows the functional outcome using the Olerud Molander Ankle Score, the time to return to work and sports, and the number of complications based on the postoperative treatment of ankle fractures. The Olerud Molander Ankle Score ranges from 0 to 100. A higher score indicates a better functional outcome. Improved function was seen at 6 weeks in the mobilization as tolerated study arm. On all other time points no significant differences were seen. In addition, Patients in the unprotected weight-bearing group demonstrated a reduced time to return to work and sports.

* ANOVA; † Chi-square; × analysis was performed on the number of patients that reported they had work respectively performed sports; Mean scores (±SD) are shown.

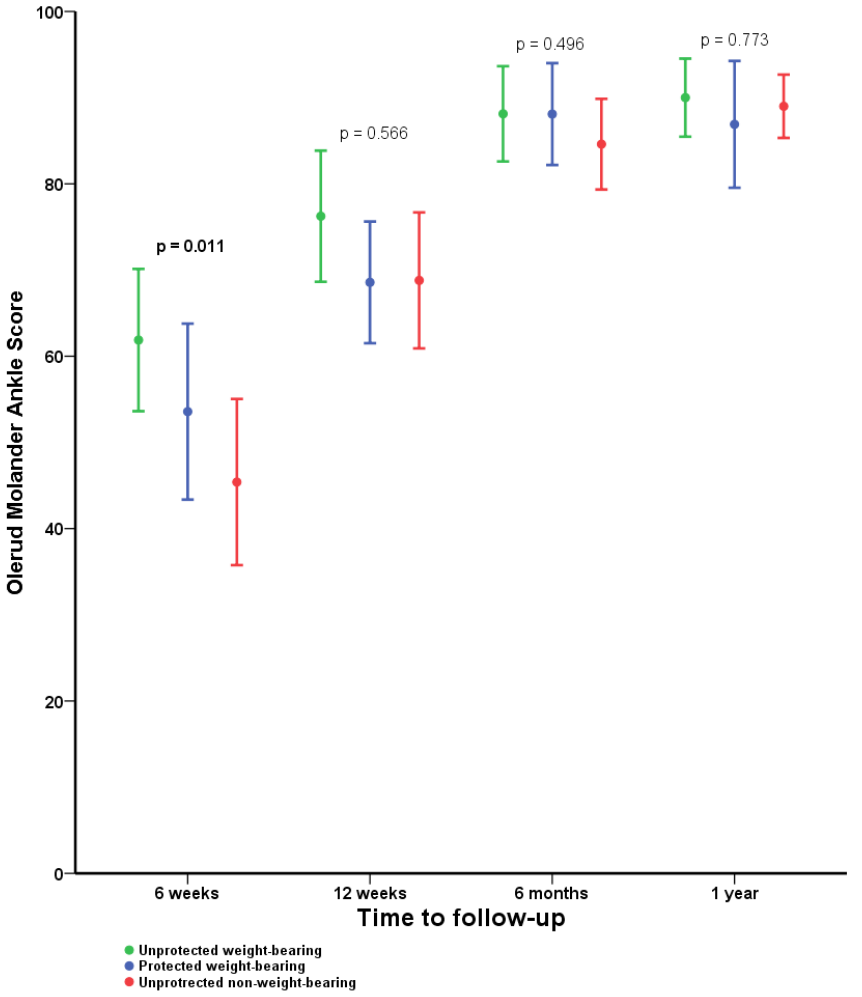

Figure 2 Functional outcome using the Olerud Molander Ankle Score based on the postoperative treatment of ankle fractures
This figure shows the functional outcome using the Olerud Molander Ankle Score based on the postoperative treatment of ankle fractures. The Olerud Molander Ankle Score ranges from 0 to 100. A higher score indicates a better functional outcome. Mean Olerud Molander Ankle Scores are shown with corresponding 95% confidence intervals of the means on the different time points.

There were no significant differences in the rate of complications between groups (p=0.639). The number and type of complications are shown in table 2 for each group. In addition, Appendix 4 included anecdotes and descriptions of the recovery pattern of patients that were included in the unprotected weight-bearing group.

Table 3 Results and differences in quality of life using the SF-36

	Unprotected non-weight-bearing (n=37)	Protected weight-bearing (n=36)	Unprotected weight-bearing (n=42)	p-value*
SF-36 score at 12 weeks				
physical functioning	74.9 (±22.8)	75.5 (±18.3)	76.8 (±21.9)	0.922
role-physical functioning	41.7 (±41.8)	31.9 (±37.7)	40.8 (±40.4)	0.575
bodily pain	76.9 (±18.7)	76.1 (±15.0)	73.2 (±22.2)	0.696
general health perception	80.9 (±17.8)	78.1 (±18.5)	77.6 (±13.2)	0.676
energy/ fatigue (vitality)	73.9 (±20.5)	72.2 (±14.1)	69.9 (±18.0)	0.629
social functioning	83.3 (±18.7)	80.6 (±21.0)	79.0 (±23.4)	0.686
role-emotional functioning	15.2 (±31.3)	11.5 (±27.1)	14.9 (±31.7)	0.869
mental health	83.3 (±14.1)	85.5 (±11.5)	81.1 (±15.8)	0.439
SF-36 score at 1 year				
physical functioning	93.1 (±10.0)	90.5 (±16.3)	88.8 (±17.1)	0.459
role-physical functioning	5.7 (±17.2)	16.7 (±33.4)	19.1 (±37.0)	0.150
bodily pain	92.1 (±16.4)	86.4 (±20.4)	84.7 (±21.7)	0.249
general health perception	81.4 (±13.7)	80.5 (±17.3)	79.2 (±17.9)	0.846
energy/ fatigue (vitality)	72.1 (±16.1)	73.8 (±16.2)	75.5 (±17.1)	0.682
social functioning	90.4 (±18.5)	93.9 (±12.1)	91.5 (±19.1)	0.675
role-emotional functioning	6.7 (±22.6)	12.1 (±31.0)	17.5 (±37.0)	0.328
mental health	80.7 (±14.2)	81.9 (±13.6)	81.6 (±16.8)	0.939

This table shows the health related quality of life using the SF-36v2 based on the postoperative treatment of ankle fractures. A higher score of the SF-36v2 indicates less disability (range from 0 to 100). No significant differences were seen.
* ANOVA
Mean scores (±SD) are shown.

Discussion

The main message of this study is "get up and walk". Orthopedic trauma surgeons tend to be careful with weight-bearing after surgical treatment of extremity injuries in order to avoid loss of reduction and implant failure. As these injuries occur often in the working population, this attitude has tremendous socio-economic implications. Patient and society might benefit from a more liberal approach towards weight-bearing after ankle fracture surgery. This study shows that unprotected weight-bearing as tolerated is a safe postoperative care regimen in adult patients with a supination external rotation type 2-4 ankle fracture who have no comorbidities.

The study methodology with a prospective expert panel is new in orthopedic trauma surgery. The expert panel confirms the fracture type prior to study inclusion. In contemporary literature, mostly an anatomic determination ("ankle") is used, instead of a specific fracture type (6;9;17). The strict selection of fracture type as used in the present study is essential, as different types of ankle fractures require a different operative and postoperative approach. Consequently, results of this study do not generalize to patients with other fracture types. This unique method of selecting fractures by a classification-guided expert panel helps to identify the right patient population in which a postoperative treatment regimen may be effective (23;24). As such, it prevents the inclusion of an overly heterogeneous patient population in whom treatment effects are equally heterogeneous. By ensuring a specific fracture type, a more solid advice regarding effectiveness of treatment can be obtained (25;26). We believe this approach of targeted treatment in carefully selected patients should be the new standard for studies in orthopedic trauma surgery.

Over time the postoperative care regimens of injuries and particularly fractures have evolved towards favoring early weight-bearing and/or mobilization in order to optimize fast and functional recovery. In addition, several studies on different lower extremity fractures did not demonstrate negative effects of early weight-bearing (27-29). However, factors such as comorbidities and injury pattern, influence the surgeon's choice of postoperative care regimen in an attempt to avoid complications (7). With respect to the postoperative treatment of ankle fractures, multiple studies investigated either early weight-bearing or early mobilization (active ankle exercises), but not a combination (8-10;17). Previously, early protected weight-bearing showed good functional outcomes without disadvantages (9;10). In addition, early mobilization showed an earlier return to work in previous reports (8;17). One retrospective cohort study examined unprotected weight-bearing and mobilization as tolerated, which revealed a significantly earlier return to work without a higher rate of complications (6). When compared to other studies, our 6-week OMAS results of the early protected weight-bearing group are similar to the comparable group in the study by Dehghan et al. However, the results of our unprotected weight-bearing group was 19 points higher on the 6-week OMAS compared to the protected early weight-bearing group in the study by Dehghan et al.(9). Hence, our study not only supports the

results of Gul et al. given an earlier return to work, but also demonstrates an earlier return to sports and improved functional outcome 6 weeks postoperatively for mobilization as tolerated. Appendix 4 highlights some of the advantages of early functional recovery in patients who were allowed to weight bear without protection immediately after surgery.

The study protocol incorporated strict criteria for early termination of the trial due to complications (19). An earlier retrospective cohort study in our region showed a 10% wound complication rate and a 4% implant failure rate (30). The results of this study showed that wound-related complications had a multifactorial origin but were not associated with the different postoperative treatment protocols. This is in contrast to Keene et al., in which early mobilization resulted in a higher rate of infection compared to immobilization and a study of Lehtonen et al. that even suggested an immobilization period of 2 weeks to reduce infectious complications (12;30;31). To prevent confounders to influence the rate of postoperative complications, the trial enforced strict in- and exclusion criteria concerning both the patient and trauma mechanism (19). This may have contributed to the lower rate of complications as compared to the historical cohort study and the above mentioned studies (12;30).

Although complications were not an issue, early termination of the study was recommended by the DSMB. An interim analysis was conducted after half of the target enrollment was reached as specified in the study protocol (19). After interim analysis, the trial was terminated based on the slow inclusion rate, in combination with the absence of any difference in the primary endpoint, and the improved function after 6 weeks in the experimental study arm without an increase in complications.

Several features were incorporated in this trial to minimize the amount of bias. Allocation to a treatment group was concealed using a computerized block randomization. In addition, a coordinating researcher performed the follow-up of all patients to keep the loss to follow-up as low as possible to prevent attrition bias. All outcomes were measured in a standardized way using patient-reported questionnaires. The protocol pre-specified our methods and statistical analysis plan, except for the statistical significance bound, for which we decided post-hoc to use the conservative O'Brien-Fleming approach (19).

The study was limited by the fact that there was no blinding of patients, treating physicians or outcome assessors; however, it is unclear whether

blinding is truly necessary in this pragmatic trial. A potential criticism also mentioned by Dehghan et al. is the potential noncompliance of patients to their designated postoperative care regimen (9;32). Patient noncompliance could lead to a higher rate of complications as described previously, although this was absent in the present study (33). Finally, the rate of randomized to screened patients was low.

Conclusion

This study suggests that unprotected weight-bearing and mobilization as tolerated results in improved short-term functional outcome and earlier return to work and sports. The postoperative care regimen of unprotected weight-bearing and mobilization as tolerated did not result in an increased rate of complications in adult patients with a supination external rotation type 2-4 ankle fracture without comorbidities. When results are implemented in common clinical practice, careful patient and fracture selection in combination with close observation is warranted.

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Appendix 1 In- and exclusion criteria and reasons for not participating

	AZN	DHU	HMC	EZH	total
Exclusion criteria					
pre-existent impaired mobility	1	3	0	1	**5**
pre-existent impaired cognitive disability	4	2	9	5	**20**
expected insufficient stable fracture fixation with standard surgical technique	0	0	0	0	**0**
necessity of a syndesmosis screw	13	3	16	7	**39**
posterior malleolar fragment requiring operative fixation	15	2	26	12	**55**
body mass index >30	18	6	4	5	**33**
diabetes mellitus	7	8	10	3	**28**
polytrauma patients	0	0	1	2	**3**
Gustilo 2 and 3 open fractures	4	3	5	1	**14**
inability to comply with one of the treatment groups	4	3	4	3	**14**
inability to comply with follow-up	2	3	3	2	**10**
inability to comply with follow-up because of language	2	1	5	2	**10**
too severe soft tissue damage and/or initial use of external fixation	0	3	6	5	**14**
pregnancy	0	1	0	0	**1**
other injuries dictating postoperative care	3	3	1	6	**13**
insufficient stable fracture fixation established during surgery as judged by the treating surgeon	1	1	3	0	**5**
No participation					
trial not discussed	36	9	92	79	**216**
refusal to participate	6	13	13	4	**36**
Included	31	60	18	6	**115**

AZN = St Antonius; DHU = Diakonessenhuis; HMC = Haaglanden Medisch Centrum; EZH = Elisabeth-TweeSteden

Appendix 2 Follow-up rate per time-point

Hospital	2 weeks		6 weeks		12 weeks		6 months		1 year	
AZN	31/31	100%	28/31	90.3%	29/31	93.5%	26/31	83.9%	29/31	93.5%
DHU	60/60	100%	54/60	90.0%	57/60	95.0%	43/60	71.7%	55/60	91.7%
HMC	18/18	100%	12/18	66.7%	12/18	66.7%	11/18	61.1%	16/18	88.9%
EZH	6/6	100%	4/6	66.7%	3/6	50.0%	1/6	16.7%	6/6	100%
Total	**115/115**	**100%**	**98/115**	**85.2%**	**101/115**	**87.8%**	**81/115**	**70.4%**	**106/115**	**92.2%**

AZN = St Antonius; DHU = Diakonessenhuis; HMC = Haaglanden Medisch Centrum;
EZH = Elisabeth-TweeSteden

Appendix 3 Group comparisons of Olerud Molander Ankle Score, time to return to work and sports

	Mean difference	95% CI of the difference	p-value
Unprotected weight-bearing (n=42) vs Protected weight-bearing (n=36)			
Olerud Molander score 6 weeks	9.4	(-.39 to 19.2)	0.059
Olerud Molander score 12 weeks	3.6	(-4.7 to 11.8)	0.391
Olerud Molander score 6 months	-0.4	(-9.5 to 8.7)	0.925
Olerud Molander score 1 year	-2.2	(-9.6 to 5.1)	0.542
Time to return to work in weeks*	-1.6	(-3.6 to 0.3)	0.105
Time to return to sports in weeks*	-3.8	(-7.6 to 0)	0.048
Unprotected weight-bearing (n=42) vs Unprotected non-weight-bearing (n=37)			
Olerud Molander score 6 weeks	15.4	(5.3 to 25.6)	0.004
Olerud Molander score 12 weeks	4.3	(-5.0 to 13.6)	0.357
Olerud Molander score 6 months	4.6	(-5.5 to 14.7)	0.362
Olerud Molander score 1 year	-1.9	(-8.3 to 4.6)	0.564
Time to return to work in weeks*	-2.9	(-5.1 to -0.7)	0.010
Time to return to sports in weeks*	-5.2	(-8.0 to -2.4)	<0.001
Protected weight-bearing (n=36) vs Unprotected non-weight-bearing (n=42)			
Olerud Molander score 6 weeks	6.0	-4.7 to 16.7	0.265
Olerud Molander score 12 weeks	0.7	-8.0 to 9.5	0.866
Olerud Molander score 6 months	5.0	-3.8 to 13.9	0.259
Olerud Molander score 1 year	0.4	-6.1 to 6.9	0.908
Time to return to work in weeks*	-1.3	-3.8 to 1.2	0.312
Time to return to sports in weeks*	-1.4	-5.5 to 2.7	0.492

Independent Samples T-test was used. Equal variances were not assumed.

Appendix 4 Anecdotes of unprotected weight-bearing participants

- Two weeks postoperatively, a patient reported that he had been catching Pokemons and thereby walking about 2 kilometres a day and riding his bike for 10 kilometres a day.
- Two weeks postoperatively, a patient arrived by motorcycle for a follow-up visit.
- Six weeks postoperatively, a patient could already walk 10 consecutive kilometres.
- Four and a half weeks postoperatively, a patient was working and playing sports again.

CHAPTER NINE

Clinical research on post-operative trauma care: Has the position of observational studies changed?

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O.A.J. van der Meijden, F. Hietbrink

Int J Surg Case Rep. 2017;41:360-365.

Abstract

Background

The post-operative care regimes of ankle fractures are studied for over 30 years and recommendations have shifted only slightly in the last decades. However, study methodology might have evolved. The aim of this study was to evaluate the changes in time in the design, quality and outcome measures of studies investigating the postoperative care of ankle fractures.

Methods

The MEDLINE and EMBASE database were searched for both RCTs and cohort studies. The original studies were divided into decades of publication over the last thirty years. The methodological quality of the studies was assessed using the 'traditional' risk of bias assessment tool provided by The Cochrane Collaboration and the 'newer' MINORS criteria.

Results

The percentage of RCTs on this subject declined from 67% to 38% in the last decades. According to the Cochrane tool, the reported quality of RCTs has improved in the last three decades whereas the reported quality of observational studies has remained unchanged. However, when quality was evaluated with the MINORS criteria, equal improvement was observed for both RCTs and observational studies. In the '80's, 67% of all studies used the range of motion as the primary outcome measure, which decreased to 45% in the '90's. In the '00's, none of the studies used the range of motion as the primary outcome.

Conclusion

For postoperative care of ankle fractures, results of this study showed a relative decrease in the published number of RCTs. The overall quality of the published articles did not decline. In addition, a gradual shift from physician measured to patient reported outcome variables was observed. However, it should be borne in mind that the findings are based on a small sample (n=25).

Introduction

In evidence based medicine, the value of observational studies, such as cohort and case-control studies, has generally been regarded as relatively insignificant (1). Randomized controlled trials (RCTs) have long been considered the gold standard (2). In the strive for optimal evidence based medicine and subsequent patient care the utility of conducting Randomized Controlled Trials (RCT) in trauma surgery has been questioned over the past years (3). In addition, observational studies are published frequently, while the number of surgical RCTs from North America have decreased over the last decade (4). This raises questions how the quality of studies evolved over the last years. In addition, as a result of evolving clinical experience and meeting patient demands, there is more emphasis on patient reported outcome measurements. Patients are more involved in the decision making process concerning their treatment, which should ultimately lead to shared decision making.

In trauma surgery, ankle fractures are among the most common fractures and the indication for surgery has not changed in the past decades 5). Furthermore the post-operative care regimes of ankle fractures are studied for over 30 years and recommendations have shifted only slightly in the last decades, as we demonstrated recently. As a consequence the circumstances in which studies were performed, did not change substantially in this field of medicine. Therefore treatment of ankle fractures can be used as an example to investigate the evolution in study methodology. The goal of this study was to evaluate the changes in time in the design, quality and outcome measures of studies investigating the postoperative care of ankle fractures.

Methods

Selection

This study included the same studies as selected in our previous meta-analysis evaluating the postoperative care regimen of ankle fractures of twenty five RCTs and cohort studies (6). The studies included were retrieved by two reviewers (DS and FH), who independently searched the MEDLINE and EMBASE electronic databases. An extensive description of the search strategy and study selection with inclusion and exclusion criteria was published in the meta-analysis (6).

Data extraction

The original studies were divided into decades of publication, for the last thirty years. The decades covered the years from 1980 until 1989, 1990 until 1999 and 2000 and onwards. Subsequently, the studies were analysed for design, number of patients, quality, primary outcome variable and other outcomes including complications. The study designs were divided into a retrospective cohort, prospective cohort, randomised controlled trial or a combination of designs. Partly prospective and partly retrospective studies were defined as a mixed cohort study. The methodological quality of the studies was independently assessed by three reviewers (DS, FH and RH) using the risk of bias assessment tool provided by The Cochrane Collaboration and the MINORS criteria (7;8). The risk of bias assessment tool provided by The Cochrane Collaboration was developed to compare the quality of RCTs and the MINORS criteria were developed to compare the quality of nonrandomized studies. A higher score indicates a higher quality. In addition, we have checked the affiliations of the authors of the included articles to check if a methodologist cooperated in the research project. The primary outcome variables were the range of motion (ROM), functional scores (such as the Olerud Molander score; a patient reported outcome) and return to work data (9). Secondary outcomes ranged from objective physician measured outcomes to more subjective patient dependent outcomes. If none of the above mentioned outcome variables were used, the study was excluded from the analysis.

Descriptive analysis

SPSS software (version 20.0, Chicago, IL, USA) was used for descriptive analysis, both statistically and graphically. Additional analyses were not performed.

Results

A total of 25 studies were included, 6 of which from the '80's, 11 from the '90's and 8 from the 21st century (Table 1). From all studies 12 (48%) were RCTs.

Study design

Fewer RCTs were published in the last decades. The relative number of RCTs decreased. The percentage of RCTs on this subject declined from 67% to 38% (Table 1 and Figure 1). The number of patients per study changed from 46 (±10) in the '80's to 51 (±13) in the '90's to 67 (±33) in the 21st century.

Table 1 Risk of bias assessment

Publication and year of publication	Study design	Positive points on Cochrane risk of bias assessment tool	MINORS criteria	Primary outcomes	Most patient dependent outcome	All outcomes	Number of included patients
Gul et al. 2007	Retrospective	1	18	RTW	RTW	RTW, FS	50
Honigmann et al. 2007	RCT	4	19	FS	RTW	RTW, FS, ROM	45
Vioreanu et al. 2007	Prospective	2	21	FS	RTW	RTW, FS, ROM	62
Simanski et al. 2006	Mixed	2	18	FS	RTW	RTW, FS	46
Siddique et al. 2005	Prospective	2	17	FS	FS	FS, ROM	44
Lehtonen et al. 2003	RCT	5	21	FS	RTW	RTW, FS, ROM	100
Egol et al. 2000	RCT	3	19	FS	RTW	RTW, FS	55
Harager et al. 2000	Mixed	0	12	ROM	NR	NR	135
Dogra et al. 1999	RCT	5	19	ROM	FS	FS, ROM	52
Laarhoven van et al. 1996	Prospective	2	18	FS	RTW	RTW, FS, ROM	81
Richter et al. 1996	Prospective	1	14	FS	FS	FS	61
Tropp et al. 1995	RCT	2	16	ROM	FS	FS, ROM	30
DiStasio et al. 1994	RCT	3	17	FS	RTW	RTW, FS, ROM	61
Hedström et al. 1994	RCT	4	18	FS	FS	FS, ROM	53
Ahl et al. 1993	Mixed	1	14	FS	FS	FS, ROM	40
Godsiff et al. 1993	Prospective	2	15	ROM	RTW	RTW, ROM	47
Cimino et al. 1991	Mixed	1	12	ROM	ROM	ROM	51
Davies et al. 1991	Prospective	1	18	ROM	RTW	RTW, ROM	41
Wetzler et al. 1991	RCT	2	11	RTW	RTW	RTW, ROM	45
Finsen et al. 1989	RCT	2	19	FS	RTW	RTW, FS, ROM	56
Ahl et al. 1988	Mixed	1	13	FS	FS	FS, ROM	51
Ahl et al. 1987	RCT	2	16	ROM	ROM	ROM	53
Ahl et al. 1986	RCT	3	17	ROM	ROM	ROM	46
Søndenaa et al. 1986	RCT	2	11	ROM	ROM	ROM	43
Lund-Kristensen et al. 1981	Prospective	2	15	ROM	ROM	ROM	28

RTW = return to work or daily activities; FS = functional score; ROM = range of motion; NR = not reported

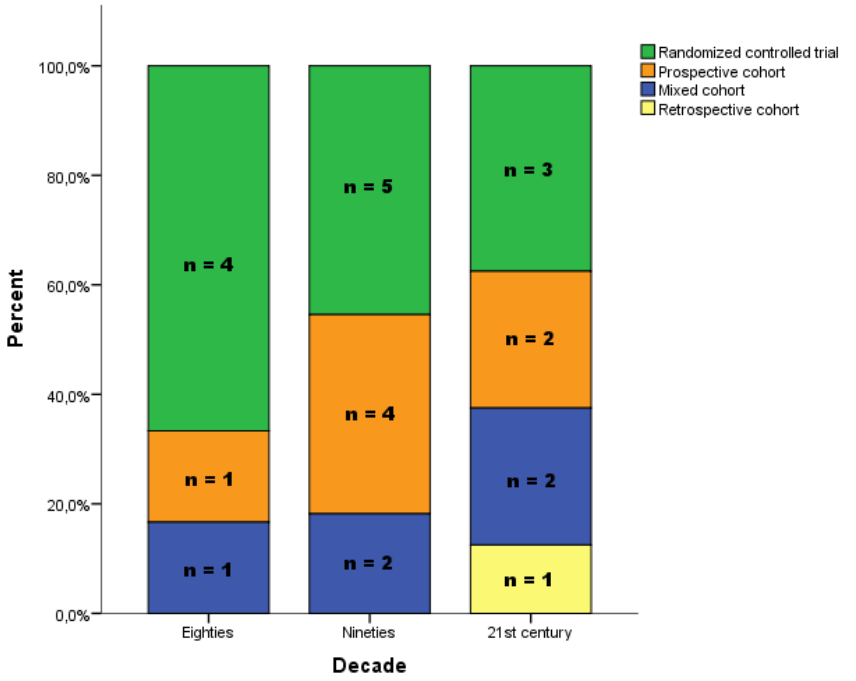

Figure 1 Study design

Quality

Over the past three decades, the overall quality of the published articles did not decline (Table 1). The mean score on the Cochrane risk of bias assessment tool was 2.2 (±1.3). The highest score was 5 out of 7 points on the Cochrane risk of bias assessment tool, which was reached by two studies. Interestingly, the reported quality of RCTs improved in the last decade, from a mean of 2.3 (±0.5) to 4.0 (±1.0) (Figure 2). The quality of prospective and mixed cohort studies remained unchanged. The mean score on the MINORS criteria was 16.3 (±2.9). When using the MINORS criteria the reported quality of RCTs improved in the last decade, from a mean of 15.8 (±3.4) to 19.7 (±1.2). In addition the quality of prospective and mixed cohort studies improved in the last decade, from a mean of 14.0 (±1.4) to 17.2 (±3.3) (Figure 3).

Two articles had one or more authors that were affiliated with a research department (10;11). Both were RCTs and had a relative high score on the Cochrane risk of bias assessment tool and the MINORS criteria.

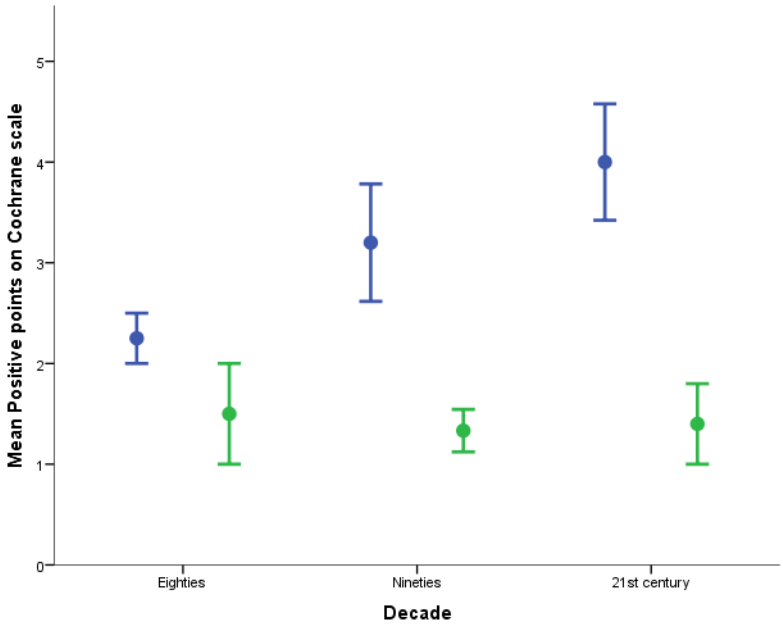

Figure 2 Quality RCT compared with non-randomised studies using Cochrane
Blue = RCTs; Green = non-randomised studies; Error bars: +/- 1 SE

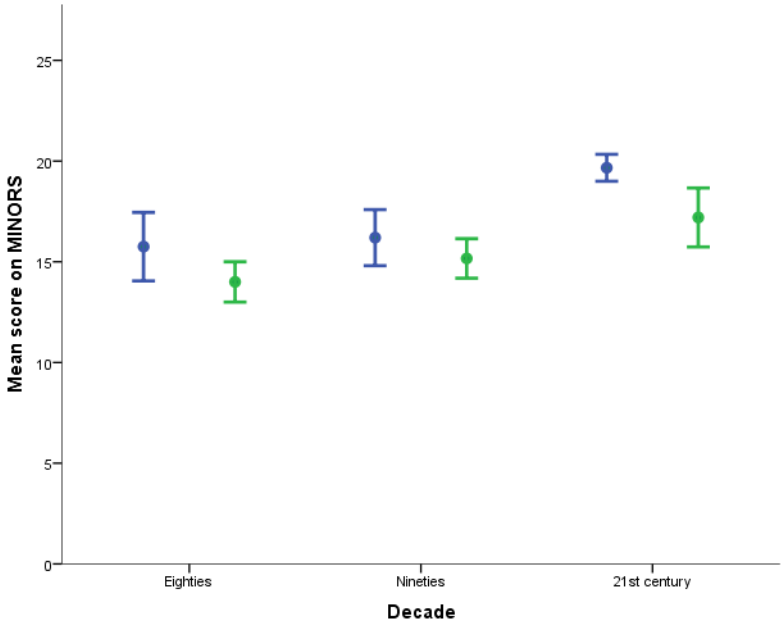

Figure 3 Quality RCT compared with non-randomised studies using MINORS
Blue = RCTs; Green = non-randomised studies; Error bars: +/- 1 SE

Primary outcome variable and most patient dependent outcome variable

A functional score was used as primary outcome in 13 (52%) studies and the range of motion was used in 10 (40%) studies as primary outcome. In the '80's, 67% of all studies used the range of motion as the primary outcome measure, which decreased to 45% in the '90's. In the '00's, none of the studies used the range of motion as the primary outcome. Less objective outcome measures and more functional scores were used over time (Table 1 and Figure 4).

The return to work was the most used patient dependent outcome variable applied in 12 (48%) studies (Figure 5). In the '80's all 6 studies used the range of motion as outcome compared to 4 studies (50%) in the '00's. In the last decade 6 studies (75%) reported "return to work" data.

A total of 2 studies did not report on complications (12;13). Six other studies did report on complications, but without reporting the treatment group to which the complications belong or without reporting exact numbers (10;14-18).

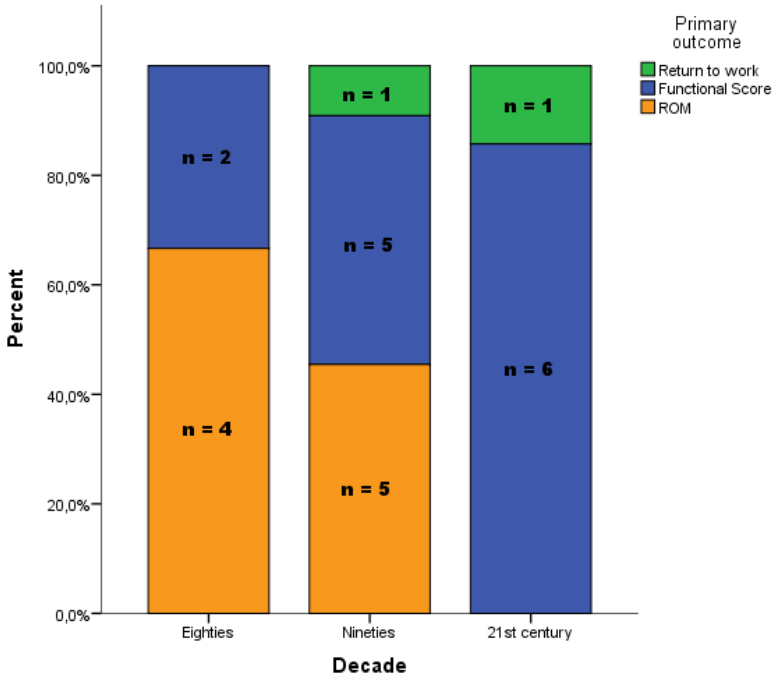

Figure 4 Primary outcomes

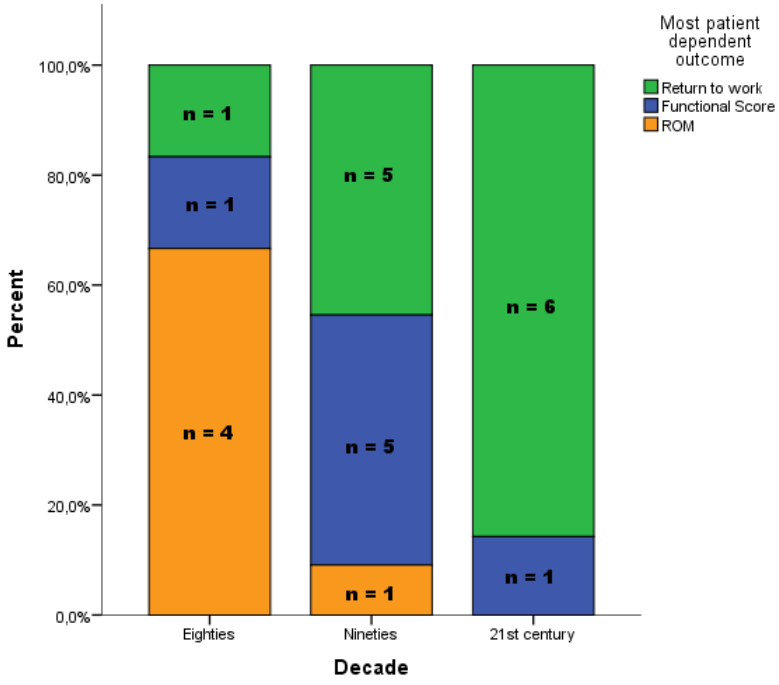

Figure 5 Most patient dependent outcome

Discussion

For postoperative care of ankle fractures a change in study design and presented outcome variables was observed over the last three decades. This study demonstrated an increase in the published number of cohort series on the treatment of ankle fractures, with increasing number of patients included. According to the Cochrane tool, the reported quality of RCTs has improved in the last three decades whereas the reported quality of observational studies has remained unchanged. However, when quality was evaluated with the MINORS criteria, equal improvement was observed for both RCTs and observational studies. Therefore evaluation of quality is under influence of the quality assessment tool used. In addition, a gradual shift from physician measured to patient reported outcome variables was observed.

There is a growing debate on the need of RCTs to evaluate the effectiveness of surgical procedures (19). Results of this study indicate a relative decrease in the number of published RCTs over the past three decades in this field of research. Literature shows that one in five surgical RCTs is discontinued early, and one in three completed trials remains unpublished (19). For (trauma) surgical research such a trend might be explained by several factors.

First, including patients in a surgical RCT has become more and more challenging (20). Both patient and surgeon have treatment preferences and surgeons may be better skilled in one of the study procedures. Ideally, randomisation distributes any unknown factors, thereby eliminating unforeseen confounders. However, patients may refuse or prefer the "new" technique and, therefore, do not wish to receive random treatment (21). In addition, blinding of both patient and surgeon is frequently impossible and/or undesired by both patient and surgeon, which also neutralizes one of the advantages of a RCT over a cohort series.

Second, in the last decade the bureaucratic burden of ethical committee approval and monitoring have increased substantially, especially for conducting RCTs. This is accompanied by an increased financial demand. These procedures were developed to increase patient consent and safety, but sometimes might seem undue. For research projects in a field with limited financial resources, it is therefore increasingly difficult to meet the intensified quality demands (20). Only a limited amount of funding went to surgical research in spite of the relatively large contribution of surgery to effective treatment (22). These practical obstacles might have caused a substantial decrease in the quantity of RCTs in surgical research compared to other fields of medicine (4;23).

However, as the goal of research remains to improve the quality of care for patients with an ankle fracture, alternatives are sought. This might reflect the subsequent increase in the number of published cohort series. An alternative explanation might be that due to the eagerness to produce papers in the highly competitive scientific world, where the number of publications counts heavily, there may be a bias towards writing more relatively inexpensive articles that describe cohort and retrospective studies. However, this was not demonstrated by the absolute number of published papers over the last three decades in this study, nor by a decrease in quality.

Reported quality of RCTs improved over time. This might be explained by several quality assessment tools that became available for RCTs in the '90's. The introduction of these tools provided guidance for constructing well-designed studies, with more standardised reporting and thereby improved reported research quality. Reporting of studies might have improved by reporting standard such as the CONSORT (2). In the current study we used the Cochrane risk of bias assessment tool to assess the quality of the studies included. This tool was primarily designed for RCTs, but is also recommended for quality assessment of observational studies (24;25). In addition, we used the MINORS criteria (8). This tool is primarily designed for non-randomized studies. A combination of both tools can provide the overall quality of studies. Due to the design of the Cochrane risk of bias assessment tool, the design of a study is decisive for the results on a domain of the tool (e.g. a randomised trial has the potential to score positive on all domains contrary to observational studies). Therefore, observational studies will inevitable have a higher risk on bias in the Cochrane risk of bias assessment tool. In addition, we used the MINORS criteria (8). This tool is especially designed for non-randomized studies. Other tools for observational studies were designed more recently, which are not frequently used (26). It should always be kept in mind that evaluation of quality is under influence of the quality assessment tool used. Similarly to RCTs, the MINORS criteria might provide guidance for constructing well-designed observational studies and further improve observational research quality. Perhaps both RCTs and cohort series are needed to provide a complete image of a disease or treatment modality. RCTs are designed to compare specific items head to head, while large cohort series are more capable of exposing rare complications or the effect of a whole package (27).

A convincing finding of the present study is the increased use of patient-relevant outcomes. The next step would perhaps consist of consensus recommendations in order to define standard outcome measures for future ankle fracture studies. If all studies applied the same set of outcome measures at the same timepoints, this would make it much easier to compare and to use study results. In rheumatology, such an initiative (called OMERACT) was highly successful (28).

In the '80's, primary outcomes were focused on radiological results and objective variables. The attending physician or investigator could measure

these objective variables. In the twentieth century, outcomes increasingly focused on the implications for the patient and were reported as primary end-point of several studies. In the last decade over half of the included studies mentioned return to work as outcome measure which is, in our opinion, a legitimate patient reported end-point.
The sample (n= 25 studies) is quite small. It is still possible that some of the observed results are attributable to the play of chance. This should be borne in mind when interpreting the results.
As ankle fractures are represented in the top five of most prevalent fractures and have an important socio-economic impact on both patient and society, the observations made in this study might be applicable to broader areas of (trauma) surgery research (29). However, results of this study might not be applicable to other non-surgical specialities. This study can be seen as a case-report and should be tested in further extent and on a larger scale in traumasurgical studies.
Results of this study indicate a relative decrease in the number of published RCTs, which might be a reflection of the practical difficulty to conduct RCTs in trauma surgery due to surgeon, patient and system based factors. Furthermore, the desire for more patients orientated outcome variables is reflected in the changes seen in the last decades.

Conclusion

For postoperative care of ankle fractures a change in study design and presented outcome variables was observed over the last three decades. RCTs were performed less frequently. According to the Cochrane tool, the reported quality of RCTs has improved whereas the reported quality of observational studies has remained unchanged. When quality was evaluated with the MINORS criteria, equal improvement was observed for both RCTs and observational studies. This shows that evaluation of quality is influenced by the quality assessment tool. In addition, a gradual shift from physician measured to patient reported outcome variables was observed. However, it should be borne in mind that these findings are based on a small sample (n=25).

Compliance with ethical requirements

There are no potential conficts of interests. The research does not directly include patients and therefore informed consent was not applicable.

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CHAPTER TEN

Plate fixation or intramedullary fixation for midshaft clavicle fractures: a systematic review and meta-analysis of randomized controlled trials and observational studies

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Abstract

Background

The last decade has shown a shift towards operative treatment of a subset of midshaft clavicle fractures. However, it is unclear if there are differences between plate fixation and intramedullary fixation regarding complications and functional outcome. The aim of this systematic review and meta-analysis was to compare plate fixation and intramedullary fixation for midshaft clavicle fractures.

Methods

The MEDLINE, EMBASE and Cochrane databases were searched for both randomized controlled trials and observational studies. The methodological quality of all included studies was assessed using the MINORS.

Results

Twenty studies were included. Ten of the 20 included studies used a fracture classification. Seven of these studies reported exclusion of patients with comminuted fractures. No difference in the total re-intervention rate was found (Odds Ratio (OR) 1.21; 95%Confidence Interval (CI) 0.71-2.04). Major re-interventions occurred more often after plate fixation (OR 1.88; 95%CI1.02-3.46). Mean implant removal rates after plate fixation were 38% and after intramedullary fixation were 73%. Re-fracture after implant removal occurred more often after plate fixation (OR 3.42; 95%CI1.12-10.42). The Constant-Murley scores showed no differences on both short- and long-term (short-term mean difference (MD) -1.18; 95%CI-13.41-11.05; long-term MD 0.15; 95%CI-1.57-1.87). No differences were observed regarding non-unions (OR 1.50; 95%CI0.82-2.75). The rate of infections showed no differences when outlier studies were excluded (OR 1.54; 95%CI0.88 – 2.69).

Conclusion

Major re-intervention and re-fracture after implant removal occurred more frequent after plate fixation of non-comminuted displaced midshaft clavicle fractures. No differences in terms of function and non-unions between plate fixation and intramedullary fixation were observed.

Introduction

Clavicle fractures are most commonly observed in males under the age of 30 years and typically as a result of a contact sport or road traffic accident. Midshaft clavicle fractures (MCF) account for approximately 80% of all clavicle fractures and 30% of these fractures are sports related injuries (29). The last decade has shown a paradigm shift towards operative treatment of MCF(7, 37). Operative fixation of clavicle fractures, for certain fracture patterns and in selected patients, may provide better long-term outcomes with respect to shoulder biomechanics and arm strength. Operative treatment is generally indicated for mid-shaft fractures that have significant shortening or displacement and are present in patients who will benefit from the possible improved strength and biomechanics of anatomic restoration (18, 37, 47).

Both plate fixation (PF) and intramedullary fixation (IMF) have shown superior results regarding the rates of non-unions compared to non-operative treatment for MCF in randomized controlled trials (RCTs) (8, 35). A recent randomized controlled trial (RCT) showed no difference in functional results one year after PF and IMF of MCF. However, no conclusions could be drawn regarding complications because the RCT design focused on functional outcomes (41).

Compared to RCTs, observational studies are generally more suitable for detecting (long-term) complications, especially for surgical procedures (17). In addition, there is growing evidence that meta-analysis of well-designed observational studies of surgical procedures may be as accurate as that of RCTs (1, 17).

The aim of this systematic review and meta-analysis is to compare plate- and IMF for MCF reported in both RCTs and observational studies. The primary outcome is the re-intervention rate defined as all re-interventions requiring general anesthesia except elective implant removal. Secondary outcomes are elective implant removal, setting of implant removal (hospital or outpatient department; under local or general anesthesia), re-fractures after implant removal, short- and long-term functional results, non-unions and infections.

Methods

Search strategy and selection criteria

RCTs and both prospective and retrospective observational studies comparing PF and IMF for acute DMCF were included in this systematic review and meta-analysis. Two reviewers (RMH and OAvdM) independently searched MEDLINE, EMBASE and The Cochrane Library on the 20th of April 2015. Articles written in English, French and German that were available in full text were included. Eligibility disagreement was resolved by discussion (RMH and OAvdM). The search syntax is provided in Appendix 1 (appendices available as supplemental material). Citation tracking and reference screening of the selected studies was performed. Figure 1 shows a flowchart of the search strategy according to the PRISMA guidelines (25).

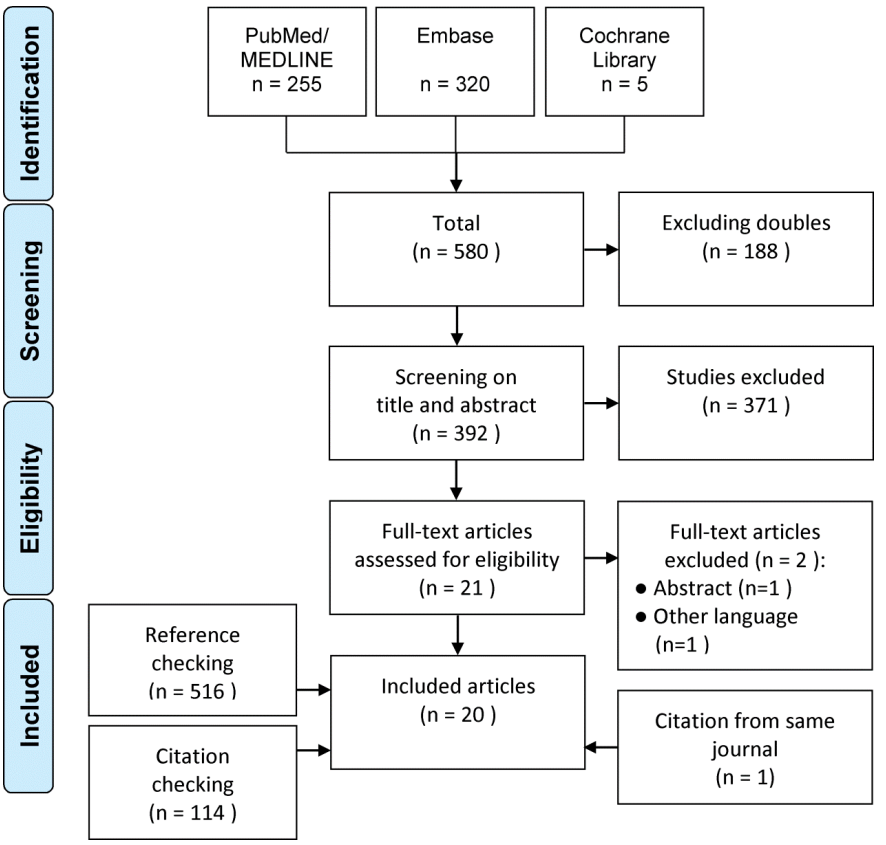

Figure 1 Flowchart search strategy
Process of search strategy following the PRISMA guidelines

Quality assessment

Two reviewers assessed the methodological quality of all included studies (RMH and OAvdM). Studies conducted by the first (RMH) and last author (OAvdM) were assessed by two other reviewers (DPJS and MCK). The MINORS methodology was used to assess the included studies (33). MINORS is an instrument designed to assess the methodological quality of observational surgical studies and was validated against the current standard for randomized trials (32).

Outcome measures

The primary outcome parameter of this meta-analysis was re-intervention rate. All re-interventions requiring general anesthesia except elective implant removal were considered major re-interventions. Minor re-interventions were defined as re-interventions at the outpatient department under local anesthesia. Secondary outcomes were elective implant removal defined as removal of the implant according to hospital protocol or according to patients wish. The location (hospital or outpatient) and the type of anesthesia used for implant removal (local or general anesthesia) were recorded when provided. The Constant-Murley score was used to collect information about long-term functional results (10). Short-term was defined as functional results within 2 months postoperatively. Long-term results were defined as functional results one year or longer after surgery (31). Non-union was defined as radiographic unsuccessful bone healing after 6 months. Infection was divided into superficial and deep infections. The definition of a superficial infection was redness, swelling and/or purulent discharge of the wound according to the used definition in the assessed studies. In case the infection required debridement or implant removal it was considered a deep infection and scored as major or minor re-intervention depending on required anesthesia. For the meta-analysis, infections were analyzed as one group.

Data extraction

Two reviewers (RMH and OAvdM) independently extracted the following baseline study data: authors, year of publication, study design, Institutional Review Board (IRB) approval, performance of sample size calculation, definition of fracture parts displacement described in methods section, classification used for inclusion, type of plate used, position of the plate, number of patients treated with PF, type of and technique used for IMF, number of patients treated with IMF and the postoperative rehabilitation protocol.

Statistical analysis

Outcomes reported by two or more studies were pooled in meta-analyses. Dichotomous and continuous outcomes were presented as odds ratios (ORs) and weighted mean differences, respectively. Data were pooled using the Mantel-Haenszel method for dichotomous outcomes and the inverse-variance method for continuous outcomes. Trials with zero events in both arms were excluded from meta-analysis. Trials with zero events in one arm were included in the analysis by adding a continuity correction of 0.5 to all cells in the 2x2 table of that study. As a robustness assessment, meta-analyses with RCTs with zero events in one arm were also performed using risk differences in a sensitivity analysis. For all analyses the 95% confidence interval (CI) was calculated. Absolute risk of re-fracture after plate and intramedullary fixation was analyzed using the Fisher Exact Test. Heterogeneity was calculated using Higgins χ^2 test, and inconsistency in study effects was quantified by I^2 values. The fixed effects model was used if no heterogeneity was present (χ^2 P value > 0.1 and I^2 < 25%). If excessive heterogeneity was present, data were first re-checked and the DerSimonian random effects model was used when heterogeneity persisted. Review Manager software (RevMan© v. 5.3.5) provided by The Cochrane Collaboration was used for data management and statistical analyses (28).

Subgroup and sensitivity analyses

After primary analysis, subgroup and sensitivity analyses were performed for the primary outcome parameter. As minor re-interventions are not possible for PF, major re-interventions were used for subgroup and sensitivity analyses. Subgroup analysis was performed for study type (RCTs versus observational). In subgroup analysis, results of both groups were presented. Sensitivity analysis was performed for study quality, type of implant for plate fixation and infections. In the sensitivity analysis on study quality, all studies with a MINORS score above 16 were included arbitrary. Biomechanical data showed inferior results of reconstruction plates compared to newer generation locking compression plates (12). Therefore a sensitivity analysis included all studies which did not use reconstruction plates. In the sensitivity analysis on infections, outlier studies were excluded. In sensitivity analyses, only results of the included group were reported.

Results

Search

The electronic search identified a total of 580 articles (Figure 1). After removal of duplicates, 378 studies were screened based on title and abstract and 21 studies were selected for full-text assessment. The study of Qia et al. was written in Chinese and the study of van Rutte et al. was an abstract and therefore excluded (27, 42). The 19 relevant studies from the initial search were checked for related citations and references, not resulting in additional relevant studies. One study was found in the same journal of one of the relevant studies. Therefore, 20 studies met the inclusion criteria (2, 5, 6, 9, 13, 15, 20-24, 26, 30, 38-41, 43-45) (Figure 1).

Baseline characteristics

Of the 20 included studies, 6 were RCTs, 4 were prospective cohort studies and 10 were retrospective cohort studies, enabling meta-analysis of a total of 1382 patients (Table 1). In 5 studies displacement was not defined. Six different types of plates and five different intramedullary (IM) devices were used. Plate position was superior, anterior-superior and inferior.

Critical appraisal

A summary of the critical appraisal of included studies is provided in Appendix 2. The total MINORS score for all studies ranged from 10 to 23 out of 24 with a mean (SD) of 15.9 (3.3). For the RCTs it ranged from 15 to 23 with a mean (SD) of 19.8 (2.9) and for the observational studies, it ranged from 10 to 17 with a mean (SD) of 14.5 (2.1). Ten of the 20 included studies used a fracture classification. Seven of these studies reported exclusion of studies with comminuted fractures.

Re-intervention

Seventeen of the 20 included studies reported re-interventions (2, 5, 6, 13, 15, 20-23, 26, 30, 39, 40, 43-45). No significant differences were found if all re-interventions were taken into account. The I^2 value for heterogeneity was 11%. When the fixed effects model was used, the calculated OR (95% CI) was 1.21 (0.71-2.04) (p = 0.48) (Appendix 3 and Figure 2).

Major re-interventions showed a significant difference to occur more often after plate fixation. The I^2 value for heterogeneity was 0%. When the fixed effects model was used, the calculated OR (95% CI) was 1.88 (1.02-3.46) (p = 0.04) (Appendix 4).

Table 1 Baseline characteristics

First author	Year	Country	Study-design	Displace-ment	Fracture type	Plate type
Andrade-Silva2	2015	Brazil	RCT	Yes	OTA B	Reconstruction plates
Assobhi5	2011	Egypt	RCT	Yes	NR	3,5mm Reconstruction plate
Bohme6	2011	Germany	PC	No	No	DCP, LCDCP & Reconstruction plates
Chen9	2012	China	RC	No	OTA A/B	Reconstruction plates
Ferran13	2010	United Kingdom	RCT	Yes	No	LCDCP
Fu15	2012	Taiwan	RC	No	No	Reconstruction
Jones20	2014	United Kingdom	RC	No	Alman 1	NR
Kleweno21	2011	United States	RC	No	OTA B1,B2	Reconstruction, LCP & Precontoured
Lee 200723	2007	Taiwan	RCT	Yes	NR	DCP
Lee 200822	2008	Taiwan	RC	Yes	NR	DCP, Tubular & Reconstruction
Liu24	2010	Taiwan	RC	Yes	NR	Reconstruction LCP
Meijden van der41	2015	The Netherlands	RCT	Yes	OTA A,B,C	Surgeon preference
Narsaria26	2014	India	PC	Yes	Robinson 2A2, 2B1	DCP
Saha30	2010	India	PC	Yes	AO B1,B2	LCP
Tabatabaei38	2011	Iran	PC	Yes	No	LCDCP & Reconstruction
Tarng39	2012	Taiwan	RC	Yes	Robinson 2A2, 2B1	Reconstruction
Thyagarajan40	2009	United Kingdom	RC	Yes	NR	LCDCP
Wenninger43	2011	United States	RC	Yes	NR	LCDCP & Reconstruction
Wijdicks44	2012	The Netherlands	RC	Yes	AO A/B/C	LCP & Reconstruction
Zehir45	2015	Turkey	RCT	No	Robinson 2B1,B2	LCP

RCT = randomized controlled trial; PC = prospective cohort; RC = retrospective cohort;
NR = not reported; LCDCP = low contact dynamic compression plate; DCP = dynamic compression plate;
LCP = locking compression plate; N = number of patients; IMF = intramedullary Fixation

Plate position	N plate	IMF type	N IMF	Rehabilitation
Superior	33	TEN	26	Sling 4wks, AROM at 2 weeks
Anterior-Inferior	19	TEN	19	Sling 2 wks, ADL 4 wks, Stenuous activities 6wks
NR	53	TEN	20	NR
NR	84	TEN	57	Sling 4 wks + PROM
Superior	15	Rockwood pin	17	Sling 2 wks 6wks PROM 90degr abd/flex
Anterior-Superior	50	Knowles pin	53	Sling 2-4wks
NR	24	TEN	25	NR
Ant, Sup & Inf	18	Rockwood pin	14	NR
NR	30	Knowles pin	32	Sling 2-4wks
NR	32	Knowles pin	56	Sing 1-3wks
Superior	59	TEN	51	NR
Anterior-Superior	58	TEN	62	Sling for comfort, early AROM
Anterior-Superior	34	TEN	32	Sling 2wks, early AROM
Anterior-Superior	37	TEN	34	Sling for comfort, early AROM
NR	25	NR	25	Velpeau, Sling, Early pendulum
NR	32	TEN	25	Sling 1wk, early AROM
NR	17	Rockwood pin	17	NR
Superior	29	Hagie pin	33	NR
Anterior-Superior	43	TEN	47	Surgeon preference
Superior	21	CRx	24	Sling 2wks, early AROM

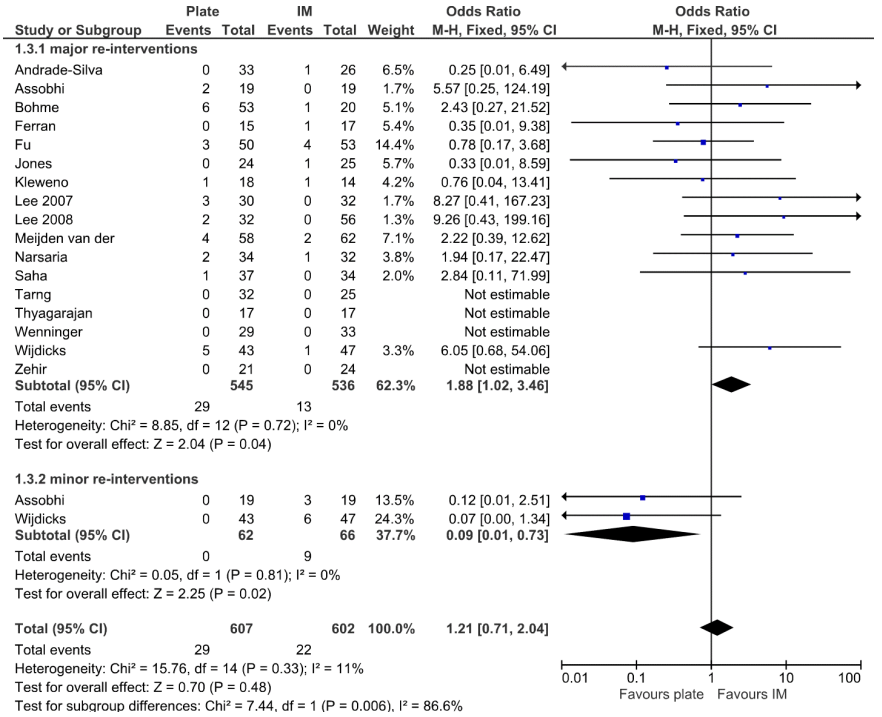

Figure 2 All re-interventions
The odds ratio (95% confidence interval) on the rate of all re-interventions is shown between the plate fixation group and the intramedullary fixation group

Subgroup analysis for study design, resulted in an OR of 1.92 (95% CI 0.70-5.25) (p = 0.21) for RCTs compared to an OR of 1.86 (95% CI 0.87-4.00) (p = 0.11) for observational studies. Sensitivity analysis for study quality resulted in an OR of 2.31 (95% CI 0.99-5.40) (p = 0.05). Sensitivity analysis for studies that did not use reconstruction plates resulted in an OR of 1.66 (95% CI 0.53-5.19) (p = 0.38).

Implant removal

Mean implant removal rates after PF were 38% and after IMF were 73%. Implant removal after IMF in the outpatient setting was reported in 3 studies under local anesthesia (23, 39, 41).

Re-fracture

Re-fracture after implant removal occurred significant more often after PF. This complication was described in 7 studies (2, 5, 6, 21, 26, 41, 44).

The I^2 value for heterogeneity was 0%. The fixed effects model was used; the calculated OR (95% CI) was 3.42 (1.12-10.42) (p = 0.03) (Appendix 5). The absolute risk of re-fracture after plate removal was 0.07, higher than the absolute risk after removal of the intramedullary device (0.01, p=0.01).

Functional outcome

Five studies reported short-term Constant-Murley scores (5, 26, 30, 39, 41). No significant differences were observed. The I^2 value for heterogeneity was 98%. The random effects model showed a mean difference of -1.18 (95% CI -13.41-11.05) (p = 0.85).

Also no significant differences were observed regarding long-term functional outcome. Constant-Murley scores were reported by 10 studies (2, 5, 9, 13, 22-24, 26, 30, 41). The I^2 value for heterogeneity was 82%. The random effects model showed a mean difference of 0.15 (95% CI -1.57-1.87) (p = 0.86) (Appendix 3, 6 and 7).

Non-unions

All included studies reported non-union rates (Appendix 3 and 8). The rates differed from 0 to 10%. No significant differences between the two procedures were observed. The I^2 value for heterogeneity was 0%. The fixed effects model was used; the calculated OR (95% CI) was 1.50 (0.82-2.75) (p = 0.19) (Appendix 8).

Infections

Reported infections occurred significantly more often after plate fixation (Appendix 3 and 9). The rates differed from 0 to 36%. Infections were described in all included studies except one45. The I^2 value for heterogeneity was 0%. The fixed effects model was used; the calculated OR (95% CI) was 1.78 (1.08 – 2.93) (p = 0.02) (Appendix 9).

Sensitivity analysis excluding outlier studies resulted in an OR (95% CI) was 1.54 (0.88 – 2.69) (p = 0.13).30, 38 The I^2 value for heterogeneity was 0%.

Discussion

In this systematic review we observed no differences in terms of re-interventions in general and function between PF and IMF. When we focus on major re-interventions, re-fracture after implant removal and infections we found an advantage for the IMF treatment. However, not all fracture types are suitable for IMF. From the 10 studies that reported

a fracture classification, 7 excluded comminuted fractures (AO type C and Robinson 2B2) (2, 9, 20, 21, 26, 30, 39). If all the papers reviewed had included comminuted fractures, the conclusions regarding the major intervention rate, nonunion rate, and overall outcomes might have been changed. The conclusions reached in this study would therefore be limited to non-comminuted, displaced mid-shaft clavicle fractures.

A recent meta-analysis on this subject by Zhu et al. included 5 studies resulting in assessment of results of 285 patients (46). A limitation of their meta-analysis is that only randomized and quasi-randomized controlled trials were included, and as a result, most analyses were performed on 1–3 studies. This leads to a reduced power to identify differences. In the current meta-analysis the study power was substantially higher since two recent published RCTs on this subject could be included.(2, 41) Furthermore, we also included observational studies, which has been suggested in previously published surgical and orthopedic papers (4, 19, 34). By including observational studies, results of this meta-analysis were based on 20 studies including 1382 patients. There is growing evidence that meta-analysis of well-designed observational studies of surgical procedures is probably as accurate as that of RCTs and a recent Cochrane review found little evidence that the results of observational studies and RCTs systematically disagreed (1, 3, 17). This premise, that observational studies are as good as RCTs to accurately detect the difference in our primary outcome measure may be reflected by the more modest effect size (= weighted difference between the conditions reported as Odds ratio in this study) in the meta-analysis of observational studies. This same finding was also reported by three other meta-epidemiological studies on surgical interventions (1, 16, 19).

Surgical treatment of DMCF can be considered a two-staged procedure. Plate fixation offers the chance that a second surgery will not be required whereas intra-medullary fixation generally mandates a second surgery. In this study implant removal rates after plate fixation vary between 3 and 100% whereas implant removal after IMF is common clinical practice in multiple studies (6, 13, 21, 26, 40, 43, 44). Regarding implant removal there seems to be an advantage of IMF: fewer re-fractures and the possibility to remove the implant in the outpatient setting under local anesthesia (23, 39, 41). Nevertheless not every patient will tolerate local anesthesia. Biomechanical data show increased weakness of the clavicle after plate

removal compared to IM removal (36). Explanations for re-fracture after plate removal might be stress shielding by the plate, stress risers at the screw holes and unrecognized non-union. Post-operative activity restrictions for a sufficient period of time may diminish re-fracture rates after plate removal.

An important confounder for re-intervention might be the use of reconstruction plates (12). As reconstruction plates were used in 12 of the 20 included studies, re-intervention rates might be influenced accordingly. A sensitivity analysis excluding studies with reconstruction plates however, showed a similar OR. This may be due to the lower sample size but since the change in effect size is minimal, one might conclude that the type of plate does not alter the effect size considerably.

Reported infections rates were shown in this study since there are likely unreported infections in both groups that might result in reporting bias. Infections occurred more after plate fixation. The much larger surgical dissection required for plate placement could in fact result in a higher surgical infection rate. Infections were analyzed as one group. However, definitions used in the various studies were heterogeneous and consequences of superficial and deep infections differ substantially. A deep infection generally resulted in a re-intervention whereas a superficial infection could be treated with oral antibiotics. Two studies used in the meta-analysis had deep infection rates after plate fixation of 11% and 36% (30, 38). The rest of the articles had an average infection rate under 2%. A sensitivity analysis excluding these studies resulted in an insignificant OR and therefore these results should be interpreted with caution.

In this study we decided deliberately not to show migration rates but the most important consequence of migration: re-intervention or implant removal. However, in the study of van der Meijden et al., all fracture types were included resulting in 50% nail migration to medial after IMF (41). Medial migration could be due to shortening which might be the result of fracture comminution. Possible solutions for medial migration might be Endcaps or locking devices for IMF (14).

The MINORS methodology was used for quality assessment of both randomized and observational studies (33). Since this quality assessment tool does not differentiate between randomized and observational studies and includes several items derived from indices focusing on the quality of randomized trials, the fact that a given study has a randomized

design is not sufficient to achieve a high score. Therefore the MINORS methodology could be an appropriate tool to assess quality of both study designs. Re-intervention is a relevant complication, which can be well defined and probably represents the most important distinction between the two techniques. Since the Clavien-Dindo classification makes a clear distinction between (re)-interventions without general anaesthesia (3A) or with general anesthesia (3B) we used this division as well(11).
A potential limitation of this study was the fact that the search strategy focused on full-text articles, and that abstracts and congress presentations were not included. We chose this approach since important information such as inclusion criteria, type and techniques of surgery and methodological quality cannot be assessed reliable based on abstract alone. Also, due to language restrictions, one article written in Chinese was excluded. Although various types of plates and IM devices were used, all studies were analyzed as a group. Consequently some in-group differences may exist. We attempted to alleviate the influence of these differences by accounting for heterogeneity when present, and by performing a sensitivity analysis for possible confounders (such as use of reconstruction plates and outlier studies for infection rates).

Conclusion

Major re-intervention and re-fracture after implant removal occurred more frequent after plate fixation of non-comminuted DMCF. No differences in terms of function and non-unions between plate fixation and intramedullary fixation were observed. Future research should focus on fracture selection for IMF and further improvement of plate and IM devices.

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Appendix 1 Search syntax

Database	Searchstring	Hits
PubMed	(((((((surgery[Title/Abstract]) OR surgical[Title/Abstract]) OR operative[Title/Abstract]) OR operation[Title/Abstract])) AND (((((clavicle[Title/Abstract]) OR clavicular[Title/Abstract]) OR collarbone[Title/Abstract]) OR clavicula[Title/Abstract]) OR claviculae[Title/Abstract])) AND (((fracture[Title/Abstract]) OR fractured[Title/Abstract]) OR fractures[Title/Abstract])) AND ((((((((((midshaft[Title/Abstract]) OR mid shaft[Title/Abstract]) OR midschaft[Title/Abstract]) OR mid schaft[Title/Abstract]) OR mid clavicular[Title/Abstract]) OR midclavicular[Title/Abstract]) OR mid clavicle[Title/Abstract]) OR midclavicle[Title/Abstract]) OR middle third[Title/Abstract]) OR mid third[Title/Abstract])	245
EMBASE	'surgery'/exp AND 'clavicle fracture'/exp AND ('midshaft' OR 'mid shaft' OR 'midschaft' OR 'mid schaft' OR 'mid clavicular' OR 'midclavicular' OR 'mid clavicle' OR 'midclavicle' OR 'middle third' OR 'mid third') AND [embase]/lim	313
Cochrane	Clavicle	5

The used searchstrings in the different databases.

Appendix 2 Quality assessment

MINORS	Andrade-Silva (2)	Assobhi (5)	Bohme (6)	Chen (9)	Ferran (13)	Fu (15)	Jones (20)	Kleweno (21)	Lee (200723)	Lee (200822)	Liu (24)	Meijden van der (41)	Narsaria (26)	Saha (30)	Tabatabaei (38)	Tarng (39)	Thyagarajan (40)	Wenninger (43)	Wijdicks (44)	Zehir (45)
Clear aim	2	2	1	1	1	2	2	1	0	2	2	2	2	1	1	2	1	2	2	1
Inclusion consecutive	2	1	2	0	2	1	2	2	2	2	1	2	0	1	1	1	2	1	2	2
Prospective collection data	2	2	2	0	2	0	0	2	2	1	0	2	2	2	1	0	0	0	0	2
Endpoint appropriate	2	2	1	2	2	2	2	0	2	2	2	2	2	2	2	2	1	2	2	1
Unbiased assessment	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Follow-up appropriate	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	0	0
Loss to follow-up < 5%	1	2	1	1	2	1	0	0	1	1	0	2	1	1	1	1	0	2	0	0
Prospective calculation size	2	2	0	0	2	0	0	0	0	0	0	2	0	0	0	0	0	0	0	1
Adequate control group	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Baseline equivalence	1	2	0	2	1	2	2	1	2	2	2	2	2	2	0	2	0	1	1	2
Adequate statistics	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	2	2
Total	20	21	13	14	20	16	16	14	18	18	15	23	17	17	12	16	10	15	13	15

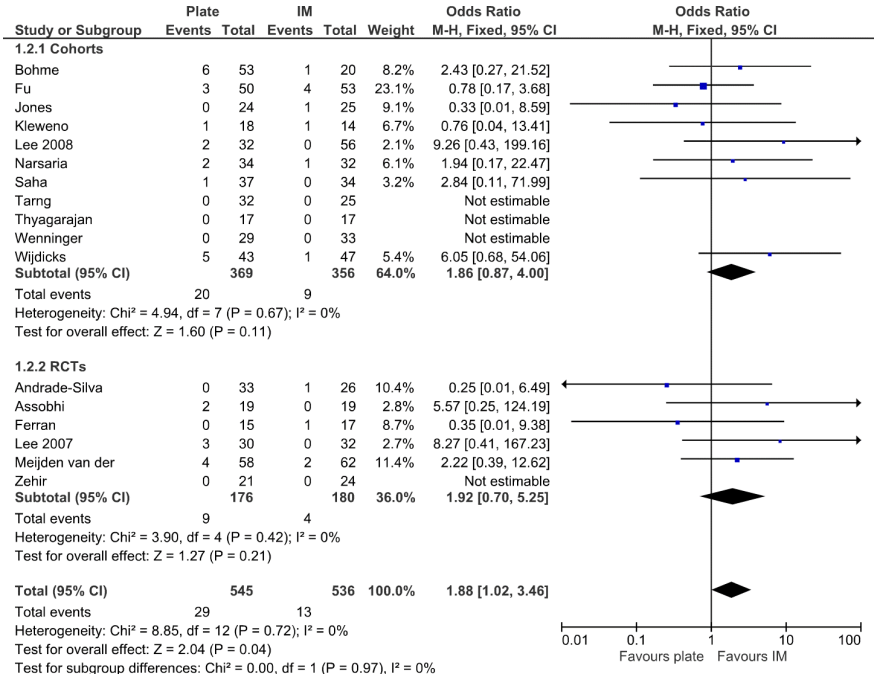
* < 20% loss to follow-up: 1 point
Follow-up appropriate: > 1 year
Unbiased assessment: 1 point if not analyzed by treating surgeon, 2 points if scars were hided with an objective investigator

Appendix 3 Results

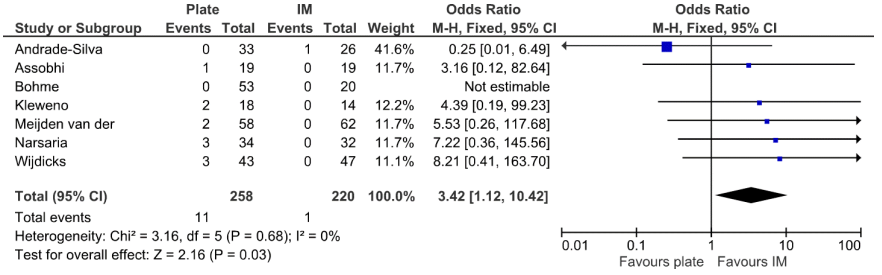
First Author	Re-intervention surgery plate		Re-intervention surgery IMF		Implant removal plate		Implant removal IMF		Refracture	
	Hospital	Out-patient	Hospital	Out-patient	Hospital	Outpatient	Hospital	Outpatient	Plate	IMF
Andrade-Silva2	0	0	1 (4%)	0	1 (3%)	0	18 (72%)	0	0	1 (4%)
Assobhi5	2 (10%)	0	0	3 (16%)	NR	NR	NR	NR	1 (5%)	none
Bohme6	6 (11%)	0	1 (5%)	0	53 (100%)	NR	20 (100%)*	NR	none	none
Chen9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ferran13	0	0	1 (6%)	0	8 (53%)	0	17 (100%)*	0	NR	NR
Fu15	3 (6%)	0	4 (8%)	0	NR	NR	NR	NR	NR	NR
Jones20	NR	NR	1 (4%)	0	NR	NR	9 (36%)	0	NR	NR
Kleweno21	1 (7%)	0	1 (5.5%)	0	3 (21%)	0	18 (100%)*	0	2 (11%)	none
Lee 200723	3 (10%)	0	0	0	22 (73%)	0	0	20 (63%)	NR	NR
Lee 200822	2 (6%)	0	0	0	NR	NR	NR	NR	NR	NR
Liu24	NR	NR	NR	NR	12 (20%)	NR	4 (8%)	NR	NR	NR
Meijden van der41	4 (7%)	0	2 (3 %)	0	11 (19%)	0	25 (40%)	8 (13%)	2 (3%)	none
Narsaria26	2 (6%)	0	1 (3%)	0	20 (59%)	NR	32 (100%)*	NR	3 (10%)	none
Saha30	1 (3%)	0	0	0	NR	NR	NR	NR	NR	NR
Tabatabaei38	NR	NR	NR	NR	8 (32%)	NR	NR	NR	NR	NR
Tarng39	0	0	0	0	12 (38%)	0	0	4 (16%)	NR	NR
Thyagarajan40	0	0	0	0	2 (12%)	NR	17 (100%)	0	NR	NR
Wenninger43	0	0	0	0	2 (7%)	0	33 (100%)*	0	NR	NR
Wijdicks44	5 (12%)	0	1 (2%)	6 (13%)	27 (63%)	0	45 (96%)*	0	3 (7%)	none
Zehir45	0	0	0	0	NR	NR	NR	NR	NR	NR

IQ: inter quartile range; SD: standard deviation; R: range; CI: Confidence Interval;
SEM: Standard Error of the Mean; NR = not reported

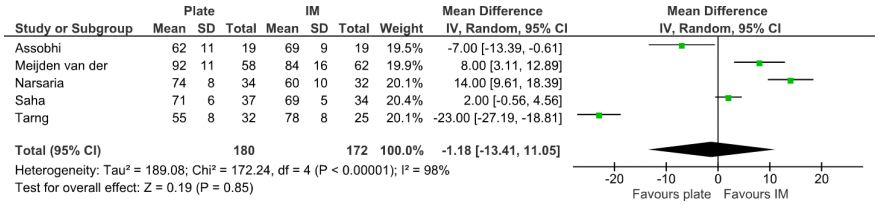
Functional results short term (< 2m)		Functional results long term (>1 y)		Non-unions		Infection			
Constant		Constant				Plate		IMF	
Plate	IMF	Plate	IMF	Plate	IMF	Super- ficial	Deep	Super-ficial	Deep
NR	NR	92 (SD 9)	92 (SD 9)	0	1 (4%)	1 (3%)	0	0	0
62 (SD 11, 95% CI 65-74)	69 (SD 9, 95% CI 65-74)	90 (SD 11, 95% CI 84-95)	96 (SD 5, 95% CI 93-98)	1 (5%)	0	1 (5%)	0	0	0
88 (SD NR)	89 (SD NR)	NR	NR	0	0	2 (4%)	0	0	0
NR	NR	95 (SD 3)	95 (SD 3)	3 (4%)	1 (2%)	3 (4%)	0	1 (1%)	0
NR	NR	89 (SD 9)	92 (SD 6)	0	0	3 (20%)	0	0	0
NR	NR	NR	NR	1 (2%)	4 (8%)	0	1 (2%)	0	0
NR	NR	NR	NR	1 (4%)	0	0	0	1 (4%)	0
NR	NR	NR	NR	0	0	0	0	1 (7%)	0
NR	NR	84 (R 60-100)	85 (R 65-100)	1 (3%)	0	1 (3%)	0	0	0
NR	NR	93 (SD 4)	95 (SD 4)	1 (3%)	0	1 (3%)	0	0	0
NR	NR	88 (SD 5)	87 (SD 5	6 (10%)	5 (10%)	6 (10%)	0	3 (6%)	0
92 (SEM 1)	84 (SEM 2)	99 (SEM 0)	91 (SEM 2)	1 (2%)	0	3 (5%)	0	0	0
74 (SD 8)	60 (SD 10)	96 (SD 3)	95 (SD 3)	0	1 (3%)	2 (6%)	0	2 (3%)	0
71 (SD 6)	69 (SD 5)	91 (SD 5)	92 (SD 5)	1 (3%)	0	0	4 (11%)	0	0
NR	NR	NR	NR	1 (4%)	0	0	9 (36%)	0	5 (20%)
55 (IQ 49-60)	78 (IQ 73-84)	NR	NR	1 (3%)	0	1 (3%)	0	0	0
NR	NR	NR	NR	1 (6%)	0	1 (6%)	1 (6%)	2 (12%)	0
NR	NR	NR	NR	0	0	0	0	1 (3%)	0
NR	NR	NR	NR	3 (7%)	0	1 (2%)	0	4 (9&)	0
NR	NR	NR	NR	0	0	NR	NR	NR	NR



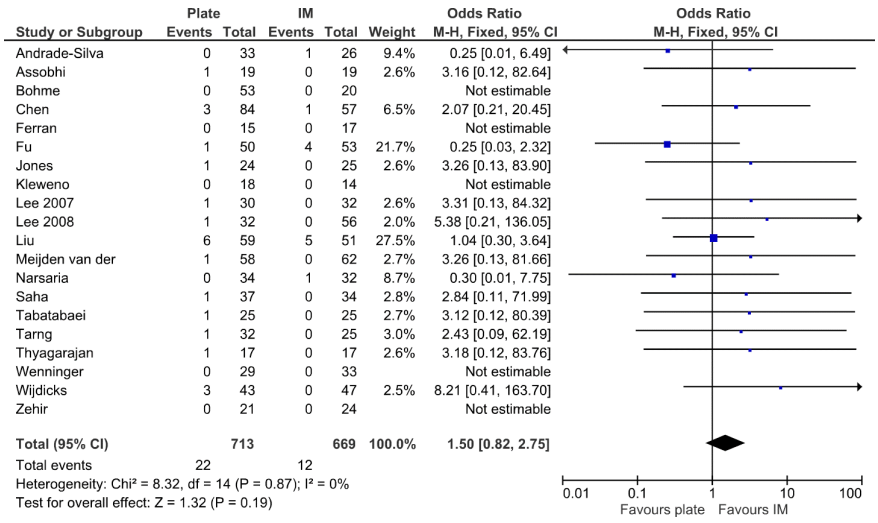
Appendix 4 Major re-interventions
The odds ratio (95% confidence interval) on the rate of major re-interventions is shown between the plate fixation group and the intramedullary fixation group



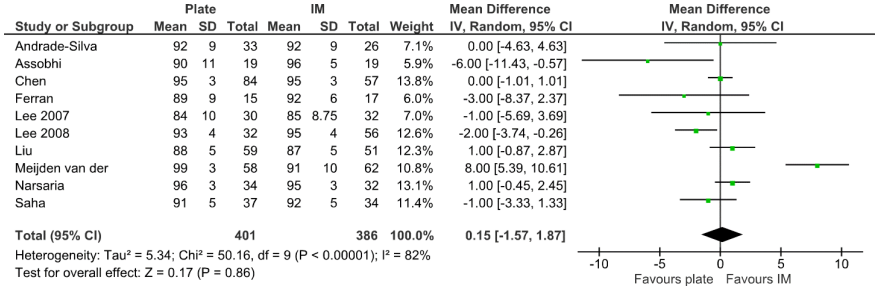
Appendix 5 Re-fracture after implant removal
The odds ratio (95% confidence interval) on the rate of re-fracture after implant removal is shown between the plate fixation group and the intramedullary fixation group



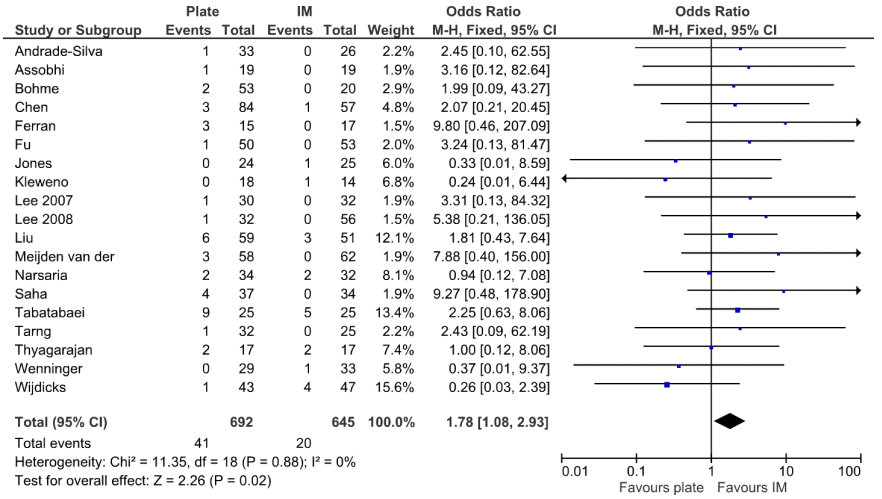
Appendix 6 Constant short-term
The mean difference (95% confidence interval) on the Constant short-term is shown between the plate fixation group and the intramedullary fixation group



Appendix 7 Constant long-term
The mean difference (95% confidence interval) on the Constant long-term is shown between the plate fixation group and the intramedullary fixation group



Appendix 8 Non-unions
The odds ratio (95% confidence interval) on the rate of non-unions is shown between the plate fixation group and the intramedullary fixation group



Appendix 9 Infections

The odds ratio (95% confidence interval) on the rate of infections is shown between the plate fixation group and the intramedullary fixation group

CHAPTER ELEVEN

Surgical versus nonsurgical treatment for midshaft clavicle fractures in patients aged 16 years and older: a systematic review, meta-analysis, and comparison of randomized controlled trials and observational studies

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M. van Heijl, M.C. Kruyt, R.H.H. Groenwold,
O.A.J. van der Meijden, R.M. Houwert

Am J Sports Med. 2017 Jul;45(8):1937-1945.

Abstract

Background

There is no consensus on the choice of treatment of midshaft clavicle fractures. The aim of this systematic review and meta-analysis was (1) to compare fracture healing disorders and functional outcome of surgical versus conservative treatment of midshaft clavicle fractures and (2) to compare effect estimates obtained from RCTs and observational studies.

Methods

A systematic review and meta-analysis was performed. The PubMed/MEDLINE, Embase, CENTRAL and CINAHL databases were searched for both randomized controlled trials and observational studies. Using the MINORS instrument all included studies were assessed on their methodological quality. The primary outcome was a nonunion. Effects of surgical versus conservative treatment were estimated using random effects meta-analysis models.

Results

A total of 20 studies were included of which 8 were RCTs and 12 observational studies including 1760 patients. Results were similar across the different study designs. Meta-analysis of 19 studies revealed that nonunions were significantly less common after surgical treatment than after conservative treatment (odds ratio (OR) 0.16; 95% confidence interval (CI) 0.09to0.26). The risk of malunions did not differ between surgical and conservative treatment (OR 0.38; 95%CI 0.12to1.19). Both the long term DASH and Constant scores favoured surgical treatment (DASH MD -2.04 (95%CI -3.56to-0.52); Constant MD 3.23 (95%CI 1.52 to 4.95)). No differences were observed regarding revision surgery (OR 0.85; 95%CI 0.42to1.73). Including only high quality studies, both the number of malunions and return to work show significant differences in favour of surgical treatment (malunions OR 0.26 (95%CI 0.07to0.92); return to work MD -8.64 (95%CI -16.22to-1.05)).

Conclusions

This meta-analysis of high quality studies showed that surgical treatment of MCFs results in less nonunions, less malunions and an accelerated return to work compared to conservative treatment. Meta-analysis of surgical treatments need not be restricted to randomized trials, provided that the included observational studies are of high quality.

Introduction

Clavicle fractures represent 2,6% to 4% of all fractures and 35% to 44% of those in the shoulder girdle.(37;41) Midshaft clavicle fractures are among the most common upper extremity injuries managed by orthopedic trauma surgeons. Midshaft fractures account for 69% of all clavicle fractures of which half are displaced.(44) Most clavicle fractures occur in young men and are caused by falls, sports and road-traffic accidents.(44) Open fractures, compromised overlying skin and presence of neurovascular damage require surgical treatment.(24) However, there is no consensus about the choice of treatment of closed midshaft clavicle fractures (MCFs) without these factors.(38;49;50) In the past decades, indications for surgical treatment seem to have broadened and operative treatment is increasingly favored, especially by shoulder specialists.(7;8;51) However, still half of the surgeons treat their patients conservatively.(50)

Several systematic reviews and meta-analyses have previously been published, with contradicting results.(4;13;31) All of these studies only included randomized controlled trials (RCTs).(29;31;42;58) Yet, the holy grail of RCTs has recently been debated.(3) Observational studies can be included in meta-analyses to increase the sample size and generalizability of findings, provided the quality (i.e., validity) of the observational studies is of the same level as that of the RCTs. Observational studies are very suitable to identify relatively rare outcomes such as infrequent complications. Recent literature shows no differences in effect estimates between RCTs and observational studies.(21) Therefore, meta-analyses including high-quality observational studies in surgery may be considered complementary to those including RCTs only.(1;3;21)

The aim of this systematic review and meta-analysis was (1) to compare fracture healing disorders and functional outcome of surgical versus conservative treatment of midshaft clavicle fractures and (2) to compare effect estimates obtained from RCTs and observational studies.

Methods

A published protocol for this review does not exist. No ethical committee approval was necessary for this literature review.

Search strategy and selection criteria

This review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and the Quality of Reporting of Meta-analyses standards (QUOROM statement).(35;36) Published RCTs and observational studies concerning the comparison of surgical and conservative treatment for acute MCFs in patients of 16 years and older were included. Two reviewers (DS and DV) independently conducted an electronic systematic search in PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL from The Cochrane Library) and CINAHL for articles published up to December 1st 2015. The search syntax is provided in Appendix 1. Duplicate articles were removed. Titles and abstracts of retrieved citations were screened, and potentially suitable studies were read in full by both reviewers. Articles were included if written in English, Dutch, German or French language. Only published data have been included. A minimum follow-up time was not required for inclusion. Letters, comments, abstracts for conferences, case reports, study protocols, reviews, biomechanical studies, animal studies, studies which included patients with (only) floating shoulders, studies describing a surgical technique and non-comparative studies were excluded. In addition, studies were excluded if only the comparison of delayed surgery versus non-surgical treatment was made. No further search restrictions or search filters were applied in the search. Citation tracking and reference screening of the selected studies was performed. Disagreements in the search were resolved by discussion with a third independent reviewer (RH).

Quality assessment

The methodological quality of all included studies was independently assessed by two reviewers (DS and DV) using the Methodological Index for Non-Randomized Studies (MINORS).(46) The MINORS is a validated instrument designed to assess the methodological quality and clear reporting of observational surgical studies.(46) The MINORS is externally validated using RCTs and, therefore, also appropriate to assess the quality of RCTs.(46) Three other reviewers (TT, OvdM and RH) independently assessed the quality of 7 out of 20 articles to improve unity on the use of the MINORS. The included study published by two of the authors (DV and TT) was assessed by two other reviewers (DS and RH).(53) Disagreements were resolved by discussion with a third independent reviewer (RH). Details on the quality scoring system are given in Appendix 2.

Data extraction

The following data were extracted: first author, year of publication, study design, country in which the study is performed, fracture displacement, type of fractures,mean follow-up, treatment groups, used type of plate or intramedullary fixation material in surgical groups, conservative treatment method, number of patients per group, outcomes including confidence interval (CI) and/or p-values.Definitions of displacement were used according to the methods section of the included studies.

Outcome measures

Fracture healing disorders in this study were nonunions and malunions. Definitions of nonunion and malunion were used according to the methods section of the included studies. The primary outcome parameter was a nonunion. The effectiveness of both the conservative and surgical treatment was evaluated using the following secondary outcome measures: functional scores (DASH and Constant-Murley scores) on both short term (<1 year) and long term (≥1 year), return to work in days, revision surgery and implant removals.(11;23)

Revision surgery was defined as a second operative fixation in the surgical treatment group and as an operative fixation after initial conservative treatment in the conservative treatment group. Return to work was defined as the number of days needed until work, duty or daily activities could be resumed. For results concerning studies which used both plate and intramedullary fixation the results of the combination of plate and intramedullary fixation were used. If these results of the whole surgical treatment group were not available, the results of the plate fixation were used which is the most common surgical treatment.(13)

Data analysis

Data management, statistical analyses and graphical representation were performed using Review Manager software (RevMan© v. 5.3.5) provided by The Cochrane Collaboration.(43) When means or stand deviations (SD) were not reported in an article, these were calculated – if possible – using the available information. If the range was available for outcome variables the standard deviation was estimated as range divided by 4.(22) The standard deviation was estimated from the standard error (SE) using the following formula: $SE = SD / \sqrt{n}$, where SD indicates the standard deviation and n is the sample size. The standard error was estimated from the 95% confidence interval (CI), by dividing the width of the confidence interval by

2 * 1.96 = 3.92. Data were converted into the same units if needed.
Outcomes reported by two or more studies were pooled in a meta-analysis. Short term and long term results were analysed separately. The assessment of statistical heterogeneity was done by visual inspection of the forest plots and estimating statistical measures of heterogeneity: Cochran's Q (chi-square test), I^2, and τ^2 (tau^2). The random effects model was used for meta-analyses. The overall effect Z-test was used to determine significance. A two-sided p-value <0.05 was considered statistically significant. All analyses were stratified by study design, i.e., cohort studies and RCTs separately. All analyses were then repeated by including all studies (i.e., irrespective of study design).
For continuous outcomes, a weighted mean difference (WMD) was estimated. The Inverse Variance (IV) statistical method was used to construct a 95%CI. A pooled odds ratio (OR) was estimated for dichotomous outcomes. The Mantel-Haenszel (M-H) statistical method was used to construct a 95%CI. Zero-event data were handled using different methods.(6) In the crude method, data of all studies was pooled and analysed without taking clustering of data within studies into account. In the inverse variance method, the log(odds ratio) of each study was weighted by the inverse of the within study variance (also known as fixed effects model). When the inverse variance method was applied with correction, 0.5 was added to each cell of the 2x2 table of that study, if one (or both) of the treatment arms experienced no events. The same correction was made for the DerSimonian Laird method (also referred to as the random effects model), but in contrast to the inverse variance method, the weighting was based on the inverse of the sum of the within study variance and the between study variance.(6) If a study had missing data, available case analysis was performed.
After the primary analyses, sensitivity analyses on the impact of study quality were performed for the primary outcome. In this sensitivity analysis on high quality, only studies with a MINORS score above 16 (out of a maximum score of 24) were included. Another sensitivity analysis was performed using only low quality studies (MINORS score of 16 or lower). (46)
Potential publication (or reporting) bias was assessed using a funnel plot, showing intervention effect estimates on the primary outcome from individual studies against their standard error.(14)

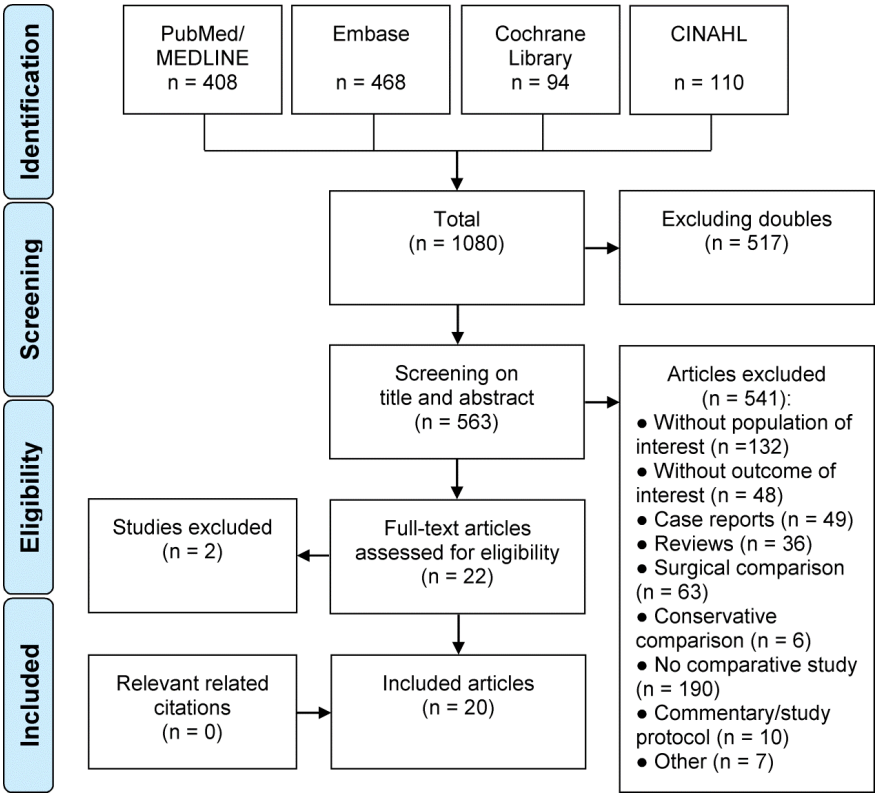

Figure 1 Flowchart of the articles included in a systematic review of MCFs comparing conservative versus surgical treatment
Two studies were excluded because of language and inclusion of medial and lateral fractures. The search string can be found in appendix 1.

Results

Search

The electronic searches detected 1080 articles. After removing duplicates 563 articles were screened on title and abstract. A total of 22 possible relevant studies from the initial search were assessed on full-text for eligibility and references were checked for suitable related citations. The study of Van der Have et al. was excluded because the study was performed on adolescents.(54) The study of Smekal et al. was excluded because of overlap in patient population with other studies from their group.(47;48) A total of 132 studies were excluded because these papers

did not describe acute MCF or included patients under the age of 16. In total, 20 studies could be included for analysis.(2;5;9;10;12;16;18;25-28;30;33;34;45;47;52;53;55;57) Of all included studies, 8 were RCTs and 12 were observational, of which 5 were prospective studies and 7 were retrospective studies. The search results, reasons for exclusion and selection process is summarized in the flowchart in Figure 1.

Quality assessment

Appendix 3 shows the distribution of study quality across the studies. The mean MINORS score was 17.2 (±3.0) with a range from 11 to 22. For the RCTs it ranged from 11 to 22 with a mean (±SD) of 18.6 (±3.5) and for the observational studies, it ranged from 11 to 19 with a mean (±SD) of 16.2 (±2.3).

Baseline characteristics

The characteristics of all included studies, their treatment groups and included type of fractures are described in Appendix 4. Studies did not handle different in- or exclusion criteria for their treatment groups. Plate fixation was compared with conservative treatment in 10 (50%) studies, intramedullary fixation was compared with conservative treatment in 6 (30%) studies and both plate and intramedullary fixation were compared with conservative treatment in 4 (20%) studies. A total of 620 patients were treated using plate fixation, 284 patients using intramedullary fixation and 856 patients were conservatively treated. The studies included in total 1760 participants (80.2%men) with a mean age of 35.5 years (range 25 to 46). The number of patients included in a study ranged between 40 and 200. In total, more patients were included in the observational studies (studies n=12; patients n=1068; mean age=36.3 years; mean age range 27.1 to 46 years) compared to the RCTs (studies n=8; n=692; mean age=34.0 years; mean age range 25 to 41 years). The mean age and male/female ratio did not appear to be different across the different study designs.

Fracture healing disorders

Nineteen (95%) of the 20 included studies reported the number of nonunions (Appendix 5).(2;5;9;10;12;18;25-28;30;33;34;45;47;52;53;55;57) George et al. was excluded because the number of nonunions was not reported.(16) In the study by Witzel et al. no events occurred in both treatment arms. (57) Nonunions occurred significantly less after surgical treatment than

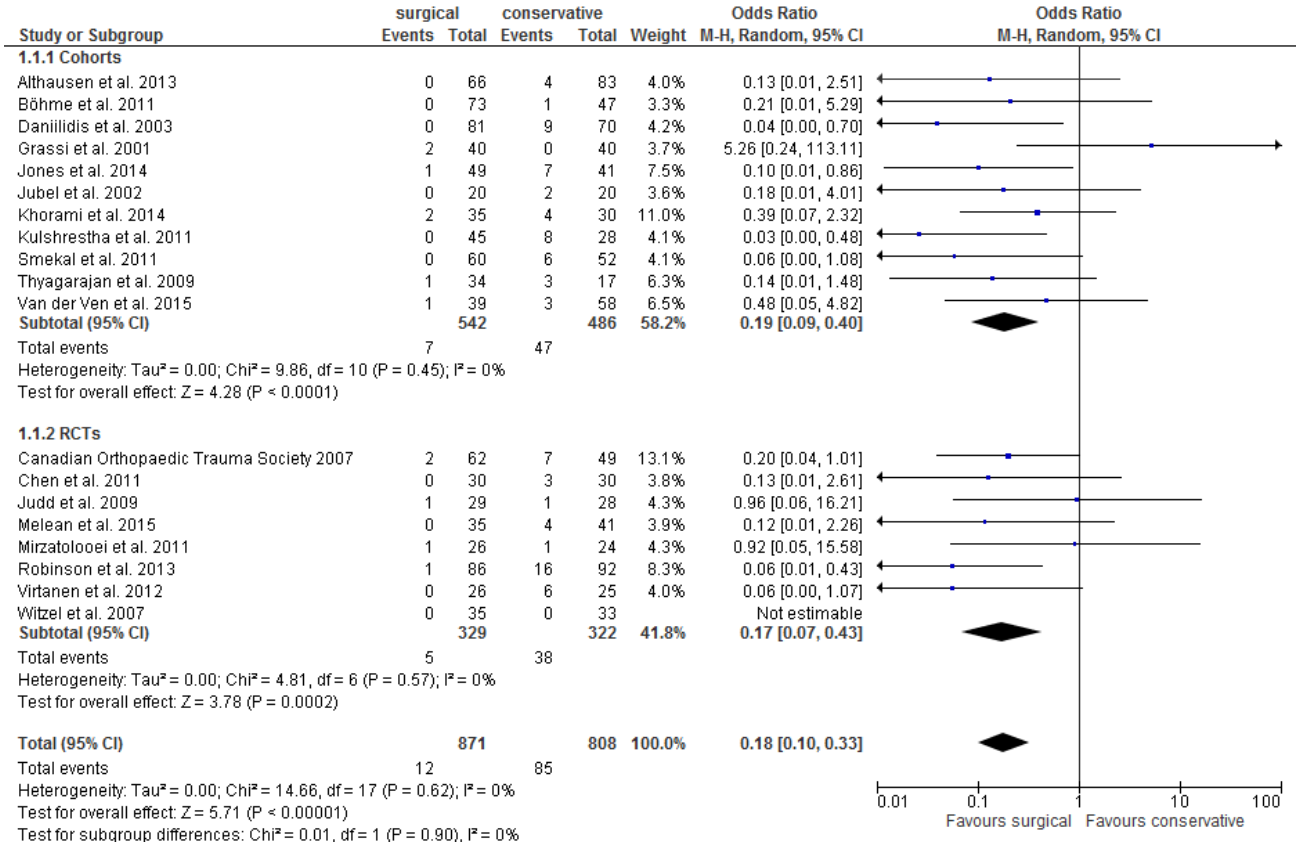

Figure 2 Nonunions in a systematic review of MCFs comparing conservative versus surgical treatment

after conservative treatment with an odds ratio of 0.18 (95%CI 0.10 to 0.33; p<0.01; Figure 2). Surgical treatment resulted in a nonunion in 1.4% and conservative treatment in 10.5%. The different methods to handle studies in which no event occurred in either (or both) of the treatment arm yielded similar results (data shown in Appendix 6).
Thirteen studies (65%) reported the risk of malunions which showed comparable results between the surgical and conservative treatment arm with an odds ratio of 0.38 (95%CI 0.12 to 1.19; p=0.10; Appendix 7) .(9;10;18;27;28;30;34;45;47;52;53;55;57) Surgical treatment resulted in a malunion in 6.4% and conservative treatment in 13.6%.

Functional scores and the return to work

Both the short term DASH scores and the short term Constant-Murley scores showed comparable results between the surgical and conservative treatment arm (Table 1). The long term results for the DASH scores and the long term Constant-Murley scores showed significant differences in favour of the surgical treatment arm compared to the conservative treatment arm (DASH MD -2.04; 95%CI -3.56 to -0.52; p=0.01; Appendix 8)(Constant-Murley MD 3.23; 95%CI 1.52 to 4.95; p<0.01; Appendix 9).
Seven studies (35%) reported the return to work or daily activities of which in 5 studies a standard deviation was documented or could be estimated. (2;5;18;28;33;45;53) Analysis showed comparable results between the surgical and conservative treatment arm (MD -2.80; 95%CI -15.03 to 9.42; p=0.65).

Table 1 Results of sensitivity analyses in a systematic review of MCFs comparing conservative versus surgical treatment

Outcome	Results	Subgroup cohorts	Subgroup RCTs	Sensitivity analysis including high quality studies	Sensitivity analysis including low quality studies
Nonunions*	0.18 (0.10; 0.33)	0.19 (0.09; 0.40)	0.17 (0.07; 0.43)	0.18 (0.09; 0.37)	0.18 (0.06; 0.50)
Malunions*	0.38 (0.12; 1.19)	0.73 (0.15; 3.61)	0.18 (0.04; 0.79)	0.26 (0.07; 0.92)	3.06 (0.44; 21.26)
DASH scores short term**	-3.09 (-10.04; 3.85)	-4.38 (-15.05; 6.29)	-0.10 (-7.74; 7.54)***	-3.09 (-10.04; 3.85)	NE
DASH scores long term**	-2.04 (-3.56; -0.52)	-0.68 (-3.69; 2.32)	-2.70 (-2.88; -2.53)	-2.04 (-3.78; -0.30)	-1.70 (-6.00; 2.60)***
Constant scores short term**	3.07 (-2.19; 8.34)	6.00 (-5.51; 17.51)	0.25 (-3.97; 4.47)	3.07 (-2.19; 8.34)	NE
Constant scores long term**	3.23 (1.52; 4.95)	3.82 (-0.47; 8.11)	4.18 (3.96; 4.41)	4.08 (3.62; 4.54)	5.44 (-2.37; 13.24)
Return to work**	-2.80 (-15.03; 9.42)	2.96 (-19.83; 25.75)	-12.26 (-33.83; 9.31)	-8.64 (-16.22; -1.05)	24.00 (18.86; 29.14)***
Revision surgery*	0.85 (0.42; 1.73)	1.16 (0.50; 2.67)	0.52 (0.16; 1.74)	0.69 (0.27; 1.78)	1.20 (0.43; 3.30)

* means that results are presented as odds ratio (95%CI); ** means that results are presented as mean difference (95%CI)
*** means that only one study with SD available or calculable can be included; NE: Not estimatable because no studies could be included

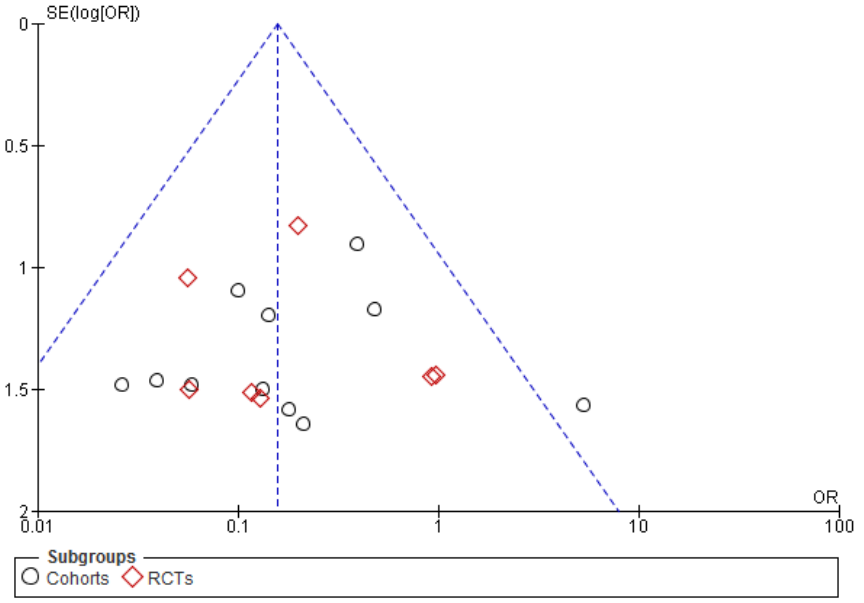

Figure 3 Funnel plot of included studies using the number of non-unions in a systematic review of MCFs comparing conservative versus surgical treatment

Revision surgery and implant removal

Eighteen studies (90%) reported the number of revision surgeries.(2;5;9;10;12;18;25;27;28;30;33;34;45;47;52;53;55;57) Analysis showed no significant differences between the surgical and conservative treatment group (OR 0.85; 95%CI 0.42 to 1.73; p=0.65; Appendix 10). Surgical treatment resulted in revision surgery in 8.2% and 9.8% required operative fixation after initial conservative treatment. Implant removal was reported in ten studies (50%).(9;12;25;27;30;33;45;52;53;57) The mean percentage of implant removal was 35.0% ranging from 3.7% to 100%.

Study design analyses

Results were similar across all included studies, when analyses were stratified by study design as shown in the forest plots (Figure 2 and Appendix 7-10). The subgroups do differ in the significance of the results in three secondary outcomes: malunions, the long term DASH scores and the long term Constant scores. In these outcomes the RCTs showed a significant result compared to the insignificant results of the observational studies. Nevertheless, in all of these studies the outcome did remain in

favour of the surgical group.

Sensitivity analysis on quality

Sensitivity analysis using high quality studies on the primary outcome – nonunions – resulted in an overall OR of 0.14 (95%CI 0.07 to 0.28; p<0.01) (table 1). There were no outcomes that changed direction, however, the number of malunions and the days to return to work became significant outcome parameters in favour of the surgical group (table 1).

Sensitivity analysis using low quality studies on the primary outcome resulted in an OR of 0.18 (95%CI 0.06 to 0.50; p<0.01). The other outcomes changed in insignificant results or were not estimatable because no studies could be included. The return to work changed to favourable results for the conservative treatment including only one study.

Assessment of publication bias

A funnel plot with the odds ratios and standard errors of the studies including nonunions is shown in Figure 3. The funnel plot asymmetry analysis showed relative symmetry, indicating no evidence or a very low risk of existing publication bias in this systematic review and meta-analysis. When excluding the outlier with an OR of 5.26 the appearance of the figure structure stays intact.(18)

Discussion

Results of this systematic review and meta-analysis including both RCTs and observational studies showed less nonunions for surgical treatment of MCFs compared to conservative treatment. Functional outcomes are statistically significant in favor of surgical treatment, yet these differences seem of little clinical importance.(4;15;19) The subgroup analysis of only RCTs and observational studies displayed similar results. In high quality studies less malunions and a faster return to work in favor of the surgical treatment group were observed.

Results of functional outcome might be statistically significant, nevertheless, a mean difference of respectively 2 points on the DASH and 3 points on the Constant Murley score are clinically irrelevant.(4;15;19) For each of these scores, a 10 point difference is deemed clinically relevant.(4;19)

More nonunions were observed after conservative treatment in this study for all groups. These numbers are in accordance with other systematic reviews and meta-analyses about this topic.(17;29;32) The earlier return to daily activities after surgical treatment also corresponds with results of

another review.(20) However, in this study Hill et al. only included 3 studies, whereas our meta-analysis included information of 20 studies.(27;47;48) In a previous review and meta-analysis, plate and intramedullary fixation were compared. No differences were found in terms of function and number of nonunions. Major re-intervention and re-fracture after implant removal occurred more frequently after plate fixation.(21)

One of the most important observations of this study is that high quality observational studies and RCTs provide similar results for this topic (Table 1). By excluding low quality observational studies, malunion and return to work became significant in favor of surgical treatment. Therefore low quality observational studies had enough impact to possibly influence recommendations from this meta-analysis. Obviously, recommendations based on a meta-analysis should be based on the quality of the included studies, not just on their study design.

This is the first review that shows an accelerated return to work after operative treatment of midshaft clavicle fractures. As patients with MCFs are generally in the working population with a peak incidence in males younger than 30 years old, this might be an important consideration.(44) On the other hand, operative treatment of all MCF would substantially increase the cost for society of treating this common injury. Three recent studies about cost-effectiveness of operative treatment emphasize this dilemma.(2;39;56) Walton et al. described the financial impact for society. They found that nonoperative treatment followed by delayed surgery resulted in approximately 11,500 USD cost savings from the perspective of a single health insurance payer. However, costs to the patients are not accounted for in their analysis.(56) Althausen et al. calculated that operative treatment resulted in approximately 5000 USD cost savings in the perspective of the patient although the initial hospital bill was higher because of surgical charges.(2) Furthermore, operatively treated patients missed fewer days from work (8 vs 35 days) and returned to full duty 25 days sooner than nonoperatively treated patients. Pearson et al. concluded that the cost-effectiveness of operative treatment depended on the durability of functional advantage compared to nonoperative treatment. When functional benefits persisted for more than 9 years, operative treatment had favorable value compared with many accepted health interventions.(39) However, no comparative studies have yet described the long-term outcome of operative versus nonoperative treatment of MCF.

Previously published meta-analyses on this topic only included RCTs for analysis.(17;42;58) Currently the value of the different study designs is being discussed.(1;3) This is the first meta-analysis comparing surgical and conservative treatment of MCF in which data on RCTs and observational studies were combined. Therefore, information of 1760 patients could be included resulting in the largest sample size in a meta-analysis on this topic, which consequently led to an increase in power. Due to this increased power effects may have been detected that would have gone unnoticed if only including RCTs. In addition, combining information from both RCTs and observational studies can provide a broader view of the available evidence, possibly leading to results that have better generalizability, which might improve the applicability of recommendations based on systematic reviews.(40) Because of the often stringent in- and exclusion criteria of RCTs, the generalizability of trial results may be hampered and finding similar effect estimates in observational studies may support the relevance of study results for clinical practice. We note, however, that the baseline characteristics of patients enrolled in the studies included in our meta-analysis did not materially differ across study designs, suggesting results of randomized trials on MCF already have wide applicability.

Observational studies inherently have a greater risk of bias due to the non-random allocation of treatment. Therefore, pooling results of studies with a different design is counterintuitive. However, we consider this approach appropriate, since RCTs and observational studies showed similar results and the potential for unmeasured confounding in the observational studies was considered small. This corresponds to an earlier performed meta-analysis including observational studies in which the primary outcome, i.e., re-interventions, showed comparable results between RCTs and observational studies when comparing the plate and intramedullary fixation of clavicle fractures.(21) The potential for bias in the observational studies included in our meta-analysis appeared to be small (given comparability of measured patient characteristics between treatment arms).

Despite a low risk of publication bias in this systematic review and meta-analysis, several factors possibly influencing our results should be mentioned. For example, definitions varied according to the included studies, such as displacement, non- and malunion. Also, time to return to work could be affected by type of occupation. In the current analysis no distinction could be made between laborers and physical demanding

occupations from sedentary occupations. Finally, both plate fixation and intramedullary have been included for analysis of 'operative treatment'. As a recently published meta-analysis comparing plate and intramedullary fixation found no significant differences regarding functional outcome and the number of nonunions, combining results of functional outcome and non-union of both techniques was justified in our opinion.(21) Furthermore, results were homogeneous across studies.

Conclusion

This systematic review and meta-analysis shows that surgical treatment of MCFs results in less nonunions, less malunions and an accelerated return to work. Functional outcomes are comparable between the groups. RCTs and observational studies showed similar results. Observational studies provide relevant data for meta-analysis as long as the quality of the included studies is taken into account and the results are interpreted in the right clinical context. The results of this meta-analysis favour the surgical treatment of MCFs. However, it should always be kept in mind that patient specific factors should be taken into account. The final decision for a surgical or conservative treatment should be based on shared-decision making.

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Appendix 1 Search strings
Searchstring PubMed/MEDLINE (n=408)
(clavicle[MeSH Terms] OR clavicle[Title/Abstract] OR clavicula[Title/Abstract] OR claviculae[Title/Abstract] OR clavicular[Title/Abstract] OR collarbone[Title/Abstract] OR collar bone[Title/Abstract]) AND
(Fractures, bone[MeSH Terms] OR fracture[Title/Abstract] OR fractured[Title/Abstract] OR fractures[Title/Abstract]) AND
(midshaft[Title/Abstract] OR mid shaft[Title/Abstract] OR midclavicular[Title/Abstract] OR mid clavicular[Title/Abstract] OR midclavicle[Title/Abstract] OR mid clavicle[Title/Abstract] OR middle third[Title/Abstract] OR mid third[Title/Abstract]) AND
(surgery[subheading] OR Fracture Healing[MeSH Terms] OR Fracture Fixation[MeSH Terms] OR Surgical Procedures, Operative[MeSH Terms] OR Physical Therapy Modalities[MeSH Terms] OR orthopedics[MeSH Terms] OR orthopedics[Title/Abstract] OR orthopaedics[Title/Abstract] OR surgery[Title/Abstract] OR surgical[Title/Abstract] OR operative[Title/Abstract] OR operation[Title/Abstract] OR conservative[Title/Abstract] OR conventional[Title/Abstract] OR non-operative[Title/Abstract] OR nonoperative[Title/Abstract] OR sling[Title/Abstract] OR figure-of-eight bandage[Title/Abstract])

Searchstring Embase (n=468)
('clavicle'/exp OR clavicle:ti,ab OR clavicula:ti,ab OR claviculae:ti,ab OR clavicular:ti,ab OR collarbone:ti,ab OR 'collar bone':ti,ab) AND
('fracture'/exp OR fracture:ti,ab OR fractured:ti,ab OR fractures:ti,ab) AND
(midshaft:ti,ab OR 'mid shaft':ti,ab OR midclavicular:ti,ab OR 'mid clavicular':ti,ab OR midclavicle:ti,ab OR 'mid clavicle':ti,ab OR 'middle third':ti,ab OR 'mid third':ti,ab) AND
('surgery'/exp OR surgery:ti,ab OR surgical:ti,ab OR operative:ti,ab OR operation:ti,ab OR 'conservative treatment'/exp OR 'conservative treatment':ti,ab OR conservative:ti,ab OR conventional:ti,ab OR 'non-operative':ti,ab OR nonoperative:ti,ab)

Searchstring CENTRAL (The Cochrane Library) (n=94)
(clavicle AND fracture)

Searchstring CINAHL (n=110)
(clavicle OR clavicula OR claviculae OR clavicular OR collarbone OR collar bone) AND
(fracture OR fractured OR fractures) AND
(midshaft OR mid shaft OR midclavicular OR mid clavicular OR midclavicle OR mid clavicle OR middle third OR mid third) AND (surgery OR surgical OR operative OR operation OR conservative OR conventional OR non-operative OR nonoperative)

Appendix 2 MINORS assessment criteria

Methodological items	**2**	**1**	**0**
A clearly stated aim	Aim or hypothesis including outcomes have been reported	Aim or hypothesis have been reported without a clear outcome	Not reported
Inclusion of consecutive patients	Explicit inclusion and exclusion criteria have been reported	Unclear or poor description inclusion and exclusion criteria have been reported	Not reported
Prospective collection of data	Prospective	Retrospective	Not reported
Endpoints appropriated to the aim of the study	Outcomes are appropriate to the aim of the study	Outcomes are not appropriate to the aim of the study	Not reported
Unbiased assessment of the study endpoint	Blind evaluation of objective outcomes and double-blind evaluation of subjective outcomes	One or more outcomes have been blinded	Blinding has not been performed or is not reported
Follow-up period appropriate to the aim of the study	≥ 1 year	< 1 year	Not reported
Loss to follow up	≤ 5%	> 5% and ≤ 20%	Not reported or more than 20%
Prospective calculation of the study size	Power analysis has been performed	Explanation for the number of included patients without a power analysis	Not reported or not performed
An adequate control group	Plate or intramedullary fixation compared with a conservative treatment	Not applicable	Not reported
Contemporary groups	Study group and controls have been managed during the same time period	Study group and controls have not been managed during the same time period	Not reported or unclear description
Baseline equivalence of groups	Baseline characteristics have been described for both groups and are comparable	Baseline characteristics have not been described thoroughly or are not comparable	Not reported
Adequate statistical analyses	Statistical analysis has been described including the type of test	Inadequate statistical analysis	Not reported

Appendix 3 Quality assessment of all included studies in a systematic review of DMCFs comparing conservative versus surgical treatment using the MINORS

Criteria	Althausen et al. (2)	Böhme et al. (5)	Canadian Orthopaedic Trauma Society (9)	Chen et al. (10)	Daniilidis et al. (12)	George et al. (16)	Grassi et al. (18)	Jones et al. (25)	Jubel et al. (26)	Judd et al. (27)	Khorami et al. (28)	Kulshrestha et al. (30)	Melean et al.(33)	Mirzatolooei et al. (34)	Robinson et al. (44)	Smekal et al. (46)	Thyagarajan et al. (51)	Van der Ven et al. (52)	Virtanen et al. (54)	Witzel et al. (55)
A clearly stated aim	2	0	2	1	2	2	1	2	1	1	2	2	2	2	2	2	1	2	2	1
Inclusion of consecutive patients	0	2	2	2	0	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2
Prospective collection of data	1	2	2	2	1	1	1	1	1	2	2	2	2	2	2	2	1	2	2	2
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1
Unbiased assessment of the study endpoint	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0
Follow-up period appropriate to the aim of the study	2	1	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	1
Loss to follow-up less than 5%	0	1	1	2	1	0	2	0	2	0	1	1	0	1	1	1	0	0	1	0
Prospective calculation of the study size	0	0	2	0	0	0	0	1	0	0	0	0	2	2	2	0	0	0	2	0
An adequate control group	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2
Baseline equivalence of groups	2	1	2	2	0	2	0	0	2	2	2	2	2	2	2	2	1	2	1	0
Adequate statistical analyses	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	0
Total quality score MINORS	16	14	21	19	14	17	16	16	16	17	18	19	18	21	22	19	11	18	20	11

Appendix 4 Baseline characteristics of included studies in a systematic review of MCFs comparing conservative versus surgical treatment

Study	Year	Study design	Country	Fracture type(s)	Displacement
Althausen et al. (2)	2013	RC	USA	No further classification applied	Yes
Böhme et al. (5)	2011	PC	Germany	Using a modified AO classification; Type A, B and C fractures	No
Canadian Orthopaedic Trauma Society (9)	2007	RCT	Canada	No further classification applied	Yes
Chen et al. (10)	2011	RCT	China	Simple, wedge and comminuted fractures according to the AO classification system	No
Daniilidis et al. (12)	2003	RC	Germany	No further classification applied	No
George et al. (16)	2015	RC	Australia	Edinburgh type 2B1	Yes
Grassi et al. (18)	2001	RC	Italy	Simple, with a butterfly fragment and comminuted	Yes
Jones et al. (25)	2014	RC	UK	Allman type 1 fractures	No
Jubel et al. (26)	2002	RC	Germany	No further classification applied	No
Judd et al. (27)	2009	RCT	USA	No further classification applied	Yes
Khorami et al. (28)	2014	PC	Iran	Robinson 2A2, 2B1, 2B2	Yes
Kulshrestha et al. (30)	2011	PC	India	Robinson 2B1, 2B2	Yes
Melean et al. (33)	2015	RCT	Chile	Robinson 2B1, 2B2	Yes
Mirzatolooei et al. (34)	2011	RCT	Iran	No further classification applied	Yes
Robinson et al. (44)	2013	RCT	UK	Edinburgh type 2B	Yes
Smekal et al. (46)	2011	PC	Austria	15B1, 15B2, 15B3, according to the AO classification system	Yes
Thyagarajan et al. (51)	2009	RC	UK	No further classification applied	Yes
Van der Ven et al. (52)	2015	PC	The Netherlands	No further classification applied	Yes
Virtanen et al. (54)	2012	RCT	Finland	15B1, 15B2, according to the AO classification system	Yes
Witzel et al. (55)	2007	RCT	Germany	No further classification applied	Yes

Follow-up (months)	Groups	No. of patients	Age (years) (±SD)	Male/ Female
32	Surgical - superior locking plate	66	40.3	47/19
	Conservative - nfs	83	41.7	65/18
8	Surgical fixation - DCP or LCDCP or reconstruction plate	53	total: men: 35 (range 18-69) women: 41 (range 22-69)	total: 95/25
	Surgical fixation - pin	20		
	Conservative - figure-of-eight-bandage	47		
12	Surgical - LCDCP or reconstruction plate or precontoured plate or other plate	62	33.5	53/9
	Conservative - sling	49	33.5	34/15
15	Surgical - TEN	30	39.0 (±11.9)	16/14
	Conservative - sling	30	38.4 (±13.3)	16/14
15	Surgical - LCP	73	40.3	64/17
	Surgical - TEN	8	27.1	
	Conservative - figure-of-eight-bandage	70	40.8	51/19
62	Surgical - plate	20	36 (range 18-63)	13/7
	Conservative - nfs	20	46 (range 22-78)	16/4
64	Surgical - intramedullary pin	40	30.2 (range 15-62)	31/9
	Conservative - figure-of-eight-bandage	40	37.2 (range 15-70)	35/5
30	Surgical - plate	24	total: 27.1 (±8)	total: 76/14
	Surgical - TEN	25		
	Conservative - nfs	41		
36	Surgical - TEN	20	37 (±16)	16/4
	Conservative - figure-of-eight-bandage	20	36 (±15)	17/3
12	Surgical - modified Hagie pin	29	28 (range 19-40)	27/2
	Conservative - sling	28	25 (range 17-41)	25/3
6	Surgical - 3.5mm plate	35	31 (±9.5)	25/10
	Conservative - figure-of-eight-bandage	30	30 (±13.0)	23/7
18	Surgical - contoured reconstruction plate	45	32.0 (±6.2)	43/2
	Conservative - sling	28	32.8 (±4.6)	24/4
12	Surgical - 3.5mm LCP	34	38.1 (±13)	NR
	Conservative - sling	42	37.2 (±11.2)	NR
12	Surgical - 3.5mm reconstruction plate	29	36.0	20/6
	Conservative - sling	31	35.3	21/3
12	Surgical - LCP	95	32.3 (95%CI 30.1-34.5)	83/12
	Conservative - collar and cuff	105	32.5 (95%CI 30.1-34.9)	92/13
24	Surgical - TEN	60	36.8 (±12.6)	54/6
	Conservative - sling	52	38.0 (±14.8)	44/8
6	Surgical - LCDCP	17	32.1 (range 17-46)	15/2
	Surgical - Rockwood pin	17	28 (range 15-56)	16/1
	Conservative - sling	17	34.5 (range 17-64)	12/5
60	Surgical - LCP	39	40.8 (±12.8)	35/4
	Conservative - sling	58	40.5 (±15.2)	49/9
12	Surgical - 3.5mm reconstruction plate	28	41 (±10.8)	24/4
	Conservative - sling	32	33 (±12.0)	28/4
19	Surgical - Prévot pin	35	34.2 (range 19-72)	22/13
	Conservative - figure-of-eight-bandage	33	NR total: 35.4 (range 18-72)	23/10

Appendix 5 Study outcomes and results in a systematic review of DMCFs comparing conservative versus surgical treatment

Study	Nonunion		Functional scores short term (<1 year)				Functional scores long term (≥ 1year)	
			DASH scores		Constant score		DASH scores	
	Surgical	Conservative	Surgical	Conservative	Surgical	Conservative	Surgical	Conservative
Althausen et al. (2)	0	4/83 (4.8%)	NR	NR	NR	NR	NR	NR
Böhme et al. (5)	0	1/47 (2,1%)	NR	NR	88.2* 94.0**	83.6	NR	NR
Canadian Orthopaedic Trauma Society (9)	2/62 (3.2%)	7/49 (14.3%)	21	40	80	69	5	14
Chen et al.(10)	0	3/30 (10%)	NR	NR	NR	NR	2.74 (±3.6)	7.91 (±12.6)
Daniilidis et al. (12)	0***	9/70 (12.9%)	NR	NR	NR	NR	7.3***	11.1
George et al. (16)	NR	NR	NR	NR	NR	NR	10.13 (±15.7)	11.22 (±18.8)
Grassi et al. (18)	2/40 (5%)	0	NR	NR	NR	NR	NR	NR
Jones et al. (25)	1/24 (4.7%)* 0/25** 1/49 (2.0%) ***	7/41 (17.1%)	NR	NR	NR	NR	10 (±15)* 1.7 (±2.9)** 5.9 (±11.5) ***	7.6 (±9.3)
Jubel et al. (26)	0	2/20 (10%)	NR	NR	NR	NR	NR	NR
Judd et al. (27)	1/29 (3.5%)	1/28 (3.6%)	NR	NR	NR	NR	NR	NR
Khorami et al. (28)	2/35 (5.7%)	4/30 (13.3%)	24.6 (range 0-88)	22.7 (range 0-87)	20.97 (±5.7)	20.53 (±7.04)	NR	NR
Kulshrestha et al. (30)	0	8/28 (28.6%)	NR	NR	90	78	NR	NR

* plate; ** intramedullary fixation; *** results of combination of patients treated with plate and intramedullary fixation; SE = Standard error; SD = standard deviation; R = range; CI = Confidence Interval; NR = not reported

Functional scores long term (≥ 1year) Constant score		malunion		Return to work in days		Revision surgery		Implant removal
Surgical	Conservative	Surgical	Conservative	Surgical	Conservative	Surgical	Conservative	Surgical
NR	NR	NR	NR	35.9	61.1	3/66 (4.5%)	0	NR
94.4* 96.7** (8 months)	90.3 (8 months)	NR	NR	34	36	4/53 (7.5%)* 1/20 (5%)**	1/47 (2.1%)	NR
96	90	0	9/49 (18.4%)	NR	NR	3/62 (4.8%)	16/49 (32.7%)	5/62 (8.1%)
97.0 (±4.2)	94.0 (±5.4)	0	2/30 (6.7%)	NR	NR	1/30 (3.3%)	5/30 (16.7%)	NR
91.7 (SE: 1.1) ***	88.1 (SE: 1.4)	NR	NR	NR	NR	9/81 (11.1%) ***	9/70 (12.9%)	3/81 (3.7%) ***
NR	NR	NR	NR	NR	NR	NR	NR	NR
82.9 (range 63-95)	84.4 (range 52-95)	2/40 (5%)	0	40.7 (range 20-60)	16.7 (range 7-60)	1/40 (2.5%)	0	NR
NR	NR	NR	NR	NR	NR	NR* 1/25** NR***	1/41 (2.4%)	10/25 (40%)**
97 (±4)	78 (±23)	NR	NR	NR	NR	NR	NR	NR
NR	NR	1/29 (3.5%)	0	NR	NR	7/29 (24.1%)	1/28 (3.6%)	29/29 (100%)
NR	NR	18/35 (51.4%)	7/30 (23.3%)	59.5 (±13.3)	61.6 (±13.3)	3/35 (8.6%)	4/30 (13.3%)	NR
94	84	2/45 (4.4%)	10/28 (35.7%)	NR	NR	2/45 (4.4%)	8/28 (28.6%)	4/45 (8.9%)

Appendix 5 Continued

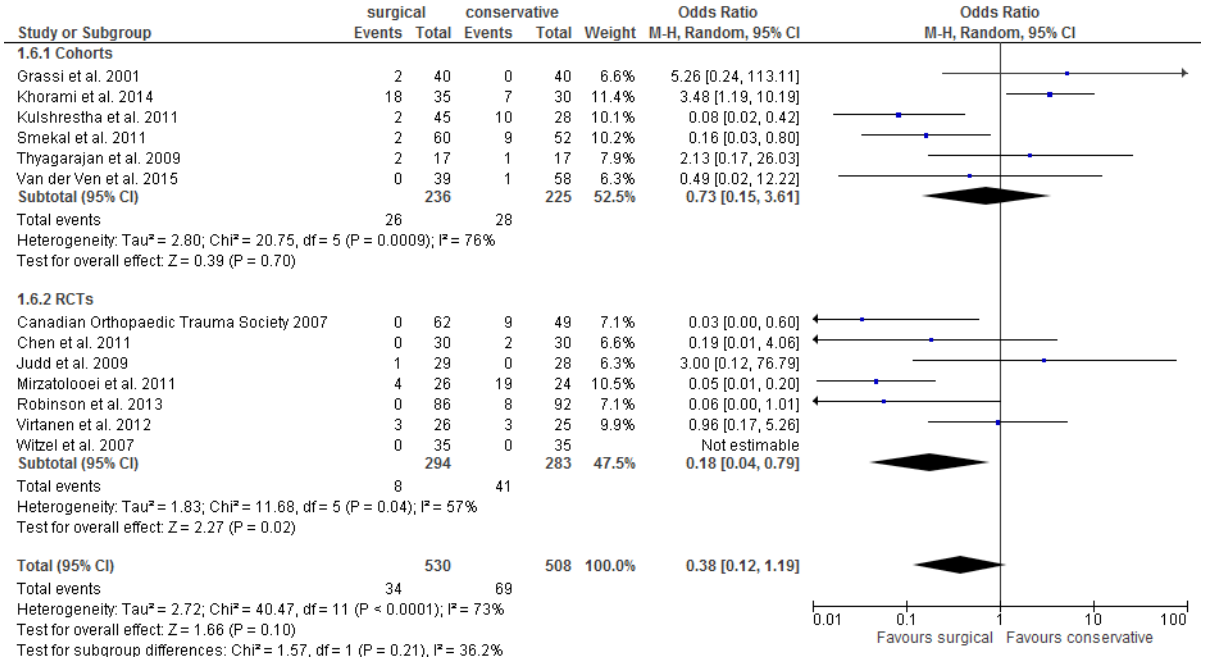
Study	Nonunion		Functional scores short term (<1 year)				Functional scores long term (≥ 1year)	
			DASH scores		Constant score		DASH scores	
	Surgical	Conservative	Surgical	Conservative	Surgical	Conservative	Surgical	Conservative
Melean et al.(33)	0	4/41 (9.6%)	NR	NR	76 (range 48-93) (3 months)	74 (range 31-95) (3 months)	NR	NR
Mirzatolooei et al. (34)	1/26 (3.8%)	1/24 (4.2%)	NR	NR	NR	NR	8.6	21.3
Robinson et al. (44)	1/86 (1.2%)	16/92 (17.4%)	22	28	70	67	3.4 (R1.9 -4.9)	6.1 (R4.1 -8.1)
Smekal et al. (46) 2011	0	6/52 (11.5%)	NR	NR	NR	NR	0.5 (±1.8)	3.1 (±7.4)
Thyagarajan et al. (51)	1/17 (5.9%)* 0/17** 1/34 (2.9%) ***	3/17 (17.6%)	NR	NR	97.8 (±2.5)* 93.7 (±4.4)** NR***	89.0 (±16.0)	NR	NR
Van der Ven et al. (52)	1/39 (2.6%)	3/58 (5.2%)	15.7 (±17.2)	24.8 (±16.7)	90.9 (±14.2)	78.7 (±17.0)	5.2 (±9.8)	2.5 (±4.9)
Virtanen et al. (54)	0	6/25 (24%)	14.2 (±13.4)	14.3 (±14.4)	78.7 (±10.9)	80.0 (±10.2)	5.0 (±6.4)	8.0 (±13.3)
Witzel et al. (55)	0	0	NR	NR	NR	NR	NR	NR

* plate; ** intramedullary fixation; *** results of combination of patients treated with plate and intramedullary fixation; SE = Standard error; SD = standard deviation; R = range; CI = Confidence Interval; NR = not reported

Functional scores long term (≥ 1year)		malunion		Return to work in days		Revision surgery		Implant removal
Constant score								
Surgical	Conservative	Surgical	Conservative	Surgical	Conservative	Surgical	Conservative	Surgical
93 (range 91-95)	87 (range 79-95)	NR	NR	88.2 (±24.3)	112.5 (±33.5)	0	4/41 (9.8%)	4/35 (11.4%)
89.8	78.8	4/26 (15.4%)	19/24 (79,2%)	NR	NR	3/26 (11.5%)	1/24 (4.2%)	NR
92 (R90.0-94.0)	87.8 (R85.2-90.3)	0	8/92 (8.7%)	22.0 (95% CI 15.1 - 28.9)	24.2 (95% CI 16.9 - 31.5)	5/86 (5.8%)	13/92 (14.1%)	10/86 (11.6%)
98.0 (±3.6)	95.1 (±7.0)	2/60 (3.3%)	9/52 (17.3%)	NR	NR	12/60 (20%)	6/52 (11.5%)	NR
NR	NR	2/17 (11.8%)* 0/17** 2/34 (5.9%) ***	1/17 (5.9%)	NR	NR	2/17 (11.8%)* 0** 2/34 (5.9%) ***	4/17 (23.5%)	2/17 (11.8%)* 17/17 (100%) ** 19/34 (55.9%) ***
NR	NR	0	1/58 (1.7%)	16.1 (±13.3)	29.4 (±21.7)	9/39 (23.1%)	3/58 (5.2%)	4/39 (10.3%)
87.3 (±6.5)	85.2 (±9.5)	3/26 (11.5%)	3/25 (12%)	NR	NR	1/26 (3.8%)	1/25 (4%)	NR
NR	NR	0	0	NR	NR	0	0	35/35 (100%)

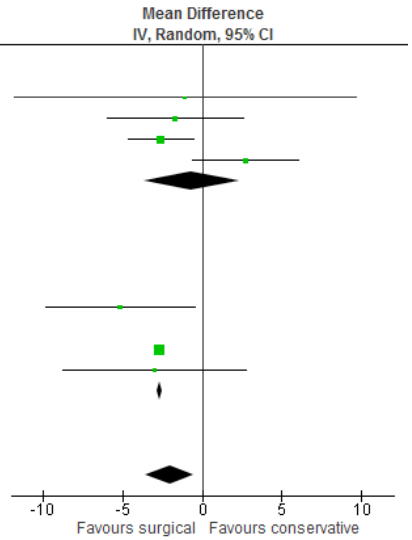
Appendix 6 Impact of different methods to handle zero-event data in the meta-analysis of conservative vs surgical treatment of DMCF and nonunions

	Observational studies	Randomised trials
Method	Pooled OR (95% CI)	Pooled OR (95% CI)
Crude	0.11 (0.04; 0.25)	0.11 (0.04; 0.29)
Inverse variance – no correction	0.20 (0.06; 0.65)	0.22 (0.08; 0.64)
Inverse variance - with correction	0.17 (0.07; 0.38)	0.17 (0.07; 0.43)
DerSimonian Laird with correction	0.16 (0.05; 0.55)	0.18 (0.05; 0.67)
Peto	0.12 (0.06; 0.23)	0.15 (0.07; 0.30)

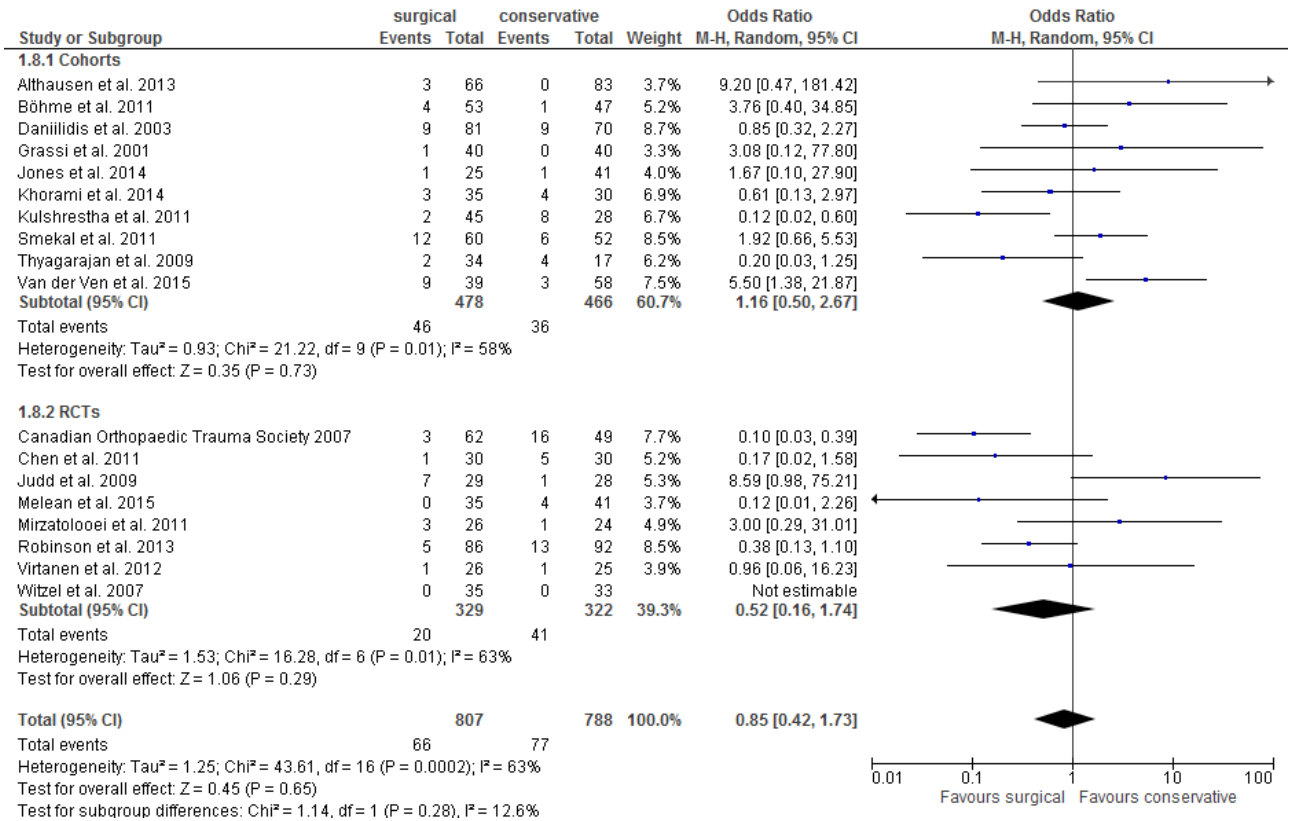


Appendix 7 Malunions in a systematic review of DMCFs comparing conservative versus surgical treatment

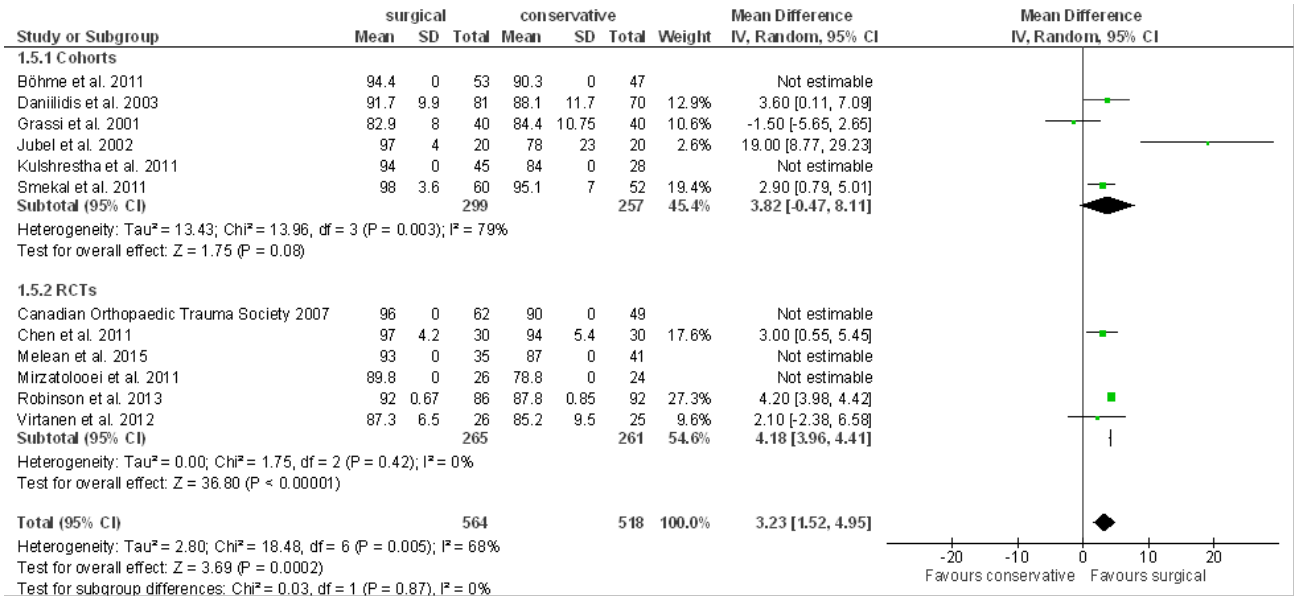
Study or Subgroup	surgical Mean	SD	Total	conservative Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Cohorts								
Daniilidis et al. 2003	7.3	0	81	11.1	0	70		Not estimable
George et al. 2015	10.13	15.7	20	11.22	18.8	20	1.9%	-1.09 [-11.82, 9.64]
Jones et al. 2014	5.9	11.5	49	7.6	9.3	41	9.4%	-1.70 [-6.00, 2.60]
Smekal et al. 2011	0.5	1.8	60	3.1	7.4	52	22.6%	-2.60 [-4.66, -0.54]
Van der Ven et al. 2015	5.2	9.8	39	2.5	4.9	58	13.5%	2.70 [-0.62, 6.02]
Subtotal (95% CI)			**249**			**241**	**47.4%**	**-0.68 [-3.69, 2.32]**
Heterogeneity: Tau² = 4.92; Chi² = 7.11, df = 3 (P = 0.07); I² = 58%								
Test for overall effect: Z = 0.45 (P = 0.66)								
1.4.2 RCTs								
Canadian Orthopaedic Trauma Society 2007	5	0	62	14	0	49		Not estimable
Chen et al. 2011	2.74	3.6	30	7.91	12.6	30	8.2%	-5.17 [-9.86, -0.48]
Mirzatolooei et al. 2011	8.6	0	26	21.3	0	24		Not estimable
Robinson et al. 2013	3.4	0.5	86	6.1	0.67	92	38.4%	-2.70 [-2.87, -2.53]
Virtanen et al. 2012	5	6.4	26	8	13.3	25	5.9%	-3.00 [-8.76, 2.76]
Subtotal (95% CI)			**230**			**220**	**52.6%**	**-2.70 [-2.88, -2.53]**
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.58); I² = 0%								
Test for overall effect: Z = 30.67 (P < 0.00001)								
Total (95% CI)			**479**			**461**	**100.0%**	**-2.04 [-3.56, -0.52]**
Heterogeneity: Tau² = 1.55; Chi² = 11.49, df = 6 (P = 0.07); I² = 48%								
Test for overall effect: Z = 2.64 (P = 0.008)								
Test for subgroup differences: Chi² = 1.73, df = 1 (P = 0.19), I² = 42.2%								



Appendix 8 DASH scores on the long term in a systematic review of DMCFs comparing conservative versus surgical treatment



Appendix 9 Constant scores on the long term in a systematic review of DMCFs comparing conservative versus surgical treatment



Appendix 10 Revision surgery in a systematic review of DMCFs comparing conservative versus surgical treatment

CHAPTER TWELVE

Summary, discussion
and future perspectives

In this chapter a reflection concerning the performed studies has been given. To begin with, the postoperative treatment of ankle fractures has been thoroughly studied in this thesis. Using these common fractures in trauma surgery, the transition in trauma surgery research has been described. Both outcomes and the type of studies have changed. This caused a discussion concerning the position of observational studies in trauma surgery.

Ankle fractures and the evolution of postoperative treatment

Ankle fractures are the most common lower extremity fractures worldwide with an incidence rate of 187 per 100.000 person-years, resulting in over 30.000 ankle fractures annually in the Netherlands (1;2). The main causes of ankle fractures are minor trauma and sports, which are typical injuries for individuals in their working age (3;4). As such, ankle fractures have high impact on both individual patients and society. Due to the occupational disability in the population at risk, ankle fractures are associated with loss of productivity and high costs for society (5-7). The disability after ankle fractures and the resulting personal and economic burden emphasize the importance of a safe and rapid functional recovery. Functional recovery of patients with operatively treated ankle fractures is highly impacted by the postoperative treatment regimen. A wide range of postoperative treatment regimens has been used (8).

In the Netherlands, ankle fractures are mostly treated by dedicated trauma surgeons, with a background in either orthopedic surgery or general surgery. This thesis has shown that trauma surgeons in the Netherlands still use different types of postoperative treatment regimens for similar ankle fractures (9). The majority of Dutch surgeons (60%) preferred a postoperative non-weight-bearing treatment with active mobilization. Others used weight-bearing with a walking cast or other postoperative treatment regimens (9). The worldwide literature confirms the use of a variety of postoperative treatment regimens (10).

In the early twentieth century, immobilization and non-weight-bearing treatment after surgery were common postoperative treatment regimens (11-13). However, immobilization in a cast might result in stiffness of the ankle and muscle atrophy, and non-weight-bearing treatment, although retaining range of motion results in a delayed functional recovery (14-16). More liberal postoperative treatment regimens were investigated

in the past decade. Several reviews concerning these postoperative treatment regimens have been published (17-20). Nash et al. concluded that immobilization provides no benefit, and Thomas et al. concluded that it is difficult to determine whether early motion is overall better or worse than cast immobilization (18;20). Smith et al. concluded that because of the little difference in outcome, the optimum time to commence weight-bearing cannot be determined (19). Black et al. suggested that early weight-bearing might allow for faster rehabilitation and earlier return to work (17). Weight-bearing and mobilization were also combined using an orthosis. However, a high rate of wound infections was reported in patients wearing these orthoses (21). In a meta-analysis in which specific aspects of postoperative treatment regimens were analyzed, instead of whole postoperative treatment regimens, we could provide a differentiated clinical advice on the effect of ankle exercises and weight-bearing (10). Direct active mobilization after surgery is advantageous compared to immobilization, and weight-bearing shows a similar trend without an increased risk for complications (10). These findings were confirmed in a recent trial (14). One small retrospective study even combined both aspects into unprotected weight-bearing and mobilization as tolerated directly after surgery with beneficial results (22). The combination of functional treatment and early weight-bearing may reduce soft tissue atrophy and development of osteoporosis and better preserve ankle range of motion (22).

In this thesis, the WOW! study was the first randomized controlled trial to investigate unprotected weight-bearing and mobilization as tolerated directly after surgery (23). We included skeletal mature patients without severe comorbidities. We excluded patients older than 65 years, patients with open fractures and patients in which initial external fixation was used as these factors are independently associated with a significant higher risk of wound related complications, the most common complications after ankle fracture surgery (24). Furthermore, we included only supination external rotation type 2 to 4 fractures. An expert panel, consisting of six experienced trauma surgeons, classified the anonymous X-rays using the Lauge-Hansen classification (13). The expert panel was implemented to minimize inter-observer variability between treating physicians. In addition, strict termination criteria were established to ensure the safety of patients participating in the trial. The WOW! study showed

that unprotected weight-bearing and mobilization as tolerated results in improved short-term functional outcome and earlier return to work and sports. The postoperative treatment regimen of unprotected weight-bearing and mobilization as tolerated did not result in an increased rate of complications in adult patients with a supination external rotation type 2 to 4 ankle fracture without comorbidities. These results can provide significant benefits for the individual patient as well as for society.

The transition in trauma surgery research to patient reported outcome measures

Besides the evolution of postoperative treatment regimens to early mobilization and early weight-bearing, studies investigating this topic have changed in the past decades (25). Fewer randomized controlled trials (RCTs) have been published, while the total number of published studies has increased. Strikingly, the quality of the published articles has not declined.

One of the most remarkable progressions to a tailor-made treatment is the gradual shift from physician measured to patient reported outcome measures (PROMs), for instance the functional outcome changed from measuring the range of motion to the Olerud Molander Ankle score (25). Outcomes are increasingly focused on the implications for patients. Numerous tools to measure PROMs have been developed over time to guide physicians (26;27). These tools should be further developed and consensus should be reached in reporting these outcome measures to enable comparison between studies. In addition, these tools can assist physicians in reaching patient expectations (28-30).

Both above-mentioned developments show that research in trauma surgery is in transition.

Quality should prevail

As indicated above, trauma surgeons in the Netherlands still use different types of postoperative treatment. This was demonstrated and specified using a questionnaire among all Dutch (orthopedic) trauma surgeons (9). Results of this questionnaire led to further investigation of the inconsistency in postoperative treatment of ankle fractures in the worldwide available literature using a meta-analysis (10). Subsequently, other issues that might influence the results of postoperative treatment

regimens were identified and further investigated (24;31). In these studies, it was demonstrated that the post-operative care regime did not influence the most relevant complications (wound problems/infections and loss of reduction). Infections were caused by comorbidities, injury characteristics and factors associated with the surgical procedure. In addition, we could demonstrate that there is a difference in high-energy and low-energy trauma mechanism. These studies demonstrated the importance of adequate patient and fracture selection. Based on these results, a protocol for an RCT was developed and the WOW! Study was performed (23). All these studies were needed to create an evidence based, high-quality answer to a research question which affects large numbers of patients. The two important observations for research in trauma surgery that were distilled from these studies are further elaborated on.

First, patient selection or knowledge about patient characteristics of those included in trauma surgery studies is essential to appraise the results of those studies. Certain patients are at risk for complications and thereby studies can be affected by the in- or exclusion of those patient groups. For example, hip fracture studies excluded substantial (22% - 36%) numbers of patients due to dementia or cognitive impairment (32-34). This is in contrast to the 28% prevalence of dementia in patients with hip fractures. The patients with dementia who suffer a hip fracture show an increase in both mortality and complications compared to patients without dementia (34). Stringent exclusion criteria may create an unrepresentative population and restrict clinical applicability of these studies. Likewise, particular groups of patients, e.g. older patients, are more likely to develop complications after ankle fracture surgery (24). This indicates that patient selection is essential and in- and exclusion criteria should be considered when using evidence for decision making.

Second, we have shown that different trauma mechanisms cause different fracture types, each requiring their own distinct approach (31;35). Although this might sound logical, most studies still include all types of ankle fractures (21;36;37). In the past decade, it seems that more awareness is created, and more studies are now focusing on a specific type of fracture (38-40). In the WOW! study an expert panel confirmed the fracture type prior to study inclusion. This unique method of selecting fractures helps to identify the right patient population, which has shown to be effective in other fields of surgery (41;42).

An RCT in trauma surgery, best available evidence?

One of the most common challenges of RCTs is the timely and efficiently recruitment of patients (43). Several studies have shown that RCTs in surgery have low patient participation rates (44). Patients are often hesitant to participate in (type 2 and 3) trials as they do not want their treatment to be decided by chance (45). As a result, these trials show high rates of patients refusing to participate, which could result in an underpowered study (46). The availability of a full-time dedicated researcher could minimize this risk, and thereby improve quality of studies in trauma surgery. The coordinating researcher is responsible for high follow-up rates. This can result in high patient commitment, as the researcher is always present at follow-up appointments. Moreover, a central trial coordinator results in better trial progression (47). If the recruitment of patients is not carried out properly, an extended trial period and increased costs are to be expected.

Inadequate recruitment of patients hampers the efficiency and validity of a trial (44). Besides low participation rates, a substantial part of the RCTs in trauma surgery are terminated early without adequate information about the reason for termination (48).

The low participation rate is also influenced by physicians in surgical trials as they often prefer one of both treatment arms (45). Treatment preference results in less participating centers or selective inclusion of patients. This is further emphasized in the high rate of patients with whom the trial is not discussed (23;49). Additionally, RCTs in general, have very strict in- and exclusion criteria. The patient population enrolled in the trial might therefore not be representative for the referred population. This hampers the generalizability of the results of (surgical) RCTs.

While adequate randomization ensures baseline comparability of treatment arms in type 2 and type 3 surgical trials, that comparability may not be preserved during follow-up (potentially confounding the results of the study), due to the complexity of the studies interventions. The technical difficulty of a surgical procedure cannot be compared to, for example, administering drugs. A surgical procedure can be influenced by many other factors, such as the expertise and experience of the surgical team, which can result in performance bias (50). Furthermore, a surgical procedure is often only a component of the whole treatment trajectory and results can be influenced by the postoperative treatment.

Last but not least, RCTs must be performed according to strict rules and require budget for approval by medical ethical committees and by monitoring of the trial. In a field with limited financial resources, such as trauma surgery, these regulations might lead to a decrease in the quantity of RCTs (25;51).

Future perspectives

The value of observational studies in trauma surgery

In the second part of this thesis the results between RCTs and observational studies have been evaluated in meta-analyses to assess the value of observational studies in trauma surgery.

The RCT design occupies the top of the evidence pyramid in the classic construction of scientific research. In circumstances of well-defined intervention, where the (only) interest lies in quantifying the effectiveness of the intervention, an RCT might be the preferred study design. However, it can be questioned whether RCTs are always the best available evidence in trauma surgery, because of before-mentioned limitations of RCTs. The shortcomings of traditional regulatory RCTs have long been debated (52-54). The presence and origin of the difficulties when performing a surgical RCT need to be recognized and possible solutions should be established. High quality observational data can sometimes be a good alternative to overcome these difficulties. In- and exclusion criteria can be less selective in observational studies to create larger and more representative cohorts. In addition, observational studies can complement systematic reviews and meta-analyses of randomized trials in clinical queries as the power can be increased and results between observational studies and RCTs are sometimes comparable (55-59). If the quality and conduct of non-randomized studies is high, meta-analyses of observational studies of surgical interventions (type 2 and type 3 surgical research) can be as accurate as meta-analyses of RCTs alone (60).

Discussion concerning the comparability of non-randomized and randomized studies still exists. Hemkens et al. conclude that studies of routinely collected health data could give different answers compared to subsequent randomized controlled trials on the same clinical questions, and may substantially overestimate treatment effects (61;62). However, other studies show that results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment

as compared with RCTs (55;63;64). This emphasizes the importance of the quality of studies, such as a prospective design (61). Studies in trauma surgery confirm that observational studies are valuable tools on the clinical effectiveness of treatment (65). Fralick et al. conclude that real-world data analyses of patients receiving routine care provided findings similar to those found in the randomized clinical trial (66). This shows, even in studies concerning medications, that high quality observational studies are also appreciated, in addition to RCTs (66). Supplementary, large databases can show rare side effects or complications. However, these studies still cause discussion in the scientific world (55;67). The study of Fralick et al. is in line with our meta-analyses in trauma surgery (58;59). These meta-analyses have shown that quality instead of the type of study should be leading when pooling evidence available from previous studies to answer a particular research question.
High quality observational studies (good constructed and well performed) might play a greater role in future research. If rare events need to be identified, large (observational) databases are needed to identify these cases. The use of quality assessment tools can be of assistance in improving both methodological and reporting quality of these (surgical) studies to ensure reproducibility. A research question should be answered using a research trajectory often consisting of a combination of several types of studies, and by combining the different research constructs, a case with best available evidence can be formulated. Future studies in trauma surgery should focus on methodological (and reporting) quality instead of the study type only and thereby appreciate the contribution of non-RCT research to surgical evidence based medicine.

In conclusion, after exploring a lack of knowledge in the postoperative treatment of the most common ankle fractures, a series of studies was performed to establish a well-designed trial. This trial has shown potential major benefits in a vast working population without an increased risk of complications. Future studies can further elaborate on this treatment in a population with different patient characteristics and a wider range of selected fractures resulting in a tailor-based treatment. The methodological focus of these studies should be on high quality (both well-designed and well-performed) instead of study design.

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CHAPTER THIRTEEN

Samenvatting, discussie en toekomstperspectieven

In dit hoofdstuk wordt een beschouwing gegeven op de uitgevoerde onderzoeken. Als eerste is in dit proefschrift de postoperatieve behandeling van enkelfracturen uitvoerig bestudeerd. Aan de hand van deze veelvoorkomende fracturen binnen de traumachirurgie is de ontwikkeling van het wetenschappelijk onderzoek binnen dit gebied beschreven. Zowel de uitkomsten van de onderzoeken als het type onderzoek zijn veranderd. Hierdoor is een discussie ontstaan over de positie van observationeel onderzoek in de traumachirurgie.

Enkelfracturen en ontwikkelingen in de postoperatieve behandeling

Wereldwijd zijn enkelfracturen de meest voorkomende fracturen aan de onderste extremiteit met een incidentie van 187 per 100.000 manjaren, hetgeen resulteert in jaarlijks meer dan 30.000 enkelfracturen in Nederland (1;2). De belangrijkste oorzaken van enkelfracturen zijn kleine trauma's en sportongevallen. Dit zijn typisch letsels voor mensen die deelnemen aan het arbeidsproces (3;4). Enkelfracturen hebben daarom een grote invloed op zowel de individuele patiënt als de samenleving. Ook worden enkelfracturen geassocieerd met verlies van productie en daardoor met hoge kosten voor de samenleving (5-7). Arbeidsongeschiktheid na een enkelfractuur en de daaruit voortvloeiende persoonlijke en economische gevolgen benadrukken het belang van een snel functioneel herstel zonder complicaties. Het functioneel herstel van patiënten met operatief behandelde enkelfracturen wordt in hoge mate beïnvloed door de postoperatieve behandelmethode. Er bestaat een breed scala aan postoperatieve behandelmethodes (8).
In Nederland worden enkelfracturen meestal behandeld door toegewijde traumachirurgen met als achtergrond de orthopedische of algemene chirurgie. In dit proefschrift komt naar voren dat traumachirurgen in Nederland nog steeds verschillende postoperatieve behandelmethodes gebruiken voor vergelijkbare enkelfracturen (9). De meerderheid van de Nederlandse chirurgen (60%) gaf de voorkeur aan een onbelaste nabehandeling met actieve mobilisatie. Anderen kozen voor belast mobiliseren in loopgips of andere postoperatieve behandelmethodes (9). Het toepassen van een verscheidenheid aan postoperatieve behandelmethodes wordt in de gehele wereld bevestigd in de literatuur (10).

In het begin van de twintigste eeuw waren immobilisatie en onbelaste behandeling na een operatie gebruikelijke postoperatieve behandelmethodes (11-13). Immobilisatie met gips kan echter leiden tot stijfheid van de enkel en tot spieratrofie. Een onbelaste nabehandeling, alhoewel hierbij het bewegingsbereik behouden blijft, leidt tot een vertraagd functioneel herstel (14-16). In de afgelopen tien jaar werden meer progressieve postoperatieve behandelmethodes onderzocht. Er zijn verschillende evaluaties van deze postoperatieve behandelmethodes gepubliceerd (17-20). Nash et. al concludeerden dat immobilisatie geen voordeel oplevert en Thomas et al. concludeerden dat het moeilijk is om vast te stellen of vroeg bewegen in het algemeen beter of slechter is dan immobilisatie met gips (18;20). Smith et al. concludeerden dat het optimale tijdstip om te beginnen met belasten niet kan worden vastgesteld vanwege het geringe verschil in resultaat (19). Black et al. opperden dat vroeg starten met belasten een bijdrage zou kunnen leveren aan een snellere revalidatie en tot eerder hervatten van werk (17). Belasten en mobilisatie werden ook gecombineerd met het gebruik van een orthese. Er wordt echter een hoog aantal wondinfecties aangetroffen bij patiënten die deze orthesen dragen (21). In een uitgevoerde meta-analyse waarbij specifieke aspecten van postoperatieve behandelmethodes werden geanalyseerd in plaats van complete postoperatieve behandelmethodes konden wij een gedifferentieerd klinisch advies geven over het effect van enkeloefeningen en het effect van het belasten van de enkel (10). Uit die meta-analyse volgde ook dat directe actieve mobilisatie na een operatie - vergeleken met immobilisatie - gunstig is en dat het belasten van de enkel een soortgelijke tendens laat zien zonder een verhoogd risico op complicaties (10). Deze bevindingen werden bevestigd in een recente trial (14). In één kleinschalig retrospectief onderzoek werden beide aspecten zelfs gecombineerd door het direct na de operatie onbeschermd belasten en mobilisatie op geleide van de klachten, met gunstige resultaten (22). De combinatie van functionele behandeling en vroeg belasten kan weefselatrofie en de ontwikkeling van osteoporose verminderen en zorgen voor het beter behoud van het bewegingsbereik van de enkel (22). In dit proefschrift was de WOW!-studie de eerste gerandomiseerde trial waarin onderzoek werd gedaan naar onbeschermd belasten en mobilisatie op geleide van de klachten direct na de operatie (23). Wij includeerden volwassen patiënten zonder ernstige co-morbiditeit.

Wij excludeerden patiënten die ouder waren dan 65 jaar, patiënten met een open fractuur en patiënten bij wie aanvankelijk externe fixatie was gebruikt omdat deze factoren - los van elkaar - geassocieerd worden met een aanzienlijk hoger risico op wond-gerelateerde complicaties, zijnde de meest voorkomende complicaties na enkeloperaties (24). Voorts hebben we alleen supinatie-exorotatie (type 2 tot 4) fracturen opgenomen in het onderzoek. Een expertpanel, dat bestond uit zes ervaren traumachirurgen, beoordeelde de anonieme röntgenfoto's waarbij gebruik werd gemaakt van de Lauge-Hansen classificatie (13). Het expertpanel werd opgezet om de 'interobserver variability' tussen de behandelende artsen te minimaliseren. Verder werden strikte beëindigingscriteria gehanteerd om ervoor te zorgen dat de veiligheid van de patiënten die deelnamen aan de trial gewaarborgd was. De WOW!-studie heeft aangetoond dat het onbeschermd belasten en mobilisatie op geleide van de klachten op korte termijn leidt tot een verbeterd functioneel resultaat en tot een sneller hervatten van werk en sport. De postoperatieve behandelmethode van onbeschermd belasten en mobilisatie op geleide van de klachten heeft niet geleid tot een verhoogd aantal complicaties bij volwassen patiënten met een supinatie-exorotatie (type 2 tot 4) fractuur zonder co-morbiditeit. Deze resultaten kunnen aanzienlijke voordelen opleveren voor zowel de individuele patiënt als de maatschappij.

De ontwikkeling in het wetenschappelijk onderzoek naar patient-gerapporteerde uitkomstmaten in de traumachirurgie

Behalve de ontwikkeling van postoperatieve behandelmethodes naar vroege mobilisatie en vroeg belasten, zijn ook de onderzoeken waarin dit onderwerp wordt bestudeerd in de afgelopen decennia veranderd (25). Er zijn minder publicaties verschenen van gerandomiseerde trials (RCT's) terwijl het totaal aantal gepubliceerde onderzoeken is toegenomen. Opvallend genoeg is de kwaliteit van de gepubliceerde artikelen niet verminderd.

Eén van de meest naar voren komende stappen in de richting van een behandeling op maat is de geleidelijke verschuiving van arts-gemeten naar patiënt-gerapporteerde uitkomstmaten (PROMs). Een voorbeeld hiervan is dat het functionele resultaat werd gewijzigd, namelijk van het meten van het bewegingsbereik naar een functionele score, de Olerud Molander Ankle score (25). Verder wordt bij onderzoeksuitkomsten steeds meer

de nadruk gelegd op de gevolgen voor de patiënt. In de loop van de tijd zijn talloze meetinstrumenten ontwikkeld voor het meten van PROMs als richtlijn voor artsen (26;27). Deze meetinstrumenten moeten nog verder worden ontwikkeld. Ook moet nog consensus worden bereikt over het rapporteren van de uitkomstmaten om een vergelijking van onderzoeken mogelijk te maken. De methodes zullen artsen kunnen ondersteunen bij het realiseren van de verwachtingen van de patiënt (28-30).
Beide bovengenoemde ontwikkelingen tonen aan dat een verschuiving plaats vindt in het wetenschappelijk onderzoek in de traumachirurgie.

Kwaliteit staat voorop

Zoals eerder aangegeven gebruiken traumachirurgen in Nederland nog steeds verschillende postoperatieve behandelmethodes. Dit bleek uit een enquête onder alle Nederlandse (orthopedische) traumachirurgen (9). De resultaten van deze enquête hebben geleid tot verder onderzoek naar de inconsistentie in het postoperatief beleid bij enkelfracturen. Dit onderzoek vond plaats door middel van een meta-analyse in de - wereldwijd beschikbare - literatuur (10). Vervolgens zijn andere zaken die invloed zouden kunnen hebben op de resultaten van postoperatieve behandelmethodes vastgesteld en verder onderzocht (24;31). Uit die onderzoeken volgde dat de keuze voor postoperatieve zorg geen invloed had op de belangrijkste complicaties (wondproblemen/infecties en materiaalfalen). Infecties werden veroorzaakt door co-morbiditeit, het trauma mechanisme en de chirurgische ingreep. Verder stelden wij vast dat een verschil bestaat in fracturen veroorzaakt door hoogenergetische en laag energetische traumamechanismen. Tot slot werd vastgesteld dat selectie van de juiste patiënt en de juiste fractuur van essentieel belang was. Op basis van deze resultaten werd er een protocol ontwikkeld voor een RCT en werd de WOW!-studie uitgevoerd (23). Al deze onderzoeken waren nodig om te komen tot een evidence-based, kwalitatief hoogstaand antwoord op een onderzoeksvraag, een antwoord dat van belang is voor grote aantallen patiënten. Twee van de uit de onderzoeken volgende belangrijke observaties voor wetenschappelijk onderzoek binnen de traumachirurgie worden nader toegelicht.
Ten eerste is patiëntselectie of kennis van patiëntkenmerken van degenen die zijn betrokken in trauma-chirurgische onderzoeken essentieel om de resultaten van die onderzoeken te beoordelen. Sommige patiënten

lopen het risico op complicaties, waardoor - de resultaten van - onderzoeken kunnen worden beïnvloed door de inclusie of exclusie van de patiëntgroepen waartoe die patiënten behoren. Bijvoorbeeld: bij onderzoeken naar heupfracturen werden grote aantallen patiënten (22%-36%) niet betrokken vanwege dementie of (andere) cognitieve stoornissen (32-34). Daartegenover staat het feit dat bij 28% van de patiënten met heupfracturen ook dementie wordt geconstateerd. Het aantal patiënten met een heupfractuur en dementie laat een stijging zien in zowel sterfte als complicaties ten opzichte van patiënten zonder dementie (34). Ook kunnen exclusiecriteria leiden tot een niet-representatieve groep en kunnen deze criteria de klinische toepasbaarheid van onderzoeken beperken. Het vorenstaande geldt ook voor specifieke patiëntengroepen, bijvoorbeeld oudere patiënten, die een grotere kans hebben op complicaties na operatie van een enkelfractuur (24). Dit geeft aan dat patiëntselectie essentieel is en dat goed moet worden nagedacht over inclusie- en exclusiecriteria indien bij de besluitvorming gebruik wordt gemaakt van de resultaten van een onderzoek.
Ten tweede hebben wij aangetoond dat verschillende traumamechanismen verschillende typen enkelfracturen veroorzaken en dat voor ieder type fractuur een specifieke aanpak is vereist (31;35). Ook al klinkt het voorgaande misschien logisch, bij de meeste onderzoeken worden nog steeds alle typen enkelfracturen opgenomen (21;36;37). In de afgelopen tien jaar lijkt wel te zijn gewerkt aan bewustwording van deze werkwijze. Tegenwoordig wordt bij steeds meer onderzoeken de nadruk gelegd op een specifiek type fractuur (38-40). In de WOW!-studie werd het type fractuur bevestigd door een expertpanel voorafgaand aan opname in het onderzoek. Deze unieke methode van selectie van fracturen draagt bij aan het bepalen van de juiste patiëntenpopulatie, hetgeen ook op andere terreinen van de chirurgie effectief is gebleken (41;42).

Een RCT in traumachirurgie, het best beschikbare bewijs?

Een van de belangrijkste uitdagingen van RCT's is de tijdige en efficiënte werving van patiënten (43). Diverse onderzoeken hebben aangetoond dat bij RCT's in chirurgie sprake is van een geringe deelname van patiënten (44). Patiënten aarzelen vaak om mee te doen aan (type 2 en 3) trials omdat zij niet willen dat hun behandeling wordt bepaald op basis van loting (45). Als gevolg hiervan is bij deze onderzoeken een hoog percentage patiënten

die afzien van deelname waardoor het onderzoek aan statistische kracht inboet (46). De beschikbaarheid van een full-time, toegewijde onderzoeker, een onderzoekscoördinator, zou de aarzeling wellicht kunnen wegnemen door de verschillende behandelmogelijkheden met de daarbij behorende voor- en nadelen nader toe te lichten en aldus patiënten eventueel kunnen overtuigen van het belang van deelname. Hoe groter het aantal deelnemers hoe meer informatie kan worden verkregen om de kwaliteit van onderzoek in de traumachirurgie te verbeteren en daarmee een zo goed mogelijke behandeling van patiënten te laten plaatsvinden. De aanwezigheid van een onderzoekscoördinator zou ook kunnen leiden tot een grotere betrokkenheid van de patiënt bij het onderzoek omdat de onderzoeker ook aanwezig kan zijn bij de follow-up afspraken. Bovendien zorgt de aanstelling van een centrale onderzoekscoördinator voor een betere voortgang van het onderzoek (47). Indien de selectie van patiënten niet zorgvuldig wordt uitgevoerd kan dit leiden tot een langere onderzoeksperiode en tot hogere kosten.

Onzorgvuldige (en onvoldoende) werving van patiënten staat de efficiency en de validiteit van het onderzoek in de weg (44).

De lage participatiegraad wordt ook beïnvloed door de artsen in chirurgische trials omdat zij vaak een voorkeur hebben voor één van beide behandelingen (45). Voorkeur voor een bepaalde behandeling kan leiden tot minder participerende centra of tot selectieve inclusie van patiënten. Dit wordt ook beïnvloed door het grote aantal patiënten met wie de trial niet wordt besproken (23;49). Daarnaast hebben RCT's over het algemeen erg strenge inclusie- en exclusiecriteria. De patiëntengroep die deelneemt aan de trial is daarom misschien niet representatief voor de referentiegroep. Dit heeft een negatief effect op de mogelijkheid tot het generaliseren van de resultaten van (chirurgische) RCT's.

Afgezien van de lage participatiegraad, wordt een aanzienlijk deel van de RCT's in de traumachirurgie gestaakt zonder kenbare informatie over de reden van dit staken (48).

Ook al zorgt goede randomisatie voor de mogelijkheid tot het vergelijken van baseline-waarden van behandelingen in type 2 en type 3 chirurgische trials, toch kan die mogelijkheid tot het vergelijken wellicht niet (langer) bestaan tijdens de follow-up (waardoor de resultaten van het onderzoek mogelijk vertekend worden) vanwege de complexiteit van de verschillende interventies van het onderzoek. Een technisch lastige operatieve ingreep

kan niet worden vergeleken met, bijvoorbeeld, het toedienen van medicijnen. Verder kan een operatieve ingreep worden beïnvloed door vele factoren, zoals de expertise en ervaring van het chirurgisch team, hetgeen kan leiden tot performance bias (50). Verder is een operatieve ingreep vaak slechts een onderdeel van het gehele behandeltraject en kunnen de resultaten ook worden beïnvloed door de postoperatieve behandeling.
Ten slotte moeten RCT's worden uitgevoerd volgens strenge regels en is een budget nodig voor goedkeuring door medisch-ethische commissies en voor het toezicht op de uitvoering van het onderzoek. Bij een specialisme met beperkte financiële middelen, zoals de traumachirurgie, zou dit kunnen leiden tot een vermindering van het aantal RCT's (25;51).

Toekomstperspectief: de waarde van observationeel onderzoek in traumachirurgie

In het tweede deel van dit proefschrift zijn de resultaten van RCT's en observationeel onderzoek geëvalueerd in meta-analyses om de waarde van observationeel onderzoek in traumachirurgie te beoordelen.
Het RCT-ontwerp staat hoog op de piramide van 'evidence' in de klassieke constructie van wetenschappelijk onderzoek. Bij een duidelijk omschreven interventie waar het (enige) belang ligt bij het kwantificeren van de effectiviteit van de interventie, zou een RCT de gewenste keuze voor het onderzoek kunnen zijn. Vanwege de eerder genoemde beperkingen van RCT's kan echter de vraag worden gesteld of RCT's altijd het beste beschikbare bewijs vormen in traumachirurgie. De tekortkomingen van traditionele, gereglementeerde RCT's zijn lange tijd onderwerp van discussie geweest (52-54). De problemen en de oorzaak daarvan bij het uitvoeren van een chirurgische trial dienen te worden erkend. Hiervoor kunnen echter oplossingen worden aangedragen. Het gebruik van gegevens uit kwalitatief hoogstaand observationeel onderzoek kan in sommige gevallen worden gebruikt. Ook kunnen inclusie- en exclusiecriteria minder streng zijn in observationeel onderzoek om zo grotere en meer representatieve cohorten te vormen. Verder kan observationeel onderzoek een aanvulling vormen op systematische reviews en meta-analyses van gerandomiseerde trials in klinische vraagstukken omdat de statistische kracht kan worden vergroot en resultaten van observationeel onderzoek en RCT's soms vergelijkbaar zijn (55-59). Als de kwaliteit en uitvoering van

niet-gerandomiseerde onderzoeken hoog zijn, kunnen meta-analyses van observationeel onderzoek van chirurgische interventies (type 2 en type 3 chirurgisch onderzoek) even accuraat zijn als meta-analyses van alleen RCT's (60).

De discussie over de vergelijkbaarheid van niet-gerandomiseerde en gerandomiseerde onderzoeken wordt nog steeds gevoerd. Hemkes et al. concludeerden dat studies waarin patiëntgegevens routinematig werden verzameld, verschillende antwoorden opleverden in vergelijking met daaropvolgende RCT's over dezelfde klinische vragen en dat behandeleffecten substantieel kunnen worden overschat (61;62). In andere onderzoeken wordt echter aangetoond dat de resultaten van goed opgezet observationeel onderzoek geen systematische overschatting laten zien van de omvang van de behandeleffecten ten opzichte van RCT's (55;63;64). Dit benadrukt het belang van de kwaliteit van onderzoeken zoals een prospectieve onderzoeksopzet (61). Onderzoeken in de traumachirurgie bevestigen dat observationeel onderzoek een waardevol instrument is om de klinische effectiviteit van een behandeling te bepalen (65). Fralick et al. concludeerden dat realistische data-analyses van patiënten die standaardzorg kregen resultaten opleverden die vergelijkbaar waren met de resultaten van de RCT (66). Dit toont aan dat observationeel onderzoek van hoge kwaliteit ook van waarde is naast RCT's, zelfs in studies naar geneesmiddelen (66). Aanvullend hierop kunnen grote databases zeldzame bijwerkingen of complicaties aantonen. Deze onderzoeken staan echter nog ter discussie in de wetenschappelijke wereld (55;67). Het onderzoek van Fralick et al. stemt in grote lijnen overeen met onze meta-analyses in de traumachirurgie (58;59). Deze meta-analyses hebben aangetoond dat kwaliteit, en niet het soort onderzoek, leidend zou moeten zijn bij het bundelen van bewijs uit eerdere onderzoeken om een bepaalde onderzoeksvraag te beantwoorden.

Observationeel onderzoek van hoge kwaliteit (goed opgezet en goed uitgevoerd) zou een grotere rol kunnen spelen in toekomstig wetenschappelijk onderzoek. Indien zeldzame incidenten moeten worden achterhaald, zijn grote (observationele) databases nodig om deze gevallen vast te stellen. Het gebruik van kwalitatief goede beoordelingsinstrumenten kan van nut zijn om zowel de methodologische als de rapportagekwaliteit van deze (chirurgische) onderzoeken te verbeteren om zo de

reproduceerbaarheid te waarborgen. Een onderzoeksvraag dient te worden beantwoord door gebruik te maken van een onderzoekstraject dat meestal bestaat uit een combinatie van verschillende soorten onderzoek. Door het combineren van de verschillende onderzoeksopzetten kan een casus met het best beschikbare bewijs worden geformuleerd. Toekomstige onderzoeken in de traumachirurgie moeten zich richten op methodologische (en rapportage-)kwaliteit in plaats van alleen op het soort onderzoek en daarmee waardering tonen voor de bijdrage van niet-RCT gebaseerd onderzoek aan chirurgische 'evidence based medicine'.
Na het onderzoeken van een kennislacune in de postoperatieve behandeling van de meest voorkomende enkelfracturen werd tot slot een aantal studies uitgevoerd om tot een goed opgezette trial te komen. Deze trial heeft potentieel belangrijke voordelen aangetoond zonder een verhoogd risico op complicaties bij een groot deel van de beroepsbevolking. Toekomstige onderzoeken kunnen voortborduren op deze behandeling bij een populatie met verschillende patiëntkenmerken en een bredere categorie van geselecteerde fracturen hetgeen kan leiden tot een behandeling op maat. De methodologische focus van deze onderzoeken dient te liggen op hoge kwaliteit (zowel goed opgezet als goed uitgevoerd) en niet op het onderzoeksontwerp.

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