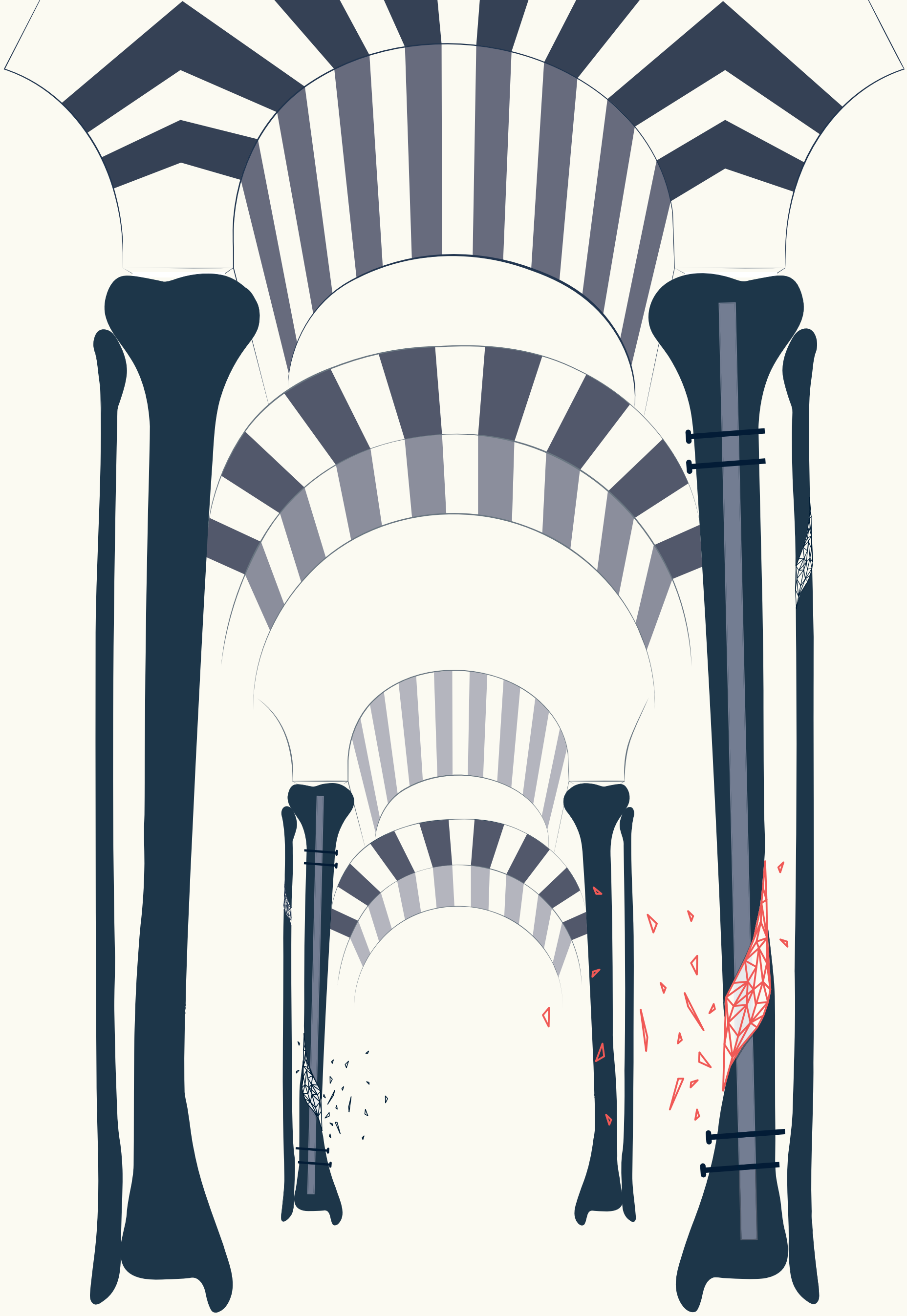

OPTIMIZING MANAGEMENT FOR TIBIA FRACTURES: DIAGNOSTIC- AND SURGICAL STRATEGIES

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OPTIMIZING MANAGEMENT FOR TIBIA FRACTURES: DIAGNOSTIC- AND SURGICAL STRATEGIES

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Nils Jan Bleeker
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Faculteit der Geneeskunde

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Voor jou pap
November 2022

PART I

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Epidemiology of tibia fractures

The human lower extremity consists of an upper- and lower part. The lower part encompasses the tibia - which is the second longest bone in human body - and the fibula. Proximally, the tibia articulates with femoral-condyles and forms the bony segments of the knee joint. Distally, the tibia plafond articulates with the talus and forms, together with the distal fibula, the ankle joint. The tibia plays an indispensable role in human movement as it fungates as full-weight bearer and distributor of weight over knee- and ankle joint. Fractures of the tibia, therefore, result in significant mobility impairments and often requires surgical intervention.

Tibia fractures are one of the most common long-bone fractures with a the peak age reported to be between 20 and 50 years.[1] Tibia fractures arise from both high energy- and low energy traumas. Most high energy injuries are caused by motor vehicle collisions involving more males than females.[2,3] Such impact often result in extensive soft tissue damage -either closed or open- and are associated with high complication rates i.e., compartment syndrome, non-union and infection.[4,5] Low energy traumas include contact sports, simple twists and insufficiency fractures in the elderly.

The gold standard fixation, where possible, is the insertion of an intramedullary nail (IMN) inside the tibia. This PhD thesis evaluates diagnostic and surgical strategies, and discusses resulting pearls and pitfalls from a spectrum of systematic review and meta-analyses, computed tomography (CT)-based imaging studies, retrospective- and prospective cohort studies, cadaveric in vitro study, and proposes a resulting randomized controlled trial (RCT) for further advancement of care for patients with tibial shaft fractures (TSF).

Should we go suprapatellar or infrapatellar for intramedullary nailing of tibia fractures?

To date, there are two main surgical approaches for IMN of TSF, including the infrapatellar (IP) - and suprapatellar (IP) approach. In case of IP-nailing, the knee is flexed 90° and the surgical incision is made medial parapatellar, lateral parapatellar or through the patellar tendon. Anterior knee pain is a frequent described complication of this approach, with high incidences reported in literature.[7-10] Based on the theoretical claim to reduce anterior knee pain, the SP-approach gained popularity and first results were considered to be promising, with less patients suffering from residual anterior knee pain.[11-14] During SP-nailing, the knee is positioned in almost full extension and the nail is introduced suprapatellar, which also facilitates a more straightforward positioning and protection of sterile fields. Early studies concluded less anterior knee pain and better alignment control. However, as of yet, little is known about the possible iatrogenic damage of the intra-articular structures of the knee[15-19] and risk of infection[20,21] since the nail is introduced superior of the proximal patellar pole and passes the articular surface of the knee joint. Moreover, more recent studies report conflicting result in terms of anterior knee pain, fueling the ongoing debate of IP- versus SP-approaches for IMN of tibial shaft fractures.

Or, should we plate them all? But what about wound problems?

Intramedullary nailing was initially suitable for fractures located in the middle part of the tibia. In case of a more distal located tibia fracture, IMN might introduce difficulties in acquiring accurate fracture reduction and proper distal locking to maintain alignment due to the short bony end-segments.[22,23] Moreover could a narrow intramedullary canal be a contra-indication for nailing. However, due to the improved (as well as more distal) locking options in modern tibia nails, the use has extended to more distal fractures, an area where plate fixation used to be the treatment of choice.[24] Therefore, there has been an increased use of IMN for a broader spectrum of fractures, making it the dominant fixation device for tibia fractures. Numbers of comparative studies on plate fixation versus IMN continue to rise[22,23,25-34], but, neither plate fixation (both open and minimal invasive plate osteosynthesis) nor IMN have evinced to be superior in definitive treatment of distal fractures of the tibia. Plate fixation might be associated with higher rates of wound problems while IMN will more likely result in anterior knee pain or malalignment.

Rotational malalignment is a frequent iatrogenic pitfall of IMN

Rotational malalignment (RM) is often an underestimated iatrogenic pitfall of IMN following TSF. RM is defined as a rotational mismatch of ≥10° compared to the non-fractured contralateral side.[35-39] It occurs when proximal and distal locking of the tibia nail is carried out while the tibia is fixed in a mal-rotated position. Severe soft tissue injury, swelling, closed reduction and fracture displacements with multiple fracture fragments might introduce difficulties in obtaining adequate alignment and hamper interpretation of fluoroscopy images. While tibia fractures are common long-bone fractures in an orthopaedic trauma surgeons' daily practice, less is known about the incidence of RM, imaging modalities to diagnose RM or how to minimize the risk of RM during tibia nailing. It has been postulated that RM may be of clinical relevance as rotational deformities can lead to cosmetical issues, functional movement disorders and might ultimately lead to osteoarthritis (OA) of the hip-, knee- and ankle joint. Moreover, from a litigation standpoint, patients suffering from RM could claim for financial compensation according to the "Guides to the Evaluation of Permanent Impairment".[40,41] An improved knowledge of the best diagnostic imaging modalities, the incidence of RM and how to avoid RM during IMN of tibia fractures will eventually help to contribute positively to the quality of tibia fracture care.

In Short: Optimizing Management of Tibia Fractures: Diagnostic- and Surgical Strategies

Orthopaedic trauma surgeons face several potential difficulties whilst taking surgical care of TSF. Firstly, in case of IMN, the surgical approach is of importance. The infrapatellar (IP)-approach is currently standard of care; however, the suprapatellar (SP)-approach has gained popularity as a promising alternative with less reported complications. Secondly, in case of a distal tibia fracture, plate fixation and IMN are both described core surgical modalities. Surgical and clinical decision making requires an understanding of clinical-, radiological- and functional outcomes as well as potential complications of both techniques. Thirdly, RM is an often-reported and possible preventable iatrogenic pitfall of IMN of tibia fractures.

The overall aim of this thesis is therefore to improve diagnostics and surgical treatment for tibia fractures, including 1) comparison of surgical approaches for IMN; 2) comparison of plate fixation vs. IMN for distal tibia fractures; and 3) evaluation and optimization of diagnostic modalities and intraoperative analytic tools to prevent RM. The thesis was structured and guided by the following parts and clinical research questions:

Part II. Chapter 1 of this thesis represents a systematic literature review comparing both the SP-approach and the IP-approach for IMN of tibia fractures. The following research questions were addressed: 1) does the SP vs. IP-approach result in less anterior knee pain?; 2) does the SP vs. IP-approach impact complication rates (patellofemoral chondropathy, infection, malalignment, non-union and secondary surgeries)?; and 3) does the SP vs. IP-approach affect physical functioning and quality of life?

Part III. In chapter 2 and 3, the focus of this thesis shifts towards evaluation of surgical treatment for distal tibia fractures by an in-depth comparison of plate fixation vs. IMN. In chapter 2, a meta-analysis of the literature comparing plate fixation (that included both open and minimal invasive plate osteosynthesis (MIPO)) and IMN. Chapter 3 elaborates on comparing MIPO and IMN. The following research questions were defined: is there a difference in plate fixation vs. IMN regarding bone healing, complications, functional and radiological results when treating distal tibia fractures?

Part IV. In this part that includes chapter 4 and chapter 5, we elaborate on rotational malalignment after IMN of tibia fractures. A prospective cohort study is presented in chapter 4, to assess the reliability of low-dose CT-assessment for early postoperative diagnosing of RM. Chapter 5 aims to clarify the incidence of RM following IMN of tibia fractures and answers the following research question: can we reliably use the contralateral uninjured limb as the reference standard to prevent RM after IMN of tibia fractures?

Part V. Chapter 6 of this thesis introduces a possible solution for RM following IMN of tibia fractures, coined the 'C-Arm Rotational View (CARV)'. The aim of this experimental cadaveric study was to develop a reliable and easy-to use fluoroscopy protocol to avoid RM by answering the following research question: how accurate is correction for RM with use of the CARV-protocol relative to rotational correction using present clinical standards? Chapter 7 closes this thesis with the presentation of the clinical protocol for a randomized controlled trial, designed to clinically validate the CARV-protocol.

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PART II

SHOULD WE GO SUPRAPATELLAR OR INFRAPATELLAR FOR INTRAMEDULLARY NAILING OF TIBIA FRACTURES?

1

DIFFERENCE IN PAIN, COMPLICATION RATES AND CLINICAL OUTCOMES AFTER SUPRAPATELLAR VS. INFRAPATELLAR NAILING FOR TIBIA FRACTURES? A SYSTEMATIC REVIEW OF 1447 PATIENTS

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ABSTRACT

Objectives

To assess the effectiveness of suprapatellar (SP)-nailing versus infrapatellar (IP)-nailing of tibia fractures in terms of anterior knee pain, complications (patellofemoral chondropathy, infection and malalignment) and physical functioning as well as quality of life. A clinical question-driven and thorough systematic review of current literature is provided.

Data source

PubMed and Embase databases were searched for studies published between 2010 and 2020 relating to SP and IP-nailing of tibia fractures. The study is performed in concordance with PRISMA-guidelines.

Study selection

Studies eligible for inclusion were randomized controlled trials, prospective and retrospective observational studies reporting on outcomes of interest.

Data extraction

Data extraction was performed independently by two assessors. Methodological quality and risk of bias was assessed according to the guidelines of the McMaster Critical Appraisal.

Data synthesis

Continuous variables are presented as means with standard deviation (SD) and dichotomous variables as frequency and percentages. The weighted mean, standardized weighted mean differences (SMD) and 95%CI were calculated. A pooled analysis could not be performed due to differences in outcome measures, time-points and heterogeneity.

Results

Fourteen studies with 1447 patients were analyzed. The weighted incidence of anterior knee pain was 29% after SP-nailing and 39% after IP-nailing, without reported significance. There was a significant lower rate of malalignment after the SP-approach (4% vs. 26%) with small absolute differences in all planes. No substantial differences were observed in patellofemoral chondropathy, infection, physical functioning and quality of life.

Conclusions

This systematic review does not reveal superiority of either technique in any of the respective outcomes of interest. Definitive choice should depend on the surgeon's experience and available resources.

Level of Evidence

Level IIa.

Key-words

intramedullary nailing, tibia fractures, suprapatellar, infrapatellar, anterior knee pain, complications, physical functioning, general quality of life.

INTRODUCTION

The number of good quality studies evaluating suprapatellar (SP)-nailing of tibia fractures is rising, and the SP-approach gained popularity in the field of Orthopaedic Trauma as an alternative surgical approach for tibia fractures. The SP-approach was first described by Tornetta et al.[1,2] and a modified technique was described by Cole in 2006.[3] Early reports suggest potentially less anterior knee pain as the main advantage, with incidences up to 71% reported after traditional infrapatellar (IP)-approach.[4-7] Secondly, straightforward positioning with less flexion of the knee may lead to better alignment control and lower rates of malalignment.[8-10] On the contrary, the SP-approach might lead to iatrogenic damage of the intra-articular structures of the knee[11-15] and potentially an increased risk for infection[16,17] as the nail will be introduced superior of the proximal patellar pole and passes the articular surface.

The potential superiority of SP-approach for intramedullary nailing (IMN) of the tibia is subject of ongoing debate.[18-22] Since its introduction, early results were considered to be promising in terms of anterior knee pain[23-26], optimal alignment control[8-10,14,24], physical functioning[23,24,26] and general quality of life.[23,26,27] However, other studies found no differences in anterior knee pain and functional outcomes if compared to IP-nailing.[10,12,28] Furthermore, data on theoretical concerns regarding patellofemoral chondropathy and infection rates after the SP versus (vs.) IP-approach is scarce. The most recent systematic review on this subject was published in 2019 in this Journal[20] and concluded that the SP-approach results in less pain and better functional outcomes if compared to IP-approach. The literature search of this systematic review was performed till august 2018, and resulted in the inclusion of five studies. However, over the last decade, several more good quality studies (both randomized controlled trials (RCT's) and cohort studies) reporting on pain, complications, physical functioning and general quality of life were published on SP vs. IP-approach for nailing of tibia fractures that improves our understanding and contribute to the ongoing debate.

Therefore, this systematic review on SP vs. IP-nailing provides an update with inclusion of these additional studies with the aim of answering the following clinical research questions: 1) does the SP vs. IP-approach result in less anterior knee pain?; 2) does the SP vs. IP-approach influence complication rates (patellofemoral chondropathy, infection, malalignment, non-union and subsequent surgeries)?; and 3) does the SP vs. IP-approach affect physical functioning and quality of life?

MATERIAL AND METHODS

This systematic review was conducted and written in concordance with the Preferred Reporting Items for Systematic Reviews (PRISMA).[29] The protocol of this systematic review is registered in the international PROSPERO-database (CRD42020181854).

Objectives and study sources

The PubMed and Embase databases were searched on 23-04-2020 for articles published between 2010 and 2020 relating to tibia fractures, IMN and nailing technique (SP and IP). A medical librarian constructed the search strategy, which is presented in supplementary material table 1.

Study selection

Studies eligible for inclusion were RCT's, prospective and retrospective observational studies reporting on: 1) tibia fractures; 2) IMN; 3) nailing technique; 4) anterior knee pain; 5) complications (patellofemoral chondropathy, infection, malalignment, non-union, subsequent surgeries and range of motion (ROM)); 6) physical functioning and quality of life, assessed with patient-reported outcome measures (PROMs); 7) minimal follow-up of 6 months; and 8) patient's age ≥18 years. Studies were excluded in case of: 1) pediatric fractures; 2) animal studies; 3) case reports, conference abstracts, systematic reviews or meta-analyses; 4) surgical treatment other than IMN; and 5) language other than English, German, Dutch, French and Spanish.

Study selection was executed in duplicate by NJB and FIJ and performed in two stages with use of Rayyan software.[30] In stage 1, title and abstract were screened. In stage 2, full text screening was performed. Disagreement was resolved by discussion according to the Cochrane Handbook for Systematic Reviews of Interventions.[29]

Data extraction

Methodological quality and risk of bias of included studies was independently assessed by NJB and IR according to the guidelines of the McMaster University Occupational Therapy Evidence-Based Practice Research Group.[31] The McMaster critical appraisal consists of eight categories including: 1) study purpose; 2) literature review; 3) study design; 4) study sample; 5) study outcome; 6) study intervention; 7) study results; and 8) conclusions and implications. Scores included: 'yes=1 point', 'no=0 points', 'not addressed (N/A)', and 'not applicable (NA)'. The total score reflects the methodological quality with a maximum score of 16 for RCT's and 14 for other designs. The definitive score may vary from 0–100%, with a higher score indicating a higher methodological quality. Scores between 75%–89% indicated good-quality studies and scores between 90%–100% indicated excellent-quality studies. Based on the quality of the studies, a best-evidence synthesis was performed. Any continued disagreements were solved during a consensus meeting with NJB, IR and FIJ.

Data extraction was performed independently by NJB and FIJ using a predefined extraction file. Patient demographics, study details, OTA classification[32], follow-up duration and outcome measures of interest were extracted from included studies.

TABLE 1. Study characteristics of included studies.

Author	Year	Country	Design	N*	Period	Group(s) (n)^	OTA-classification
Avilucea et al. [8]	2016	USA	RSC	266	2008-2014	SP (132) vs IP (134)	43-A, 43-C1, 43-C2
Cazatto et al. [23]	2018	Italy	RSC	25	2014-2016	SP (25)	42-A, 42-B, 42-C
Chan et al. [12]	2016	USA	RCT	25	2011-2012	SP (11) vs IP (14)	42-A, 42-B, 42-C
Courtney et al. [9]	2015	USA	RSC	45	2009-2013	SP (21) vs IP (24)	42-A, 42-B, 42-C
Cui et al. [41]	2019	China	RSC	50	2014-2016	SP (24) vs IP (26)	42-A, 42-B, 42-C
Fu et al. [24]	2016	China	RSC	23	2012-2013	SP (23)	41-A2, 41-A3, 42-A, 42-B, 42-C
Isaac et al. [28]	2019	USA	RSC	262	2011-2016	SP (91) vs IP (171)	NR
Jones et al. [10]	2014	UK	RSC	74	NR	SP (36) vs IP (38)	42-A, 42-B, 42-C
Leliveld et al. [42]	2012	NL	RSC	71	1998-2008	IP (72)	42-A, 42-B, 42-C
MacDonald et al. [43]	2019	UK	RCT	95	2011-2013	SP (53) vs IP (42)	NR
Marecek et al. [16]	2018	USA	RSC	282	2009-2015	SP (147) vs IP (142)	NR (open fractures)
Mitchell et al. [17]	2017	USA	RSC	135	2011-2016	SP (139)	NR (open fractures)
Ozcan et al. [27]	2020	Turkey	RSC	58	2010-2017	SP (21) vs IP (37)	NR
Sanders et al. [14]	2014	USA	PSC	36	2007-2011	SP (37)	42-A, 42-B, 42-C

*Total patients, ^total fractures
[1]Follow-up in months
SP = suprapatellar, IP = infrapatellar

Surgical technique

The SP-approach encompasses two surgical techniques described by respectively Ryan[33] and Sanders et al.[14] Ryan et al.[33] describes an incision in the midline to the superior pole of the patella. Using this incision as a mobile window a partial medial parapatellar arthrotomy is performed. The entry-point is reached by subluxating the patella laterally. The technique described by Sanders et al.[14] uses a longitudinal incision proximal of the superior pole of the patella. The entry point is reached by splitting the distal quadriceps and lifting the patella. The knee is 20°–30° flexed and potential damage to the intra-articular structures of the knee is avoided by using a sleeve.[34] The entry point at the anteromedian side of the proximal tibia is determined under fluoroscopy assistance.[34]

The traditional IP-approach encompasses three main surgical approaches distal of the inferior pole of the patella, including the medial parapatellar, lateral parapatellar and tendon-splitting approach. The definitive choice depends on the surgeon's preference and is usually not reported on in studies. The knee is positioned in 90° flexion. The longitudinal incision is made from the distal pole of the patella towards the tibia tubercle. The entry point for the intramedullary nail is equal to the SP-approach.

Definition(s) of outcome measures

Anterior knee pain is defined as discomfort located anteriorly of the affected knee which occurred after tibia nailing. Anterior knee pain is presented as a percentage of patients suffering

	Follow-up[1] (mean +- SD)	
Outcomes	**SP**	**IP**
Complications	>6	>6
Complications, physical functioning, QoL	29 (6)	NR
Pain, complications, QoL	16 (5)	
Complications, physical functioning	8 (8)	13(10)
Pain, physical functioning	24 (7)	23 (7)
Complications, physical functioning	16 (3)	NR
Pain	43 (18)	50 (19)
Pain, complications, physical functioning, QoL	23 (6)	28 (5)
Pain, complications, physical functioning	NR	84 (37)
Pain, complications, physical functioning	>6	>6
Complications	9 (9)	11 (13)
Complications	9 (13)	NR
Pain, physical functioning	16 (4)	33 (19)
Pain, complications, physical functioning, QoL	19 (9)	NR

RSC = retrospective cohort, PSC = prospective cohort, RCT = randomized controlled trial
NR = not reported
QoL = quality of life

from knee pain, or objectified with use of PROMs. The PROMs reporting on pain are listed in supplementary material.

Complications include patellofemoral chondropathy, infection, malalignment, non-union, subsequent surgeries and impaired ROM of the knee joint. Patellofemoral chondropathy is defined as iatrogenic damage to the patellofemoral joint after SP-nailing detected by per-operative arthroscopy and postoperative MRI of the knee. Infection is categorized into superficial and deep infections and encompassed septic arthritis.[35] Malalignment is divided into angular deformities in the coronal or sagittal plane and rotational malalignment. Angular deformities are defined as a deformity of ≥5° in the coronal or sagittal plane[8,36,37] and rotational malalignment is defined as a rotation of ≥10° in comparison to the unaffected side.[38,39] Non-union includes no signs of cortical healing after 6 months. Subsequent surgeries include screw(s) removal, implant removal and revision for complications. ROM is extracted as reported in included studies and includes the flexion and extension of the affected or/and unaffected knee joint.

PROMs encompassed multiple questionnaires reporting on two constructs, predefined for this study: 1) physical functioning; and 2) quality of life. The different PROMs are described in supplementary material.

Data synthesis

Continuous variables are presented as means with standard deviation (SD) and dichotomous variables as frequency and percentages. In case of more than two reported continuous variables in more than one group, the weighted mean and weighted SD was calculated. For dichotomous variables presented as frequency or percentage, the weighted mean frequency or percentage was calculated.

For comparative studies, the differences in continuous outcomes were calculated by using the inverse variance weighting method and presented as standardized weighted mean difference (SMD) and 95% confidence interval (95%CI). Differences of dichotomous variables within comparative studies were calculated by use of the X^2-test according to the Cochrane Handbook for Systematic Reviews of Interventions.[40] P-values below 0.05 were considered to indicate statistical significance.

RESULTS

Search

The literature search resulted in 201 articles of which eventually 25 full-text articles were screened. A total of 14 studies met inclusion criteria and were eligible for further analysis (figure 1).[8-10,12,14,16,17,23,24,27,28,41-43]

Study characteristics

A total of 1447 patients were included in this systematic review, including 760 fractures treated with the SP-technique and 700 fractures treated with the IP-technique (table 1). Nine studies were comparative studies[8-10,12,16,27,28,41,43] and four non-comparative studies reporting on either the SP-approach[14,17,23,24] or IP-approach.[42]

Methodological quality and risk of bias

There were two RCTs[12,43], one prospective single cohort study[14], seven retrospective comparative cohort series[8-10,16,27,28,41] and four retrospective single cohort series.[17,23,24,42] The mean overall score of RCT's was 94 (SD 0) and of other designs 75 (SD 7), respectively. The results of the methodological quality assessments are presented in supplementary material table 2.

Anterior knee pain

Eight studies reported on anterior knee pain, including six comparative studies[10,12,27,28,41,43] and two non-comparative studies (table 2).[14,42] The weighted incidence of anterior knee pain was 29% after the SP-approach (range 0–38%)[10,12,27] and 39% after the IP-approach (range 14–46%).[10,12,27,42] No substantial differences were reported on VAS, NRS and HSS pain scores & Lysholm pain scores for the SP-approach and IP-approach (table 2).

Best-evidence synthesis showed that five out of eight studies that reported on knee pain were of good[10,28,42] or excellent quality.[12,43] MacDonald et al.[43] reported a significant difference between the SP and IP-group in the AWT-K test after 12 months during fully weight-bear kneeling for 60 seconds. No other relevant differences were observed.

Complications

Two studies reported on patellofemoral chondropathy after the SP-approach.[12,14] Chan et al.[12] reported chondropathy in three out of 11 (27%) patients based on pre and post SP-nailing arthroscopy. One had preexisting chondromalacia; one sustained small iatrogenic scratches of the trochlea and one had some damage to the undersurface of the patella. All patients with post SP-nail arthroscopic changes had a full recovery at 1-year follow-up. Sanders et al.[14] reported grade II chondromalacia at the trochlea groove – probably due to pressure of insertion cannula – in two out of 37 (5%) patients based on immediate arthroscopy after SP-nail insertion. Two patients exhibiting arthroscopic changes had normal MRI's at 1-year follow-up (table 3).

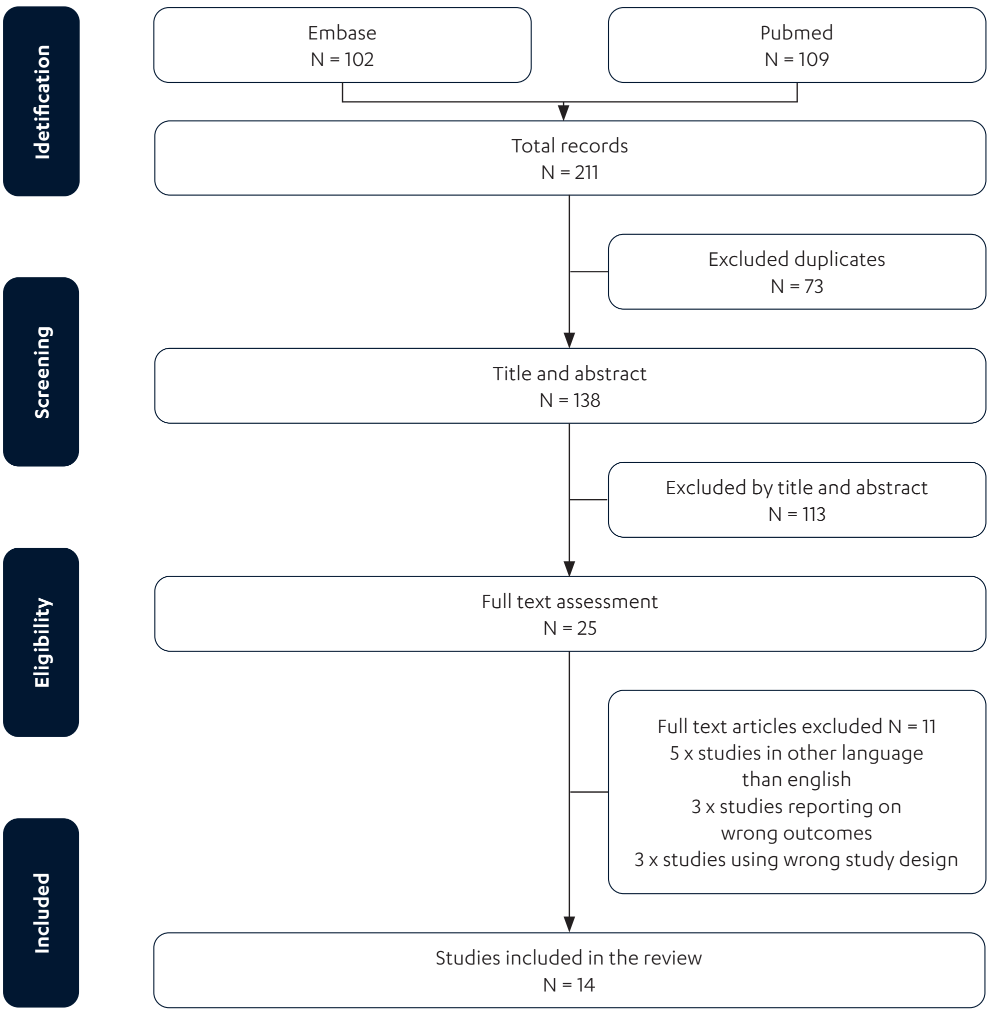

FIGURE 1. Search syntax.

Eight studies reported on infection,[12,14,16,17,23,24,42,43] including three good-quality studies[16,24,42] and two excellent-quality studies.[12,43] The weighted infection rate was 12% after the SP-approach (range 0–18%)[12,14,16,17,23,24,43] and 9% after the IP-approach (range 0–20%)[12,16,42,43], with most infections occurring after nailing of open fractures (SP 18% vs. IP 14%).[16,17] None of the patients included by Mitchell et al.[17] developed septic arthritis of the knee after the SP-approach, while Marecek et al.[16] reported 2 cases (1%) out of 147 patients after the SP-approach.

Seven studies reported on alignment,[8-10,12,14,24,42] including five good and excellent-quality studies.[8,10,12,24,42] Avilucea et al.[8] reported 15% malalignment (40 of 266 patients) in the overall study population, with a significant difference between SP-group (5 patients, 4%) and IP-group (35 patients, 26%) ($p < 0.005$). The mean difference in alignment in comparison to the unaffected side in the coronal plane after SP-nailing was 3.2° (SD 1.1°) vs. 5.7° (SD 1.8°) after IP-nailing (SMD -1.7°). The mean difference alignment in the sagittal plane was 2.9° (SD 1°) vs. 5.5° (SD 2.3°) after the IP-approach (SMD -1.5°). Rotational malalignment was not reported. Courtney et al.[9] reported significant differences in the sagittal plane (SMD 0.6°) and Jones et al.[10] reported significant differences in the coronal plane (SMD -0.6°), both in favor of the SP-approach (table 3).

TABLE 2. Anterior knee pain after suprapatellar and infrapatellar approach for nailing of tibia fractures.

		0-12 months	
Study and outcome	**Groups (n)**	**SP**	**IP**
Anterior Knee Pain			
Cases %			
Chan et al. 2016[12]	SP (11) vs IP (14)	NR	NR
Jones et al. 2014[10]	SP (36) vs IP (38)	NR	NR
Leliveld et al. 2012[42]	IP (71)	NR	NR
Ozcan et al. 2020[27]	SP (21) vs IP (37)	NR	NR
VAS			
Chan et al. 2016[12]	SP (11) vs IP (14)	NR	NR
MacDonald et al. 2019[43]	SP (53) vs IP (42)	mild 36; moderate 1; severe 0*	mild 22; moderate 1; severe 0*
Sanders et al. 2014[14]	SP (36)	NR	NR
NRS			
Isaac et al. 2019[28]	SP (91) vs IP (171)	NR	NR
AWT-K			
MacDonald et al. 2019[43]	SP (53) vs IP (42)	36/37[1]	18/23[2]
HSS pain score			
Cui et al. 2019[41]	SP (24) vs IP (26)	NR	NR
Lysholm pain score			
Chan et al. 2016[12]	SP (11) vs IP (14)	NR	NR
Sanders et al. 2014[14]	SP (36)	NR	NR

SMD = standardized weighted mean difference, 95%CI = 95% confidence interval
NR = not reported, NA = not applicable
*Mild (0-39), moderate (40-79), severe (80-100)
VAS (Visual Analogue scale, 0(no pain)– 10(worst pain)),

Three studies reported on fracture healing[10,12,14] including one good-quality study[10] and one excellent quality study.[12] The incidence of non-union based on measurements on plain radiographs ranged from 1% to 9% after SP-nailing[10,12,14] and was 0% after IP-nailing[10,12] and did not statistically differ between the SP- and IP-approach (table 3).

Eight studies reported on subsequent surgeries[10,12,14,16,23,24,42,43], of which six studies were of good to excellent-quality.[10,12,16,24,42,43] The weighted rate of subsequent surgeries was 21% after the SP-approach (range 3–48%)[10,12,14,16,23,24,43] and 26% after the IP-approach (range 0–62%).[10,12,16,42,43] None of the comparative studies[10,12,16,43] showed significant differences in rates of subsequent surgeries. A specification of subsequent surgeries is presented in supplementary material table 3.

Three studies reported on ROM (table 3)[12,14,24] including one good-quality study[24] and one excellent-quality study.[12]

Fu et al.[24] reported a significant difference between ROM preoperatively and postoperatively at last follow-up after SP-approach (26.7° vs. 117.9°). Other studies reported no substantial differences in knee ROM between the affected and unaffected side at clinical follow-up (table 3).[12,14]

> 12 months		P-value /SMD [95%CI]
SP	**IP**	
0 (0%)	2 (14%)	P 0.3
12 (33%)	16 (42%)	P 0.4
NR	27 (38%)	NA
8 (38%)	17 (46%)	P 0.6
mean 0.4	mean 1.5	NA
NR	NR	NA
0	NR	NA
kneeling 4 (4); resting 2 (3); walking 3 (3)	kneeling 4 (4); resting 2 (3); walking 3 (3)	NA
NR	NR	NA
29 (2)	28 (3)	SMD 0.4 [-0.2 – 0.9]
24	20	NA
22	NR	NA

NRS (Numeric Rating scale, 0(no pain)–10(worst pain)),
AWT-K (Aberdeen weightbearing test) 1,2 Proportion of patients who completed the AWT-K as secondary outcome measurer of the test.
HSS pain score (Hospital Special Surgery pain score, 0(complete discomfort)–100(no discomfort))
Lysholm pain score (0(heavy pain)–25(no pain))

TABLE 3. Complications after suprapatellar versus infrapatellar nailing for tibia fractures.

Complications	Study	Outcome(s) SP	IP	P-value / SMD [95%CI]
Retropatellar chondropathy				
Cases (%)				
	Chan et al. 2016[12]	3 (27%)	0 (0%)	P 0.1
	Sanders et al. 2014[14]	2 (5%)	NR	NA
Infection				
Cases (%)				
	Cazatto et al. 2018[23]	0 (0%)	NR	NA
	Chan et al. 2016[12]	0 (0%)	0 (0%)	NA
	Fu et al. 2016[24]	0 (0%)	NR	NA
	Leliveld et al. 2012[42]	NR	Total 4 (6%); deep 1 (1%); superficial 3 (4%)	NA
	MacDonald et al. 2019[43]	2 (4%)	0 (0%)	P 0.4
	Marecek et al. 2018[16]	Total 24 (16%); deep 16 (11%); superficial 8 (5%)	Total 20 (14%); deep 14 (10%); superficial 6 (4%)	P 0.6
	Mitchell et al. 2017[17]	Total 25 (18%); deep 16 (12%); superficial 9 (7%)	NR	NA
	Sanders et al. 2014[14]	2 (5%)	NR	NA
Primary angular malalignment				
Cases (%)				
	Avilucea et al. 2016[8]	5 (4%)	35 (26%)	P <0.005*
	Chan et al. 2016[12]	1 (not specified)		
	Leliveld et al. 2012[42]	NR	3 (4%)	NA
	Sanders et al. 2014[14]	1 (3%)	NR	NA
(Mal)alignment coronal plane				
Mean +- SD°				
	Avilucea et al. 2016[8]	3.2° (1.1°)	5.7° (1.8°)	SMD -1.7°* [-2° – 1.4°]
	Courtney et al. 2015[9]	2.5° (1.9°)	3.2° (2.0°)	SMD -0.4° [-0.9° – 0.2°]
	Fu et al. 2016[24]	1.6° (1°)	NR	NA
	Jones et al. 2014[10]	1° (0.8°)	2° (2.3°)	SMD -0.6°* [-1° – 0.1°]
(Mal)alignment sagittal plane				
Mean +- SD°				
	Avilucea et al. 2016[8]	2.9° (1°)	5.5° (2.3°)	SMD -1.5°* [-1.7° – 1.2°]
	Courtney et al. 2015[9]	2.9° (2.6°)	4.6° (2.7°)	SMD 0.6°* [-1.2° – 0°]
	Fu et al. 2016[24]	2.1° (1.3°)	NR	NA
	Jones et al. 2014[10]	0° (2.2°)	0° (5.2°)	SMD 0° [-0.5° – 0.5°]

TABLE 3. (continued)

Complications	Study	Outcome(s) SP	IP	P-value / SMD [95%CI]
Rotational (mal)alignment				
Cortical width(s) in mm				
	Courtney et al. 2015[9]	0.3 (0.4)	0.3 (0.3)	SMD 0.2 [-0.4 – 0.8]
Non-union				
Cases (%)				
	Chan et al. 2016[12]	1 (9%)	0 (0%)	P 0.4
	Jones et al. 2014[10]	1 (1%)	0 (0%)	P 0.5
	Sanders et al. 2014[14]	1 (3%)	NR	NA
Subsequent surgeries				
Cases (%)				
	Cazatto et al. 2018[23]	6 (24%)	NR	NA
	Chan et al. 2016[12]	1 (9%)	0 (0%)	P 0.4
	Fu et al. 2016[24]	11 (48%)	NR	NA
	Jones et al. 2014[10]	1 (3%)	0 (0%)	P 0.5
	Leliveld et al. 2012[42]	NR	44 (62%)	NA
	MacDonald et al. 2019[43]	13 (25%)	4 (10%)	P 0.1
	Marecek et al. 2018[16]	28 (19%)	30 (21%)	P 0.7
	Sanders et al. 2014[14]	7 (19%)	NR	NA
Range of Motion				
F/E (flexion/extension)				
Mean arc +- SD				
	Chan et al. 2016[12]	F/E affected side 131°/0.4° F/E unaffected side 129°/0.4°	F/E affected side 137°/0.8° F/E unaffected side 138°/0.8°	NA
	Fu et al. 2016[24]	117.9° (5.31°)	NR	NA
	Sanders et al. 2014[14]	Affected side 124.2° (SD NR) Unaffected side 127.2° (SD NR)	NR	NA

* = statistically significant, NR = not reported, NA = not applicable

Physical functioning and general quality of life

Ten studies reported on physical functioning of the knee[9,10,12,14,23,24,27,41-43], of which five studies were of good or excellent quality.[10,12,24,42,43] Only MacDonald et al.[43] determined a statistically significant difference in Lysholm scores after 12 months between the SP and IP-approach (SMD 0.6) (table 4). There were no differences observed with almost equal outcomes for the SP and IP-approach in terms of IKDC, OKS, Kujala Knee score, HSS, OMAS and Irrgang scores (table 4).

Four studies reported on general quality of life[10,12,14,23] including two studies with good or excellent methodological quality.[10,12] No relevant differences were observed in SF-36 and SF-12 scores between the SP and IP-approach.

TABLE 4. Physical functioning and quality of life after the suprapatellar approach versus the infrapatellar approach.

Study and outcome	Group(s)	0-12 months SP	0-12 months IP	> 12 months SP	> 12 months IP	P-value / SMD [95%CI]
Physical functioning						
IKDC						
Cazatto et al. 2018[23]	SP (25)	NR	NR	77 (6)	NR	NA
OKS						
Cazatto et al. 2018[23]	SP (25)	NR	NR	42 (6)	NR	NA
Courtney et al. 2015[9]	SP (21) vs IP (24)	36 (12)	40 (9)	NR	NR	SMD -0.4 [-0.9 – 0.2]
Kujala score						
Cazatto et al. 2018[23]	SP (25)	NR	NR	85 (4)	NR	NA
Jones et al. 2014[10]	SP (36) vs IP (38)	NR	NR	68 (23)	75 (19)	SMD 0.3 [-0.8 – 0.1]
Leliveld et al. 2012[42]	IP (71)	NR	NR	NR	83(16)	NA
Ozcan et al. 2020[27]	SP (21) vs IP (37)	NR	NR	80 (9)	83 (8)	SMD -0.4 [-0.9 – 0.2]
Lysholm score						
Chan et al. 2016[12]	SP (11) vs IP (14)	NR	NR	98	86	NA
Cazatto et al. 2018[23]	SP (25)	NR	NR	99 (7)	NR	NA
MacDonald et al. 2019[43]	SP (53) vs IP (42)	93 (11)	84 (20)	NR	NR	SMD 0.6* [-0.2 – 1]
Ozcan et al. 2020[27]	SP (21) vs IP (37)	NR	NR	85 (8)	83 (8)	SMD 0.3 [-0.3 – 0.8]
Sanders et al. 2014[14]	SP (36)	NR	NR	Excellent 14; good 8; fair 7; poor 8;[+] mean 82.2	NR	NA
HSS						
Cui et al. 2019[41]	SP (24) vs IP (26)	NR	NR	97 (5)	97 (6)	SMD 0 [-0.5 – 0.5]
Fu et al. 2016[24]	SP (23)	NR	NR	92 (4)	NR	NA
OMAS						
Fu et al. 2016[24]	SP (23)	NR	NR	94 (4)	NR	NA
Irrgang						
MacDonald et al. 2019[43]	SP (53) vs IP (42)	Total 73 (8); symptoms 32 (4); function 41 (6)	Total 68 (13); symptoms 30 (7); function 38 (7)	NR	NR	SMD 0.5 [0.1 – 0.9]
QoL						
SF-36						
Cazatto et al. 2018[23]	SP (25)	NR	NR	79 (6)	NR	NA
Chan et al. 2016[12]	SP (11) vs IP (14)	NR	NR	PCS 46 MCS 47	PCS 38 MCS 47	NA

TABLE 4. (continued)

Study and outcome	Group(s)	0-12 months SP	0-12 months IP	> 12 months SP	> 12 months IP	P-value / SMD [95%CI]
Sanders et al. 2014[14]	SP (36)	NR	NR	PCS 42 MCS 48	NR	NA
SF-12						
Jones et al. 2014[10]	SP (36) vs IP (38)	NR	NE	PCS 40 (13) MCS 49 (12)	PCS 43 (12) MCS 51 (9)	SMD -0.2 [-0.7 – 0.2] SMD 0.2 [-0.3 – 0.6]

SP = suprapatellar, IP = infrapatellar
NR = not reported, NA = not applicable
+Excellent 95–100, good 84–94, fair 65–83, poor <65.
IKDC (international knee documentation committee, scale 0–100, 100=no pain, no limitations in sports and daily activities),
OKS (Oxford knee score, scale 0–48, 48=no restrictions in terms of pain and function)
Kujala Knee score (scale 0–100, 100=excellent physical functioning)
Lysholm Knee score (scale 0–100, 100=no disability)
HSS (hospital special surgery score, scale 0–100, 100=no discomfort)
OMAS (Olerud-Molander Ankle score, scale 0–100, 100=no symptoms and normal physical functioning)
Irrgang (scale 0–80, 80=no symptoms and excellent function)
SF-36 (short-form 36), SF-12 (short-form 12), physical component scale (PCS), mental component scale (MCS)

DISCUSSION

The rationale for choosing a suprapatellar (SP) instead of infrapatellar (IP)-approach for IMN of tibial fractures is potentially less anterior knee pain. Clinical concerns of the SP-approach, however, may include iatrogenic damage to articular cartilage[11,13-15] and infection.[16,17] This is the first systematic review in which inclusion criteria were not limited by study design and that provides a comprehensive overview of current literature published over the last decade regarding complete spectrum of outcomes measures following SP or IP-nailing for tibia fractures.

This systematic review found no substantial decrease in the incidence of anterior knee pain with regard to the SP vs. IP-approach (29% vs. 39%). In terms of complications, only the rate of malalignment was significantly different (5% vs. 26%) with small absolute differences in the coronal and sagittal plane in favor of the SP-approach. No differences were observed in risk on patellofemoral chondropathy, infection, non-union and subsequent surgeries. Self-reported physical functioning and quality of life were comparable in both groups.

Does the SP vs. IP-technique results in less anterior knee pain?

The weighted incidence of anterior knee pain among studies after SP-nailing was 29% vs. 39% after IP-nailing. There was a higher rate of anterior knee pain after IP-nailing, however, the studies that compared outcomes after SP to IP-nailing[10,12,27] reported no significant differences. The incidence of anterior knee pain ranged from 0% to 38% after SP-nailing and 14% to 46% after IP-nailing.[10,12,27,42] The wide range might be explained by the multifactorial nature of anterior knee pain. Etiologies may include iatrogenic damage to the infrapatellar nerve[42], to Hoffa's fat pad[44], periosteal irritation of the entry point, patellar tendinopathy or nail prominence.[45] Moreover, knee pain persists after nail removal in up to 60% of the cases.[5,42,46] It might be noteworthy that the IP-approach is used for implant removal, even after initial SP-nailing. Further research is needed to clarify the etiology of anterior knee pain and elucidate pain perception.

Does the SP vs. IP-technique influence complication rates?

Another concern that may arise with SP-nailing is potential iatrogenic damage to intra-articular structures and cartilage as the nail passes the knee-joint.[2,3,34] Several cadaveric studies reported conflicting results.[13,15,47] Only Sanders et al.[14] and Chan et al.[12] reported on clinical evaluation of patellofemoral chondropathy after SP-nailing with an average follow-up of 16 and 19 months, respectively . They found no cartilage damage, gouges, or pressure changes from the SP-nail insertion cannula in the patellofemoral joint based on per-operative arthroscopy and MRI after 12-months. However, good quality long-term data is limited which might improve our understanding regarding this clinical concern.

The infection rates after the SP-approach and IP-approach were comparable and showed no relevant differences (12% vs. 9%). Most infections occurred after nailing of open fractures with comparable rates following SP or IP-nailing, indicating that open fractures are more decisive for infection instead of the nailing technique. The chance on developing knee sepsis after SP-nailing of open fractures was considerably low in comparison to IP-nailing.[16,17]

There is low evidence that SP-nailing leads to lower rates of malalignment. The current review showed significant differences in malalignment in the sagittal and coronal plane in favor of the SP-technique.[8-10] SP-nailing might be beneficial in facilitating reduction and obtaining accurate alignment in more proximal- and distal tibia fractures[14] as showed by Avilucea et al.[8] who assessed distal tibia fractures. Fu et al.[24] included proximal as well as distal tibia fractures, but all were treated with SP-nailing and no comparison to IP-nailing was made. It is noteworthy, however, that the absolute differences were small (reported SMD's ranged from -1.7° to 0.6°) and therefore clinically irrelevant.[8-10] Moreover, radiographs were used to measure alignment while CT-scans are superior in detecting malalignment.[13,38,39] The included studies in this review did not report on rotational malalignment based on CT-measurements. Low dose-CT based data on rotational malalignment after SP-nailing is lacking and might be of added value to the ongoing debate on SP or IP-nailing of tibial fractures as incidences up to 35% were reported after the IP-approach.[38,39]

Finally, this review illustrates that the SP-approach does not substantially decrease the complication rate in comparison to the traditional IP-approach in terms of non-union, subsequent surgeries and impaired ROM.

Does the SP vs. IP-approach affect physical functioning and quality of life?

There is little evidence whether the SP-approach leads to superior physical functioning and quality of life in comparison with the IP-approach. MacDonald et al.[43] reported a significant difference between SP and IP-nailing by using Lysholm scores after 12 months with an excellent score for the SP-group and good score for the IP-group (93 vs. 84). Overall, the recovery of physical functioning and quality of life following SP and IP-nailing seems good. Although, nine different outcome measures were used making is difficult to compare study results.

Strengths and limitations

This systematic review contains strengths and limitations. This is the first review that encompassed the complete spectrum of outcome measures, including pain, complications, physical functioning and general quality of life after SP and IP-nailing. Secondly, search criteria were not limited by study design (e.g. cohort study, RCT's), which provides a complete overview of all outcomes of interest published over the last decade. Thirdly, this study provides a clinically question-driven overview about the ongoing debate on the nailing technique of tibial fractures.

Due to heterogeneity, inconsistent time-points and a varying range of methodological quality, a pooled-analysis was not possible. However, results presented in this study were not subjected to any form of heterogeneity, and therefore validated and statistically reliable.

CONCLUSION

The suprapatellar and infrapatellar approach are both good techniques in tibial nailing with comparable results in terms of anterior knee pain, complication rates (including patellofemoral chondropathy, infection, malalignment), physical functioning and general quality of life. The definitive choice should depend on the surgeon's experience and available resources.

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PART III

OR, SHOULD WE PLATE THEM ALL? BUT WHAT ABOUT WOUND PROBLEMS?

2

PLATE VS. NAIL FOR EXTRA-ARTICULAR DISTAL TIBIA FRACTURES: HOW SHOULD WE PERSONALIZE SURGICAL TREATMENT? A META-ANALYSIS OF 1332 PATIENTS

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Injury. 2020.

ABSTRACT

Background

Treatment for distal diaphyseal or metaphyseal tibia fractures is challenging and the optimal surgical strategy remains a matter of debate. The purpose of this study was to compare plate fixation with nailing in terms of operation time, non-union, time-to-union, mal-union, infection, subsequent re-interventions and functional outcomes (quality of life scores, knee- and ankle scores).

Methods

A search was performed in PubMed/Embase/CINAHL/CENTRAL for all study designs comparing plate fixation with intramedullary nailing (IMN). Data were pooled using RevMan and presented as odds ratios (OR), risk difference (RD), weighted mean difference (WMD) or weighted standardized mean difference (WSMD) with a 95% confidence interval (95%CI). All analyses were stratified for study design.

Results

A total of 15 studies with 1332 patients were analysed, including ten RCTs (n=873) and five observational studies (n=459). IMN leads to a shorter time-to-union (WMD: 0.4 months, 95%CI 0.1 – 0.7), shorter time-to-full-weightbearing (WMD: 0.6 months, 95%CI 0.4 – 0.8) and shorter operation duration (WMD: 15.5 minutes, 95%CI 9.3 – 21.7). Plating leads to a lower risk for mal-union (RD: -10%, OR: 0.4, 95%CI 0.3 – 0.6), but higher risk for infection (RD: 8%, OR: 2.4, 95%CI 1.5 – 3.8). No differences were detected with regard to non-union (RD: 1%, OR: 0.7, 95%CI 0.3 – 1.7), subsequent re-interventions (RD: 4%, OR: 1.3, 95%CI 0.8 – 1.9) and functional outcomes (WSMD: -0.4, 95%CI -0.9 – 0.1). The effect estimates of RCTs and observational studies were equal for all outcomes except for time to union and mal-union.

Conclusion

Satisfactory results can be obtained with both plate fixation and nailing for distal extra-articular tibia fractures. However, nailing is associated with higher rates of mal-union and anterior knee pain while plate fixation results in an increased risk of infection. This study provides a guideline towards a personalized approach and facilitates shared decision-making in surgical treatment of distal extra-articular tibia fractures. The definitive treatment should be case-based and aligned to patient-specific needs in order to minimize the risk of complications.

Key-words

distal tibia fractures, personalized approach, plate fixation, intramedullary nailing, meta-analysis, mal-union, infection, shared decision-making.

INTRODUCTION

Surgical treatment of distal diaphyseal or metaphyseal tibia fractures is challenging and the optimal surgical strategy remains a matter of debate. Two core surgical modalities have been described including intramedullary nailing (IMN) and plate fixation.

In the search of defining which treatment is better, the main focus of past meta-analyses has been on pooling data from randomized controlled trials (RCTs). Recently, evidence is growing that the study population and effect estimates of observational studies tend to be quite similar to that of RCTs. Adding observational data in a meta-analysis increases sample size and might improve generalizability of results[1-6] as RCTs frequently have stringent inclusion criteria resulting in a selective study population.[7-9]

The aim of this meta-analysis is to provide a complete and comprehensive overview on the optimal surgical treatment of distal tibia fractures by 1) analysing a broad pallet of outcome measures and 2) including both observational studies and RCTs comparing plate fixation to IMN. Outcomes of interest include operation time, non-union, time to union, mal-union, infection, subsequent re-interventions and functional outcomes (quality of life scores and knee- and ankle scores). Sub-group analysis is performed to compare outcomes derived from RCTs as well as observational studies.

MATERIAL AND METHODS

This systematic review and meta-analysis is performed and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist.[10,11] Ethical approval was not required for current study.

Search strategy and selection criteria

In order to answer the research question, a search in PubMed/Medline, Embase, CENTRAL and CINAHL was performed for studies comparing plate fixation (either open (ORIF) or minimal invasive plate osteosynthesis (MIPO)) and IMN for meta- or distal diaphyseal extra-articular fractures of the tibia (for search syntax see supplementary material table 1). A junior doctor (NJB) and a consultant trauma surgeon as well as epidemiologist (BvdW) independently reviewed the title and abstract for suitability and both observational studies and RCTs were included. After screening for title and abstract, NJB and BvdW independently performed the full-text screening. Inclusion criteria of the study were meta- or distal diaphyseal extra-articular fractures of the tibia (type 42-A, 42-B, 42-C and 43-A), comparison of plate (either ORIF or MIPO) to IMN fixation, minimal follow-up of 6 months and reporting on relevant outcomes including operation time, non-union, time to union, mal-union, infection, subsequent re-interventions and functional outcomes (quality of life scores and knee- and ankle scores). Studies reporting on intra-articular fractures (43.B1- 43.C3), secondary or tertiary referrals for non-union or mal-union revision surgery, pathologic fractures or contra-indication for IMN (total knee arthroplasty) were excluded. Studies with languages other than English were also excluded. In case of disagreement on eligibility, a consensus meeting was organized with an independent third reviewer and senior consultant trauma surgeon (FJPB). References of all included studies were screened to identify studies not found in the original literature search.

Data extraction

Data extraction was performed by the two same independent reviewers (NJB, BvdW) with use of a predefined data extraction file. Conflicting data entries were resolved by discussion, and continued disagreement was resolved with the senior author. The following characteristics were extracted from the included studies: authors, year of study, year of publication, country, study design, study period, study subject and included patients. Furthermore, data on patient- and fracture characteristics such as gender, age, injured side, OTA/AO-classification[12], open/closed fractures according to the Gustilo classification[13] were collected.

Quality assessment

The methodological quality of each included study was independently assessed by NJB and BvdW according to the Methodological Index for Non-Randomized Studies (MINORS).[14] The MINORS is considered to be a reliable and validated instrument for assessment of methodological quality of observational cohort studies.[14] RCTs were appraised using the same tool as well in order to measure quality on the same scale as observational studies (supplementary material table 2).[1-6] The MINORS contains 12 items, in which each item can be scored with ''reported and adequate'' = 2 points, ''reported but inadequate'' = 1 point and ''not reported = 0 points''. A total of 0 points indicated poor methodological quality and 24 indicated excellent methodological quality. Disagreements on this topic were resolved by organizing a consensus meeting.

Study outcomes

Outcome measures included: operation time, non-union, time to union, mal-union, infection, subsequent re-interventions and functional outcomes (quality of life scores, knee- and ankle scores). Non-union is defined as a lack of tricortical continuity after 6 months of fracture fixation. Mal-union was an angulation more than 5º in any plane or as a rotational deformity of >10º[15]. Infection included both superficial and deep surgical wound infections[16] and subsequent re-interventions included all reoperations during follow-up. General quality of life scores included the EuroQol-5D (EQ-5D), Disability Rating Index (DRI) and ShortForm-36 (SF-36). Functional ankle scores encompassed the Olerud Molander Ankle score (OMAS), Lowa Ankle score, American Orthopaedic Foot and Ankle Society score (AOFAS), Mazur Ankle score and Foot Ankle Index. Functional knee scores included Lysholm Knee Scoring Scale, Knee Injury and Osteoarthritis Outcome Score (KOOS), Oxford Knee Score (OKS), Kujala score, International Knee Documentation Committee (IKDC), Hospital for Special Knee Surgery score (HSS) and Irrgang Knee Outcome Survey Activities of Daily Living Scale. The quality-of-life scores and functional scores were pooled for each field (general quality of life, ankle function and knee function) separately. In case different scoring instruments were used within one field, than the scores were standardised for pooled analysis.

Statistical analysis

Statistics were performed using RevMan (version 5.3.5). Continuous variables are presented as means with standard deviation (SD) and dichotomous variables as counts and percentages. We used a method described in the Cochrane Handbook for Systematic Reviews of Interventions[17] to convert the reported range or interquartile range (IQR) to SD. The Mantel-Haenszel method was used to pool effects of plating or IMN on dichotomous outcomes and results were reported as weighted odds ratio (weighted OR), risk difference (weighted RD) with corresponding 95% confidence interval (95%CI). In case of zero-cell counts in one of the two treatment groups, 0.5 was added to all cells of contingency table of treatment and the outcome of those studies in which this occurred. The influence of plating or IMN on continues outcomes were pooled using the inverse variance weighting method. These outcomes were presented as weighted mean difference (WMD) or weighted standardised mean difference (WSMD) with 95%CI. Heterogeneity between studies was assessed for all reported outcomes by the I^2 statistic for heterogeneity. All analyses were stratified according to study design, i.e., RCTs and observational studies. Differences in effect estimates between RCTs and observational studies were assessed using the χ^2-test as described in the Cochrane Handbook for Systematic Reviews of Interventions. A p-value below 0.05 was considered statistically significant. Publication bias was assessed by visual inspection of funnel plots. All funnel plots can be found in the supplementary material figures A-J.

Sensitivity analysis

A sensitivity analysis was performed to determine the influence of type of approach (MIPO or ORIF) and AO-classification (type 42 and type 43) on all outcomes of interests. Additionally, a sensitivity analysis on high quality studies was performed. High quality studies were defined as studies with a MINORS score of 16 or higher (range 0 – 24).[1,2]

RESULTS

Search

The search and literature selection are presented in figure 1. A total of 34 articles were screened for full text. Finally, 15 studies were found to be eligible for inclusion (figure 1).[18-32] The reported outcomes of Vallier et al. 2011 and Vallier et al. 2012 were based on the same cohort and therefore merged.

Baseline study characteristics

A total of 1332 patients were included in this meta-analysis: 634 patients (48%) were treated with plate fixation and 698 (52%) patients with an IMN. The mean follow up ranged from 11 to 33 months. The mean weighted age of the total study population was 39 years (range 31 – 52 years) with 866 (66%) being males. The patient- and fracture characteristics per included study are presented in table 1&2.

Ten of the included studies were RCTs[19-26,29,31] including a total of 873 patients. The weighted mean age was 42 years (range 35 – 45 years) with 603 (69%) males. A total of 432 (49%) patients

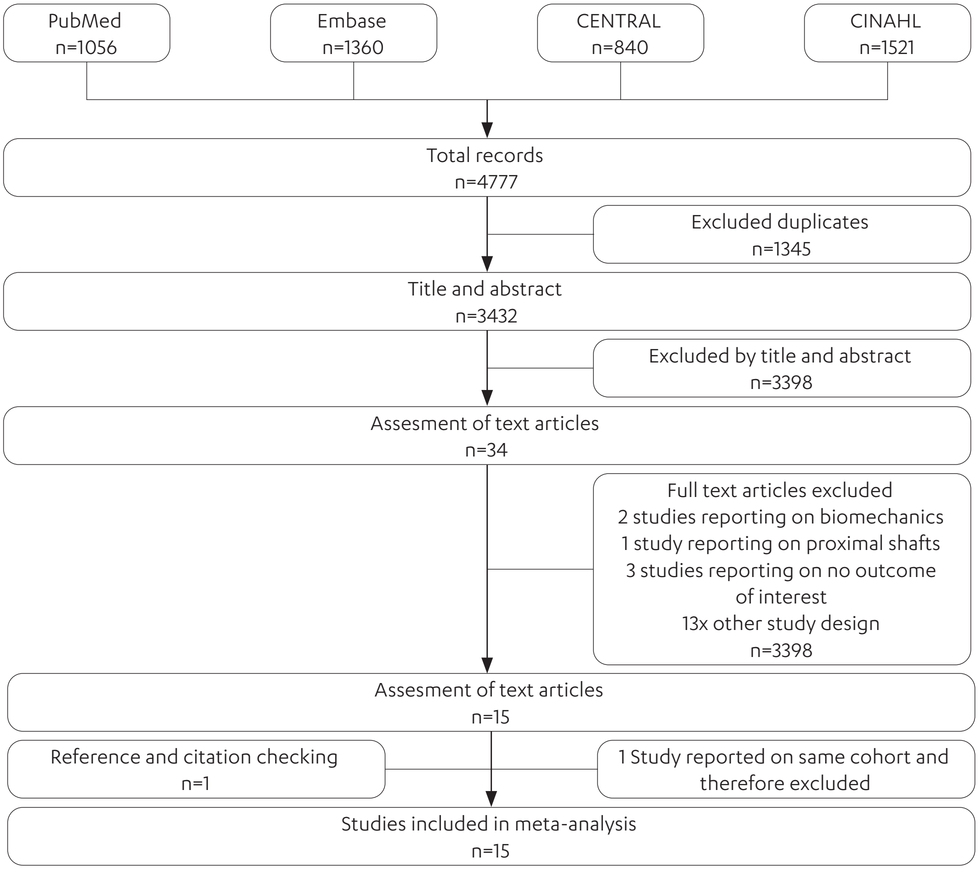

FIGURE 1. Search.

were treated with plate fixation with a weighted mean age of 42 years (range 33 – 46 years). IMN was performed in 441 (51%) patients. The weighted mean age in this group was 42 years (range 34 – 50 years). Nine studies reported on surgical approach for both treatment groups. Two studies used an open anteromedial approach for plate fixation[23,29] and seven studies used the medial minimal invasive approach.[19-22,24,26,31] For IMN, all studies used an infrapatellar approach.[19-24,26,29,31]

Five retrospective observational studies were included with a total of 459 patients.[18,27,28,30,32] The overall weighted mean age was 41 years (range 31 – 52 years) with 263 (57%) being male. A total of 202 (44%) patients were treated with plate fixation and 257 (56%) patients with an IMN. In the plate group, patients had a weighted mean age of 40 (range 31 – 55). This was 42 years (range 31 – 48 years) in the IMN group. Bisaccia et al. used an open anteromedial approach for plate fixation and Vaienti et al. used a medial minimal invasive approach.[18,28] Three studies reported on surgical approach for IMN and all described an infrapatellar approach.[18,28,32]

TABLE 1. Study characteristics of included studies.

Author	Year	Country	Design	Study period	Total N	Plate	IMN	Follow up (mean +- SD) months
Im-Gun et al.	2005	S-Korea	RCT	1998-2001	64	30	34	>6
Yang et al.	2006	Taiwan	Cohort	1999-2003	27	14	13	33 (11)
Vallier et al.	2008	USA	Cohort	1999-2003	113	37	76	>6
Guo et al.	2010	China	RCT	2005-2008	85	41	44	>6
Vallier et al.	2011	USA	RCT	2002-2008	104	48	56	>6
Mauffrey et al.	2012	USA	RCT	2008-2009	24	12	12	>6
Seyhan et al.	2013	Turkey	Cohort	2004-2009	61	36	25	21 (12)
Li et al.	2014	Japan	RCT	2002-2012	92	46	46	14.9 (1.1)
Polat et al.	2015	Turkey	RCT	2009-2012	25	15	10	23.1 (9.4)
Fang et al.	2016	China	RCT	2005-2013	56	28	28	28.9 (10)
Wani et al.	2017	India	RCT	2014-2016	60	30	30	11.5 (4.5)
Doalagupu et al.	2017	India	RCT	2014-2015	42	21	21	>6
Costa et al.	2017	UK	RCT	2013-2016	321	160	161	>6
Bisaccia et al.	2018	Italy	Cohort	2009-2015	75	34	41	>6
Vaienti et al.	2018	Italy	Cohort	2008-2017	183	81	102	>6
Total					1332	634	698	

Quality assessment

The MINORS scores are shown in table 3. The overall mean MINORS score for RCTs was 19 (range 15 to 22 points). The overall mean MINORS score for observational studies was 15 with a range from 13 to 16 points.

Outcome measure – operation time (minutes)

Eight studies reported on operation time (minutes), including two observational studies and six RCTs[18,20-24,26,28] with an overall weighted mean operation time of 97 minutes (range 51 – 114 minutes) in the plate group and 77 minutes (range 57 – 88 minutes) in the IMN group. The operation time was significantly longer for plate fixation in comparison to IMN (WMD 15.5 minutes, 95%CI 9.3 – 21.7, I^2 90%). There were no significant differences observed in effect estimates between observational studies (WMD 23.8 minutes, 95%CI 4.2 – 43.4, I^2 98%) and RCTs (WMD 11.8 minutes, 95%CI 6.3 – 17.4, I^2 57%) (test for subgroup difference p=0.3) (figure 2).

Outcome measure – non-union

Seven studies reported on non-union, including two observational studies and five RCTs.[21,23-25,27,29,30] There was no difference in risk for non-union between the two treatment groups (weighted OR 0.7, 95%CI 0.3 – 1.7, I^2 0%) and the effect estimates of observational studies (weighted OR 0.7, 95%CI 0.1 – 3.5, I^2 0%) and RCTs (weighted OR 0.8, 95%CI 0.3 – 2.1, I^2 0%) were equal (test for subgroup difference p=0.9) (figure 3). Non-union occurred in 4.3% of patients treated with plate fixation and 5.9% after IMN (weighted RD 1%, 95%CI -5% – 2%, I^2 0%).

TABLE 2. Patient and fracture characteristics of included studies.

		Mean age		Open fractures	
Author	**Design**	**Plate**	**Nail**	**Plate**	**Nail**
Im-Gun et al.	RCT	40(10.8)	42(11.5)	5	8
Yang et al.	Cohort	54.6(18)	48.2(19)	NR	
Vallier et al.	Cohort	39.8(12.5)	38.4(15.3)	12	22
Guo et al.	RCT	44.4(11.5)	44.2(10.1)	NR	
Vallier et al.	RCT	38.3(13)		19	21
Mauffrey et al.	RCT	33(14.1)	50(15.6)	NR	
Seyhan et al.	Cohort	39.7(12.7)	40.3(14.2)	5	7
Li et al.	RCT	43(15)	44(15)	14	17
Polat et al.	RCT	36.4(10.7)	34(9.7)	NR	
Fang et al.	RCT	38.6(7.5)	35(9.2)	6	4
Wani et al.	RCT	38.4(8.7)	36.4(9.7)	NR	
Doalagupu et al.	RCT	39.1(10.1)	35.2(9.2)	NR	
Costa et al.	RCT	45.8(16.3)	44.3(16.3)	NR	
Bisaccia et al.	Cohort	31(13.3)		NR	
Vaienti et al.	Cohort	42.6(13)	47.2(14.8)	19	34

*NR= not reported

Outcome measure – time to union

Eleven studies – four observational studies and seven RCTs – reported on time to union[18,20-24,26,28,30-32] with an overall weighted mean time to union of 4.5 months (range 3.5 – 6.4 months) in the plate group and 4.2 months (range 3.6 – 5.2 months) in the IMN group. The time to union in the IMN group was significantly shorter compared to the plating group (WMD 0.4 months, 95%CI 0.1 – 0.7, I^2 88%). Furthermore, the effect estimates of observational studies (WMD 0.9 months, 95%CI 0.6 – 1.2, I^2 34%) and RCTs (WMD 0.2 months, 95%CI -0.1 – 0.5, I^2 59%) were significantly different (test of subgroup difference, p=<0.005) (figure 4).

Outcome measure – mal-union

Thirteen studies reported on mal-union (five observational studies and eight RCTs).[18,20,21,23-32] There was a significant lower risk of mal-union for plate fixation (weighted OR 0.4, 95%CI 0.3 – 0.6, I^2 0%) with a significant difference in effect estimates of observational studies (weighted OR 0.2, 95%CI 0.1 – 0.4, I^2 0%) and RCTs (weighted OR 0.6, 95%CI 0.3 – 1,0 I^2 0%)(test for subgroup difference p=0.03)(figure 5). Mal-union occurred in 7% of the patients with plate fixation and 18% after IMN (weighted RD -11%, 95%CI -15% – -7%, I^2 0%).

Outcome measure – infection

Fourteen studies reported on infection, including four observational studies[18,27,28,30] and ten RCTs.[19-26,29,31] There was a significantly higher risk for infection among patients treated with plate fixation (weighted OR 2.4, 95%CI 1.5 – 3.8, I^2 3%). There was no difference in effect estimates of

<table>
<tr><th colspan="2">AO 42</th><th colspan="2">AO 43</th><th colspan="2">Fibula fractures</th></tr>
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C1-5</td><td>A1-15 | A2-9 | A3-5
C1-5</td><td>15</td><td>22</td></tr>
<tr><td>NR</td><td></td><td>A 13</td><td>A 14</td><td>NR</td><td></td></tr>
<tr><td>A 17 | B 5 | C 15</td><td>A 38 | B 19 | C 19</td><td>NR</td><td></td><td>100</td><td></td></tr>
<tr><td></td><td></td><td>A1-13 | A2-12 | A3-16</td><td>A1-13 | A2-16 | A3-15</td><td>NR</td><td></td></tr>
<tr><td>A 31 | B 10 | C 7</td><td>A 32 | B 17 | C 7</td><td>NR</td><td></td><td>NR</td><td></td></tr>
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<tr><td>A 28 | B 4 | C 4</td><td>A 19 | B 3 | C 3</td><td>NR</td><td></td><td>34</td><td>25</td></tr>
<tr><td>A 37 | B 7 | C 2</td><td>A 33 | B 8 | C 5</td><td>NR</td><td></td><td>NR</td><td></td></tr>
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<tr><td>A1-20 | A2-2 | A3-8</td><td>A1-18 | A2-9 | A3-3</td><td>NR</td><td></td><td>8</td><td>6</td></tr>
<tr><td>NR</td><td></td><td>A1-10 | A2-9 | A3-2</td><td>A1-11 | A2-6 | A3-4</td><td>NR</td><td></td></tr>
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</table>

TABLE 3. MINORS-Criteria.

MINORS-criteria	RCTs	Im-Gun et al.	Guo et al.	Vallier et al.	Mauffrey et al.	Li et al.	Polat et al.	Fang et al	Wani et al.	Doalagupu et al.	Costa et al.	Observational studies	Yang et al.	Vallier et al.	Seyhan et al.	Bisaccia et al.	Vaienti et al.
Clearly stated aim		2	1	2	2	2	2	2	2	0	1		2	2	2	2	2
Inclusion of consecutive patients		2	2	2	2	2	2	2	2	2	2		0	2	2	1	2
Prospective data collection		2	2	2	2	2	2	2	2	2	2		0	0	0	0	0
Appropriate endpoints		1	2	2	2	2	2	2	2	2	2		2	2	2	0	2
Unbiased assessment endpoints		2	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Appropriate follow-up (>1year)		2	2	2	1	2	2	2	1	1	2		2	2	2	2	1
Loss-to-follow up <5%		1	1	2	1	1	2	0	0	0	1		0	0	0	0	0
Prospective calculation study size		0	0	2	0	0	0	0	0	0	2		0	0	0	0	0
Adequate control group		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
Baseline equivalence of groups		2	2	2	2	2	2	2	2	2	2		2	2	2	2	2
Adequate statistical analysis		2	2	2	2	2	2	2	2	2	2		2	2	2	2	2
Total		**20**	**18**	**22**	**18**	**19**	**20**	**18**	**17**	**15**	**20**		**14**	**16**	**16**	**13**	**15**

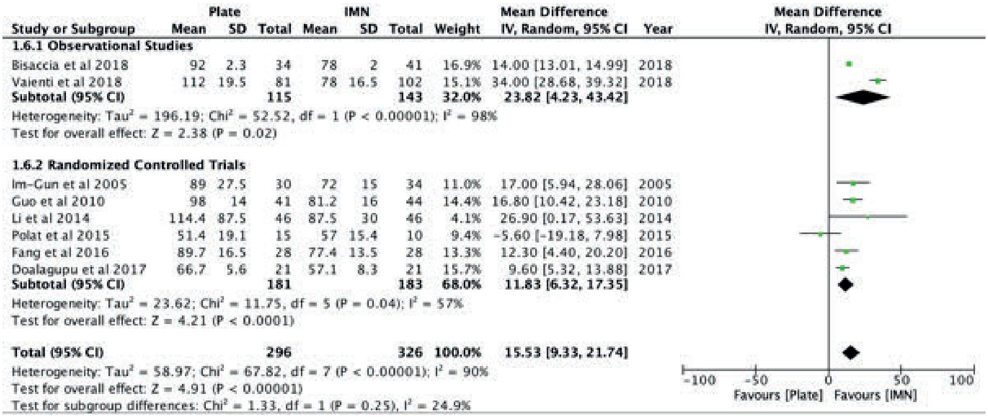

FIGURE 2. Forest plot for operation time in minutes.

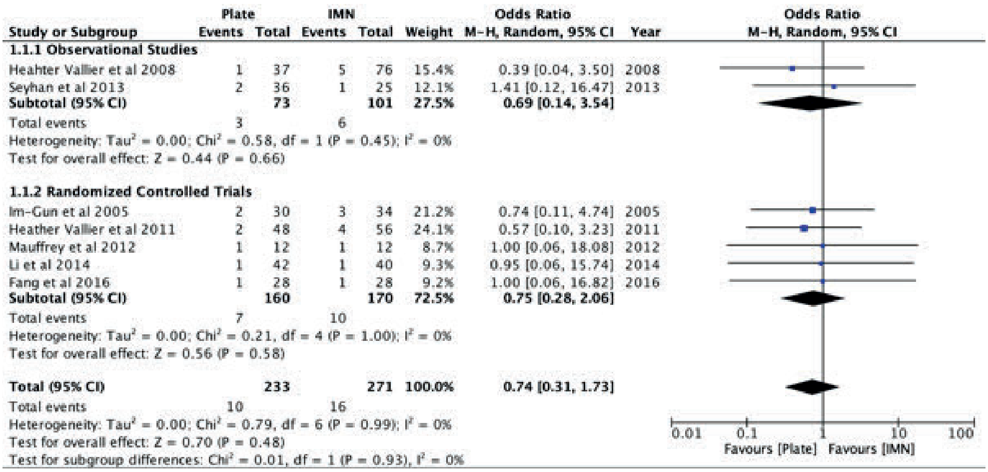

FIGURE 3. Forest plot for non-union after plate- or IMN fixation.

observational studies (weighted OR 3.3, 95%CI 0.7 – 16.4, I^2 26%) and RCTs (weighted OR 2.3, 95%CI 1.4 – 3.7 I^2 2%) (test for subgroup difference p=0.7) (figure 6). Infection occurred in 14% of patients surgically treated with plate fixation and 5% after IMN (weighted RD 8%, 95%CI 4% – 12%, I^2 48%).

Seven studies divided infection into superficial and deep infection[19-21,23-25,27] and five studies reported on deep infections only.[18,26,28-30] The prevalence of deep infections was 3.7% after plate fixation and 1.3% after IMN. The prevalence of superficial infections was 10.2% after plate fixation and 4.1% after IMN.

Outcome measure – subsequent re-interventions

Subsequent re-interventions were reported in fourteen studies, including five observational studies and nine RCTs.[18,19,21-32] There was no difference in risk of subsequent re-interventions between plate

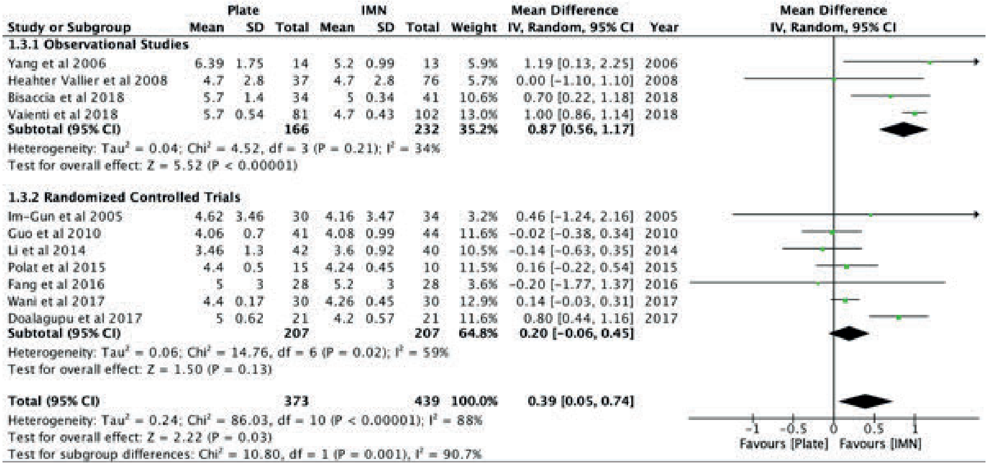

FIGURE 4. Forest plot for time to union (months) for plate fixation versus IMN.

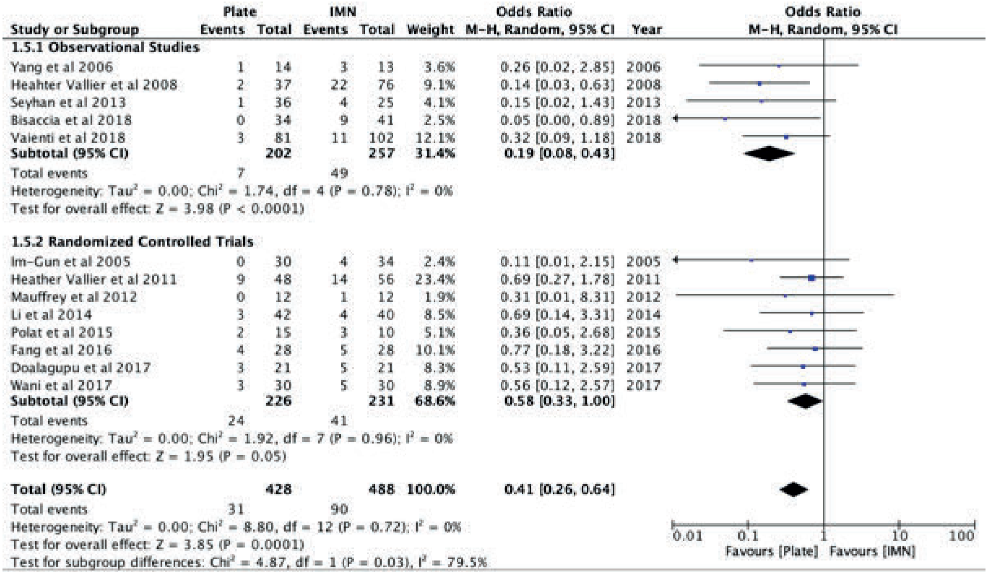

FIGURE 5. Forest plot for risk for mal-union after plate- or nail fixation.

fixation and IMN (weighted OR 1.3, 95%CI 0.8 – 1.9, I^2 45%). The effect estimates of observational studies (weighted OR 1.4, 95%CI 0.4 – 4.3, I^2 73%) were equal to the effect estimates of the RCTs (weighted OR 1.3, 95%CI 0.9 – 1.9, I^2 5%) (test for subgroup difference p=1.0) (figure 7). A subsequent re-intervention was required in 38% of the plate fixation group and 33% in the IMN fixation group (weighted RD 4%, 95%CI -3% – 11%, I^2 59%). The majority of subsequent re-interventions included implant removal (72% versus 75%) and revisions (6% versus 12%). The indications for re-intervention are listed in table 4 and supplementary material table 3.

Outcome measure – time to weightbearing (months)

Six studies evaluated time to weightbearing, including three observational studies and three RCTs.[18,20,26-28,31] The weighted mean time to full weightbearing for patients treated with plate fixation was 2.9 months (range 1.4 – 3.5 months) and 2.3 months (range 1.2 – 3.0 months) for patients treated with an IMN. Time to weightbearing was significantly shorter for patients treated with an IMN (WMD 0.6 months, 95%CI 0.4 – 0.8, I^2 72%) with no difference between observational studies (WMD 0.7 months, 95%CI 0.5 – 0.9, I^2 45%) and RCTs (WMD 0.4 months, 95%CI 0.0 – 0.9, I^2 84%) (test for subgroup difference p=0.3)(figure 8).

Outcome measure – anterior knee pain

Seven studies reported on anterior knee pain – three observational studies and four RCTs.[18,20,21,24,26,28,32] Anterior knee pain was reported in 20% of the patients treated with IMN (weighted RD -25%, 95%CI -41% – -9%, I^2 89%) and 0% after plate fixation.

Outcome measure – general quality of life scores (6 to 12 months postoperatively)

Only three studies – one observational study and two RCTs – reported on general quality of life and all used the Disability Rating Index.[19,25,28] The overall weighted mean score for plate fixation was 30 points (range 21.5 – 39.8) and also 30 points (range 29.8 – 31.2) for IMN (0 points indicating no disability and 100 points indicating complete disability). This outcome did not differ significantly between both treatment groups (WMD -1.9, 95%CI -13.3 – 9.6, I^2 84%) (figure 9). Subgroup analysis stratified for study design was not possible as only one observational study was available for comparison to RCTs.

Outcome measure – functional ankle scores (6 to 12 months postoperatively)

Eight studies reported on functional ankle scores – two observational studies and six RCTs – using the OMAS, AOFAS score and Foot Ankle Index.[19,21,22,25,26,28,31,32] There was no significant difference in functional ankle scores between both treatment groups (WSMD -0.4, 95%CI -0.9 – 0.1, I^2 88%) and there was no difference observed between observational studies (WSMD -1, 95%CI -2.2 – 0.1, I^2 87%) and RCTs (WSMD -0.2, 95%CI -0.3 – 0.0, I^2 0%) (test for subgroup difference: p=0.1) (figure 10).

Outcome measure – functional knee scores (6 to 12 months postoperatively)

None of the included studies reported on functional knee scores.

Sensitivity analysis

The weighted effects of both treatment groups on different outcomes stratified by quality of studies, AO-classification and surgical approach for plate fixation (ORIF and MIPO) did not significantly differ between the main analysis and the stratified analyses (table 5).

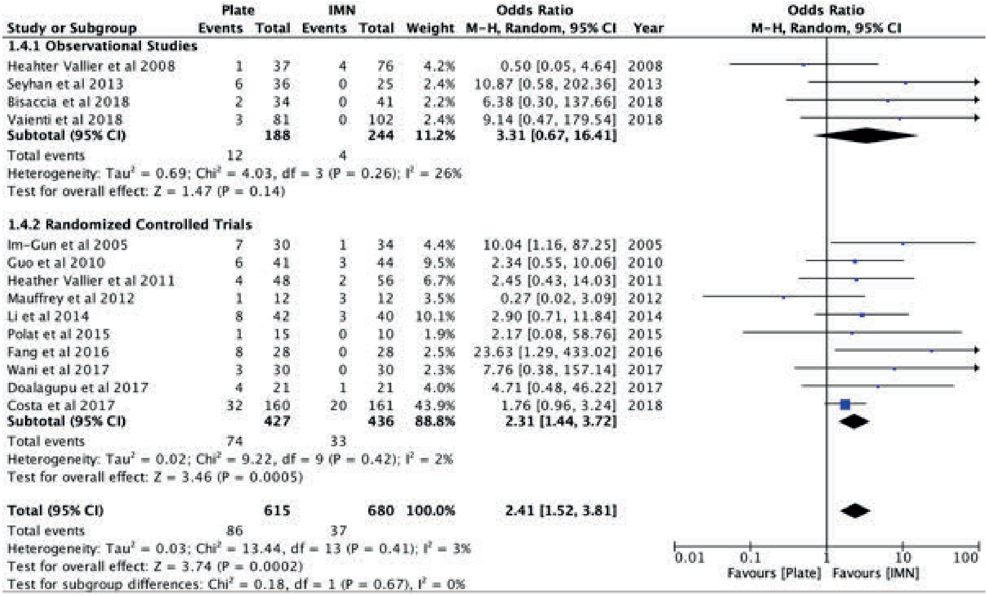

FIGURE 6. Forest plot for risk of infection.

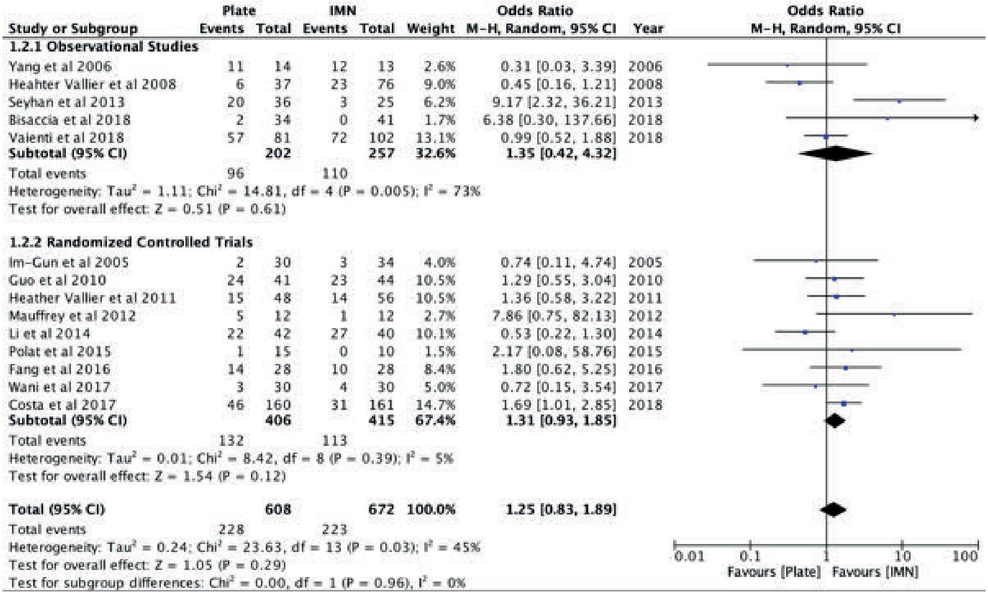

FIGURE 7. Forest plot for subsequent re-interventions.

TABLE 4. Specification of subsequent re-interventions after plate- or IMN fixation.

Study	Revision		Infection		Implant removal		Not specified	
	Plate	Nail	Plate	Nail	Plate	Nail	Plate	Nail
Observational Studies								
Yang et al.	NR		NR		11	12	NR	
Vallier et al.	2	13	1	4	3	6	NR	
Seyhan et al.	3	1	4	0	13	2	NR	
Bisaccia et al.	NR		2	0	NR		NR	
Vaienti et al.	NR		NR		57	72	NR	
Total (plate, n=96) (nail, n=110)	**5 (5%)**	**14 (12%)**	**7(7%)**	**4(4%)**	**84(88%)**	**92(84%)**	**NR**	
RCTs								
Im-Gun et al.	1	3	1	0	NR		NR	
Guo et al.	NR		NR		24	23	NR	
Vallier et al.	3	5	4	2	4	6	4	1
Mauffrey et al.	NR		1	0	4	1	NR	
Li et al.	NR	1	NR	1	22	25	NR	
Polat et al.	NR		1	0	NR		NR	
Fang et al.	NR	1	1	NR	13	9	NR	
Wani et al.	NR		NR		NR		3	4
Costa et al.	5	2	5	1	14	11	22	17
Total (plate, n=132) (nail, n=113)	**9(7%)**	**12(11%)**	**13(10%)**	**4(4%)**	**81(61%)**	**75(66%)**	**29(22%)**	**22(19%)**
Total Observational & RCTs (plate, n=228) (nail, n=223)	**14(6%)**	**26(12%)**	**20(9%)**	**8(3%)**	**165(72%)**	**167(75%)**	**29(13%)**	**22(10%)**

DISCUSSION

The aim of this meta-analysis was to determine the optimal surgical strategy for distal tibia fractures by comparing plate fixation to IMN using both observational studies and RCTs and analysing a broad pallet of outcome measures. Time to union, time to full weightbearing and operation duration was significantly shorter and the infection rate lower among patients treated with IMN. On the contrary, there was a lower risk for mal-union and anterior knee pain for patients treated with plate fixation compared to IMN. No significant differences were detected with regard to non-union, of patient reported quality of life scores, ankle scores and subsequent re-interventions. Subsequent re-interventions were mostly performed for implant removal in both groups. Although the effect estimates of observational studies and RCTs pointed in the same direction for all outcomes, the magnitude was different for the outcomes time to union and mal-union. Sensitivity analysis for

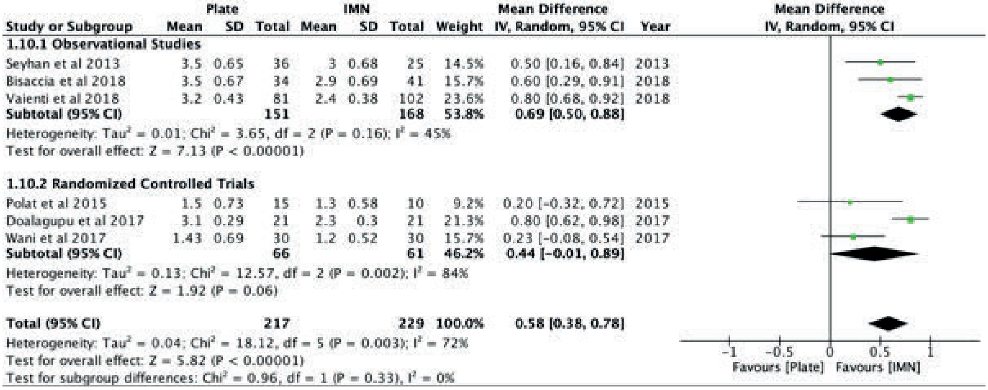

FIGURE 8. Forest plot for time to full weightbearing in months.

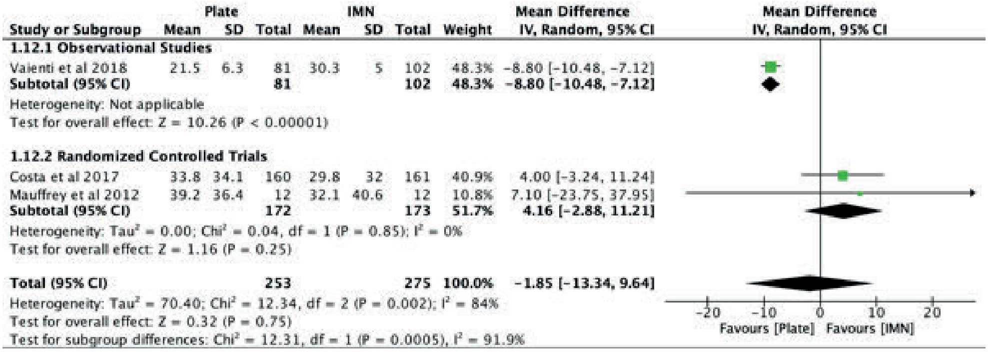

FIGURE 9. Quality of Life Scores.

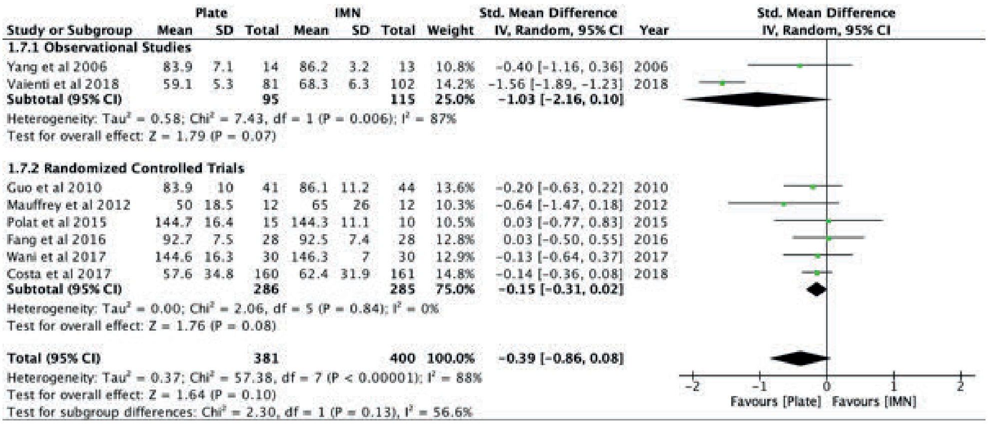

FIGURE 10. Functional Ankle Scores.

high/low quality studies, AO-classification and surgical approach for plate fixation (MIPO or ORIF) showed no relevant differences in all outcomes.

Comparison to previous literature

The present meta-analysis differs from previous meta-analyses in several ways. Firstly, we included observational studies in the pooled analysis and stratified for design. Adding observational studies increases sample size and the ability to detect small differences not previously detectable in previous meta-analyses (e.g., time to union and operation duration).[1-4] Stratification creates the possibility to study differences in effect estimates between observational studies and RCTs which, as shown in the present and previous meta-analyses comparing surgical treatments[1-4], tend to be quite similar. Secondly, the purpose of this study was to provide a comprehensive overview and comparison on plate fixation versus IMN of distal tibia fractures by analysing a broad pallet of outcomes measures ranging from operation time to complications and functional outcomes. Thirdly, there are several questionnaires for measuring, for example, ankle function. As such, different questionnaires measure functionality on a different scale. For pooled analysis, one can either pool the scores of the same questionnaire together or standardize the scores of questionnaires in the same field (for example general quality of life or ankle function). The previous meta-analyses used the first method and the present study the latter. Both have their advantages and disadvantages with regard to statistical power and precision. As both methods have led to the same conclusion, it is fairly certain that there truly is no difference in functional outcomes between the two treatments.

TABLE 5. Sensitivity analysis for quality of studies, AO-classification and surgical approach for plate fixation.

	Non-union	Time to union (months)	Mal-union	Infection	Subsequent re- interventions	Functional ankle scores
All studies	OR 0.7 [0.3 – 1.7]	MD 0.4 [0.1 – 0.7]	OR 0.4 [0.3 – 0.6]	OR 2.4 [1.5 – 3.8]	OR 1.3 [0.8 – 1.9]	SMD -0.4 [-0.9 – 0.1]
High quality studies	OR 0.7 [0.3 – 1.7]	MD 0.1 [0.0 – 0.2]	OR 0.5 [0.3 – 0.8]	OR 2.3 [1.3 – 4.1]	OR 1.3 [0.8 – 2.2]	SMD -0.2 [-0.3 – 0.1]
Low quality studies	*	MD 1.0 [0.8 – 1.1]	OR 0.3 [0.1 – 0.7]	OR 6.1 [1.3 – 29.1]	OR 1.0 [0.4 – 2.5]	SMD -1.0 [-2.2 – 0.1]
AO type 42	OR 0.7 [0.3 – 2.0]	MD 0.1 [0.0 – 0.3]	OR 0.5 [0.3 – 0.8]	OR 3.1 [1.3 – 7.0]	OR 1.2 [0.6 – 2.6]	SMD -0.0 [-0.4 – 0.3]
AO type 43	OR 0.7 [0.1 – 4.7]	MD 0.7 [0.3 – 1.0]	OR 0.3 [0.1 – 0.6]	OR 4.4 [1.5 – 12.6]	OR 1.1 [0.7 – 1.7]	SMD -0.7 [-1.7 – 0.3]
MIPO	OR 1.1 [0.2 – 5.3]	MD 0.3 [-0.1 – 0.7]	OR 0.5 [0.3 – 0.9]	OR 2.3 [1.4 – 3.6]	OR 1.4 [0.8 – 2.2]	SMD -0.4 [-1.1 – 0.3]
ORIF plate	OR 0.6 [0.2 – 1.7]	MD 0.7 [0.3 – 1.1]	OR 0.3 [0.1 – 0.7]	OR 1.8 [0.5 – 6.8]	OR 1.0 [0.5 – 2.5]	SMD -0.5 [-1.1 – 0.1]

OR – odds ratio
MD – mean difference
SMD – standardised mean difference
[...] – 95% confidence interval
* Less than 2 studies available for pooled analysis

This meta-analysis found a significant higher rate of mal-union and anterior knee pain after IMN and a significant higher rate of infection after plate fixation for distal tibia fractures. Furthermore, significant differences were found in terms of time to union, time to full weightbearing and operation duration in favour of IMN. Previous studies found almost equal outcomes with regard to IMN leading to a higher rate of mal-union and anterior knee pain and that plate fixation is leading to a significant higher rate of wound complications.[9,33-36] Two studies came to different conclusions about the mal-union rate, which was not significantly different in both groups.[7,37] It is noteworthy, however, that Wang et al. merged the rates of mal-union and non-union and that Goh et al. included a selected group consisting of closed or Gustilo I open extra-articular (43-A) fractures. As this meta-analysis included the entire spectrum of distal tibia fractures and pooled data on mal-union and non-union separately, a reliable comparison with these studies was not possible.

Interpretation of results

There were several pronounced differences between plate fixation and IMN.

There was a fairly large difference in risk of infection between the two treatment groups: in the plate fixation group, 14% developed an infection versus 5% after IMN. It should however be acknowledged that this encompasses both superficial and deep infections combined. From a clinical point of view, deep infections are the most relevant of the two as they frequently lead to re-intervention and/or prolonged durations of antibiotic treatment. Deep infections were rare and occurred in 3.7% of patients treated with plate fixation versus 1.3% for nailing.

Minimally invasive techniques tend to have less risk for infection. Interestingly, this concept did not apply in the sensitivity analysis on type of approach. The risk for infection was equally high in the comparison of MIPO to IMN and ORIF to IMN. This may be subscribed to the slender soft tissue envelope on the medial aspect of the tibia. Introducing the plate in a MIPO fashion on the medial side of the tibia as well as its prominence might compromise the insertion wounds. Therefore, the outcomes might be not as promising as compared to MIPO techniques of the femur as there is sufficient more soft tissue coverage. However, the current study was designed to compare plate fixation (ORIF and MIPO) versus IMN. Direct comparison of MIPO to ORIF is outside of the scope of this study. This study also sought to establish the relation between open fracture type and infection through a sensitivity analysis. However, as the included studies had a mix of both open and closed fractures, this sensitivity analysis was not possible.

Mal-union occurred in 18% of the patients after IMN and 7% after plate fixation. The difference could be subscribed to the difficulty in establishing correct alignment during IMN due to soft tissue injury, swelling, often closed reduction without direct vision of the fracture, displacement of multiple fracture fragments and difficulties in interpretation of fluoroscopy images as opposed to direct reduction techniques when applying a plate.

IMN shortens the time to union and full weightbearing with approximately two weeks. It should be acknowledged that assessment of time to union and time to full weightbearing depends on a few factors. Firstly, measuring radiographic union on plain radiographs is challenging and susceptible to high degrees of inter-observer variability.[38] Secondly, full weightbearing is a subjective outcome which ideally should be measured on day-to-day basis. The ability to fully weight bear was determined at fixed intervals due to the nature of the studies included in this meta-analysis. Therefore, it is difficult to ascertain how this two-week difference translates into a clinical setting and how patients experience this contrast.

It is widely considered that IMN leads to high rates of anterior knee pain. Anterior knee pain was found up to 20% of cases and is the leading cause for implant removal. If anterior knee pain would have been a temporary issue, treatable with nail removal, then this high percentage need not be a decisive factor in the choice between plate fixation or IMN. However, previous studies have shown that patients still suffer from ongoing knee pain even after nail removal up to 58%.[39-41] As the incidence of anterior knee pain is equally high for both an infra-patellar and supra-patellar approach, this problem applies to both nailing techniques.[42-46]

The operation duration was significantly shorter for IMN in comparison to plating (77 minutes versus 97 minutes). However, the absolute difference is small and the analysis showed high degrees of heterogeneity. The source of the heterogeneity is most likely caused by the fact that operation duration is very dependent on the surgeon's experience and hospital logistics.

All in all, the choice of implant based on the results found in this meta-analysis, is not straight forward and should be made on a case-by-case basis. Patients who have a high risk for infection (due to high age, co-morbidities, smoking, severe soft tissue injury) should preferably be treated with a nail. Young, active and healthy patients who are less prone for infection, might benefit more from plate fixation as is minimalizes risk of knee pain and mal-union.

Finally, the effect estimates of observational studies and RCTs did not differ for the majority of outcomes. However, for time to union and the occurrence of mal-union, observational studies tend to overestimate the difference.

Implications for further research

In current literature there is sufficient evidence that both plate fixation and IMN are suitable for treatment of distal tibia fractures. Future studies should focus more on aligning the optimal treatment with the potential for infection, mal-union and anterior knee pain as important parameters. Data on treatment through a case-by-case basis is limited and subsequent research should therefore center surgical decision making on individual factors such as comorbidities, physical state and social factors. Good quality prospective data for such risk stratification to personalize trauma care is currently scarce, but in other fields of medicine Machine Learning algorithms have shown promising results to facilitate shared decision making by data driven risk stratification.

Limitations

This study has several limitations that should be addressed. The first restriction is the limited value of the pooled analysis of time to union (I^2=88%), operation duration (I^2=90%), anterior knee pain (I^2=89%), general quality of life scores (I^2=84%) and functional ankle scores (I^2=88%) caused by heterogeneity. These results should be interpreted with caution. Secondly, baseline characteristics seemed similar across treatment groups. This however does not fully rule out selection bias. There might still be unmeasured characteristics which might be different across treatment groups causing residual selection bias among the observational studies. Thirdly, the majority of the included studies used the terms "superficial and deep" to indicate infection rates, which is clearly subjective to heterogeneity. Since the establishment of the consensus definition of fracture-related infection, introduced by Metsemakers et al. in 2018, more uniformity might be expected in future studies with regard to this diagnosis.[47]

CONCLUSION

Plate fixation and IMN are both viable options with implant specific merits and demerits. IMN leads to a higher rate of mal-union and anterior knee pain and plate fixation is associated with an increased risk of infection. This study provides a guideline towards personalized treatment and facilitates shared decision-making in future treatment of distal tibia fractures. The surgical treatment should be based on a case-by-case basis and dictated by whether surgeons want to prevent mal-union and anterior knee pain versus the potential of infection. Logically, the definitive interpretation and how to integrate this evidence into clinical practice is up to the treating surgeon/reader.

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3

MIPO VS. NAIL FOR EXTRA-ARTICULAR DISTAL TIBIA FRACTURES AND THE EFFICACY OF INTRA-OPERATIVE ALIGNMENT CONTROL: A RETROSPECTIVE COHORT OF 135 PATIENTS

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ABSTRACT

Introduction

Definitive treatment of distal extra-articular fractures of the tibia is challenging and both minimal invasive plate osteosynthesis (MIPO) and intramedullary nailing (IMN) are considered to be feasible surgical modalities with their own implant-specific merits and demerits. This retrospective study was designed to compare MIPO versus IMN in terms of fracture healing, complications, functional and radiological outcomes and to assess the efficacy of intra-operative alignment control in order to reduce the rate of malalignment after definitive fixation of distal extra-articular fractures of the tibia.

Materials and Methods

All consecutive adult patients with extra-articular distal meta- or diaphyseal tibia fractures that were treated between January 2012 and September 2019 either with MIPO or IMN were included. Outcome measures included fracture healing, complications (infection, malalignment, subsequent surgeries), functional and radiological outcomes. Intra-operative alignment control encompassed bilateral draping of the lower extremities.

Results

A total of 135 patients were included out of which 72 patients (53%) were treated with MIPO and 63 patients (47%) underwent IMN. There was a significantly higher incidence of non-union for fractures treated with IMN (13 (22%) vs. 4 (6%), p=0.04). There was no significant difference between both groups in terms of rotational malalignment (3% vs. 10%) and angular malalignment (4% vs. 5%). A significantly higher rate of infection was found after MIPO after correction of significant differences in baseline characteristics. No differences were found in subsequent surgeries or functional outcomes.

Conclusion

Both MIPO and IMN are reliable surgical techniques. IMN is associated with higher rates of non-union whereas MIPO results in a higher risk for infection. The incidence of malalignment was surprisingly low endorsing the utility of the intra-operative alignment control.

Key-words

Distal tibia fractures, MIPO, IMN, postoperative outcomes, bilateral draping, malalignment.

INTRODUCTION

Definitive treatment of extra-articular distal tibia fractures remains challenging. The poor soft tissue envelope, the proximity to the ankle joint and the underlying trauma mechanisms ensure that these fractures are prone to complications.[1-4] For this reason, minimally invasive techniques, such as minimally invasive plating (MIPO) and intramedullary nailing (IMN), are the preferred treatment options, both with their own merits and demerits. Studies have shown that MIPO might be associated with higher rates of infection and implant related complications.[5,6] IMN, however, is associated with anterior knee pain[7-10] and with a tendency towards malalignment.[2,3,11-15] In addition, distal extra-articular fractures of the tibia are more susceptible for malalignment due to difficulties in acquiring and maintaining correct alignment of the distal bony segment[3,15]

The authors feel that both surgical modalities encompass implant-specific pros and cons and that the choice is often based on the surgeon's personal preference and hospital logistics. This clinical decision making should be, however, based on an understanding of implant-specific outcomes, complications as well as functional and radiological results. Therefore, this retrospective study was designed to provide a comprehensive comparison between MIPO and IMN for definitive treatment of distal extra-articular tibia fractures by answering the following primary research question: is there a difference in MIPO and IMN with regard to bone healing, complications, functional and radiological results when treating distal tibia fractures?

The second aim of this study was to assess the efficacy of bilateral draping of the extremities to reduce the rate of malalignment. Bilateral draping of both extremities is routinely used for MIPO and IMN in the study hospital. It is hypothesized that the risk of malalignment can be reduced if these measures are taken routinely.

MATERIAL AND METHODS

This study was written according to the STROBE-statement.[16] The Ethical board of Nord-West and Central Switzerland (EKNZ) waived approval for this retrospective study in accordance to the Declaration of Helsinki (2020-00694).

Study design, setting and participants

For this retrospective study all consecutive adult patients with open or closed extra-articular distal meta- or diaphyseal tibia fractures (AO 42-A, 42-B, 42-C, 43-A) that were treated in a Level-1 Trauma Center in Switzerland between January 2012 and September 2019 either with MIPO or IMN were included. All medical records and imaging were extracted from the hospital's electronic patient records. Patients with intra-articular fractures (43.B1- 43.C3), secondary or tertiary referrals for revision surgery, pathologic fractures or contra-indication for nailing (total knee arthroplasty) were excluded. Further, we excluded patients that were transferred to other hospitals for the postoperative care and those for whom follow-up information was incomplete (<6 months).

Surgical technique and intra-operative alignment control

All operations were performed by board certified surgeons. Patients with closed fractures received a single dose of 2000mg cefazoline 30 min prior to surgery as an antibiotic prophylaxis. Patients with open fractures all received 2200mg amoxicillin with clavunate in the emergency department. Grade 1 and 2 fractures according to the Gustilo classification[17] were given amoxicillin with clavunate for 24 hours, grade 3 fractures were treated for 72 hours. In case of a reported allergic reaction to the above-mentioned antibiotics, clindamycin was given according to our local guidelines.

Patients were positioned in supine position on a radiolucent table with both extremities draped free as part of the intra-operative alignment control protocol. Patients underwent MIPO as described by Babst et al. in 2007.[18] IMN (Expert Tibia Nail, ETN) was performed with the knee flexed 90° for an infra-patellar approach. After determination of the nail-entry point, the intra-medullary canal was reamed 1.0-1.5mm larger than the diameter of the chosen nail and the nail was inserted. The alignment and rotation were checked by comparing the operated leg to the healthy contra-lateral side as a reference by bending both knees 90° for rotational control prior to locking. The nail was then locked both distally and proximally with 2 standard locking screws proximally (in the static and dynamic hole). The decision to use either two (parallel) or three interlocking screws distally was left to the discretion of the treating surgeon.

On the first day after surgery standard AP and lateral radiographs were obtained. The MIPO-group was instructed to limit weight bearing to a maximum of 15kg for 6 weeks. Within the nail group, weight bearing as tolerated was allowed immediately. Radiographic- and functional routine follow-up was performed 6 weeks, 12 weeks, 6 months and 1 year after trauma.

Data measurement

Fracture classification were performed according to the AO/OTA-classification[19] by a junior surgical resident (NJB) and two independent board certified surgeons (NvV, BvdW). Discrepancies were resolved during a consensus meeting with a third independent board-certified trauma surgeon (FB). The proximal- and distal segments of the tibia were defined using the Müller square[20] in which the square had an equal length as the largest horizontal distance between the lateral and medial border of the tibia plateau and tibia plafond. The bony-area outside both squares was defined as true-shaft. The length of the shaft was measured and divided by three. Each fracture located outside the square but within the range of the distal 1/3 was defined as distal diaphyseal fracture and included. Fractures located in the distal square were defined as metaphyseal fractures and were included. Fractures located in the proximal segment were excluded.

Fracture consolidation was assessed on x-rays obtained during follow up. Radiologic union was defined as tricortical continuity in the AP- and lateral plane[21] Delayed-union was defined as union between six to twelve months.[22] Non-union was defined as failure of fracture consolidation after twelve months.[22]

Complications included malalignment, infection and subsequent re-interventions. Rotational malalignment was defined as an iatrogenic rotational deformity of ≥10° based on clinical- and low-dose CT measurements.[23,24] The involved surgeon and a 2nd uninvolved consultant clinically assessed the rotational alignment the day after fracture fixation as part of the standardized hospital protocol. In case of uncertainty concerning the alignment, a low-dose CT was performed. The clinical assessment of the alignment was presumed adequate if there was no low-dose CT indicated. CT-measurements were performed according to the reliable measurement technique described by Bleeker et al.[23]. Angular malalignment was defined as angular deformities of 5º or more in the coronal or sagittal plane.[3,15,25] Surgical site infections were divided in superficial surgical site infections (SSSI) and deep surgical site infections (DSSI) according the definition of the Centre of Disease Control (CDC).[26] Subsequent re-interventions include nail dynamization, screw removal/change/addition for issues such as irritation or to gain extra stability, total implant removal, revision for non-union, delayed-union, malalignment, infection and fasciotomy wound management.

The functional outcome measures include the time to full weight bearing, occurrence of anterior knee pain, time to return to sports and time to return to work. We defined full weight bearing as pain free walking without aids and return to sports as the ability to perform a preferred sport activity.

Statistical methods

Statistical software package SPSS 23.0 was used to analyze the results. Descriptive statistics were provided of all baseline characteristics and study endpoints. Continuous variables were described as means with standard deviation (SD) or medians with interquartile range (IQR) depending on distribution. Differences were analyzed using the independent T-test for normally distributed and Mann-Whitney-U-test for non-normal data. For categorical variables, the counts and percentages were calculated. Differences were analyzed using the Fischer exact test. Cox regression was used for time-dependent outcomes of interest and logistic regression for non-time dependent binominal outcomes to investigate the difference between MIPO and IMN. All analyses were also corrected for AO/OTA and Gustilo classification in a multivariate model to yield both the uncorrected and corrected hazard ratio's (HR) and odds ratio's (OR) with corresponding 95% confidence interval (95%CI). Analyses were limited to outcomes which occurred more than ten times during follow-up ensuring sufficient number of events for the degrees of freedom in de Cox or logistic model. A p-value under 0.05 was considered statistically significant.

RESULTS

Participants

Between 2012 and 2019, 325 patients with a tibia fracture were treated in our Level-1 Trauma Center. Based on the above-mentioned exclusion criteria, 135 patients could ultimately be included in this study. Seventy-two patients (53%) were treated with MIPO and 63 patients (47%) underwent IMN. In case of IMN, 55% (35 out of 63 patients) underwent tripe locking distally. The mean follow-up was 14 months (range 5 – 44 months). Baseline characteristics and surgical data are described in table 1 and 2. There were several significant differences between the two treatment groups. Significantly more high-energy traumas ($p=0.02$) and more open fractures ($p<0.001$) were treated with IMN.

The incidence of 42-A1 and 43-A1 type fractures was higher in the MIPO-group whilst 42-A2 and 42-A3 fractures were more prevalent in patients treated with IMN (p=0.03) (table 1).

Fracture healing

Median time to union was significantly shorter in the MIPO-group with 5.7 months (IQR 3.5) vs. 6.6 months (IQR 6.9) for the IMN-group (p=0.03) (table 3). Furthermore, there was a significantly

TABLE 1. Baseline characteristics*.

	MIPO-Group (n=72)	**IMN-Group (n=63)**	**P-value**
Age (Mean ± SD)	47.8 (16.7)	44.7 (17.2)	0.28
Gender			
Male	46 (64%)	44 (67%)	0.72
Female	26 (37%)	19 (30%)	
High Energy Trauma	33 (46%)	42 (67%)	0.02
Polytrauma	10 (14%)	17 (27%)	0.08
Fracture side			
Right	40 (56%)	29 (46%)	0.30
Left	32 (44%)	34 (54%)	
Open or Closed			<0.001
Closed	65 (80%)	35 (56%)	
Gustilo 1	4 (6%)	6 (10%)	
Gustilo 2	1 (1%)	12 (19%)	
Gustilo 3	2 (3%)	10 (16%)	
AO/OTA			0.03
42-A1	24 (33%)	16 (25%)	
42-A2	6 (8%)	11 (18%)	
42-A3	1 (1%)	10 (16%)	
42-B2	19 (26%)	14 (22%)	
42-B3	7 (10%)	4 (6%)	
42-C1	0 (0%)	1 (2%)	
42-C2	2 (3%)	2 (3%)	
42-C3	0 (0%)	1 (2%)	
43-A1	8 (11%)	1 (2%)	
43-A2	1 (1%)	1 (2%)	
43-A3	4 (5%)	2 (3%)	
External Fixator (Fix. Ex.)	16 (22%)	20 (32%)	0.25
Fibula fracture	66 (92%)	55 (87%)	0.57
Follow-up duration (months) (median and range)	14.4 (5.4 – 33.3)	13.7 (5.4 – 43.5)	0.94

*All outcomes were presented as n (%) unless stated otherwise.

higher incidence of non-union for fractures treated with an IMN (13 (22%) vs. 4 (6%), p=0.04). Other parameters with regard to bone healing are described in table 3.

TABLE 2. Surgical data.

	MIPO-Group (n=72)	**IMN-Group (n=63)**	**P-value**
Time to surgery (days) (median and range)	0 (0 – 11)	0 (0 – 15)	0.88
Time to Fix. Ex removal (days) (median and range)	5 (3 – 11)	5 (2 – 15)	0.61
Operation duration (hours) (median and range)	2.3 (1.0 – 6.5)	3.0 (1.5 – 6.6)	0.06
Blood loss (cc) (median and range)	50 (5 – 500)	100 (10 – 500)	0.10
Compartment syndrome	7 (10%)	11 (17%)	0.21

TABLE 3. Postoperative outcomes.

	MIPO-Group (n=72)	**IMN-Group (n=63)**	**P-value**
Time to Union (months) (median and IQR)	5.7 (3.5)	6.6 (6.9)	0.03
Union			0.04
1-3 months (union)	11 (15%)	3 (5%)	
4-6 months (union)	30 (43%)	22 (38%)	
7-9 months (delayed-union)	15 (21%)	11 (19%)	
10-12 months (delayed-union)	10 (14%)	9 (16%)	
>12 months (non-union)	4 (6%)	13 (22%)	
Infection Tibia*	9 (13%)	4 (6%)	0.21
– SSSI	3 (4%)	3 (5%)	
– DSSI	6 (8%)	1 (2%)	
Implant removal	36 (50%)	28 (44%)	0.61
Subsequent surgeries			0.02
None	23 (32%)	20 (33%)	
1	42 (58%)	23 (37%)	
2	7 (10%)	15 (24%)	
>2	0 (0%)	4 (6%)	
Rotational Malalignment	2 (3%)	6 (10%)	0.14
Malalignment in coronal or sagittal plane	3 (4%)	3 (5%)	1.00

*SSSI = Superficial Surgical Site Infection, DSSI= Deep Surgical Site Infection

Infection

In total thirteen infections were observed, nine (13%) in the MIPO-group and four (6%) in the IMN-group (p=0.21) (table 3). Within the MIPO-group there were six (8%) deep surgical site infections. Three of these patients (one closed fracture (AO/OTA 43-A3), two Grade III open fractures (AO/OTA 42-B3) developed osteomyelitis and underwent a revision according to the Masquelet technique[27] after which all fractures healed. In two patients, the infection was treated with antibiotics and surgical debridement. Both patients achieved union within a year. In one case, union had already been achieved at the time of infection diagnosis, after which the implant was removed. Three of the patients in the MIPO-group had a superficial surgical site infection. One of these patients (closed fracture) required surgical debridement, the other two were treated solely with antibiotics.

Four infections (6%) were observed in the IMN-group including one deep surgical site infection after a grade III open fracture (AO/OTA 42-A1) resulting in a chronic osteomyelitis and amputation. The fracture did not show union prior to amputation. One patient with a superficial surgical site infection after a grade II open fracture (AO/OTA 42-B2) underwent additional surgical debridement and skin grafting. The fracture healed after eleven months. The remaining two superficial surgical site infections were treated with antibiotics.

Subsequent surgeries.

Subsequent surgery was more often required after IMN (p=0.02) (table 3). A total of 42 patients in the nail group underwent 71 additional interventions and a total of 49 patients underwent 59 re-interventions within the MIPO-group. Indications for subsequent surgeries are described in table 4. A total of 13 non-unions were found after IMN; four patients, in whom the nail was previously dynamized due to delayed union, required additional surgeries in order to promote bone healing. These patients underwent a fibula osteotomy, nail revision or secondary plate fixation after removing the initial implant. Three patients underwent dynamization as primary treatment for their non-union. Five patients achieved union without any subsequent surgical intervention. The last patient with a non-union underwent limb amputation as a result of chronic osteomyelitis.

Functional outcomes

There was no difference in time to full weightbearing between both groups (p=0.57). The median time to full weightbearing after MIPO was 3.80 months (IQR 2.80) and 3.40 (IQR 3.10) after IMN (table 5). No relevant differences between the two groups were observed in range of motion of knee and ankle joint or the percentage of patients able to return to work and sport. Anterior knee pain was present in 6% of the patients treated with IMN (p=0.05).

Multivariate analysis of MIPO versus IMN

Only the outcome measures time to union, infection, revision, implant removal and time to weightbearing were eligible for analysis. The analysis is presented in table 6 and outcome measures are presented with and without adjustment for AO/OTA fracture classification and Gustilo

TABLE 4. Subsequent Surgeries.

	MIPO-Group	IMN-Group
Dynamization	0 (0%)	16 (22%)
Screw removal/change	3 (5%)	4 (5%)
Revision		
Non-union	2 (3%)	4 (5%)
Delayed-union	-	1 (1%)
Mal-union	-	3 (4%)
Rotational malalignment	1 (2%)	2 (3%)
Other	1 (2%)	-
Infection Tibia	9 (15%)	2 (3%)
Fasciotomy wound management	7 (12%)	11 (15%)
Total:	59	71

TABLE 5. Functional outcomes 1-year after trauma.

	MIPO-Group (n=73)	IMN-Group (n=62)	P-value
Time to weightbearing (months) (median and IQR)	3.80 (2.80)	3.40 (3.10)	0.57
ROM Knee[1]	67 (92%)	60 (97%)	0.62
ROM Ankle[2]	62 (85%)	53 (85%)	0.80
Return to work[3]	57 (78%)	44 (71%)	0.46
Return to sport[4]	55 (75%)	38 (61%)	0.17
Anterior Knee Pain	0 (0%)	4 (6%)	0.05

[1] Patients with flexion >90 degrees. Total four patients (3%) missing.

[2] Patients with dorsal flexion >20 degrees. Total four patients (3%) missing.

[3] Defined as return to work within a year.

[4] Defined as return to sports within a year.

classification. There were two significant differences observed. Firstly, the Hazard-Ratio (HR) described for time to union showed a significantly longer time to union after IMN in comparison to MIPO (HR 1.50, p=0.03) (figure I). However, after correction for the AO/OTA- and Gustilo classification this difference was no longer significant. Secondly, the Odds-Ratio (OR) described for infection showed a higher risk for infection after MIPO in comparison to IMN (p=0.03) after correction for AO/OTA fracture classification and Gustilo classification.

The efficacy of the intra-operative alignment control

There was no significant difference between both groups in terms of rotational malalignment and angular malalignment. Rotational malalignment was seen in 2 (3%) patients treated with MIPO and 6 (10%) after IMN, without showing significance (p=0.14). Angular malalignment occurred in 3 (4%) patients treated with MIPO and 3 (5%) patients treated with IMN (p = 1.0) (table 3).

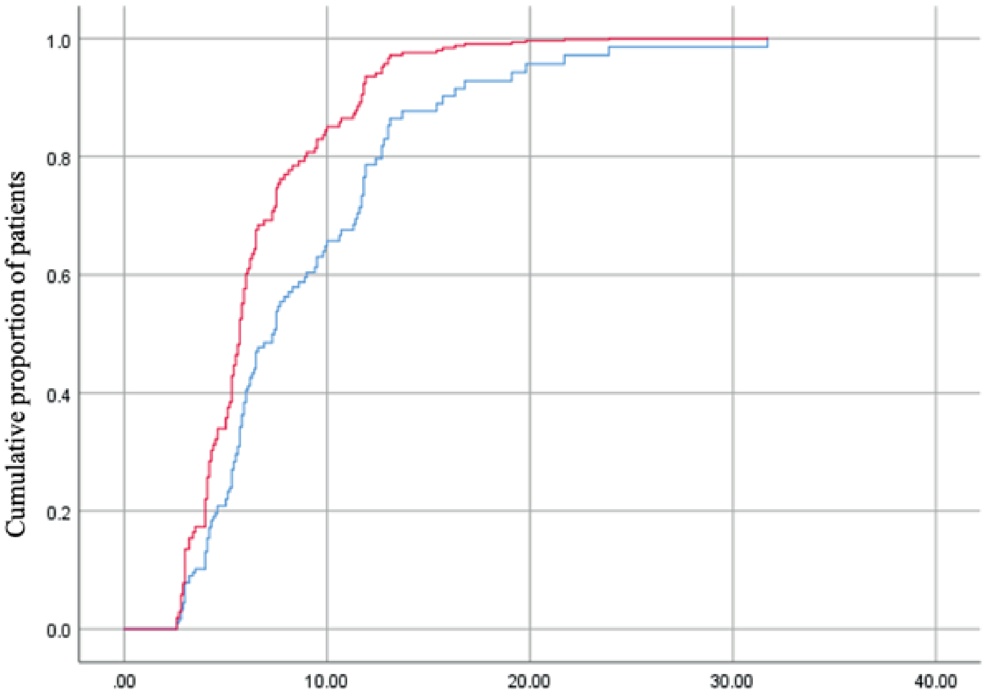

FIGURE 1. Time to union (weeks) for MIPO vs. IMN for treatment of distal extra–articular tiba fractures. The red line indicates the time to union after MIPO. The blue line represents time to union after IMN.

TABLE 6. Analysis of MIPO versus IMN for Postoperative Complications.

	Time to Union	**Infection**[2]	**Revision**[3]	**Implant Removal**[4]	**Full weight bearing**
Uncorrected Effect Estimates	HR 1.50 (95%CI 1.01 – 2.10) p-value = 0.03	OR 2.27 (95%CI 0.68 – 7.63) p-value = 0.18	OR 0.74 (95%CI 0.35 – 1.56) p-value = 0.42	OR 1.00 (95%CI 0.51 – 1.95) p-value = 1.0	HR 0.98 (95%CI 0.68 – 1.41) p-value = 0.93
Corrected Effect Estimates[1]	HR 1.30 (95%CI 0.90 – 1.90) p-value = 0.16	OR 6.22 (95%CI 1.22 – 31.72) p-value = 0.03	OR 1.04 (95%CI 0.43 – 2.51) p-value = 0.93	OR 0.86 (95%CI 0.40 – 1.85) p-value = 0.69	HR 0.75 (95%CI 0.62 – 1.40) p-value = 0.64

[1]Corrected for significant difference in baseline characteristics such as AO/OTA- and Gustilo Classification.
[2]Superficial and deep surgical site infections
[3]Revision for true complications (non-union(n=6), mal-union(n=3), rotational malalignment(n=3), delayed union (n=1) and fasciotomy wound management(n=18)).
[4]Implant removal (removal of plate, screw(s) or nail).

DISCUSSION

MIPO and IMN are both established minimal invasive surgical modalities for the definitive treatment of distal extra-articular tibia fractures. The primary principle finding of this study illustrates that IMN is associated with a significantly higher rate of non-union in comparison to MIPO (22% vs. 6%). Further, there was a higher rate of infection among patients treated with MIPO vs. IMN (OR 6.22). The incidence of subsequent surgeries and functional outcomes such as time to full-weightbearing, range of motion of the knee and ankle, return to work and return to sports showed no significant differences.

The secondary outcomes illustrate the potential beneficial effect of bilateral draping in order to minimize the rate of malalignment. Firstly, there was no difference in rates of malalignment between both groups and, secondly, the overall rate of malalignment was lower than rates presented in previous studies.[23,24,28-34]

This study showed that distal extra-articular fractures of the tibia treated with IMN are associated with a significantly higher non-union rate in comparison to MIPO (13 patients out of 63 (22%) vs. 4 patients out of 72 (6%)). Multiple meta-analyses pooled data on non-union rates following MIPO and IMN and found no significant differences.[30,32,33,35,36] The higher rate in this study could be attributed to the fact that significantly more high energy traumas and open fractures were treated with IMN. The time to radiological union was also longer after IMN in comparison to MIPO (5.7 months vs. 6.6 months). This difference was no longer significant after correction for differences in baseline characteristics such as AO/OTA classification and Gustilo classification, illustrating that AO/OTA fracture type and Gustilo classification play a crucial role in the occurrence of non-union, independent of the treatment modality.[37] Other cohort series as well as RCTs showed equal times to union for both treatment modalities[38-41] and are in line with the findings presented in this study.

The secondary finding of this study is that there was no difference in the rate of malalignment between the two groups, although there was a non-significant tendency towards more rotational malalignment after IMN in comparison to MIPO (10% vs. 3%). The angular malalignment rate was also not statistically different between the groups (4% vs. 5%). These findings are not in line with numbers previously published in literature as significantly higher rates of malalignment were found after IMN[15,23,24,28-34] in up to 35% of the cases. This difference can possibly be attributed to several factors: for all cases in this study draping of both extremities took place to allow both clinical and radiological comparison with the healthy non-fractured side during the operation. Furthermore, clinical assessment of alignment by two consultant surgeons took place in order to indicate the necessity for a low-dose CT for rotational control. Subsequently, revision rates for malalignment were low, endorsing the utility of the alignment protocol used in this Level-1 Trauma Center.

This study initially found no difference in infection rates between the two groups. However, after correction for AO/OTA fracture type and Gustilo classification, there was a significant difference ($p=0.03$). More deep infections were seen after MIPO (8% vs. 2%) while the rate of superficial infections was almost equal in both groups (4% vs. 5%). The higher rate of infection after plate fixation is extensively reported on[1,6,11,38,42,43] and can be explained by the poor soft tissue envelope on the medial side of the distal tibia, the less soft tissue compromise during IMN and the probably less direct reduction techniques.[44]

Patients that underwent MIPO were more likely to undergo implant removal due to the subcutaneous location of the implant. Patients that underwent IMN were more susceptible for two or more additional surgical interventions as the majority of the implants were dynamized after 3 months and removed after a year.

Anterior knee pain is inherent to nailing and occurred in only 6% of patients in the present study. Previous studies reported incidences from 14% up to 46%[7-10] after infrapatellar nailing. The exact underlying aetiology of anterior knee pain is not yet clarified and might be multifactorial. We could not identify any reasons why the incidence in our study was lower than previous literature. A study performed in 2014 by Kuhn et al.[45] presented promising biomechanical results of a retrograde tibia nail (RTN). The RTN avoids the infrapatellar approach and offers a different entry-point. It might hypothetically limit the risk of anterior knee pain. However, clinical results are currently unavailable.

There are a few strengths and limitations that need to be addressed. The main limitation is the retrospective design of this study. The second limitation is the significant difference in AO/OTA-fracture type and Gustilo classification. Although a correction for these differences was made, residual confounding cannot be ruled out. The third limitation is the substantial dissimilarity in postoperative weightbearing protocols after either MIPO or IMN with regard to time to full weightbearing and possible delays in consecutive radiographs. Final, in this study, it was standard procedure to ream 1mm to 1.5mm larger than the chosen nail. “Ream-to-fit” may be biomechanically more stable as is enhances the fit of the nail and lowers the risk of motion, however, reaming 1mm (or 1.5mm) larger creates the possibility to introduce a larger nail yielding increased stability through nail diameter (instead of press-fitting in case of ream-to-fit). Future studies should aim to clarify this biomechanical matter. The main strength is that this cohort study is one of the largest non-randomized studies focussing on the surgical treatment of extra-articular distal tibia fractures. Secondly, this study analysed the whole spectrum of outcome measures, ranging from fracture healing to infection and functional outcomes with a minimal follow-up of 6 months.

CONCLUSION

Based on these findings, satisfactory results can be obtained with both MIPO or IMN. However, IMN is associated with a higher rate of non-union while MIPO is associated with higher rates of infection. The definitive choice should be at the discretion of the involved clinician respecting fracture pattern and soft tissue condition. Secondly, bilateral draping might be effective in reducing malalignment after definitive treatment of distal extra-articular tibia fractures and future studies should aim to compare fractures treated with and without comparative intraoperative alignment control.

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PART IV

ROTATIONAL MALALIGNMENT IS A FREQUENT IATROGENIC PITFALL OF INTRAMEDULLARY NAILING

4

BILATERAL LOW-DOSE COMPUTED TOMOGRAPHY ASSESSMENT FOR POST-OPERATIVE ROTATIONAL MALALIGNMENT AFTER INTRAMEDULLARY NAILING FOR TIBIAL SHAFT FRACTURES: RELIABILITY OF A PRACTICAL IMAGING TECHNIQUE

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ABSTRACT

Introduction

The purpose of this study is to evaluate the intra- and inter-observer reliability of low-dose protocolled bilateral postoperative Computed Tomography (CT)-assessment of rotational malalignment after intramedullary nailing (IMN) of tibial shaft fractures.

Materials and methods

A total of 156 patients were prospectively included with tibial shaft fractures that were treated with IMN in a Level-I Trauma Centre. All patients underwent post-operative bilateral low-dose CT-assessment (effective dose of 0.03784 – 0.05768 mGy) as per hospital protocol. Four observers performed the validated reproducible measurements of tibial torsion in degrees, based on standardized techniques. The Intra-Class Coefficient (ICC) was calculated to evaluate intra- and inter-observer reliability. The intra- and inter-observer reliability was categorized according to Landis and Koch.

Results

Intra-observer reliability for quantification of rotational malalignment on post-operative CT after IMN of tibial shaft fractures was excellent with 0.95 (95% CI = 0.92-0.97). The overall inter-observer reliability was 0.90 (95% CI = 0.87-0.92), also excellent according Landis and Koch.

Conclusion

Firstly, bilateral post-operative low-dose –similar radiation exposure as plain chest radiographs– CT assessment of tibial rotational alignment is a reliable diagnostic imaging modality to assess rotational malalignment in patients following IMN of tibial shaft fractures and it allows for early revision surgery. Secondly, it may contribute to our understanding of the incidence-, predictors- and clinical relevance of post-operative tibial rotational malalignment in patients treated with IMN for a tibial shaft fracture, and facilitates future studies on this topic.

Key Word

tibial shaft fractures, intramedullary nailing, rotational malalignment, bilateral low-dose CT assessments and reliability measurement technique

INTRODUCTION

Rotational malalignment is a preventable iatrogenic complication for patients undergoing intramedullary nailing (IMN) of tibia shaft fractures.[1-8] Previous studies reported an incidence ranging from 19 to 41%[2,5-7,9] based on (standard-dose) Computed Tomography (CT) assessment of bilateral complete tibiae.[5] Prior to the use of CT assessment of rotational malalignment, the reported incidence was based on clinical assessment and reported to be much lower, ranging from 0-8%. Several in vitro- and in vivo diagnostic imaging studies have been performed in order to optimize assessment of rotational malalignment in the early post-operative phase: techniques range from fluoroscopy[10], MRI[11], ultrasonography[12] to CT.[5,13-18]

Presently, CT assessment of tibial rotational malalignment is considered the gold standard. The definition of rotational malalignment has been uniformly accepted as a longitudinal malrotation of the axes through the affected proximal tibia and distal tibia[14,16,18] as compared to the unaffected limb.[5] Rotational malalignment can be disabling for patients, though to what extent is still unclear.[7] Prospective studies on this subject are scarce, given that protocolled (standard dose) post-operative diagnostic CT imaging of complete tibiae (without limited selected axial scanning), has not been common practice after IMN in the majority of high volume Level-I trauma centers to date, due to impracticability, costs and radiation exposure for patients.[7,19,20]

Puloski and colleagues coined a reproducible measurement technique for quantifying rotational malalignment using (standard-dose) CT assessment by two observers in 25 patients involving CT scanning of complete tibiae (without limited selected scanning) in 2004. To the best of our knowledge, there are no subsequent reports on intra- and inter observer reliability of their measurement technique using protocolled low-dose (effective dose of 0.03784 – 0.05768 mGy; compared to chest radiographs = 0.06 mGy) CT assessment for post-op rotational malalignment after IMN by obtaining limited axial cuts of the proximal tibiofibular- and distal tibiotalar joints in a large prospective series of patients with more than 2 observers.[5,13-18]

Therefore, the purpose of this study was to evaluate intra- and inter- observer reliability of protocolled low-dose post-operative CT assessment of limited selected axial CT scanning for rotational malalignment in patients following IMN for tibial shaft fractures in a large prospective cohort with multiple observers of varying levels of training. We hypothesized that intra- and inter-observer reliability of protocolled low-dose CT imaging technique for the assessment of malalignment would be good according to the categorical rating by Landis and Koch.

Our Institutional Review Board (IRB) waived approval for the use of CT scans for this diagnostic imaging study, as post-operative bilateral CT-scanning is part of hospital protocol in our Level-I Trauma Centre, in accordance to the Declaration of Helsinki.

MATERIAL AND METHODS

Study subjects

Between January 2009 and September 2016, we included 156 patients, with unilateral tibial shaft fractures treated with intramedullary nailing, who underwent a protocolled postoperative CT assessment for rotational malalignment of the tibia. There were 112 males (72%), 44 female (28%)

with an average age of 41 (median 37.5). A total of 82 right tibia fractures (53%) and 74 left tibia fractures (47%) were included. There were 7 proximal tibial shaft (4%), 35 middle shaft (22%), 104 distal shaft (67%) and 10 segmental (6%) fractures. According to the AO/OTA fracture group classification[21], there were 107 simple fractures (69%), 26 wedge fractures (17%) and 23 complex fractures (15%). In 42 patients (26%) the fracture was associated with a compound injury, whilst the remaining 114 patients (74%) had a closed injury. In 129 cases (83%) there was an associated fibula fracture, including 32 proximal fibula fractures (25%), 37 shaft fractures (29%), 46 distal fractures (36%) and 14 segmental fibula fractures (11%).

Surgical technique

Patients were treated using modern IMN techniques (TRIGEN META-Nail Smith & Nephew, USA), with technique and positioning specifics as per the surgeon's routine.[22] The average nail diameter was 10 mm (range, 8.5 to 13 mm) with an average length of 340 mm (range, 260 to 400 mm). Distal screw locking was performed using the Smith & Nephew TRIGEN SURESHOT Distal Targeting System, with a median number of distal locking screws of two (range, one to three screws). The median number of proximal interlocking screws was two (range, one to four screws).

Computed Tomography (CT-) scanning protocol

As per hospital protocol a postoperative low-dose limited axial cut CT assessment for rotational malalignment of the tibia was undertaken for all 156 patients. Scans were made with patient supine with neutral hip rotation, knees extended, and with ankles stabilized in gutter in order to optimize reproducibility. Plain CT scans were then performed with helical blocks, through the proximal and distal tibia to minimize radiation exposure.

Limited (usually 2-3) axial cuts were taken from the proximal tibiofibular joint to 2-3 mm above the tibiofibular joint. A similar scanning method was used for the distal tibia, 2-3 mm proximal the tibiotalar joint. In our study the average Total-DLP (mGy.cm) of the proximal and distal CT-slices was half the Total-DLP (mGy.cm) required to image the whole tibia (range 94.6-144.3 mGy.cm). Our low-dose bilateral CT protocol was then defined on the length that is scanned, converting to an effective dose of 0.03784 – 0.05768 mGy. In comparison to plain chest radiographs of 0.02 mGy for AP dose and 0.04 mGy for lateral, totaling 0.06 mGy (http://pubs.rsna.org/doi/full/10.1148/radiol.14132903).

Assessment of rotational malalignment of the tibia

These protocolled bilateral CT scans were used to measure degrees of malrotation of the tibia (Figure 1). This measurement technique is based on a standardized reproducible technique in completely scanned tibiae as described by Puloski and colleagues, based on preliminary work of others.[5,14,15,17,18,23,24] All CT-assessments were performed in our Carestream Vue Picture Archiving Communication System (PACS) version 11.4.1.0324.

Proximal rotation is measured by taking the angle of the line tangential to the posterior tibial plateau, 2-3 mm above the proximal tibiofibular joint and the horizontal reference as

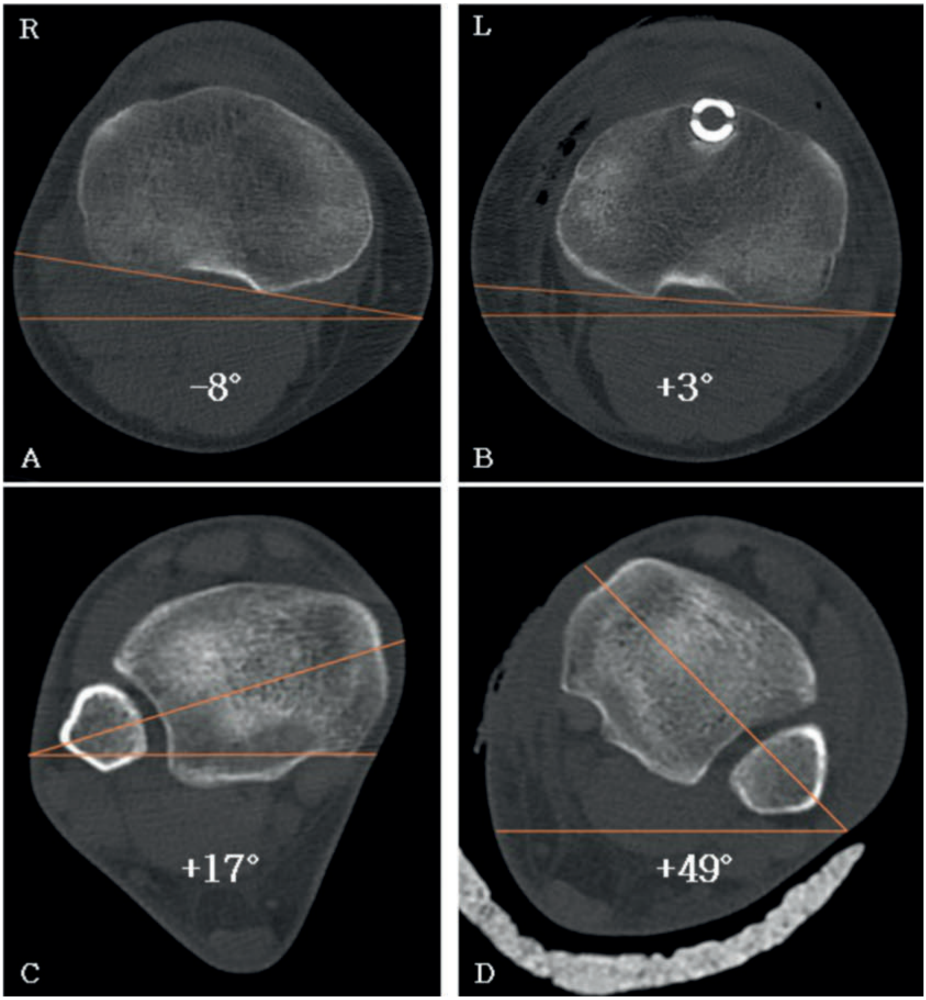

FIGURE 1. Assessment of postoperative Computed Tomography-slices taken 2-3 mm proximal the tibiofibular and tibiotalar joint of both the affected and unaffected limb. The proximal lines are drawn tangential of the dorsal tibia and the distal lines are drawn through the middle of the tibia and fibula. **A** and **C** are the angles of the unaffected side and **B** and **D** are the angles of the affected side. The rotational difference of the unaffected side is 25˚ (17˚(**A**) - -8˚(**C**)) and the rotational difference in the affected side is 46˚ (49˚(**B**) - 3˚ (**D**)). The rotational malalignment is calculated by taking the difference between the affected (+46˚) and unaffected side (+25˚). This means a rotational malalignment of +21˚ (46˚- 25˚), which is defined as an external rotational malalignment.

described by Jend and colleagues[18] (Figure 1A and 1B). We standardized this axial CT-image to improve repeatability by defining it as the first slice proximal to the proximal tibiofibular joint that does not include the fibular head in the image.

Distal rotation is measured by taking the angle of the line drawn trough the axis of the tibial plafond and fibula as described Ulm[25], 2-3 mm proximal to the ankle joint[16] (Figure 1C and 1D).

This was defined as the first axial CT image proximal to the ankle joint that shows the complete intact distal tibia (above the talar dome).

Thus, rotational malalignment is the difference between the proximal- and distal angles of the affected limb compared with the difference between the proximal and distal angles of the uninjured limb. A negative angle indicates a relative internal (mal)rotation as compared to the uninjured limb, whilst a positive angle represents a relative external (mal)rotation. Previous studies[2,3,5-7] define rotational malalignment as a rotational difference of 10° or higher.

Intra- and inter-observer reliability of CT-assessment of malalignment

To determine the reliability of CT-assessment of tibial rotational alignment (torsion), we used four independent observers, not involved in the care for the study patients. Observers evaluated the bilateral postoperative limited axial CT-images of the proximal- and distal tibia as described above, and had respective varying levels of training: two medical doctors in training (PhD Research Fellows) and two Orthopaedic Registrars. Regarding intra- and inter-observer reliability, the four observers performed the evaluation independently on two separate occasions. On first occasion each observer performed 156 CT measurements. On second occasion, two weeks later to avoid recall bias, each observer measured 50 randomly selected CT-scans of the 156 CTs from the first round.

Statistical analysis

The intraclass correlation coefficient (ICC) as described by Shrout and Fleis[26] was used in order to calculate the reliability of the CT assessments by the same observer on two separate occasions (inter-observer reliability), and by different observers on the same occasion (intra-observer reliability). It is the most common used statistic method to describe agreement of continues data since its introduction by Shrout and Fleis.[26] Due the individual differences in identifying the reference points of tibia and the fibula by each observer, the ICC of the distal and proximal tibia line is also calculated. ICC values were interpreted using the categorical rating proposed by Landis and Koch[27]: values of 0.01 to 0.20 indicate slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and more than 0.81, almost perfect agreement. Zero indicates no agreement beyond that expected due to chance alone, – 1.00 means total disagreement, and + 1.00 represents perfect agreement.[27,28] Furthermore, the average Standard Error of Measurements (SEM) was calculated to determine the amount of variability causes by measurement error.

RESULTS

Intra-Observer reliability (Tables 1 and 2)

The overall level of agreement for quantification of rotational malalignment after IMN on low-dose axial CT scan between one observer on two separate occasions was 0.95 (range 0.92 – 0.97; with a 95% CI of 0.92-0.97 (Table 1). ICCs for each respective observer are excellent according to the rating by Landis and Koch. Intra-reliability for determining the axes trough the proximal tibia and distal tibiofibular joint were 0.98 and 0.99 respectively with a 95% CI of 0.96-0.99 and 0.97-1 (Table 2).

Inter-Observer reliability (Table 3)

Overall inter-observer reliability of CT-assessment of rotational malalignment after IMN of tibial shaft fractures was 0.90 with a 95% CI of 0.87-0.92. Inter-observer reliability of determining the proximal tibia axis, 2-3 mm above the tibiofibular joint was 0.99 with a 95% CI of 0.99-0.99, and for the distal axis 0.97 with a 95% CI of 0.93-0.99.

Standard error of measurement (Table 4)

Table 4 shows the measurement error of paired measurement for each observer. To obtain the total SEM of all observers, the mean SEM is calculated by taking the average of the SEM of each observer, as reported in Table 4. We found an average SEM of 2.4°. Practically, this means that outcomes obtained within the range of 2.4° were considered as measurement error. Outcomes obtained out of this range are considered as 'true' rotational difference.

TABLE 1. Level of agreement between one observer on separate two occasions (intra-observer reliability)

Observers	Total ICC	95% CI	Landis & Koch Categorical
1	0,96	0.93 - 0.97	Excellent
2	0,92	0.87 - 0.96	Excellent
3	0,96	0.93 - 0.98	Excellent
4	0,97	0.95 - 0.98	Excellent
Average	**0,95**	**0.92 - 0.97**	**Excellent**

TABLE 2. Intra-Observer reliability proximal tibial and distal Tibiofibular axes

Observer	ICC Proximal Line	95% CI	Category	ICC Distal Line	95% CI	Category
1	0,98	0,96 - 0,99	Excellent	0,99	0,98 - 0,99	Excellent
2	0,98	0,96 - 0,99	Excellent	0,99	0,98 - 0,99	Excellent
3	0,96	0,94 - 0,98	Excellent	0,99	0,94 - 1,00	Excellent
4	0,99	0,99 - 1,00	Excellent	1,00	0,99 - 1,00	Excellent
Average	0,98	0,96 - 0,99	Excellent	0,99	0,97 - 1,00	Excellent

TABLE 3. Inter-Observer Reliability

	ICC	95% CI	Category
Total	0,90	0.87-0.92	Excellent
Proximal Line	*0,99*	*0.99-0.99*	*Excellent*
Distal Line	*0,97*	*0.93-0.99*	*Excellent*

Absolute rotational differences (Table 5)

Table 5 shows the absolute rotational differences measured by the four observers. Each observer has calculated the absolute rotational difference for each patient. In order to improve accuracy, we took the average of four measurements for each patient. Table 5 shows that a total of 56 patients ended up with a rotational difference with 10° or higher, including 48 patients with a difference up to 20°, 6 patients with a difference more than 20° and 2 patients with a rotational difference of 30° or higher. Additional, four patients went back to theatre for revision surgery in order to revise the rotational deformity. The rotational deformity was then reduced to an acceptable difference.

DISCUSSION

In the vast majority of patients with tibial shaft fractures, intra medullary nailing (IMN) is the treatment of choice with functional outcomes in the short- and long term.[20,29,30] This is ascribed to the minimally invasive approach, rapid fracture healing and excellent recovery.[3,5,6,31]

Previous studies described rotational malalignment as a potential iatrogenic pitfall of IMN, but prospective data on 1) incidence of malalignment; 2) predictors of patients at risk; and 3) impact on functional outcome on this subject are scarce.[1-7] In order to diagnose rotational malalignment in an early stage, radiological assessment with postoperative CT-scans may be considered[14,16,32], but has not been common practice after IMN in the majority of high volume Level-I trauma centers to date, due to impracticability, costs and radiation exposure for patients.[7,19,20] The presented prospective diagnostic imaging study shows that practical low-dose CT assessment by obtaining limited axial cuts of the proximal- and distal tibiofibular joints[5,13-18], as protocolled in our hospital (effective dose of 0.03784 – 0.05768 mGy; compared to chest radiographs = 0.06 mGy) is a reliable diagnostic imaging modality to assess rotational malalignment in patients following IMN of tibial shaft fractures.

This study should be interpreted in the light of strengths and weaknesses. A potential weakness is the prospective design, but the fact that analyses for this diagnostic imaging study were truly

TABLE 4. Intra- and Inter-observer variability, using the Standard Error of Measurement (SEM)

	Observer 1	Observer 2	Observer 3	Observer 4	Average
SEM	2.2°	3.0°	2.3°	1.9°	2.4°

TABLE 5. The rotational deformities

Rotation	10° - 20°	20° - 30°	≥ 30°	Total
Internal	25	2	0	27
External	23	4	2	29
Total	48	6	2	56
Total revisions	0	2	2	4

retrospectively performed, may potentially cause an unknown bias. Strengths include: the largest series to date with routine postoperative CT-imaging of 156 patients; four observers of varying levels of experience improving the reproducibility of this study to other Centers; a potential technical improvement assessing the axis of the proximal tibia by drawing a reproducible line along the posterior proximal tibia cortices[5] (Figure 1), which minimizes inaccuracies in the somewhat subjective determination of the proximal axis[14]; and finally our low-dose CT protocol that limits radiation exposure to our patients similar to the dose of plain chest radiographs, simultaneously improving practicability for implementation and reduces costs.

To date, there are several studies reporting on radiological assessments of CT-scans for anatomical tibial torsion.[5,14,16,18,23]. Madadi and colleagues published the most recent study, focusing on measurement methodology to assess and improve reliability of tibial torsion assessment in non-fractured tibiae.[14] However, studies on standardized and practical techniques for postoperative CT-assessment of tibial rotational alignment have been scarce in the last decade.[14,15,18,24] In 2004, Puloski and colleagues[5] stated that postoperative CT-assessment is a reliable method to determine rotational malalignment after IM-nailing of tibial shaft fractures: with an intra-observer variability of 3.4° and inter-observer variability of 3.9°, and a repeatability coefficient of 8° for 2 observers in 22 patients.

We build on the work of Puloski and colleagues[5] with upgraded contemporary study methodology studying a large prospective cohort of 156 patients, with > 2 observers (4 observers with varying levels of experience), and reporting Intra-Cass Coefficient (ICC) as a statistical measure for an excellent level of agreement. But most importantly, we feel that our advanced CT-scanning protocol by obtaining limited axial cuts of the proximal- and distal tibiofibular joints[5,13-18] (rather than complete tibiae) with an effective dose of 0.03784 – 0.05768 mGy (compared to chest radiographs = 0.06 mGy), does not only improve measurement accuracy with an average standard error of measurement to 2.4°; moreover, it greatly improves practicability, facilitating implementation and reduces costs.

Our study also illustrates the rate of rotational deformities after intra-medullary nailing of tibial shaft fractures. However, extensive reporting on the incidence may distract from the primary research question and therefore the rotational deformities are for illustration purposes of the imaging technique. Furthermore, we are aware of the surprisingly low revision rate. Correction surgery was performed in four cases with RM over 20 degrees. In our current practice we are more aggressive and use 15 degrees as the cut off for offering revision surgery.

In 2012, Theriault and colleagues[7] presented their landmark article on functional impact of tibial rotational malalignment after IMN for tibial shaft fractures in the largest series to date of 72 patients, out of 288 identified patients with tibial shaft fractures. These patients were retrospectively followed-up after an average of 58 months, and had tibial rotation assessed on CT scans of both tibiae. 41% of these patients had malrotation, but did not have compromised functional outcome as compared to the group without malrotation.[7] Although the largest series to date, our understanding of 1) incidence-; 2) predictors-; and 3) functional impact-of malalignment is limited due to the lack of prospective cohort data with protocolled post-operative CT-assessment of rotational malalignment and comprehensive outcome data.[1-7]

Therefore, the clinical relevance is that firstly, protocolled bilateral CT assessment is a practical and proven reliable diagnostic imaging modality with low-dose radiation exposure for our patients, in order to identify patients with iatrogenic malalignment that may require revision surgery. And secondly, protocolled CT assessment of rotational alignment may contribute to our understanding of the incidence-, predictors- and clinical relevance of post-operative tibial rotational malalignment in patients treated with IMN for a tibial shaft fracture, and facilitates future studies on this topic.

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5

PREVALENCE OF ROTATIONAL MALALIGNMENT AFTER INTRAMEDULLARY NAILING OF TIBIAL SHAFT FRACTURES: CAN WE RELIABLY USE THE CONTRALATERAL UNINJURED SIDE AS THE REFERENCE STANDARD?

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ABSTRACT

Background

Intramedullary nailing (IMN) is the treatment of choice for most tibial shaft fractures (TSF). However, an iatrogenic pitfall may be rotational malalignment (RM). The aims of this retrospective analysis were to determine 1) incidence of RM using post-op Computed Tomography (CT) as the reference standard; 2) average baseline tibial torsion of uninjured tibiae; in order to answer 3) can we reliably use the contralateral uninjured limb as the reference standard?

Methods

Included were 154 patients (male/female - 71%/29%) median age 37 years. All patients were treated for a unilateral TSF with an IMN and underwent a low-dose bilateral post-op CT to assess RM.

Results

Over one-third of patients (n = 55; 36%) had post-operative RM >10°. Right-sided TSF were significantly more likely to display external RM; in contrast, left-sided fractures predisposed to internal RM. Subsequently, we assessed the variability within the reference standard to determine if there was a left-right difference in baseline tibial torsion. This revealed a left-right rotational difference of 4° (right 41.1° ± 8.0° versus left 37.0° ± 8.2°; p<0.01), with the right tibia being on average 4° more externally rotated. Applying this 4° correction to our cohort not only reduced the incidence of RM (n = 45; 29%); it equalized the internal- and external-RM distribution between left and right tibiae. Moreover, 20 patients (36%) previously classified as having RM >10°, no longer had RM after correction; and 11 patients (18%) previously categorized as normal, now had RM.

Conclusions

This study reveals apart from a high incidence of RM following IMN for TSF (36%), a pre-existing 4° left-right difference in tibial torsion which, sheds a different light on previous studies-, current clinical practice- and could have significant implications in the diagnosis and management of tibial RM. It should be considered when labelling our patients with a post-operative iatrogenic “RM”.

INTRODUCTION

Intramedullary-nailing (IMN) is the treatment of choice for most patients with tibial shaft fractures (TSF). Nailing of tibia fractures is recognized for their reproducibility, minimally invasive surgical technique, predictable fracture healing and rapid recovery.[1-5] However, IMN has been associated with higher rates of iatrogenic rotational malalignment (RM) when compared to open reduction and internal fixation.[6-8] RM is defined as a longitudinal internal- or external rotation of the injured tibiae compared to the uninjured contralateral side.[4] Most previous studies[2-5,9,10], have defined tibial RM as a rotational difference of >10˚, which is similar to what has been reported for femoral malrotation.[1,11-13] Computed tomography (CT) has been found to be the most reliable method for assessing RM.[2,14,15] Previous studies demonstrate a low rate of RM based on clinical examination (0%-7%)[2,4] whilst, with use of advanced imaging techniques such as CT, the reported incidence increases to 19%-41%.[1-4,9,10,16] Iatrogenic RM is correlated with patients' medicolegal reimbursement: in the United States patients with a RM of ≥10° are eligible for compensation in keeping with the "Guides to the Evaluation of Permanent Impairment".[17] Thus, identification of RM following IMN may have significant financial consequences,[18] as well as potential functional impact.[19-22] Medico-legally long bone malrotation is a common reason for litigation, of which 90% of cases are proven to be based on negligence.[18] However, data on the correlation of post-operative RM and patients' functional impairment or the presumption that the uninjured contralateral limb is the correct reference standard, are scarce. The landmark paper by Theriault et al.[10], currently provides the best evidence reporting a RM (>10°) incidence of 41% of patients with bilateral lower limb CT scanning, using the contralateral uninjured limb as the reference standard. No significant difference in 'lower extremity functional scale' was identified in this relatively small cohort study. Therefore, the purpose of this study was to improve understanding of RM after IMN for TSF by addressing the following research questions: 1) What is the current incidence of RM? 2) What is the average baseline tibial torsion of uninjured limbs; and subsequently answer the overall research question: 3) can we reliably use the contralateral uninjured limb as the reference standard? The answers to these questions are clinically relevant for decision-making in patient care.

MATERIAL AND METHODS

The institutional Review Board waived the requirement for approval of this study in accordance to the declaration of Helsinki, given post-operative rotational profiling with CT is part of the hospital protocol for patients undergoing intramedullary-nailing of tibial shaft fractures.

Study Subjects

We performed a retrospective review on a consecutive series of patients that underwent an IMN for a TSF between January 2009 and September 2016. To be included, the 154 patients were required to have undergone a protocolled low-dose postoperative CT for assessment of RM. This protocol was implemented in 2009, with an initial CT-scan rate of 43%; which has since improved to 83%. Included were 110 males (71%) and 44 females (29%), with a median age of 37 years. Patient and fracture characteristics are represented in Table 1.

Surgical Technique

All patients in this study were treated with the TRIGEN IMN system (Smith & Nephew, Andover, MA USA). Nailing was performed as per routine and extensively published techniques.[23-26] Evaluation of fracture reduction was performed intra-operatively using simple fluoroscopy (assessment of cortical contact/continuity) and clinical judgement, though this was not standardized between surgeons. Protocolled postoperative low-dose CT-scans were undertaken an average of 2 days postoperatively.

TABLE 1. Demographic Data and Injury Details (N=154)

Variable	
Age*	41 ± 18.6 (14-90)
Male	110 (71%)
Female	44 (29%)
Polytrauma†	
Yes	29 (19%)
No	125 (81%)
Fracture Side†	
Right	82 (53%)
Left	72 (47%)
Open or Closed Fracture†	
Open	41 (27%)
Closed	113 (73%)
Fracture Classification†	
Simple	95 (62%)
Wedge	35 (23%)
Complex	24 (16%)
Fracture location†	
Proximal third	6 (4%)
Middle third	47 (31%)
Distal third	91 (59%)
Segmental fracture	10 (6%)
Fibula Fracture†	
Present	127 (82%)
Absent	27 (18%)
Fibula Fracture Location†¥	
Proximal third	30 (24%)
Middle third	43 (34%)
Distal third	38 (30%)
Segmental	16 (13%)

* Values are given as the mean and standard deviation with the range in parentheses.
† Values are given as the number, with the percentage in parentheses.
¥ The percentages are based on 127 fibula fractures.

CT Scanning Protocol

All 154 patients underwent postoperative bilateral short segment tibial CT-scanning as per institution protocol. The CT-scans were made in supine position with neutral hip rotation, knees extended, and ankles stabilized in a gutter in order to optimize reproducibility and reliability of scans. Plain CT-scans were then performed with helical blocks, through short segments of the proximal (including tibiofibular joint) and distal (including the tibiotalar joint) tibiae to minimize radiation exposure. The Total DLP was 94.6-144.3mGy.cm, which is an effective dose of 0.03784-0.05768mGy; equivalent to a plain chest radiograph (AP dose =0.02, lateral dose=0.04, totaling 0.06mGy).

CT Assessments of Tibial Rotational Torsion

Proximal angle measurements were made from CT-slices taken 2-3mm proximal to the tibiofibular joint. The angle determined by the horizontal reference and the line tangential to the dorsal tibia plateau[24] (Figure 1A and B). Distal angle measurements were made from CT-slices taken 2-3mm proximal to the tibiotalar joint. The angle determined by the horizontal reference and the line through the anatomic axis of distal tibia and the fibula (Figure 1C and D). Tibial torsion is the difference between the proximal and distal angle. We found excellent inter-observer and intra-observer reliability of this imaging method in a previous study (ICC = 0.92-0.97 and 0.87-0.92 respectively).[14] RM was defined as the longitudinal rotational difference between the injured-and the non-injured limb.[1-5,9,10,16,23-25,27] A rotational difference of >10˚ was classified as "RM" as per previous studies.[3-5,9,10,28] According to this definition, one assumes there is no pre-existing baseline difference between the uninjured and now injured tibia in terms of rotational alignment. Puloski et al.[4] and Johner et al.[29] applied categorical ratings to RM and we adapted these adding a category of RM ≥ 30˚ (Table 2). Mean tibial torsion of the contralateral (non-injured) tibiae in our cohort was also assessed to determine whether previous assumptions regarding left-right tibial rotation had been valid, given the contralateral limb serves as the reference standard in all studies on this subject to date.[2-4,10,16,27,30-33]

Statistical Analysis

Continuous data is presented as a mean when normally distributed; otherwise, the medians are reported. Baseline characteristics of study patients are summarized as frequencies and percentages for categorical variables and with means and standard deviations for continuous variables. Student's t-tests were performed to assess differences in RM between the injured and uninjured tibia, as well as comparison between uninjured tibiae to evaluate the value of the contralateral tibia to serve as the reference standard. The ordinal scores were compared by use of a Mann Whitney-U test. Pearson correlations coefficients were calculated to assess the association between continuous measurements and ordinal scores. A p-value ≤0.05 was considered statistically significant. Statistical analysis was performed by use of IBM SPSS Statistics for Macintosh, version24.0 (Armonk, NY; IBM Corp).

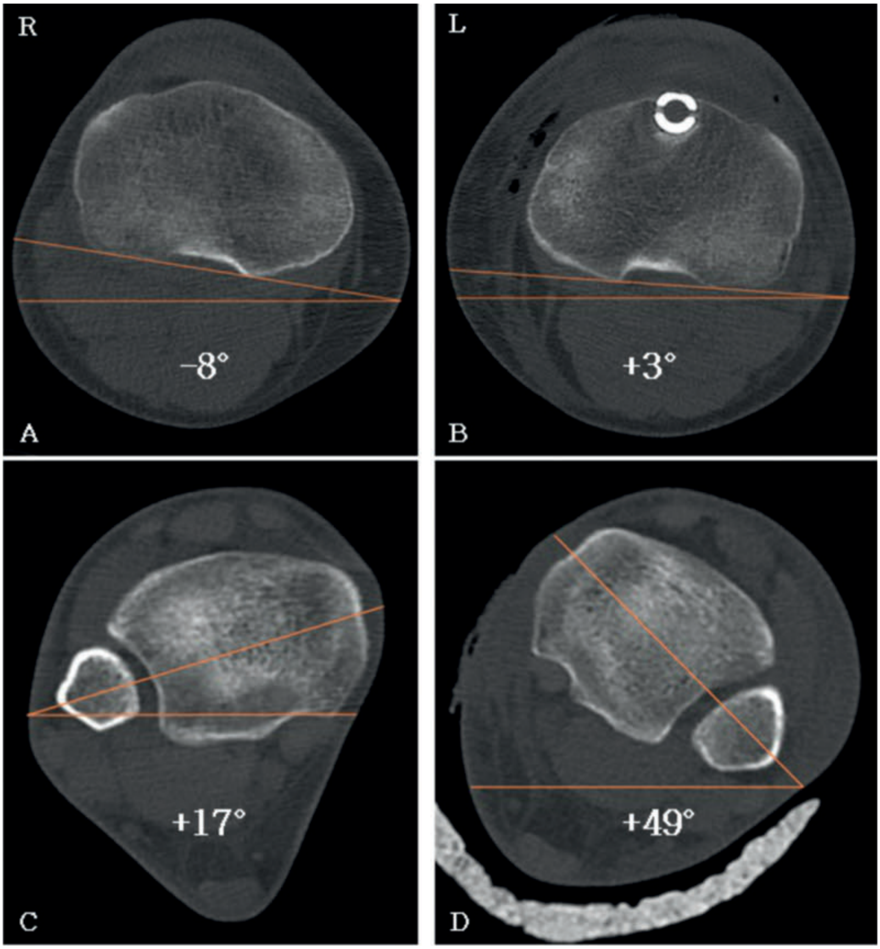

FIGURE 1. Assessment of post-operative Computed Tomography-slices taken 2-3 mm proximal the tibiofibular and tibiotalar joint of both the affected and unaffected limb. The proximal lines are drawn tangential of the dorsal tibia and the distal lines are drawn through the middle of the tibia and fibula. A and C are the angles of the healthy side and B and D are the angles of the injured side. The rotational difference of the healthy side is 25˚ (17˚(A) - -8˚(C)) and the rotational difference in the affected side is 46˚ (49˚(B) - 3˚ (D)). The rotational malalignment is calculated by taking the difference between the affected (+46˚) and unaffected side (+25˚). This means a rotational malalignment of +21˚ (46˚- 25˚), which is defined as an external rotational malalignment.

TABLE 2. Classification of Rotational Malalignment when comparing to contralateral limb using CT

Johner & Wruhs	Puloski	Our Definition
Excellent (± 0-5°)		
Good (± 6-10°)	± <10°	± <10°
Fair (±11-20°)	± 10-15°	± 10-19°
Poor (± >20°)	± >15°	± 20-29°
Unacceptable		± >30°

Source of Funding

No external source of funding.

RESULTS

Incidence of RM using the Uninjured (Contralateral) Limb as the Reference Standard (Table 3).

According to the 'classic' definition of RM:[4,10,29] 55 (36%) out of 154 patients were categorized as having RM (>10˚) after IMN. According to our categorical rating (Table 2): 46 patients (30%) had RM of 10-19˚, 7 patients (5%) had RM of 20-29˚ and 2 patients (1%) had RM of ≥30˚. The injured tibia was internally malrotated in 26 cases (47%) and externally malrotated in 29 (53%).

Distribution of RM According to Injury Side (Left versus Right) using the Contralateral Uninjured Limb as the Reference Standard (Table 4)

Assessment of RM distribution according to the side of the fracture revealed that IMN of left-sided TSF consistently resulted in a mean internal rotation (-4.5° ±9.5°), compared to the uninjured right limb. In contrast, IMN of right-sided TSF resulted in a mean external rotation (5.5° ±9.4°) when compared to the uninjured left tibia. This mean rotational difference of 10° between the injured left tibia (-4.5° ±9.5°) versus the injured right tibia (5.5° ±9.4°) was statistically significant ($p<0.001$). More specifically, 28 (39%) of 72 patients with a left-sided TSF had RM, of which, 79% were internal oriented. RM for patients with a right-sided injury was the opposite: 27 (33%) of 82 patients with right-sided TSF had RM, of which, 85% were externally rotated (Figure 2).

TABLE 3. Rotational Malalignment Data (N=154)

Variable	
Rotational Malalignment Degrees*	0.8˚ ±10.7˚ (-23.3˚ – 30.3˚)
Rotational Malalignment Incidence†	
No rotational malalignment	99 (64%)
10-19˚ rotational malalignment	46 (30%)
20-29˚ rotational malalignment	7 (5%)
>30˚ rotational malalignment	2 (1%)
Internal and External Rotational Malalignment†¥	
Internal rotational malalignment	26 (47%)
External rotational malalignment	29 (53%)

† Values are given as the number, with the percentage in parentheses.

* Values are given as the mean and standard deviation with the range in parentheses.

¥ The percentages are based on 55 cases of rotational malalignment.

Significant Difference in -Baseline- Physiological Tibial Torsion of Contralateral Uninjured Left and Right Limbs (Table 5)

A significant left-right difference in terms of physiological tibial torsion of the uninjured limb was noted: the mean tibial torsion in 72 uninjured right tibiae was 41.1° ±8.0°, versus a mean tibial torsion of 37.0° ±8.2° in 82 uninjured left tibiae (p<0.01). In other words, uninjured right tibiae were on average 4.1° more externally rotated than the uninjured left tibias. Given this, we "modified" our classification of RM – instead of <10°, the right would start at a baseline of +4°, thus "good" would be -6° to +14°, whilst left starts as a baseline of -4°, meaning "good" would be -14° to +6° and so on. A negative value representing internal rotation and positive external rotation.

Revised Incidence of RM accounting for average baseline difference of 4° (left vs right) in the Reference Standard (Table 6)

A total of 45 (29%) of 154 patients were now categorized as having RM. 23 (32%) out of 72 patients with left-sided TSF now had RM; 12 (52%) internally and 11(48%) externally malrotated. Of those with right-sided TSF, 22 (26%) out of 82 patients now had RM; 9 (41%) internally and 13 (57%) external malrotated (p=0.59) (Figure 3). The revised calculations of RM

TABLE 4. Left Right Distribution Rotational Malalignment (N=154)

Variable	Left-sided Fracture (n=72)	Right Sided Fracture (n=82)	P-value
Rotational Malalignment Degrees*	-4.5° ± 9.5° (-23.3° – 18.5°)	5.5° ± 9.4° (-15.1° – 30.3°)	<0.001
Rotational Malalignment Incidence†			
No rotational malalignment	44 (61%)	55 (67%)	0.45
10-19° rotational malalignment	25 (34%)	21 (26%)	
20-29° rotational malalignment	3 (4%)	4 (5%)	
>30° rotational malalignment	0 (0%)	2 (2%)	
Internal and External Rotational Malalignment†			
No rotational malalignment	44 (61%)	55 (67%)	<0.001
Internal rotational malalignment	22 (31%)	4 (5%)	
External rotational malalignment	6 (8%)	23 (28%)	

* Values are given as the mean and standard deviation with the range in parentheses.
† Values are given as the number, the percentage in parentheses are based on the total number of left- sided or right-sided fractures.

TABLE 5. Tibial Torsion Data Injured and Non-injured side (N=154)

Variable	Left-sided Fracture (n=71)	Right-sided fracture (n=82)	P-value
Torsion Non-Injured Tibia*	41.1° ± 8.0° (25.7° – 59.4°)	37.0° ± 8.2° (19.7° – 57.5°)	<0.01
Torsion Injured Tibia*	36.4° ± 8.9° (14.0° – 60.0°)	42.5° ± 10.2° (17.7° – 67.0°)	<0.01

* Values are given as the mean and standard deviation with the range in parentheses.

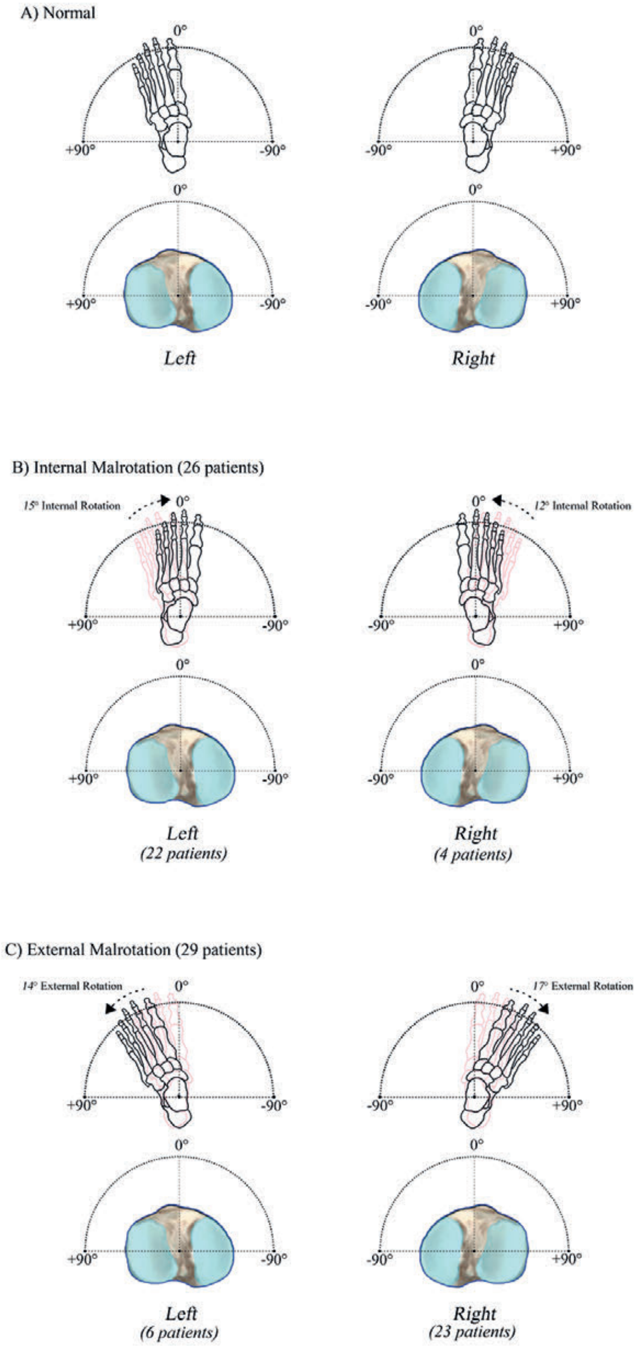

FIGURE 2. Representation of the average foot progression angle/rotational alignment in **A)** Normal individuals, **B)** in the 26 patients who sustained an internal RM following tibial IMN, and **C)** in the 29 patients who sustained an external RM following tibial IMN. In **B)** it can be seen of the 22-left sided TSF with internal RM they had an average RM of 15˚, whilst in the 4 with an internal RM following a right sided fracture their average RM was 12˚.

in our cohort, utilizing the corrected baseline measures revealed that the mean rotational difference of left (-0.5° ±9.5°) and right (1.5° ±9.4°) TSF managed with IMN, no longer differed significantly.

Alteration in Rotational Alignment Category (Table 7)

According to our modified classification of RM[4,29]: 20 patients who initially had RM using the assumption that left-right tibial torsion is equal no longer did when considering the 4° baseline rotational difference. Whilst, 11 patients initially classified as "normal", on re-calculation, now fell outside the accepted 10° rotational difference. Thus, 20% of patients within our cohort changed category of rotational alignment following adjusting for this 4° rotational difference.

TABLE 6. Left Right Distribution Rotational Malalignment According to Renewed Criteria^π^ (N=154)

Variable	Left-sided Fracture (n=72)	Right Sided Fracture (n=82)	P-value
Rotational Malalignment Degrees* π	-0.5° ±9.5° (-19.3° – 22.5°)	1.5° ±9.4° (-19.1° – 26.3°)	0.75
Rotational Malalignment Incidence† π			
No rotational malalignment	49 (68%)	60 (73%)	0.84
10-19° rotational malalignment	21 (29%)	20 (24%)	
20-29° rotational malalignment	2 (3%)	2 (2%)	
>30° rotational malalignment	0 (0%)	0 (0%)	
Internal and External Rotational Malalignment† π			
No rotational malalignment	49 (68%)	60 (73%)	0.59
Internal rotational malalignment	12 (17%)	9 (11%)	
External rotational malalignment	11 (15%)	13 (16%)	

* Values are given as the mean and standard deviation with the range in parentheses.

† Values are given as the number, the percentage in parentheses are based on the total number of left- sided or right-sided fractures.

π Compared to a baseline of -4° for left sided tibial shaft fractures and +4° for right-sided tibial shaft fractures

TABLE 7. Alteration in Rotational Malalignment Category with 4° Adjustment

	Number of patients	
No change in category of RM	124	
>10° External RM à NORMAL	10	20 (36%) of those initially eligible for compensation no longer are
>10° Internal RM à NORMAL	10	
NORMAL à >10° External RM	5	11 (11%) of those initially not eligible for compensation now are
NORMAL à >10° Internal RM	6	

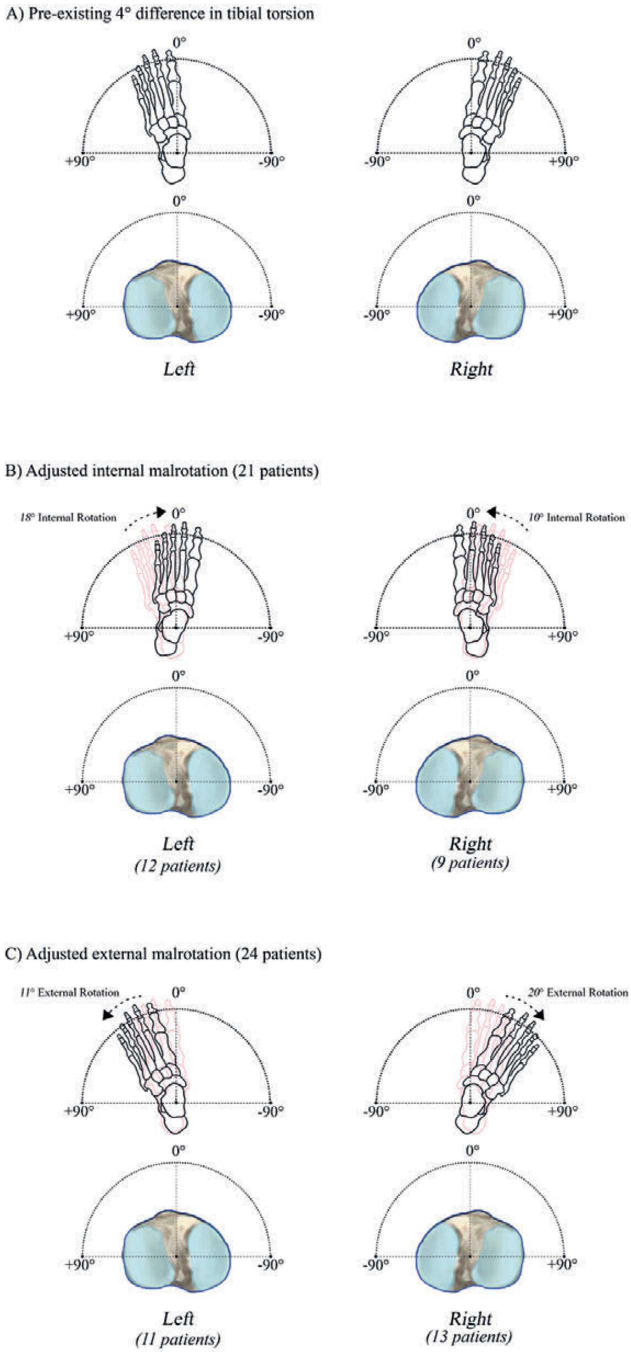

FIGURE 3. Representation of the average foot progression angle/rotational alignment when considering the right tibia is 4˚ more externally rotated than the left. A) The "adjusted normal" whereby the right foot is 4˚ more externally rotated than the left at baseline, B) The 21 patients now exhibiting internal RM following adjust for left-right difference. C) The 24 patients now exhibiting an external RM following adjustment for left-right differences.

DISCUSSION

This large retrospective review of a consecutive series of patients was developed to substantiate the incidence of RM following IMN for TSFs. We found a high incidence (36%) of RM after tibial IMN, but also showed that the side (left/right) of the TSF is associated with the direction of RM: left-sided TSFs are prone to internal RM whereas right-sided TSFs resulted in external RM. We hypothesized that a pre-existing 4° left-right difference in tibial torsion may account for this association. Re-analysis of our data considering this 4° difference drastically changed our results. It not only lowered overall incidence of RM (29%), but also lead to a similar distribution of internal/external RM for left- and right-sided TSFs. Importantly, cases previously labelled as significant RM were now found to have rotational alignment within normal ranges. Our results should be interpreted in the light of their strengths and weaknesses. Strengths included: 1) a large series (154 patients), with cohort characteristics fitting those previously reported in the epidemiological study by Larsen et al.[34] when looking at incidence and mechanism of TSF, making results generalizable. 2) The CT protocol for assessing RM has been found to be accurate, reliable and is associated with minimal radiation exposure.[14] 3) We were able to minimize bias by including all patients who had undergone an IMN for TSF with a post-operative CT scan. Weaknesses of the study included: 1) the study was limited to CT findings and hospital records. The findings represent results of a single level-1 trauma center using a single implant. 3) There were multiple surgeons involved with varying levels of training. 4) We were unable to comment on the overall clinical implication of tibial rotational malalignment. 5) This remains a retrospective study subject to the potential bias and residual confounding from unmeasured or inadequately adjusted variables associated with such research designs. In previous literature several different methods have been reported for measuring RM of the tibia.[28,35-38] However, CT is currently gold standard for radiologic assessment of tibial RM due to its ease of interpretation, imaging detail and reproducibility.[3,4,23-25,27,39] The CT protocol we utilized encapsulated a short segment only of the proximal and distal tibia limiting radiation dose to that equivalent to an antero-posterior and lateral chest radiograph. Having previously validated this protocol with an intra- and inter-reliability study[14], we feel it can be used confidently to determine RM of the tibia following an IMN. Contradictory to the low incidence of RM determined by clinical measurements[2,4] various studies have reported high incidences (19%-41%) based on CT-assessments.[1,4,9,10,16] These studies had population sizes ranging from 22-81 patients, and each utilized a slightly different CT technique for determining RM. This study used a validated CT protocol[14] on a large cohort to confirm RM is indeed a serious iatrogenic complication of IMN affecting approximately 1 in 3 patients treated with an IMN for a TSF. Alterations in lower extremity alignment have been associated with increased risk of both acute and chronic lower extremity injuries including stress fractures, patellofemoral maltracking[40,41], cruciate ligament injuries[42,43] and osteoarthritis.[44] None of these studies though, have been conducted on patients who have undergone an IMN for TSF. The main study assessing RM following tibial IMN, conducted by Theriault et al.[10], reported 'lower extremity functional scale' scores to be similar in patients with RM or without RM, and subsequently concluded that RM does not have a significant short- to medium-term functional impact. They hypothesized this was due to a number of intrinsic compensatory mechanisms of the hip, knee and ankle joints, as has previously been demonstrated in RM of femoral shaft fractures.[1] Future studies could assess whether functional outcome of IMN indeed is not affected by tibial RM, and whether the compensation mechanisms of femoral RM (for example internal RM is better tolerated than external RM)[13] are the same for tibial RM. The significant association between the side of the tibial fracture and the direction of RM came unexpected and has not been reported in literature before. We are aware that a more comprehensive study including other potential predictors of (the direction of) RM should be undertaken to assess whether the side of the fracture is an independent predictor. In our large cohort the baseline rotation of all uninjured limbs, had a ±8° range. Despite this fairly large individual variation, we felt that the large group size and for the purpose of this study, would allow averaging to a significant 4° difference in left-right rotation ($p<0.01$). This could explain the association between the side of fracture and direction of RM. This difference is in line with various other studies[31-33,45,46], reporting a left-right difference in tibial torsion in healthy subjects with the right-side being 2.1-4.9° more externally rotated on average.[33,45,47] No translation of this reported anatomical left-right torsional difference into day-to-day clinical practice has been made. Our study aims to enable this, as it could imply that our current assessment of RM is inaccurate. It may explain the higher incidence of internal RM for left-sided TSFs and external RM for right TSFs. This 4° difference in tibial torsion should be considered when assessing RM. Such analysis led to a marked reduction in the incidence of RM in this cohort. Moreover, many cases previously labelled as having RM were now within normal ranges of rotational alignment, and vice versa. Misdiagnosing RM could also have potential consequences when determining impairment ratings: in the USA a RM of ≥10° may entitle the individual to a financial reimbursement under the "Guides to the Evaluation of Permanent Impairment".[17] This finding will not necessarily change nailing practices, though it is important to consider that left-sided TSFs are more likely to be mal-reduced internally where right-sided fractures are likely to be mal-reduced externally. This awareness on its own should reduce the incidence of iatrogenic RM. Conversely, changing the idea of "normal" (left = right) may have an impact on future whole body impairment rating calculations and claims.

CONCLUSION

This study reveals an overall high rate of RM (>10°), in patients undergoing IMN of a TSF, as well as a pre-existing 4° difference in baseline tibial torsion (right more externally rotated). Applying this finding to our patient cohort not only reduced the incidence of RM (36% to 29%), it also sheds a different light on results of previous studies, current clinical practice and could have significant consequences in the diagnosis and management of tibial RM.

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PART V

INTRODUCTION OF THE CARV-PROTOCOL TO AVOID ROTATIONAL MALALIGNMENT DURING INTRAMEDULLARY NAILING

6

INTRAOPERATIVE FLUOROSCOPIC PROTOCOL TO AVOID ROTATIONAL MALALIGNMENT AFTER NAILING OF TIBIA SHAFT FRACTURES: INTRODUCTION OF THE 'C-ARM ROTATIONAL VIEW (CARV)'

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ABSTRACT

Purpose

Rotational malalignment (≥10°) is a frequent pitfall of intramedullary-nailing of tibial shaft fractures. This study aimed to develop an intraoperative fluoroscopy protocol, coined 'C-Arm Rotational View (CARV)', to significantly reduce the risk for rotational malalignment and to test its clinical feasibility.

Methods

A cadaver and clinical feasibility study was conducted to develop the CARV-technique, that included a standardized intraoperative fluoroscopy sequence of predefined landmarks on the uninjured and injured leg in which the rotation of the C-arm was used to verify for rotational alignment. A mid-shaft tibia fracture was simulated in a cadaver and an unlocked intramedullary-nail was inserted. Random degrees of rotational malalignment were applied by using a hand-held goniometer via reference wires at the fracture site. Ten surgeons, blinded for the applied rotation, performed rotational corrections according to 1) current clinical practice after single-leg and dual-leg draping, and 2) according to the CARV-protocol. The primary outcome measure was the accuracy of the corrections relative to neutral tibial alignment. The CARV-protocol was tested in a small clinical cohort.

Results

In total, 180 rotational corrections were performed by 10 surgeons. Correction according to clinical practice using single-leg and dual-leg draping resulted in a median difference of respectively 10.0° (IQR 5.0°) and 10.0° (IQR 5.0°) relative to neutral alignment. Single-leg and dual-leg draping resulted in malalignment (≥10°) in respectively 67% and 58% of the corrections. Standardized correction using the CARV resulted in a median difference of 5.0° (IQR 5.0°) relative to neutral alignment, with only 12% categorized as malalignment (≥10°). The incidence of rotational malalignment after application of the CARV decreased from 67% and 58% to 12% (p=<0.001). Both consultants and residents successfully applied the CARV-protocol. Finally, three clinical patients with a tibial shaft fracture were treated according to the CARV-protocol, resulting all in acceptable alignment (<10°) based on postoperative CT-measurements.

Conclusion

This study introduces an easy-to-use and clinical feasible standardized intraoperative fluoroscopy protocol coined 'C-arm rotational view (CARV)' to minimize the risk for rotational malalignment following intramedullary-nailing of tibial shaft fractures.

Key-words

intramedullary-nailing, tibia shaft fractures, rotational malalignment, 'C-Arm Rotational View (CARV)'

INTRODUCTION

Rotational malalignment remains an iatrogenic pitfall of intramedullary-nailing of tibial shaft fractures which occurs in up to 30% of the cases.[1-7] Alignment control is challenging and visual assessment for adequate alignment is difficult as tibia fractures are often accompanied by soft tissue injury, swelling, and various respective positions of the leg on the operating table.[7] Furthermore, the use of closed reduction techniques and presence of multiple fracture fragments may complicate adequate alignment and interpretation of fluoroscopy images.[8]

Rotational malalignment is defined as a rotation ≥10° if compared to the contralateral side[1-9] and may lead to functional impairments.[10-14] Patients with rotational malalignment qualify for monetary compensation according to the "Guides to the Evaluation of Permanent Impairment".[15] Knowledge on intraoperative identification and how to avoid rotational malalignment is therefore of paramount importance. However, studies on how to avoid rotational malalignment during intramedullary-nailing are scarce.[16-19] Postoperatively, low-dose CT-assessment is considered the gold standard and allows for early detection and revision of rotational errors.[7,8] Hence, CT-assessment is performed postoperatively in case of a clinical suspicion when the opportunity for direct revision has passed. In contrast, for patients with femoral shaft fractures, multiple studies described various intraoperative fluoroscopic strategies and protocols to avoid rotational malalignment during intramedullary-nailing.[20-24] However, an intraoperative fluoroscopic protocol to avoid rotational malalignment during intramedullary-nailing following tibia shaft fractures is still lacking.

The purpose of this cadaver and clinical feasibility study was to develop an easy-to-use intraoperative fluoroscopy protocol, coined 'C-Arm Rotational View (CARV)', using a standard C-arm image-intensifier in order to reduce the risk of rotational errors during intramedullary-nailing of tibia fractures. The following primary research question was posed: can we improve the accuracy of rotational alignment during intramedullary-nailing of tibia shaft fractures utilizing our CARV-protocol relative to present clinical standards?

MATERIAL AND METHODS

A cadaver study was performed in the Skills Center of the University Medical Center Groningen between March 2021 and July 2021. Fresh-frozen cadaveric specimens were used and CT scans of both extremities confirmed that there were no preexistent physiological rotational differences between the left and right tibia. Ten orthopedic trauma surgeons (five residents, five consultants) participated in this study. A standard C-arm image-intensifier (General Electric OEC 9800, Salt Lake City, USA) was used to obtain fluoroscopic images. The total exposure of radiation during the experiment ranged between 0.001 mSv and 0.003 mSv. Approval of the Medical Ethic Review Board of the University Medical Center Groningen was obtained with number 201900721 in accordance to the Declaration of Helsinki.

Research setting

In this cadaver study, a 4 cm longitudinal incision was made at the mid-shaft of the tibia and a transverse tibia fracture and same-height fibula fracture was created with an osteotomy. An unlocked intramedullary-nail (Expert Tibial Nail; DePuy Synthes, Switzerland) was introduced. The unlocked nail press-fitted the isthmus, allowing to rotate the distal tibia over the nail and to apply various degrees of internal and external rotation. Two parallel wooden reference wires were placed on each side of the fracture in order to measure the rotation-angle with a hand-held goniometer (figure 1). The fracture and reference wires were covered with a sterile drape in order to blind the observers to the wire positions.

Rotation of 0° to 30° – both internal and external – were applied by NJB and FIJ. Statistical software package SPSS was used to generate a randomized sequence of applied rotations in order to correct for possible learning effects. The observer, blinded to the applied rotation, first had to estimate the degree of rotation. Hereafter, the observer had to perform a rotational correction by rotating the distal tibia over the nail until the observer was convinced that neutral alignment was obtained. The tibia was fixed in this position and the reference wires were exposed by removing the sterile drape. The angle between the reference wires was measured and recorded. The rotational corrections were first performed according to current clinical practice (as described in the next paragraph) and secondly by using the CARV-protocol (as described in the subsequent paragraph).

How accurate can surgeons estimate and correct tibia (mal)rotation according to current clinical practice?

Present clinical standards included first estimation and correction of tibia (mal)rotation with only the injured leg exposed (single-leg draping) and second estimation and correction of tibia (mal) rotation with two legs being exposed (dual-leg draping). Correction techniques were according to the surgeons' preferences and included clinical assessment of the position of the leg, palpating the anteromedial rim of the tibia, fluoroscopy assessment of the cortical width at the fracture site, or a combination of techniques.

Can we improve the accuracy of rotational alignment by use of the CARV-protocol?

The CARV-technique is a standardized intraoperative fluoroscopic algorithm in which an anteroposterior (AP)-view of the knee at the contralateral side is combined with a perfect mortise-view of the ankle, obtained by rotating the C-arm without manipulating the ankle. The standardized fluoroscopic views at the contralateral side combined with rotation of the C-arm itself were used as an example to align the tibia at the injured side (figure 2.1 & figure 2.2). The detailed workflow of CARV includes (figure 1):

Determination of the fluoroscopy landmarks at the contralateral side. First, the C-arm was positioned in neutral position (0°) and an AP-view of the knee was obtained, defined by the exact intersection of the lateral cortex of the proximal tibia trough the tip of the proximal fibula (figure 1.1).[25] Hereafter, the C-arm shifted to the ankle while the surgeon kept the knee in exact AP-position (figure 1.2). A mortise-view was obtained by rotating the C-arm 20°–30° without manipulating the ankle. The mortise-view was defined as an AP-view of the ankle joint with equal medial, lateral and superior clear spaces[26,27] (figure 1.2). Both images were saved and converted to the output window of the C-arm. The degree of rotation of the C-arm was recorded.

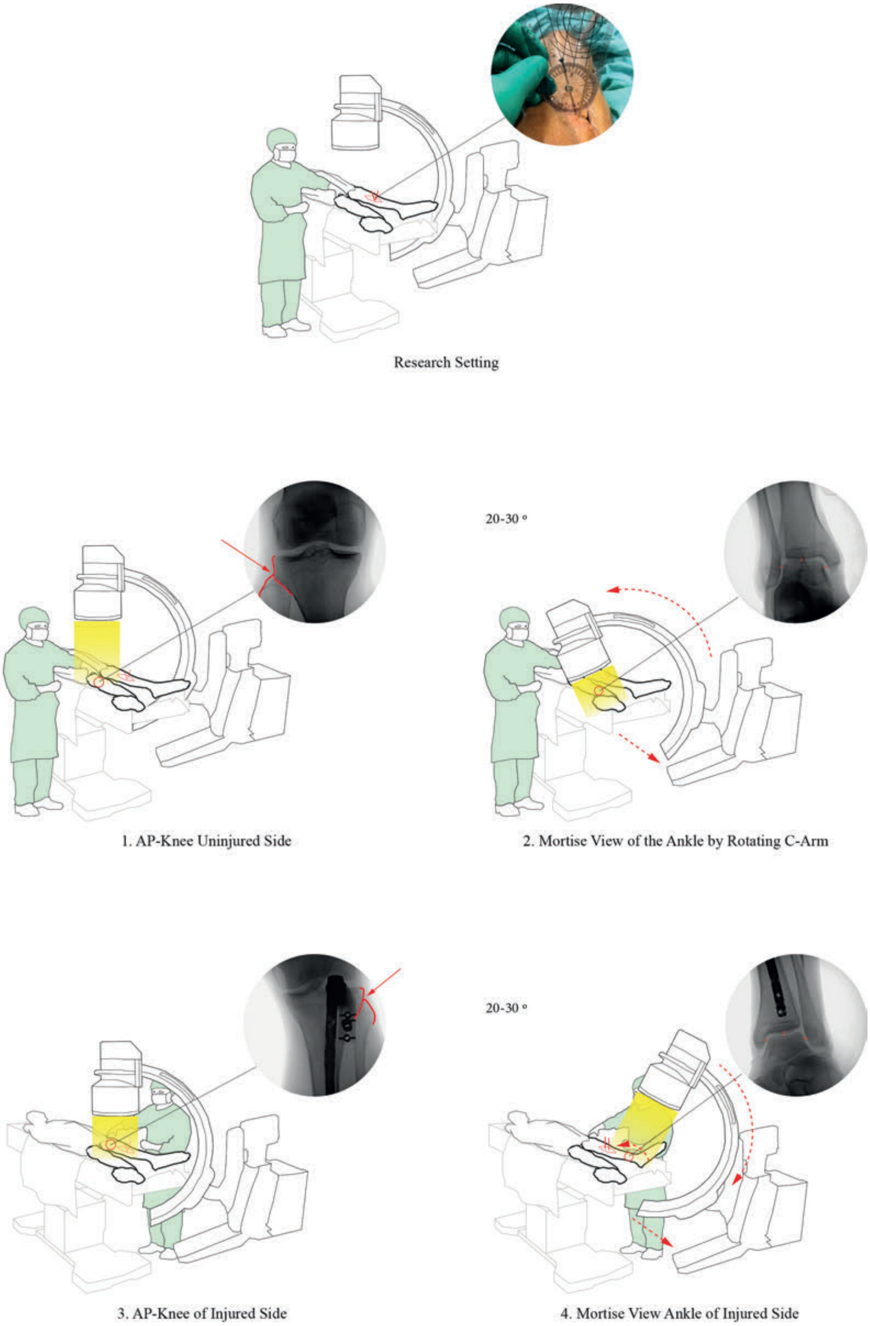

FIGURE 1. Schematic overview of the ''C-arm Rotational View (CARV)''. The CARV is an intraoperative fluoroscopy sequence comparing the uninjured and injured leg in which the degree of rotation of the C-arm itself is used to correct for rotational malalignment of the tibia. At the uninjured leg, a perfect mortise-view is taken with the knee in AP position by rotating the C-arm between 20-30°. At the injured leg, the C-arm is rotated to the same extent in the opposite direction while the knee is in AP position and subsequently the distal part of the lower leg is rotated until a perfect mortise-view is achieved, indicating symmetrical tibial alignment.

Determination of the fluoroscopy landmarks of the injured side. An identical AP-knee as compared to the contralateral side was obtained (figure 1.3). Subsequently, a mortise-view of the ipsilateral ankle was obtained by rotating the C-arm in the exact opposite position as determined on the opposite side (figure 1.2, figure 1.4). In case of an adequate tibial alignment, the mortise-view should appear and be identical to the contralateral reference mortise-view of the ankle. Any discrepancies indicated rotational malalignment and subsequent correction was performed by rotating the distal tibia over the nail while the knee remained in AP-position until and identical mortise-view was established, indicating neutral alignment (figure 1.4).

Definition of outcome measures

Ten observers performed a total of 180 rotational corrections (60 unstandardized corrections after single-leg draping; 60 unstandardized corrections after dual-leg draping; 60 corrections according to the standardized CARV-technique). The primary outcome was the accuracy of rotational correction, assessed with a hand-held goniometer and measured in degrees at the level of the tibia fracture (figure 1). Neutral alignment of the tibia was defined as an angle of 0° between the reference wires at the level of the tibia fracture as compared to the contralateral reference. The results were categorized into acceptable (<10°) and unacceptable (≥10°) rotational alignment.

Clinical feasibility

The clinical feasibility of the CARV-protocol was tested in a small prospective cohort representing a total of three patients treated with intramedullary-nailing for a tibial shaft fracture (supplementary materials). Patients were positioned in supine position and both extremities were draped free. No traction was applied. Rotational correction was performed using the standardized CARV-protocol after insertion of the unlocked intramedullary-nail. After obtaining the correct predefined fluoroscopy landmarks, definitive locking was performed. All patients underwent post-operative CT-assessment in order to verify the alignment of the tibia according to our standardized measurement technique [8].

Statistical analyses

Statistical software package SPSS 28.0 was used for analyzing data. The rotational accuracy was presented as median with interquartile range (IQR). The differences in rotational accuracy between CARV and present clinical standards were calculated by use of the Mann-Whitney-U test. The categorical data for acceptable and unacceptable alignment was presented as counts and percentages. Differences in incidences of malalignment were analyzed using the Pearson's Chi-square test. A p-value under 0.05 was considered statistically significant.

RESULTS

How accurate can surgeons estimate and correct tibia (mal)rotation according to present clinical standards?

The observers' clinical judgement of the (mal)rotated injured limb with use of single-leg draping deviated 10.0º (IQR 15.0º) from the rotation that was applied. Subsequent correction, based on one leg being available to judge the reduction, resulted in a median malalignment of 10.0º (IQR 5.0º) (table 1). A total of 33% of the attempts resulted in acceptable rotational alignment (<10º) whereas the remaining 67% resulted in an unacceptable alignment (>10º) (table 1). In terms of the accuracy of clinical assessment, there was no difference between consultant surgeons and residents with regards to clinical judgment and correction for malalignment with use of single-leg draping (p=0.89) (table 2).

Clinical estimation with use of dual-leg draping, allowing for direct comparison of the rotational profiles of both limbs, deviated 12.5º (IQR 15.0º) from the rotation that was applied. Subsequent correction, allowing for making the appearance of the legs identical, resulted in a median deviation of 10.0º (IQR 5.0º) from neutral alignment (table 1). A total of 42% of the corrections represented acceptable rotational alignment (<10º). The remaining 58% accounted for unacceptable alignment (≥10º) (table 1). We found no relationship between the level of experience and the accuracy of correction after dual-leg draping (p=0.98) (table 2).

TABLE 1. The accuracy of correction for rotational malalignment according to present clinical standards and the CARV-protocol.

	Single-leg draping	Dual-leg draping	CARV
Rotation relative to neutral alignment **(**median ± IQR)	10.0º (5.0º)	10.0º (5.0º)	5.0º (5.0º)
Acceptable alignment (<10º) (n, %)	20 (33%)	25 (42%)	53 (88%)
Unacceptable alignment (≥10º) (n, %)	40 (67%)	35 (58%)	7 (12%)
10º – 19º (n, %)	*35 (60%)*	*29 (48%)*	*7 (12%)*
20º – 29º (n, %)	*5 (7%)*	*5 (8%)*	*0 (0%)*
≥ 30º (n, %)	*0 (0%)*	*1 (2%)*	*0 (0%)*

TABLE 2. The relationship between level of experience and accuracy of correction for rotational malalignment by using CARV, single-leg or dual-leg draping respectively.

	Correction		
Method	**1. Consultant**	**2. Resident**	**P-value**
1. Single-leg draping (median ± IQR)	10.0º (6.3º)	10.0º (5.0º)	0.89
2. Dual-leg draping (median ± IQR)	10.0º (6.3º)	10.0º (5.0º)	0.98
3. CARV (median ± IQR)	5.0º (5.0º)	5.0º (5.0º)	0.73

Can we improve the accuracy of rotational alignment by use of the CARV-protocol?

To answer the primary research question with regards to the accuracy of CARV, we found that correction with use of the CARV-protocol deviated at a median of 5.0º (IQR 5.0º) from neutral alignment (table 1). A total of 88% of the attempts resulted in a rotation of <10º indicating acceptable alignment. Only 12% was categorized as an unacceptable alignment (≥10º) (table 1). Both residents and consultants were able to apply the CARV-technique without differences in performance between groups (p=0.73) (table 2). Application of the CARV-protocol showed a significantly lower proportion of unacceptable rotational alignment compared to unstandardized correction with use of single-leg draping, (67% vs 12%, p<0.001) and unstandardized correction with use of dual-leg draping (58% vs 12%, p<0.001) (table 3).

Clinical feasibility of the CARV-protocol

A total of three consecutive patients (43yrs, 43yrs, 19yrs) underwent intramedullary-nailing with application of the CARV-protocol. Different fracture patterns were included (AO/OTA [28] type 42-B2, 42-C2, 42-B3). We were able to apply the CARV-protocol clinically as proposed in our experimental study set-up. The clinical cases demonstrate the feasibility of CARV in clinical practice. The rotational outcomes based on postoperative CT assessment are presented in the supplementary materials. The rotational alignment in cases 1-3 were respectively 3º, 4º and 8°, indicating acceptable tibial alignment in all cases.

DISCUSSION

There is a high incidence of rotational malalignment following intramedullary-nailing for tibia shaft fractures with incidences up to 30%.[1-7] An intraoperative fluoroscopy protocol to increase accuracy of alignment control during intramedullary-nailing of these fractures is still lacking. This study is the first to present an accurate and clinically feasible standardized intraoperative fluoroscopy protocol coined 'C-Arm Rotational View (CARV)' in order to minimize the risk on rotational malalignment, and to avoid rotational outliers during intramedullary-nailing of tibia shaft fractures.

Our primary findings demonstrate that tibial alignment during intramedullary-nailing of tibia shaft fractures can be significantly improved by using the CARV-protocol. Only 12% of

TABLE 3. The incidence of rotational malalignment after application of the CARV versus single-leg and dual-leg draping.

	CARV	Single-leg draping	Dual-leg draping	CARV vs. Single-leg draping	CARV vs. Dual-leg draping
Acceptable (<10º)	53 (88%)	20 (33%)	25 (42%)		
Unacceptable (≥10º)	7 (12%)	40 (67%)	35 (58%)		
				p<0.001	p<0.001
Total observations	**60**	**60**	**60**		

the corrections were categorized as unacceptable rotational alignment (≥10°). Secondly, we found that clinical estimation of rotation followed by realignment of the tibia according to present clinical standards is inaccurate. A total of 67% of the rotational corrections after single-leg draping and 58% after dual-leg draping resulted in unacceptable rotational alignment (≥10°). Application of the CARV relative to current clinical practice decreased the rate of rotational alignment from 67% and 58% to 12% respectively ($p<0.001$).

This study should be interpreted considering strengths and weaknesses. The CARV-protocol was tested in cadaveric specimens in which only a transverse mid-shaft fractures was simulated instead of different fracture patterns. We felt that incorporating a mid-shaft fracture in the study-set up allowed for adequate measuring of tibia (mal)alignment using reference wires on both fracture sites. We believe that the simplified nature of our test set-up does not disqualify our findings. Moreover, CARV was successfully applied in the case series that included different fracture patterns. Although proven to be clinically feasible, prospective clinical studies are needed to clinically validate the CARV-protocol on a larger scale. Secondly, the CARV-method works under assumption that each individual has almost symmetric tibias leading to symmetric radiographic landmarks. A previous study by our group demonstrated a potential physiological difference of 4° between the right and left tibiae.[7] We believe that the small difference between the right and left tibiae does not have compromised the performance of CARV-protocol in this experimental study.

In femoral shaft fractures, multiple simple intraoperative fluoroscopy protocols have been described to avoid rotational malalignment after intramedullary-nailing.[20-24] Similarly, the potential of rotational malalignment following intramedullary-nailing for tibia shaft fractures can be minimized by simple application of the CARV-protocol. Some methods for avoiding rotational malalignment have been described in literature. Recently, a case-report reported on the perfect lateral view of the ankle in order to obtain adequate alignment during intramedullary-nailing for tibia shaft fractures.[18] However, this technique was not tested or validated in a research setting confirming its accuracy and useability. Clementz et al.[16] introduced a fluoroscopy-technique in 1989 measuring the angle between femur and ankle by assessing the overlap of the anterior and posterior cortex of the medial malleolus. This technique did not find its way in standard clinical practice despite multiple attempts to endorse its feasibility.[29,30]

Correction according to present clinical standards using either single-leg or dual-leg seemed to be insufficient in this experimental study, and has proven insufficient in multiple clinical prospective cohort studies.[1-7] This inaccuracy may be caused by 1) difficulties in clinical estimation and 2) the absence of a standardized fluoroscopy protocol to obtain adequate alignment. Among observers the cortical step sign (CSS) and diameter difference sign (DDS) was used for alignment control[17]. Although Keppler et al.[19] proved the CSS and DSS to be reliable landmarks to detect and correct for malrotation, we feel that the clinical feasibility is limited due to differences in fracture patterns and possible axial translation of the tibia caused by the eccentric position of the intramedullary-nail in the tibia-shaft.

The first advantage of the CARV-protocol was the use of the C-arm as simple and accurate indicator for rotational malalignment rather than inaccurate clinical judgment. The C-arm was able to detect a 5° rotational difference between both injured and uninjured limb by revealing sufficient small fluoroscopy alterations of the proximal tibiofibular overlap and mortise-view of the ankle (figure 2). A second asset of the CARV-protocol includes the simple standardization of rotational correction techniques. The need for such was strengthened by the existence of a wide range of insufficient correction techniques among observers which resulted in relatively high rates of unacceptable rotational outcomes. We found no relationship between level of experience and successful application of the CARV-technique, and finally, the CARV-protocol has proven to be accurate in a clinical setting with different fracture patterns underlying its potential practicability and reproducibility in clinical practice.

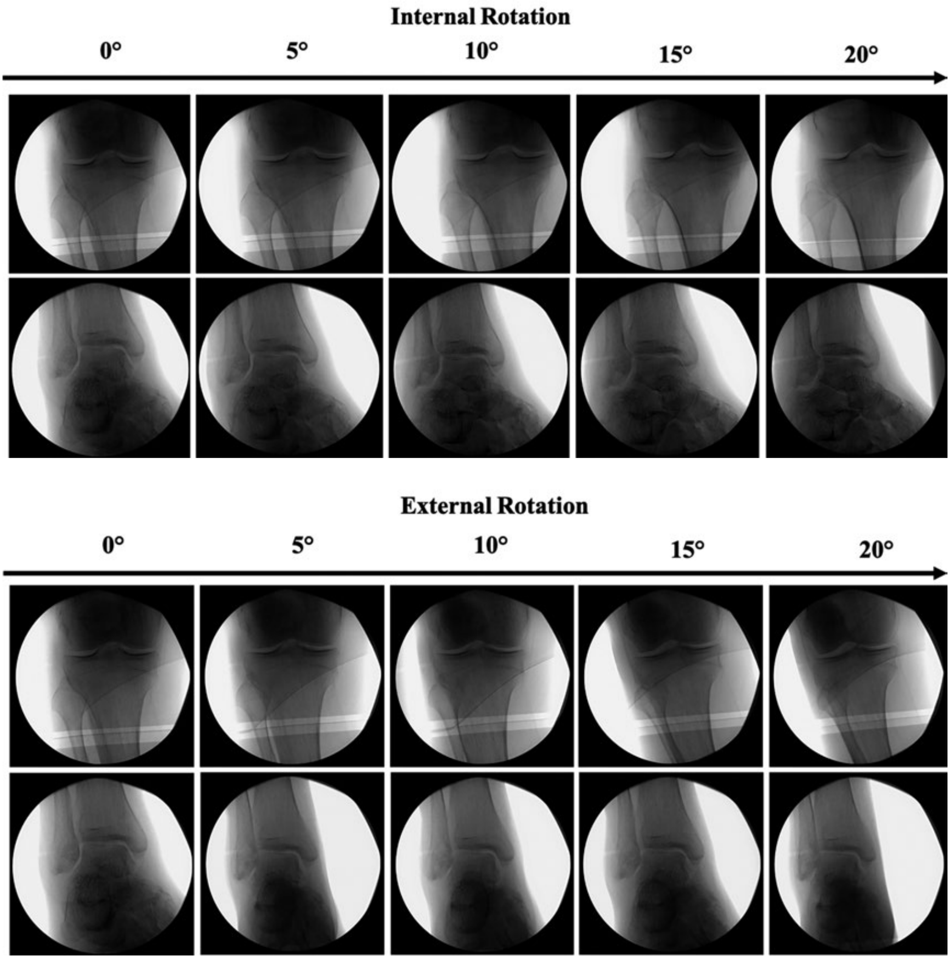

FIGURE 2.1 & 2.2. Schematic overview of alterations of the proximal- and distal landmarks of the CARV protocol after applying different degrees of both internal- and external rotation. After application of internal rotation, the proximal fibula head is more exposed while the medial clear space of the ankle-joint minimizes. After application of external rotation, there was an increased superimposement of the proximal fibula head by the lateral tibia plateau with lesser distance of the lateral clear space of the ankle joint.

CONCLUSION

This experimental study is one of the first to present a simple standardized intraoperative fluoroscopy protocol named the 'C-arm Rotational View (CARV)' to reduce iatrogenic rotational malalignment following intramedullary-nailing for patients with a tibia shaft fracture. The CARV-protocol has proven accurate and reproducible in cadaveric specimens and feasible in several clinical cases. Both consultants and residents successfully applied the CARV-protocol. Future prospective cohort studies are needed to determine the diagnostic performance characteristics in clinical practice.

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7

CLINICAL VALIDATION OF THE 'C-ARM ROTATIONAL VIEW (CARV)': STUDY PROTOCOL OF A PROSPECTIVE MULTI-CENTER RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Introduction

Rotational malalignment occurs in up to 30% of cases after intramedullary-nailing of tibial shaft fractures. The aim of this study is to assess the clinical feasibility of a new introduced standardized intraoperative fluoroscopy protocol coined 'C-Arm Rotational View (CARV)' in order to reduce the risk of rotational malalignment during intramedullary-nailing of tibial shaft fractures. The CARV includes predefined fluoroscopy landmark-views of the uninjured side to obtain correct alignment of the injured side with use of the rotation of the C-arm.

Methods and analysis

This multicenter randomized controlled trial will be conducted in two level-1-trauma centers. Adult patients with an open or closed tibial fracture, eligible for intramedullary-nailing, will be enrolled in the study. The interventional group will undergo intramedullary-nailing guided by the CARV protocol to obtain accurate alignment. The control group undergoes intramedullary-nailing according to current clinical practice, in which alignment control of the tibia is based on clinical estimation of the treating surgeon. The primary endpoint is defined as the degree of rotation measured on low-dose postoperative CT-scans.

Ethics and dissemination

The study-protocol will be performed in line with local ethical guidelines and the Declaration of Helsinki. The results of this trial will be disseminated in a peer-reviewed manuscript. Future patients are likely to benefit from this trial as it aims to provide a clinical feasible and easy-to-use standardized fluoroscopy protocol to reduce the risk for rotational malalignment during intramedullary-nailing of tibial shaft fractures.

Key-words

Tibial shaft fractures, intramedullary-nailing; rotational malalignment; C-Arm Rotational View (CARV); multi-center randomized controlled trial.

SUMMARY – STRENGTHS & LIMITATIONS

» This multi-center randomized controlled trial is the first to determine the clinical feasibility of a new introduced fluoroscopy protocol coined 'C-Arm Rotational View (CARV)' in order to reduce the risk of rotational malalignment during intramedullary-nailing of tibial fractures.

INTRODUCTION

Tibial shaft fractures are common long bone fractures in the field of Orthopaedic Trauma. In the USA, approximately half a million tibial fractures were registered per year by the National Center of Health Statistics (NCHS).[1] Intramedullary-nailing is the treatment of choice for shaft fractures. However, rotational malalignment defined as a rotation of ≥10° relative to the contralateral side remains a problem with a prevalence up to 30%.[2-10]

From a clinical point of view, there is limited knowledge on how to reduce the risk of rotational malalignment. Clinical estimation and intraoperative judgment of tibial alignment is difficult, often resulting in underestimated alignment errors.[11] This might also be the contributive factor to relatively high incidences reported in literature.[2-10] Low-dose CT-assessment is considered the gold standard to objectify rotational malalignment, but it is only performed after surgery when the opportunity for direct revision has passed. Both difficulties in intraoperative clinical judgement of tibial alignment as well as postoperative detection of rotational malalignment when the possibility for direct revision has passed, do support the need for an easy-to-use intraoperative fluoroscopy protocol to minimize the risk for rotational malalignment during intramedullary-nailing of tibial shaft fractures.

Recently, a standardized protocol named the 'C-Arm Rotational View (CARV)' was developed in order to improve the accuracy of tibial alignment during intramedullary-nailing of tibial shaft fractures. The CARV includes predefined fluoroscopy landmarks of knee and ankle of the uninjured side to obtain correct alignment of the tibia at the injured side using the rotation of the C-arm to verify the degree of rotation. Promising preliminary results were found to reduce the risk of rotational malalignment following intramedullary-nailing of tibial shaft fractures in a recent cadaver and clinical feasibility study. A prospective trial is needed to determine the performance of CARV in clinical practice. Therefore, a prospective multi-center randomized controlled trial is designed to assess the potential clinical benefits of the CARV-protocol. The following primary research question was defined: does the CARV-protocol reduce the risk of rotational malalignment following intramedullary-nailing of tibial shaft fractures?

PRIMARY ENDPOINTS

1. Determine the incidence of rotational malalignment using validated postoperative CT-assessment.[9] Rotational malalignment is defined as a rotation ≥10° relative to the contralateral side.[2-10]

MATERIAL AND METHODS

Study setting

To answer the primary research question, a multi-center prospective randomized controlled trial is designed. The protocol is structured and written according to the SPIRIT checklist.[12] The study will be conducted in two level-1 trauma centers; of the University Medical Centers Groningen, Netherlands and Flinders Medical Center, Flinders University, Adelaide, Australia.

Eligibility criteria

All consecutive patients (≥18 years) with an open or closed tibia shaft fracture, who are eligible for intramedullary-nailing, will be asked to participate in the study. The following exclusion criteria will be used: age <18 years, fractures not suitable for intramedullary-nailing and pathological fractures.

Intervention

Patients will undergo intramedullary-nailing performed by board-certified orthopaedic trauma surgeons in the level-1 trauma centers. Fluoroscopy imaging will be performed with use of a C-arm Image Intensifier (II) (GE (General Electric) OEC 9800, Salt Lake City, USA). Patients assigned to the intervention group will be treated according to the local guidelines in which alignment control is guided by the 'C-Arm Rotational View' (CARV). Patients will be positioned in supine position with both extremities draped free allowing for comparison of the injured and the uninjured leg (figure 1).

First, the fluoroscopy references of the uninjured side are determined by an anteroposterior (AP)-view of the knee and mortise-view of the ankle (figure 1). The AP-knee is defined as exact intersection of the lateral cortex of the proximal tibia through the tip of proximal fibular head.[13] The knee is kept in perfect AP-position while the C-arm is moved towards the ankle. The mortise-view, which is defined as an AP-view with equal lateral, medial and superior clear spaces,

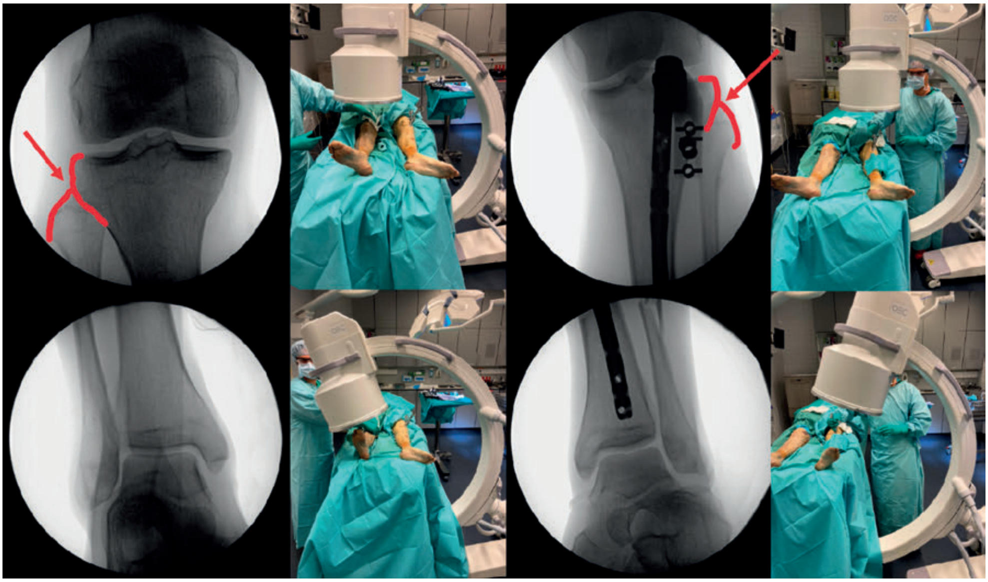

FIGURE 1. The CARV-protocol consists of predefined fluoroscopic landmarks of the injured and uninjured side. The first landmark is the proximal tibiofibular overlap of the uninjured side with the knee positioned in perfect AP. The second landmark is the mortise-view of the uninjured ankle, obtained by rotating the C-arm. The aim of the CARV-protocol is to mimic these landmarks on the injured side by first obtaining a perfect AP-knee with an equal tibiofibular overlap. The second step is obtaining a mortise-view of the ankle by rotating the C-arm in exact opposite direction. Discrepancies in the mortise-view indicate rotational malalignment and subsequent correction can be performed until the mortise-views of the injured and uninjured side appeared to be identical.

is obtained by rotating the C-arm 20 – 30° over the ankle while the leg is remained in its initial neutral position. Both reference images are saved and the degree of C-arm rotation is recorded (figure 1). Subsequently, the C-arm is moved towards the injured side. Intramedullary-nailing (Expert Tibia Nail, Depuy Synthes or Trigen Meta-Nail, Smith and Nephew) will be performed according to the surgeons' routine. When necessary, open reduction of the fracture is allowed and will be left to the discretion of the surgeon. It is part of standard clinical practice and allowance is important for the generalizability of the findings in this study. Due to randomization, open fracture reductions will probably be performed equally in both study arms and therefore not cause any selection bias. If the number of open fracture reductions is not equally distributed in both study arms, we will perform correction using a multivariate analysis. First, an identical AP-view of the knee is obtained as compared to the contralateral side. Second, a mortise view is obtained by rotating the C-arm in exact opposite gradual position in order to mimic the mortise view of the contralateral ankle (figure 1). Any discrepancies between mortise views of the uninjured and injured side indicate incorrect alignment. Adequate alignment is obtained by rotating the distal part of the tibia until an exact mortise-view of the ankle is attained as compared to the reference images. When adequate tibial alignment is obtained according to CARV, definitive locking is performed.

Control group

Patients assigned to the control group will undergo an identical surgical procedure as patients assigned to the interventional group. The only difference with the intervention group is that tibial alignment will be obtained according to present unstandardized clinical standards that included clinical assessment of the position of the leg, palpating the anteromedial rim of the tibia, fluoroscopy assessment of the cortical width at the fracture site, or a combination of techniques.

Outcomes

Postoperatively, patients in both groups will undergo low-dose CT-assessment in order to objectify the degree of (mal)rotation of the nailed tibia with the contralateral leg as a reference. Low-dose CT-assessment is part of the standard of care and radiation exposure is negligible (0.04mGy – 0.06mGy).[9] A schematic overview of the study is presented in figure 2. The measurement technique, as described by Bleeker et al.[9], will be used to measure the degree of (mal)rotation on the postoperative CT-images. The inter-observer reliability of this measurement technique is 0.95 and the intra-observer reliability is 0.90, both indicating excellent accuracy according to the categorization of Landis & Koch.[14] To avoid confirmation bias, the CT-assessments will be performed by two researchers who are unaware of the treatment allocation. The average of both measurements will be taken.

Additional data

Baseline data will be collected, including patient characteristics, trauma mechanism, open/closed fracture according to the Gustilo classification[15], OTA/AO classification[16], whether open/closed fracture reduction is performed, surgical approach, single-leg or dual-leg draping, the gradual

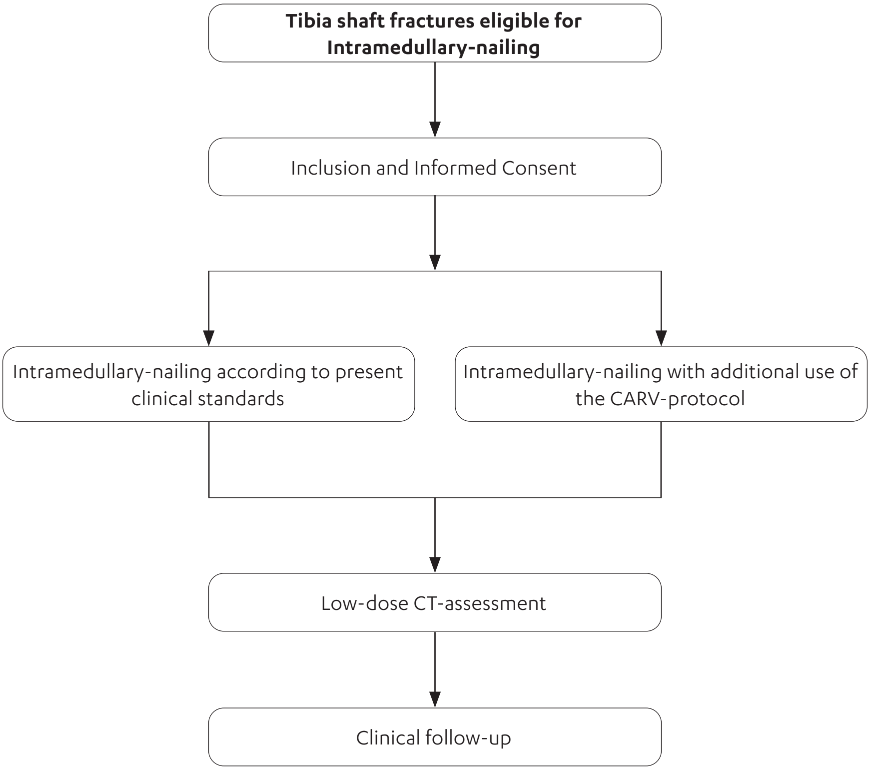

FIGURE 2. Flow-chart of the trial.

position of the C-arm and how surgeons performed rotational control during the operation according to present clinical standards.

Participant timeline

Patients enrolled in the study will undergo intramedullary-nailing at T0 of the trial. Patients will undergo postoperative low-dose CT-assessment within 2 weeks after surgery for assessment of the degree of rotation of the nailed tibia relative to the contralateral side. Routine radiographic and functional follow-up using validated patient reported outcome measures will be performed according to standardized timepoints used in the hospital (figure 3). During these outpatient clinic visits, standard radiology imaging of the fractured tibia is performed. The end of study participation is when patients complete the 1-year follow-up (figure 3).

Sample size calculation

The main outcome measure encompasses rotational malalignment. The incidence of rotational malalignment based on data of a historic prospective cohort was 36%.[8] This trial aims to reduce the prevalence from 36% to 15% or less. The power analysis calculated that approximately 132 patients

	Study Period					
	Enrollment	Allocation	Post-allocation			Close-out
TIMEPOINT**	t_0		t_1	t_2	t_3	T_6
			2w	*6w*	*3m*	*1y*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocations	X					
INTERVENTIONS:						
Intervention group: IMN with CARV	X					
Confront group: IMN without CARV	X					
ASSESSMENTS:						
Baseline characteristics	X					
Postoperative CT-assesment		X				
Routine radiographic and functional follow-up			X	X	X	X

FIGURE 3. Study mapping.

(66 per arm) are needed to decrease the incidence of rotational malalignment to 15% with a power of 80%, confidence interval of 95% and alpha of 0.05. A total of 20% extra patients will be enrolled to recompense for a potential loss to follow-up resulting in total of 160 patients (80 per arm).

Recruitment and feasibility

Patients presenting at the emergency department of the participating level-1 trauma centers with a tibial shaft fracture eligible for inclusion will be approached by orthopaedic trauma residents or orthopaedic trauma consultants for participation in this trial. Written study information is handed. Once written informed consent is obtained, patients will be randomly assigned to the intervention group or control group.

In total, about 80 – 100 patients are treated yearly with an intramedullary-nail for a tibial shaft fracture in the study hospitals. We believe that approximately 80% of the patients are willing to participate in the trial. Based on the sample size calculation, the total inclusion period will be approximately 2 years which makes the total duration of the study feasible.

Assignment for interventions

Patients will be randomly assigned to the intervention group (CARV-group) or the control group with a 1:1 distribution without stratification of patient characteristics using a sealed opaque envelope. Random numbers will be generated by a computer assisted random number generator. The randomization process meets the requirements of allocation concealment. Each study hospital does have a local study-coordinator whom guides and verifies the process of randomization. Patients will be enrolled in the trial by the researcher of the treating clinician. The trial is blinded for patients by not enlighten them about the allocation for either the interventional- or control group. As this trial includes similar surgical procedures in both arms, we feel that this blinding-method is justifiable.

Data collection and management

The data will be electronically stored on a secured file according to the local data protection guidelines. Access to the data is only possible by NJB, FIJ and RJ or after authorization of the senior researcher (FIJ). The data is not traceable to an individual participant by anonymization and encryption. The data will only be used for this research project and will not be used for other research purposes. The quality of data will be ensured by NJB, FIJ and RJ, and, in case of uncertainties, a fourth independent researcher will be consulted. The data will all be removed after fifteen years of storage.

Statistical analyses

Statistical analyses will be performed using SPSS version 28.0.0.0. Descriptive statistics will be provided for the outcomes of interest. Normal distributed continuous data are presented as means with standard deviation (SD). Not normally distributed data will be presented as median with interquartile range (IQR). In order to determine the rotational differences between both groups, the Chi-squared test or Fisher exact test will be used. Correction for confounders such as Gustilo classification[15], OTA/AO classification[16], whether open/closed fracture reduction is performed and surgical approach (infrapatellar of suprapatellar) will be performed with a multivariate regression analysis.

Monitoring

Intramedullary-nailing is a well-established and often-applied surgical modality for tibia shaft fractures. Besides the potential for recognized health-risk related to this treatment modality, the participants in the intervention group will not be exposed to additional health risks in comparison to the control group. We therefore believe that appointment of a data monitor committee (DMC) is of non-contributing value as well as an interim analyses. Potential adverse effects are immediately reported by NJB, FIJ and RJ. NJB, FIJ and RJ are responsible for reporting the adverse effects to the local ethical committee according to the local guidelines.

Ethics and dissemination

This study-protocol will be performed in line with local ethical guidelines and the Declaration of Helsinki. The protocol is currently under review by the ethical committee and the committee will be informed if there are any sufficient changes which may impact the study participants. Informed consent will be obtained by orthopaedic trauma residents or board-certified orthopaedic trauma surgeons, all familiar with the study protocol. The involved clinician is able to provide the necessary information as well as the information provided by the written information-forms.

Personal data will be handled strictly confidential and only NJB, FIJ and RJ will have access to the data-sets. Participation in this trial is completely voluntary and participants are able to withdraw from study site at any moment.

Patients allocated to the interventional group are not exposed to additional health risk when compared to patients allocated to the control-group. All surgeons participating are board-certified surgeons with ample surgical experience. Patients in both groups undergo identical surgical treatment except for the additional fluoroscopy imaging (4 images) which is unlikely to introduce extra potential health related threats. The exposure of radiation is negligible. Furthermore, participants in both groups receive postoperative a rotational profile CT, which is part of our current tibia nailing protocol. Exposure to radiation during low-dose CT rotational planning is comparable to a chest X-ray (0.04mGy – 0.06mGy) and, therefore, very minimal.[9] During follow-up, participants in both groups visit our outpatient clinic for routine radiographic follow-up and patient-reported measures at 6 weeks, 3 months and 1 year. There are no extra visits required for patients in the intervention group if compared to the control group (i.e., current standard of care).

Future patients with a tibial shaft fracture are likely to benefit from the study outcomes. By performing this multi-centered randomized controlled trial, we aim to clinically implement the CARV-protocol in daily practice and provide an evidence-based method to reduce the risk for rotational malalignment during intramedullary-nailing of tibia fractures. The trial aims to start in September 2022.

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PART VI

GENERAL DISCUSSION / CONCLUSION

SUMMARY

NEDERLANDSE SAMENVATTING

GENERAL DISCUSSION / CONCLUSION

Part II. Should we go suprapatellar or infrapatellar for intramedullary nailing of tibia fractures?

Dealer's choice: no statistically significant differences between IP- and SP-nailing were found with regards to anterior knee pain, rotational malalignment, complications rates and physical outcomes. We recommend to use either the SP-approach or IP-approach depending on surgeon's preference and hospital logistics.

The SP-approach gained popularity as promising alternative for the traditional IP-approach. This was due to the possible reduction of anterior knee pain[1-4] and better alignment control by a more extended position of the leg on the operating table.[5-7] High incidences of anterior knee pain were reported after the IP-approach and the flexed position of the leg on the operation table might have introduced difficulties in alignment control. In contrast for the SP-approach, there were also few clinical concerns, including patellofemoral chondropathy and infection due to the passing of the nail superior of the proximal patellar pole and the articular surface of the knee.[8-14] In chapter 1 of this thesis, we found that both the SP- and IP-approach are reliable surgical techniques for IMN of tibia fractures with, interestingly, statistically comparable rates of anterior knee pain after the SP-approach (29%) and IP-approach (39%). In case of malalignment, evidence was found that the SP-approach might allow for better alignment control in proximal and distal located tibia fractures. However, the absolute differences were nihil when malalignment was measured on plain radiographs, as most studies lacked CT-measures of RM. Furthermore, only 2 cohort studies addressed the potential of patellofemoral chondropathy based on a 12-months MRI and arthroscopy. No iatrogenic damages were found to the cartilage layer after the SP-approach. The last clinical concern, including infection, was also not of significant difference between both surgical approaches. Most of the fracture-related-infections occurred after nailing of open tibia fractures. The potential for developing a knee sepsis after SP-nailing of open tibia fractures was negligible if compared to IP-nailing.

Part III. Or, should we plate them all? But what about wound problems?

When soft tissue complications are not a threat, perform plate fixation of distal tibia fractures. It also reduces the risk for anterior knee pain and alignment errors. Perform IMN when soft tissues are compromised by crush or high energy injury, in patients with comorbidities to reduce the risk for infection or with a low-demanding physical state.

In the search of defining which treatment is better for definitive treatment of distal tibia fractures, both plate fixation and IMN have been described as core surgical modalities. In chapter 2, a meta-analysis of the literature was performed in order to determine the optimal surgical strategy. The search was not limited by study design to increase sample size and generalizability of results.[15-20] There were several differences between the two surgical modalities: first, a higher rate of infection was observed after plate fixation compared to IMN. In the literature superficial- and deep surgical site infections were often merged, whilst from a clinical point of view their relevance is quite different. Deep infections far more often result in prolonged hospital admissions and surgical reinterventions. As also espied in part III of this thesis, anterior knee pain was more frequent reported after IMN. There was evidence for a higher risk of developing mal-union in patients treated with IMN as compared to plate fixation. Chapter 3 represents an extension of chapter 2. A retrospective study was performed focusing on MIPO vs. IMN regarding clinical-, radiological and functional outcomes. A higher rate of infection after MIPO and higher rate of anterior knee pain after IMN was found, but not new in the light of the previous findings in chapter 2. Contrary to the findings in chapter 2, a higher rate of non-union among patients treated with IMN was found compared to MIPO. The possible reason included that more high-energy traumas and more open fractures were treated with IMN instead of MIPO. In chapter 3, bilateral draping of both extremities was routinely used to limit the risk of RM during IMN of tibia fractures. The hypothesis included that the risk for RM can be reduced if bilateral draping of both extremities is performed allowing for intra-operative comparison of the rotational profiles of both tibiae.

Based on the studies presented in part III of this thesis, we conclude that both IMN and plate fixation are viable surgical options for treatment of distal tibia fractures. Both modalities do have their own specific disadvantages while the definitive choice is not straightforward. Surgical decision making requires sufficient knowledge on these specific outcomes and should be aligned with patient specific demands. If there is a high risk for infection, for example in obese or diabetic patients, IMN should be the treatment of choice with immediate full weightbearing as allowed depending on the fracture pattern. On the other hand, young active patients or patients less prone for infection might benefit from plate fixation as it has a lower risk for anterior knee pain and potential alignment errors.

PART IV. Rotational malalignment is a frequent iatrogenic pitfall of intramedullary nailing

In part IV of this thesis, we elaborate on RM after IMN of tibia fractures. There is a high incidence of RM after tibia nailing reported in literature, with percentages up to 41%.[21-25] Full length CT-assessment of the tibiae is considered as golden standard for early diagnosis, but has not been mainstream in clinical practice. This might be ascribed to costs, impracticality and assumed high radiation exposure. Relatively low incidences of RM were reported after clinical assessment (0-8%), and significantly differed from reported incidences based on CT-assessment up to half of patients, indicating the challenging aspect of diagnosing RM with just use of clinical assessment.[26] In chapter 4, we concluded that low-dose postoperative CT-assessment (few proximal and few distal axial slices) for RM is a reliable measure to detect RM after tibia nailing. By limited axial scanning of the proximal tibia and distal tibia, the exposure to radiation was comparable to a chest x-ray and therefore a lot lower than often assumed. Protocolled low dose limited scanning of both tibiae after IMN might not only contributes to our understanding and diagnostic accuracy for RM after IMN, but also allows for early and simple revision, within the same hospital admission. The study presented in chapter 5, is performed in line with the findings in chapter 4. Based on the CT-measurements of four independent observers, the incidence of RM (>10°) was calculated. Our incidence of 36% RM was concurrent with available studies. We identified that right tibiae were prone for external RM whereas left sided tibiae were predisposed to internal RM. As per described standard[21-25], the contralateral side was used as reference standard during our measurements, under the assumption that both legs have the same rotational profile. However, on further evaluation, a pre-existent average rotational difference of 4° was found between left- and right sided non-fractured tibiae, with the right side being 4° more externally rotated. Incorporating this newly identified physiological difference not only decreased the incidence of RM from 36% to 29%, but also balanced the differences in incidence of external and internal RM in right and left tibiae. Although practically difficult, since we would normally not have a rotational profile CT of a patient before they break their tibia, this physiological difference now identified, still introduces a new view on findings in literature and might have aftereffects on diagnostics and revision surgery for RM.

Part V. Introduction of the CARV-protocol to avoid rotational malalignment during intramedullary-nailing

In the previous chapters, we concluded that RM is a frequent and possible underdiagnosed iatrogenic pitfall of RM of tibia fractures. To what extend patients might experience mobility problems of RM is unclear, but patients suffering from RM are eligible for monetary compensation.[27,28] Limited axial CT-scanning is considered as golden standard, but is performed after surgery when the direct possibility of revision has passed. In multiple femoral studies, different intra-operative protocols and strategies have been described to increase accuracy of intra-operative rotational control.[29-33] In contrast, in tibia studies, an intra-operative protocol to avoid RM is lacking. We therefore introduced the 'C-Arm Rotational View' (CARV)-protocol in cadaveric specimens. The CARV is an easy-to-use intraoperative fluoroscopy sequence of the uninjured and injured leg in which the rotation of the C-arm is used to verify rotational alignment of the tibia. Although the 4° of difference found between the left- and right leg, the study was – from a practical perspective – performed under the assumption that the contralateral side would have had the same rotational profile and was therefore used as reference standard. Correction according to clinical practice using single-leg and dual-leg draping resulted in a median difference of respectively 10.0º (IQR 5.0º) and 10.0º (IQR 5.0º) relative to neutral alignment. Single-leg and dual-leg draping resulted in malalignment (≥10º) in respectively 67% and 58% of the corrections. Standardized correction using the CARV resulted in a median difference of 5.0º (IQR 5.0º) relative to neutral alignment, with only 12% categorized as malalignment (≥10º). The incidence of rotational malalignment after application of the CARV decreased from 67% and 58% to 12% (p=<0.001). The need for standardizing rotational correction during IMN was strengthened by the existence of a wide range of insufficient and unstandardized correction maneuvers. Standardizing rotational correction according to the CARV-protocol proved to be accurate and reliable without differences between consultant surgeons and residents observed. The CARV-protocol was tested in a small clinical patient cohort in order to test its day-to-day feasibility. Not only were we able to carry out the CARV in clinical practice in the OR, but in all 3 cases, acceptable alignment was obtained (<10º). In literature, only one case report described a new technique using the lateral view of the ankle to minimize the potential of RM following IMN without being validated in a clinical research setting.[34] We are aware of the key weaknesses of our study that includes the use of cadaveric specimens rather than patients. Although the CARV was tested in a small prospective cohort, future prospective data needs to validate its clinical feasibility and practicability before final implementation can take place.

CONCLUSION

This thesis titled ''optimization of management for tibia fractures: diagnostic- and surgical strategies'' aimed to improve essential surgical aspects in definitive treatment of tibia fractures. In the first part of this thesis, a comparison of the SP-approach and IP-approach for tibia fractures was provided reporting on clinical outcomes of interest. We can conclude that both the SP- and IP-approach are reliable surgical approaches for tibia nailing without sufficient differences in rates of anterior knee pain and surgical complications as patellofemoral chondropathy, alignment errors and infection. We tried to clarify the ongoing debate with regards to definitive surgical treatment of distal fractures of the tibia. Both plate fixation and IMN are two well-established surgical modalities. In the last parts, aiming to clarify the essential aspects of RM after IMN of tibia fractures, we improved the understanding of RM. We feel that RM is an often-underestimated iatrogenic pitfall of IMN. Based on reliable post-operative low-dose CT-assessment, high incidences of RM were identified. Therefore, we designed, developed and introduced the 'C-arm rotational view (CARV)', a reliable and easy-to-use fluoroscopic protocol to minimize the potential of RM during IMN of tibia fractures.

Recommendations

1. Both the SP- and IP-approach are reliable surgical approaches for IMN. We recommend to use either the SP-approach or IP-approach depending on surgeon's preference and hospital logistics: dealer's choice.
2. Perform plate fixation of distal tibia fractures in case of young and active patients to reduce the risk of anterior knee pain and alignment errors, when soft tissue complications are not a threat.
3. Perform IMN of distal tibia fractures in patients with comorbidities to minimize the risk for infection, in patients with a low-demanding physical state, or when soft tissues are compromised by crush or high energy injury.
4. Perform routinely low-dose CT-assessment to early identify RM after IMN of tibia fractures.
5. The CARV-protocol can be adapted as an easy-to-use fluoroscopy protocol to improve rotational accuracy during IMN and minimize the risk for RM. Prospective data is needed before definitive implementation in clinical practice.

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SUMMARY

PART II. Should we go suprapatellar or infrapatellar for IMN of tibia fractures?

Chapter 1 presents a clinical-question driven systematic literature review of two different surgical approaches for IMN of tibia fractures. The suprapatellar (SP) approach gained popularity as a promising alternative relative to the infrapatellar (IP) approach. The main rationale includes a possible reduction of anterior knee pain. Clinical concerns however may include uncertainties in complication rates (patellofemoral chondropathy, infection, malalignment), physical functioning and quality of life if compared to the traditional IP-approach. The following research questions were posed: 1) does the SP vs. IP-approach result in less anterior knee pain?; 2) does the SP vs. IP-approach impact complication rates (patellofemoral chondropathy, infection, malalignment, non-union and secondary surgeries)?; and 3) does the SP vs. IP-approach affect physical functioning and quality of life?

A study of the literature was performed in which both observational studies and randomized controlled trials were included for analysis. A total of fourteen studies representing 1447 patients were reviewed. There were no significant differences in the incidence of anterior knee pain between the two approaches (29% vs. 39%). A significant lower rate of RM after the SP-approach was reported (4% vs. 26%), but with small and clinical irrelevant absolute differences. There were no differences in patellofemoral chondropathy, infection, non-union and subsequent surgeries. Self-reported physical functioning and quality of life were comparable in both groups.

This systematic review, thus, revealed no superiority of either technique in any of the respective outcomes of interest. Both surgical approaches are good techniques for IMN of tibia fractures with comparable outcomes. The definitive choice should depend on surgeons' preference and available resources.

PART III. Or, should we plate them all? But what about wound problems?

Part III encompasses two chapters aiming to answer the following research question: is there a difference in plate fixation vs. IMN regarding bone healing, complications, functional and radiological results when treating distal tibia fractures? In defining which treatment modality is better, in chapter 2 we designed a meta-analysis of the literature in which both observational studies and randomized controlled trials were included. A total of 15 studies with 1332 patients were analysed, including ten RCTs and five observational studies. We found that satisfactory results can both be obtained with IMN and plate fixation with both modalities having their own merits and demerits. IMN resulted a higher risk for anterior knee pain and shorter time to union. Plate fixation that included both open and minimal invasive plate osteosynthesis was associated with a lower risk of mal-union, but a higher risk of infection. In chapter 3, we conducted a retrospective study comparing minimal invasive plate osteosynthesis (MIPO) and IMN for the definitive treatment of distal tibia fractures. A total of 135 patients were included. We conducted an analysis of the efficacy of bilateral draping in minimizing the risk of RM after IMN. The primary finding of this study was that IMN resulted in a significant higher rate of non-union if compared to MIPO (22% vs. 6%).

Furthermore, we identified a higher rate of infection in patient treated with MIPO when compared to IMN (OR 6.22). There were no differences in rates of RM between both groups (10% vs. 3%).

PART IV. Rotational malalignment is a frequent iatrogenic pitfall of intramedullary nailing

Chapter 4 presents a prospective study on the reliability of low-dose protocolled bilateral CT-assessment following IMN for tibia fractures in order to optimize the diagnostic strategy for rotational errors. The aim of this prospective study was to evaluate the intra- and inter-observer reliability of protocolled low-dose CT-assessment for RM in patients following IMN for tibia fractures. A total of four independent observers participated in this study with 156 patients prospectively included. We found, for both the intra- and inter-observer reliability, excellent ICCs (0.95 and 0.90) indicating high diagnostic accuracy of low-dose CT-assessment for RM. Using protocolled CT-assessment in clinical practice ensures that patients with RM are diagnosed in an early stage and if required undergo simple revision within the same hospital admission. It also contributes to the understanding of the incidence of RM following IMN. In chapter 5, we described a prospective study in order to determine the incidence of RM following IMN. There was a surprisingly high incidence of RM (36%) after IMN of tibia fractures. Although the contralateral side was used as a reference standard, we found a pre-existence gradual difference of 4° between left and right tibias.

PART V. Introduction of the CARV-protocol to avoid rotational malalignment during intramedullary nailing

In the last part of this thesis, we present a possible solution for RM after IMN. In chapter 6, we conducted an experimental study aiming to minimize the risk for RM during IMN. The purpose of this study was to develop a user-friendly intraoperative fluoroscopy protocol coined the 'C-Arm Rotational View (CARV)' that included a standardized intraoperative fluoroscopy sequence of predefined landmarks on the uninjured and injured leg in which the rotation of the C-arm was used to verify for rotational alignment. The following research question was answered: can we improve the accuracy of rotational alignment during intramedullary-nailing of tibia shaft fractures utilizing our CARV-protocol relative to present clinical standards? A mid-shaft tibia fracture was simulated and an unlocked intramedullary-nail was inserted. Random degrees of RM were applied by using a hand-held goniometer via reference wires at the fracture site. Ten surgeons, blinded for the applied rotation, performed rotational corrections according to 1) current clinical practice after single-leg and dual-leg draping, and 2) according to the CARV-protocol. The primary outcome measure was the accuracy of the corrections relative to neutral tibial alignment. The CARV-protocol was also tested in a small clinical cohort. Correction according to clinical practice using single-leg and dual-leg draping resulted in a median difference of respectively 10.0º (IQR 5.0º) and 10.0º (IQR 5.0º) relative to neutral alignment. Single-leg and dual-leg draping resulted in RM (≥10º) in respectively 67% and 58% of the corrections. Standardized correction using the CARV resulted in a median difference of 5.0º (IQR 5.0º) relative to neutral alignment, with only 12% categorized as malalignment (≥10º). The incidence of RM after application of the CARV decreased from 67% and

58% to 12% (p=<0.001). Both consultants and residents successfully applied the CARV-protocol. Finally, three clinical patients with a tibial shaft fracture were treated according to the CARV-protocol, resulting all in acceptable alignment (<10°) based on postoperative CT-measurements. Further more extensive prospective data on clinical implementation is needed, and therefore a randomized controlled trial was designed in which the study protocol closes this thesis.

NEDERLANDSE SAMENVATTING

Chirurgische behandeling van tibia fracturen is uitdagend. De orthopedisch traumachirurg dient kennis te hebben van de chirurgische benadering, de mogelijke behandelingsmodaliteiten en bijbehorende potentiële complicaties. Dit proefschrift heeft als doel huidige chirurgische behandeling van tibia fracturen te optimaliseren met focus op diagnostische- en chirurgische strategieën. Het beschrijft de chirurgische benadering voor penosteosynthese en vergelijkt twee verschillende behandelingsmodaliteiten voor distale fracturen van de tibia. Het gaat verder in op de diagnostiek van rotatiefouten na penosteosynthese. Er wordt in deze thesis een algoritme geïntroduceerd om rotatiefouten tijdens penosteosynthese te minimaliseren. De thesis eindigt met een studieprotocol voor een RCT om dit algoritme te implementeren in de klinische praktijk.

Deel 2. Moeten we suprapatellair of infrapatellair benaderen voor penosteosynthese?

Hoofdstuk 1 focust zich op de chirurgische benadering voor intermedullaire penosteosynthese. Het bevat een systematische review van de literatuur waarin de suprapatellaire (SP)- en infrapatellaire (IP) benadering worden vergeleken. De SP-benadering is in populariteit toegenomen vanwege het mogelijke positieve effect op anterieure knie klachten en malrotatie. Niettemin zijn er een aantal klinische bezwaren, waaronder de kans op patellofemorale chondropathie en infectie. Daarbij is er weinig bekend over fysiek functioneren en kwaliteit van leven na deze benadering. De volgende onderzoeksvragen werden derhalve opgesteld: 1) leidt de SP-benadering vs. IP-benadering tot vermindering van anterieure knie pijn? 2) leidt de SP-benadering vs. IP-benadering tot een verhoogde kans op complicaties? 3) Beïnvloedt de SP-benadering vs. IP-benadering het fysiek functioneren en kwaliteit van leven?

We hebben een literatuuronderzoek gedaan waarin zowel observationele- als gerandomiseerde studies zijn geïncludeerd. In totaal zijn er 14 studies met 1447 patiënten geanalyseerd. Er was geen verschil in de incidentie van anterieure knie klachten tussen beide groepen (29% vs. 39%). Wel werd er een significant verschil gezien in het percentage rotatiefouten (4% vs. 26%), echter met kleine absolute en klinisch irrelevante verschillen. Er werd geen verschil gezien in complicaties, fysiek functioneren en kwaliteit van leven tussen beide groepen.

Concluderend bestaat er op basis van deze uitkomsten geen superioriteit tussen de SP-benadering en IP-benadering voor intramedullaire penosteosynthese van tibia fracturen. Beide technieken resulteren in goede uitkomsten en de definitieve keuze is afhankelijk van de ervaring van de chirurg en de aanwezige middelen in het desbetreffende ziekenhuis.

Deel 3. Of, Moeten we alle fracturen platen? En hoe zit het met de wondproblematiek?

Deel 3 bestaat uit 2 hoofstukken. In het eerste hoofdstuk (hoofdstuk 2) worden de resultaten gepresenteerd van een meta-analyse van de huidige literatuur over plaatosteosynthese vs. intramedullaire penosteosynthese. Doordat het technisch mogelijk is om de pen steeds distaler te vergrendelen, worden steeds meer distale tibia fracturen behandeld middels penosteosynthese.

Normaliter werd dit type fractuur behandeld met een plaat. In de zoektocht naar welke behandeling beter is, hebben we een meta-analyse van de bestaande literatuur verricht. Zowel observationele- als gerandomiseerde studies werden geïncludeerd. In totaal werden er 15 studies geïncludeerd met 1332 patiënten, waaronder 10 gerandomiseerde studies en 5 observationele studies. Beide behandelingsmodaliteiten kennen goede uitkomsten, waarbij er wel modaliteit-specifieke complicaties werden gevonden. Zo was er een hogere kans op mal-union en anterieure knie pijn na penosteosynthese en leidt plaatosteosynthese tot een verhoogde kans op infectie. Kennis van radiologische-, klinische- en functionele uitkomsten na plaat vs. penosteosynthese voor distale tibia fracturen zou tot passend maatwerk kunnen leiden voor de patiënt. We adviseren daarom om de definitieve keuze af te stemmen op de wensen en karakteristieken van de patiënt om de risico's op complicaties te minimaliseren.

Hoofdstuk 3 ligt in het verlengde van hoofdstuk 2. In dit hoofdstuk hebben we een retrospectieve studie verricht naar de resultaten van minimaal invasieve plaat- vs. penosteosynthese voor distale tibia fracturen. Daarbij zijn er 135 patiënten geïncludeerd. Ook hebben we een analyse verricht naar de effectiviteit van het bilateraal afdekken van beide extremiteiten en het risico op een rotatiefout na penosteosynthese. Wat bleek, penosteosynthese leidt tot een significant hoger percentage non-union vergeleken met plaatosteosynthese (22% vs. 6%). Er was tevens een hogere kans op infectie na plaatosteosynthese. Er werd geen verschil gevonden in malrotatie, mogelijk door de effectiviteit van het bilateraal afdekken.

Deel 4. Rotatie-afwijkingen zijn een onderschat probleem na intramedullaire penosteosynthese

Hoofstuk 4 allereerst bevat een prospectieve studie naar de betrouwbaarheid van een postoperatieve CT-scan voor het diagnosticeren van een rotatie-afwijking na intramedullaire penosteosynthese. Het doel van deze prospectieve studie was om de intra- en inter-observator betrouwbaarheid te bepalen van CT-metingen van geselecteerde axiale CT-coupes in een cohort van 156 patiënten. Vier observatoren participeerden in de studie. Uit de resultaten bleek dat de CT-scan voor het diagnosticeren van een rotatie-afwijking een zeer accuraat medium is met excellente ICCs. Doordat het tevens geselecteerde axiale coupes betrof, werd de blootstelling aan radiatie geminimaliseerd. Het geprotocolleerd verrichten van CT-scans verbetert de diagnostiek van rotatie-afwijkingen en faciliteert een vroege revisie binnen dezelfde ziekenhuisopname. De uitkomsten in deze studie dragen ook bij aan kennis over de incidentie van dit probleem. Hier gaat hoofdstuk 5 verder op in. In dit hoofdstuk wordt een prospectieve studie naar de incidentie van rotatiefouten verricht op basis van de CT-uitkomsten van 154 patiënten. Bij maar liefst 36% (n=154) van de geopereerde patiënten bleek er sprake te zijn van een rotatiefout. Tevens werd er een fysiologisch verschil gevonden van 4 graden tussen beide extremiteiten. Gezien de contralaterale zijde in huidige praktijk vaak wordt gebruikt als referentie, zorgt deze bevinding voor nieuwe inzichten met betrekking tot de incidentie, diagnostiek en eventuele revisie chirurgie van een rotatie-afwijking.

Deel 5. Rotatie controle tijdens de operatie middels de 'C-Arm Rotational View'

Het laatste deel van dit hoofdstuk bevat 2 hoofdstukken. In hoofdstuk 6 hebben we een studie verricht waarin we een protocol ontwikkelen om rotatiefouten tijdens intramedullaire penosteosynthese te voorkomen. Het doel was om een gebruiksvriendelijk doorlichtingsalgoritme te ontwikkelen, genaamd de 'C-Arm Rotational View (CARV)'. De CARV is een protocol waarbij gestandaardiseerde röntgenafbeeldingen van de gezonde zijde worden gebruikt als referentie. Daarbij wordt de rotatie van de C-boog gebruikt om de rotatiefout in te schatten. Er werd een klinische situatie nagebootst middels een penosteosynthese van een gesimuleerde mid-schacht tibia fractuur. De tibia kon geroteerd worden over de pen. Zodoende konden er diverse rotatiefouten worden aangebracht. Tien chirurgen en opleidingsassistenten participeerden in deze studie. In totaal zijn er 180 correcties uitgevoerd met behulp het CARV-protocol en middels de huidige klinische standaard. Dit betrof onder andere unilateraal- en bilateraal afdekken. Het gestandaardiseerd corrigeren van rotatiefouten met behulp van het CARV-protocol leidde tot een verschil van 5.0° (IQR 5.0°) vergeleken met de gezonde zijde. Correctie volgens huidige klinische standaarden resulteerde in een verschil van 10.0° (IQR 5.0°). De incidentie van tibia malrotatie daalde van 67% en 58% naar 12% na het toepassen van het CARV-protocol vergeleken met huidige klinische standaard ($p=<0.001$). Deze experimentele studie laat dus zien dat het CARV-protocol gebruikt kan worden om de kans op rotatiefouten te minimaliseren. Het protocol is tevens getest in een klinische setting om de klinische toepasbaarheid te bepalen. In geen enkele casus was er sprake van malrotatie. Verder prospectief onderzoek moet uitwijzen of dit protocol definitief in de klinische praktijk geïmplementeerd kan worden. Derhalve eindigt deze thesis met een studieprotocol van een prospectieve gerandomiseerde studie om het CARV-protocol te implementeren in dagelijkse klinische praktijk.

APPENDIX

SUPPLEMENTARY MATERIALS

Difference in Pain, Complication Rates and Clinical Outcomes afterSuprapatellar vs. Infrapatellar Nailing for Tibia Fractures? A Systematic Review of 1447 Patients

Patient related outcome measures (PROMs)

Pain

Visual Analogue Scale (VAS)

The VAS pain score provides a simple and reliable self-reported pain measure and has been widely used to objectify pain intensity (1). A score of 0 indicates ''no pain'' and a score of 10 indicates ''the heaviest pain ever experienced''.

Numeric Rating Scale (NRS)

The NRS is similar to the VAS, with scores ranging from 0-10. A score of 0 reflects no pain and a score of 10 indicates worst possible pain (2).

Aberdeen Weightbearing Knee Test (AWK-T)

The AWK-T is developed by MacDonald et al. (3) and is a specific test for anterior knee pain which is assessed by weight bearing. The patient kneels on a scale during 60 seconds with full weight bearing on each knee. The ratio of total body weight on each knee at different time points (every 15 seconds) is calculated and compared to contralateral side. The ability to fulfill the test is a secondary reported outcome.

Physical functioning

International Knee Documentation Committee score (IKDC)

The IKDC is a questionnaire that objectifies knee impairment in three domains (4). The first domain includes symptoms such as pain, swelling or instability. The second domain includes sports and daily activities and the third domain reports on knee function. Scores range from 0-100, with a reported score of 100 indicating no pain, no limitations in sports or daily activities and excellent knee function.

SUPPLEMENTARY MATERIAL TABLE 1. Search strategy.

PubMed (n=109)	"Tibial Fractures"[Mesh] OR (tibia*[tiab] AND ("Fractures, Bone"[Mesh] OR fracture*[tiab])) AND (suprapatellar[tiab] OR infrapatellar[tiab]).
Embase (n=102)	(Tibia*:ti,ab AND ('fracture'/exp OR fracture*:ti,ab) OR 'tibia fracture'/exp) AND (suprapatellar:ti,ab OR infrapatellar:ti,ab)

Oxford Knee score (OKS)

The OKS is a 12-item questionnaire, initially developed to objectify pain and function after total knee replacements (5), but the modified version is used for multiple purposes (6). On each item, a score between 1 to 4 can be given (1 indicating ''no restrictions'' and 5 indicating sufficient problems). The sum of all items reflects the total score, with a maximum of 48 points.

Kujala Knee score/Anterior Knee Pain Scale (AKPS)

The Kujala Knee score or AKPS was published by Kujala in 1993 (7) and is a self-reported 13-item questionnaire to objectify patellofemoral complaints with an ascending scale from 0 to 100. A score of 0 indicates poor outcomes and a score of 100 indicates excellent physical functioning.

Lysholm Knee score

The Lysholm Knee score is developed to objectify physical functioning after knee ligament surgery and includes eight items regarding pain, instability, locking complaints, stair climbing, support, swelling, walking pattern and squatting (8). The total score is the sum of all items with a maximum of 100 points. A total of 100 points indicates no disability. Scores between 95-100 points are considered to be excellent, 84-94 as good, 64-83 as fair and scores <64 as poor.

Hospital for Special Surgery score (HSS)

The HSS is developed to assess physical functioning after total knee replacement (9) and is divided into seven categories (pain, function, ROM, muscle strength, flexion deformity, instability and substraction). The maximum score is 100 indicating no discomfort.

Olerud-Molander Ankle score (OMAS)

The OMAS is a scoring system to objectify discomfort after ankle fractures (10) and includes nine categories (pain, stiffness, swelling, stair climbing, running, jumping, squatting, supports and work). The maximum score is 100 points and indicates no symptoms and normal physical function.

Irrgang Outcome Survey Activities of Daily Life Scale

The Irrgang Outcome Survey Activities of Daily Life Scale (11) is divided into two subcategories: symptoms and function. The symptoms subcategory includes pain, grinding or grating, stiffness, swelling, instability and weakness. The function subcategory includes walking, climbing the stairs, stand, kneeling, squatting and sitting. The score is presented as percentage. In order to calculate the percentage, the score on each separate scale is summed up and divided by the maximum score of 80 points.

General quality of life

Short-Form 36 (SF-36)

The SF-36 is developed to objectify general quality of life by measuring two distinct components (physical component and mental component) and includes eight scales (12). Scores can be given between 0 and 100, with a higher score representing less discomfort. Each scale contributes proportionally to the total score of the physical- and mental component.

Short-Form 12 (SF-12)

The SF-12 is a shortened version derived from the SF-36 and uses the same domains as the SF-36 (13).

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Plate vs. Nail for Distal Tibia Fractures: How Should We Personalize Surgical Treatment? A Meta-Analysis of 1332 Patients

SUPPLEMENTARY MATERIAL TABLE 1. Search syntax.

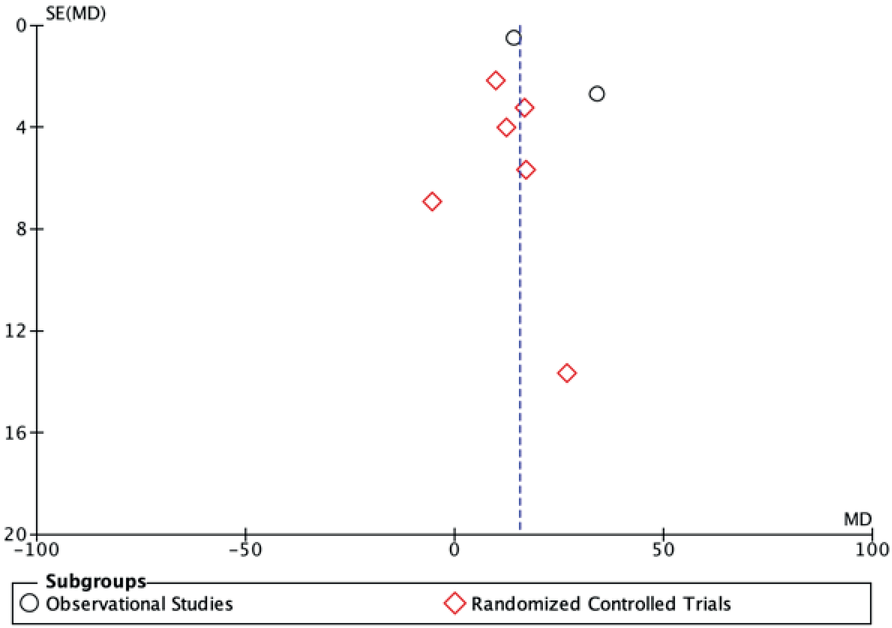
Database	Search terms
PubMed (n=1056)	((((((((“plate”[Title/Abstract]) OR “plating”[Title/Abstract]) OR “nail”[Title/Abstract]) OR “nailing”[Title/Abstract]) OR “mipo”[Title/Abstract]) OR “orif”[Title/Abstract]) OR “open reduction internal fixation”[Title/Abstract])) AND ((((“tibia shaft”[Title/Abstract]) OR “tibial shaft”[Title/Abstract])) OR ((((“distal tibia fractures”[Title/Abstract]) OR “distal tibial fractures”[Title/Abstract]) OR “distal tibia fracture”[Title/Abstract]) OR “distal tibial fracture”[Title/Abstract]))
Embase (n=1360)	((‘plate fixation’:ab,ti OR ‘intramedullary nailing’:ab,ti) AND ‘tibia fracture’:ab,ti OR ‘tibial shaft’:ab,ti OR ‘distal tibia fracture’:ab,ti) AND [2000-2020]/py
CINAHL (n=1521) **Central** (n=840)	TI tibia fracture OR TI distal tibia fracture AND TI intramedullary nail OR TI intramedullary nailing OR TI intramedullary fracture fixation AND TI orif OR TI open reduction internal fixation

SUPPLEMENTARY MATERIAL TABLE 2. MINORS-criteria for methodological assessment.

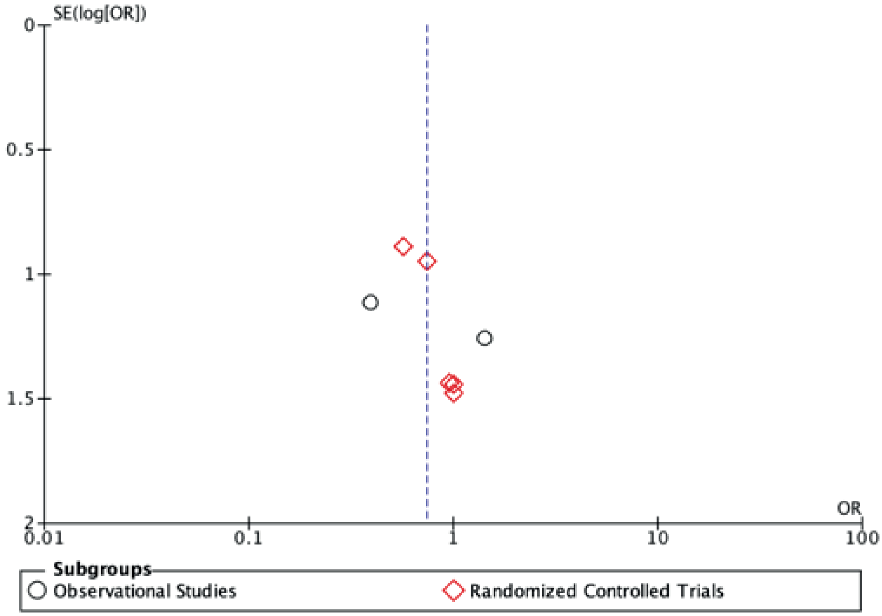
Criteria	Reported and adequate (2)	Reported but inadequate (1)	Not reported (0)
Clearly stated aim	Aim including outcomes reported	Aim reported without outcomes	Not reported
Inclusion consecutive patients	Inclusion/exclusion criteria reported	Unclear description inclusion/exclusion criteria	Not reported
Prospective collection data	Prospective	Not applicable	Not applicable
Appropriate endpoints	Appropriate endpoints to aim study	Endpoints not appropriate to aim study	Not reported
Unbiased assessment	Blinded evaluation of outcomes	Reason not blinding stated	Not reported
Appropriate follow-up	≥ 1 year	< 1 year	Not reported
Loss to follow-up < 5%	≤ 5%	> 5%	Not applicable
Prospective calculation study size	Prospective power-analysis performed	Prospective calculation without power-analysis	Not applicable
Adequate control group	Operative versus nonoperative treatment	Not applicable	Not applicable
Contemporary groups	Study/control group managed during same period	Study/control not managed during same period	Not reported
Baseline equivalence groups	Baseline characteristics described and comparable	Baseline characteristics not comparable	Not reported
Adequate statistical analyses	Statistical analysis described including type of analyses	Inadequate description statistical analysis	Not reported

SUPPLEMENTARY MATERIAL TABLE 3. Specification of revisions after plate fixation and IMN.

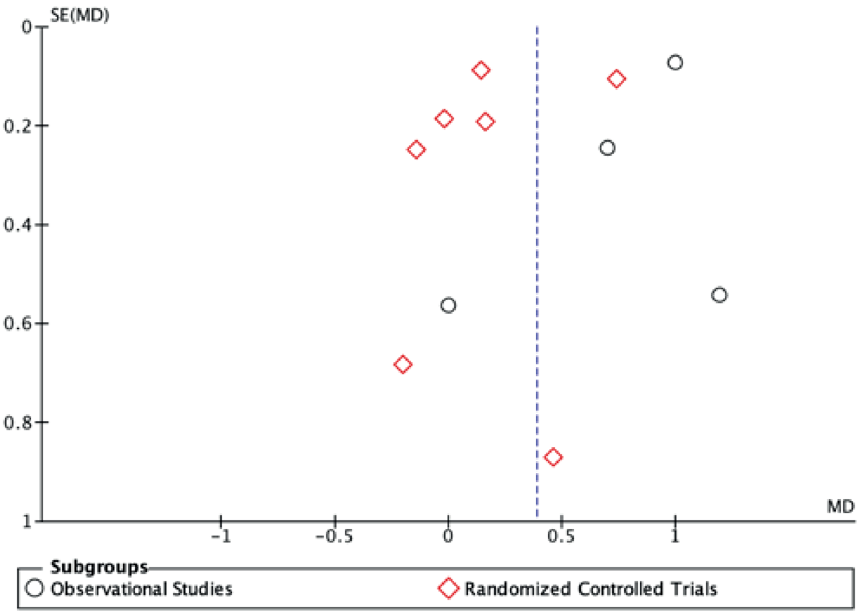
Study	Revision total		Revision non-union/ delayed union		Revision mal-union		Revision not specified	
	Plate	Nail	Plate	Nail	Plate	Nail	Plate	Nail
Observational Studies								
Vallier	2	13	2	9	NR		NR	4
Seyhan	3	1	1	NR	NR	1	2	NR
Total	**5**	**14**	**3**	**9**	**NR**	**1**	**2**	**4**
RCTs								
Im-Gun	1	3	1	3	NR		NR	
Vallier	3	5	2	4	NR		1	1
Li	0	1	NR	1	NR		NR	
Fang	NR	1	NR	1	NR		NR	
Costa	5	2	NR		NR		5	2
Total	**9**	**12**	**3**	**9**	**NR**	**NR**	**6**	**3**
Total Observational & RCTs	**14**	**26**	**6**	**18**	**NR**	**1**	**8**	**7**



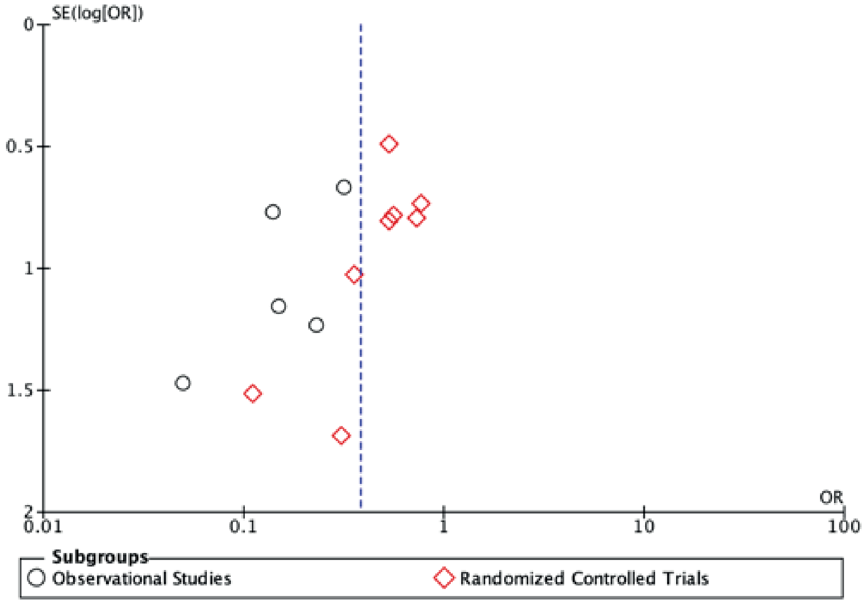
SUPPLEMENTARY MATERIAL FIGURE A. Funnel plot of operation time in minutes between plate fixation and IMN for distal tibia fractures.



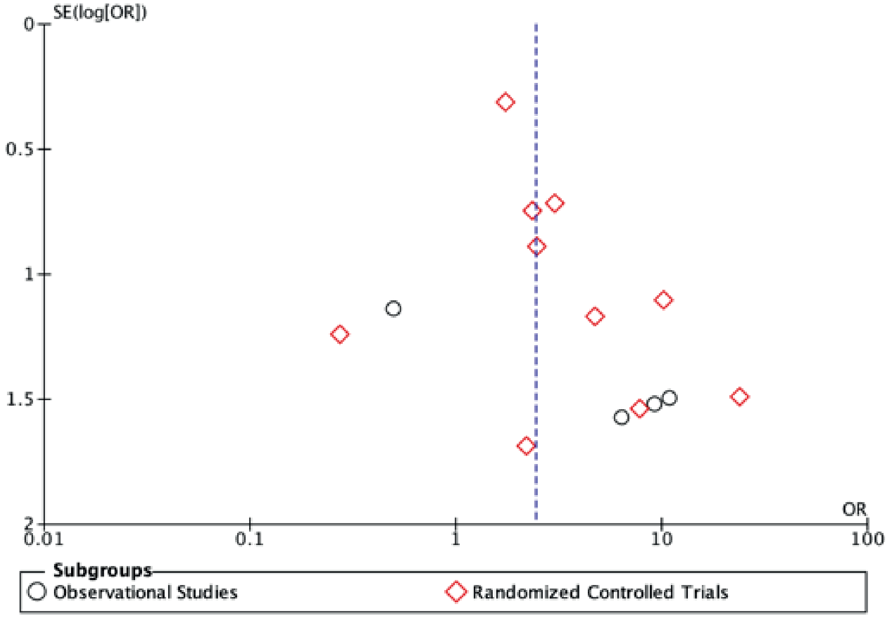
SUPPLEMENTARY MATERIAL FIGURE B. Non-union rates for distal tibia fractures treated with plate or nail fixation.



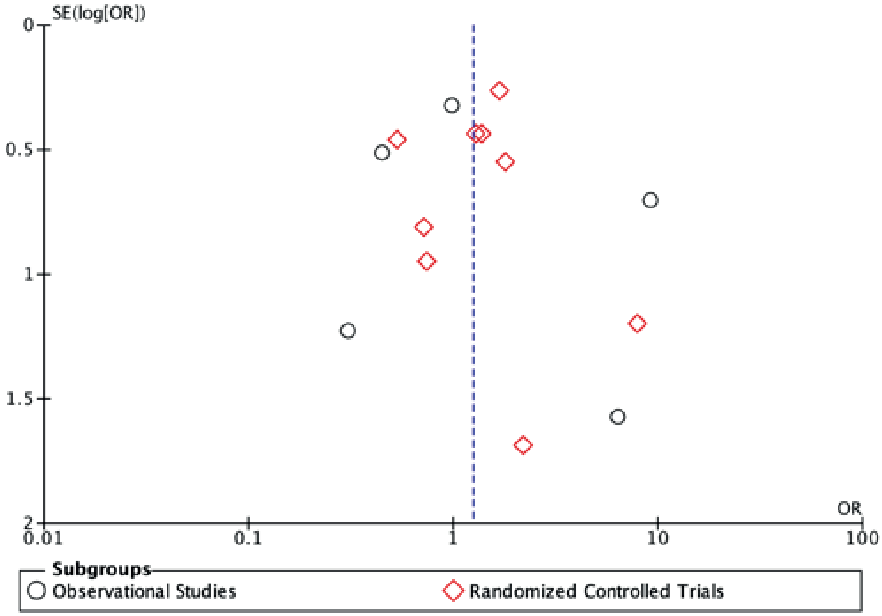
SUPPLEMENTARY MATERIAL FIGURE C. Funnel plot for time to union for distal tibia fractures treated with plate fixation or intramedullary nailing.



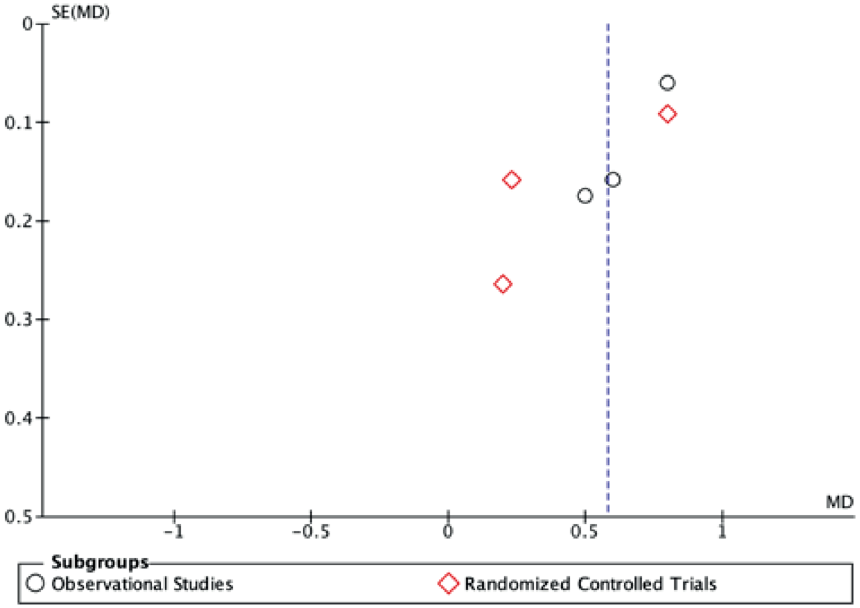
SUPPLEMENTARY MATERIAL FIGURE D. Funnel plot for rate of mal-union after plate fixation versus IMN.



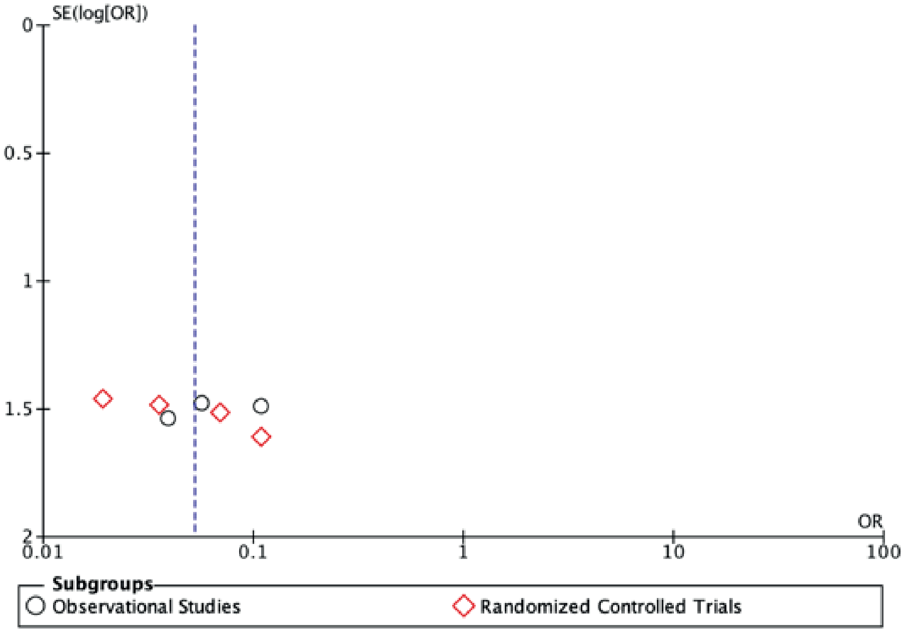
SUPPLEMENTARY MATERIAL FIGURE E. Funnel plot for infection.



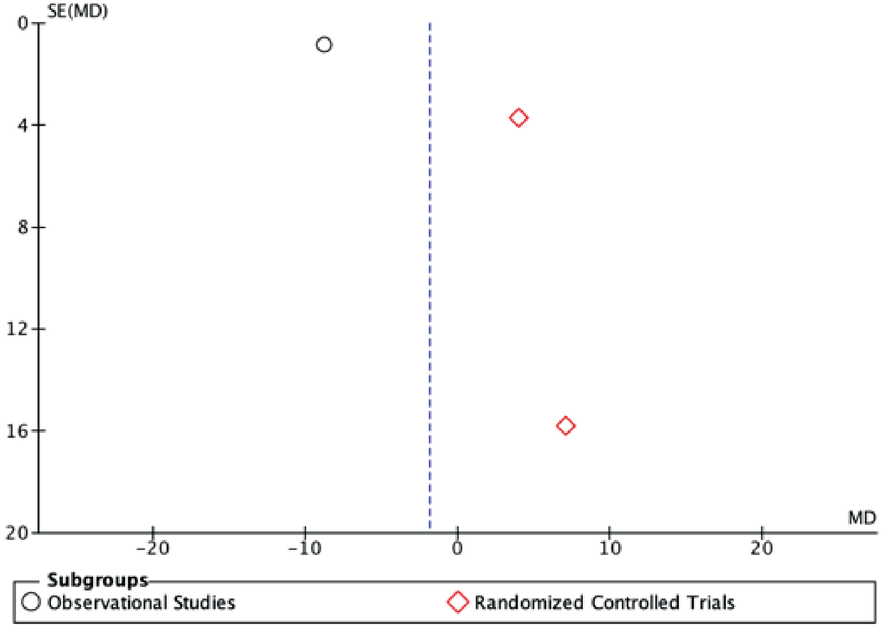
SUPPLEMENTARY MATERIAL FIGURE F. Funnel plot for subsequent re-interventions after initial treatment with plate- or intramedullary nail fixation.



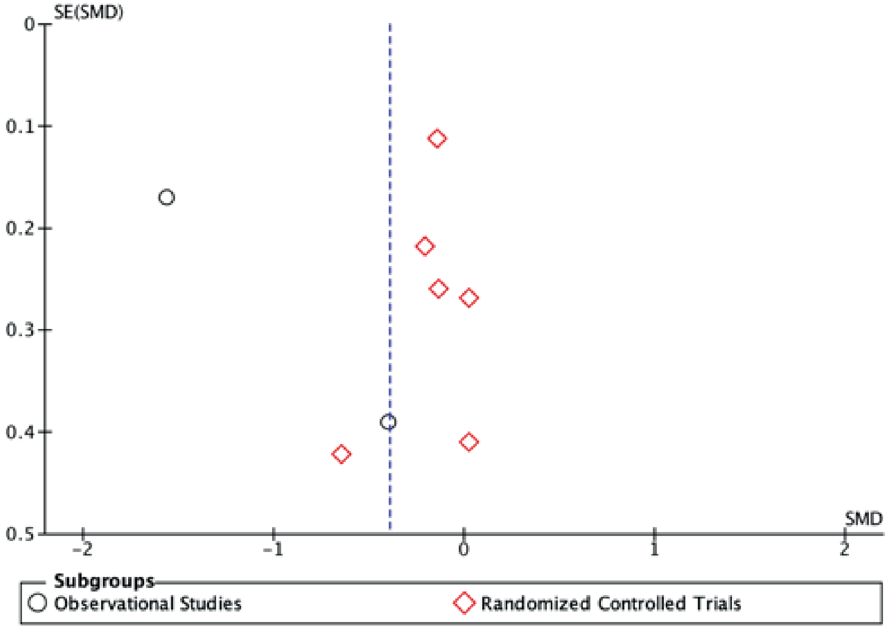
SUPPLEMENTARY MATERIAL FIGURE G. Funnel plot for time to full weightbearing after fracture fixation.



SUPPLEMENTARY MATERIAL FIGURE H. Funnel plot for anterior knee pain after plate fixation versus IMN of distal tibia fractures.



SUPPLEMENTARY MATERIAL FIGURE I. Funnel plot for general quality of life scores.



SUPPLEMENTARY MATERIAL FIGURE J. Funnel plot for functional ankle scores.

Intraoperative Fluoroscopic Protocol to Avoid Rotational Malalignment after Nailing of Tibia Shaft Fractures: Introduction of the 'C-Arm Rotational View (CARV)'

Supplementary data file 1: clinical cases

Case 1: Male, 43 years, left sided tibia fracture.

Injury mechanism: motorcycle accident.

Preoperative radiographs / clinical impression: tibia fracture, AO/OTA 42-B2.

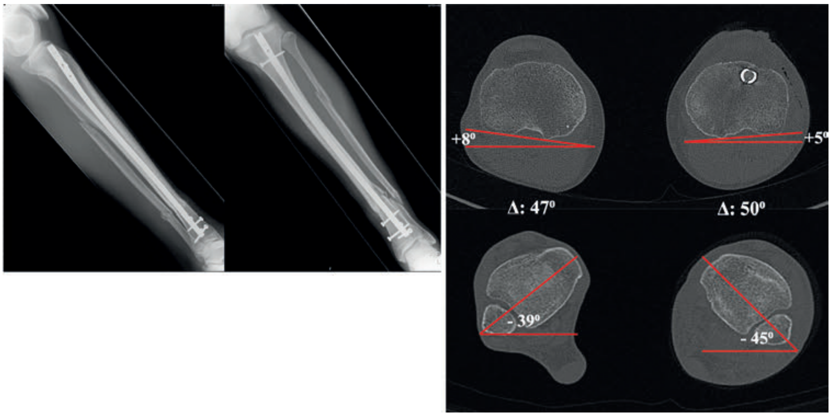
(Appendix figure 1)

APPENDIX FIGURE 1.

Operation: Intramedullary-nailing with C-Arm Rotational View (CARV)
(Appendix figure 2)

APPENDIX FIGURE 2.

Postoperative radiographs and CT-assessment:
(Appendix figure 3)



APPENDIX FIGURE 3. The rotational (mal)alignment is the rotational difference between the injured- and uninjured side. In this case, the rotation of the injured side is 50° (- 45° - 5°). The rotation of the uninjured side is 47° (- 39° - 8°). The rotation is thus 3° (injured side (50°) – uninjured side (47°)) and indicated *acceptable* alignment.

Case 2: Male, 43 years, with a Gustilo grade 3 open right sided tibia fracture and a segmental defect of the tibia

Injury mechanism: car accident, polytrauma.

Pre-operative CT / clinical impression: tibia fracture with a 7 cm segmental defect, AO/OTA 42-C2. (Appendix figure 4)

APPENDIX FIGURE 4.

Operation 1: temporary external fixator, cement spacer, radialis flap.

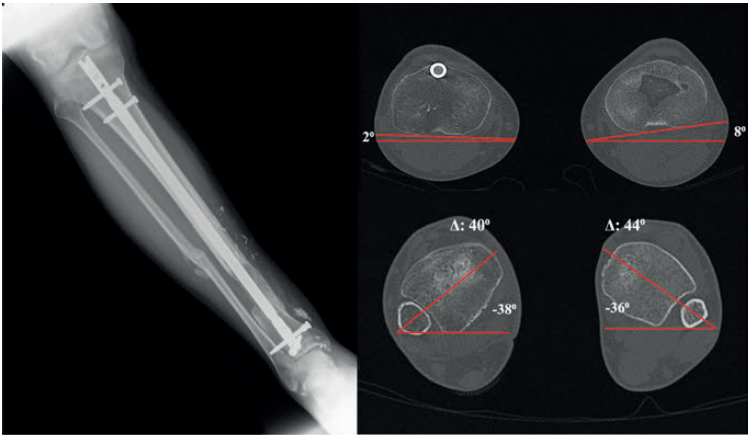
Operation 2: intramedullary-nailing with C-Arm Rotational View (CARV) and cancellous bone grafting.

(Appendix figure 5)

APPENDIX FIGURE 5.

Postoperative radiographs and CT-assessment:

(Appendix figure 6)



APPENDIX FIGURE 6. The rotational (mal)alignment is the rotational difference between the injured- and uninjured side. In this case, the rotation of the injured side is 40° (- 38° - 2°). The rotation of the uninjured side is 44° (- 36° - 8°). The rotation is thus 4° (injured side (40°) – uninjured side (44°)) and indicated *acceptable* alignment.

Case 3: Male, 19 years, with a right sided comminuted tibia fracture

Injury mechanism: motorcycle accident.

Pre-operative radiographs: tibia shaft fracture, AO/OTA 42-B3.

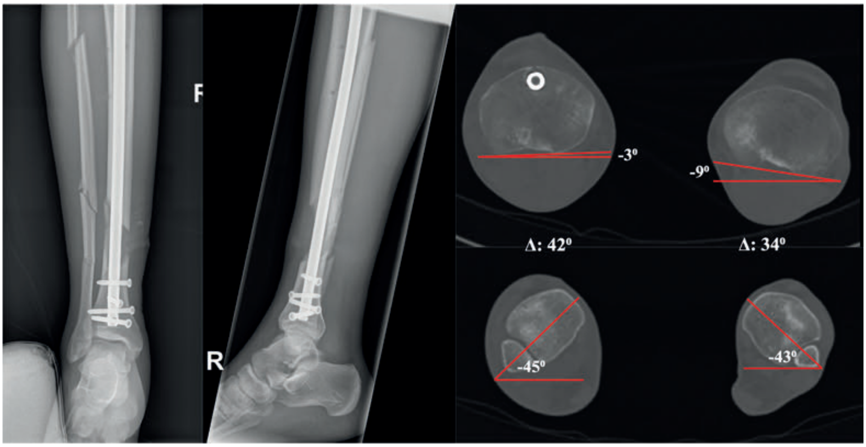
(Appendix figure 7)

APPENDIX FIGURE 7.

Operation: intramedullary-nailing with C-arm Rotational View (CARV).
(Appendix figure 8)

APPENDIX FIGURE 8.

Postoperative radiographs and CT-assessment:
(Appendix figure 9)



APPENDIX FIGURE 9. The rotational (mal)alignment is the rotational difference between the injured- and uninjured side. In this case, the rotation of the injured side is 42° (- 45° - -3°). The rotation of the uninjured side is 34° (- 43° - -9°). The rotation is thus 8° (injured side (42°) – uninjured side (34°)) and indicated *acceptable* alignment.

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	Year	ETCS
Research fellowships		
Flinders Medical Centre, Flinders University, Adelaide, Australia.	2017	
Cantonal Hospital Lucerne (LUKS), Lucerne, Switzerland.	2020	
University Medical Centers Groningen, Groningen, the Netherlands.	2020-2021	
Specific Courses		
Advanced Trauma Life Support (ATLS)	2021	4
AO Trauma Webinar – Intraoperative Evaluation of Torsion Malalignment after Nailing of the Femur and Tibia.	2020	0.5
AAOS workshop – Get Better at Scientific Writing	2019	0.5
Organization / Teaching		
4th Traumaplatform Symposium "Challenges in Trauma" and Challenge "Triathlon for Trauma"	2019	4
(Inter)national conferences		
AOA Scientific Meeting Adelaide, Australia	2017	1
OTA Annual Meeting, Vancouver, Canada	2017	3
Traumadagen, Amsterdam, the Netherlands	2018	1
AAOS Annual Meeting, Las Vegas, USA	2019	3
Symposium Tibia Plateau Fracturen Onder De Knie, Alkmaar, the Netherlands	2019	0.5
Symposium Challenges in Trauma, Leeuwarden, the Netherlands	2019	0.5
Symposium Experimenteel Onderzoek Heelkundige Specialismen (SEOHS)	2019	0.5
Resident Symposium Dutch Society for Trauma Surgery, Amsterdam, the Netherlands	2020	0.5
European Society for Trauma and Emergency Surgery (ESTES), Oslo, Norway (Cancelled due to COVID-19)	2020	0.1
German Congress of Orthopedics and Traumatology	2021	0.1
(Inter)national presentations		
Bilateral Low-Dose Computed Tomography Assessment for Post-Operative Rotational Malalignment after Intra Medullary Nailing of Tibial Shaft Fractures: Reliability of Practical Imaging Technique.		
AOA Scientific Meeting Adelaide, Australia	2017	0.5
AAOS Annual Meeting, Las Vegas, USA	2019	0.5
Symposium Challenges in Trauma, Leeuwarden, the Netherlands	2019	0.5
European Society for Trauma and Emergency Surgery (ESTES), Oslo, Norway (Cancelled due to COVID-19)	2020	0
Incidence of Rotational Malalignment after Intramedullary Nailing of Tibial Shaft Fractures		
OTA Annual Meeting, Vancouver, Canada	2017	0.5
Traumadagen, Amsterdam, the Netherlands	2018	0.5
AAOS Annual Meeting, Las Vegas, USA	2019	0.5

PHD PORTFOLIO. (continued)

	Year	ETCS
Symposium Challenges in Trauma, Leeuwarden, the Netherlands	2019	0.5
European Society for Trauma and Emergency Surgery (ESTES), Oslo, Norway (Cancelled due to COVID-19)	2020	0
MIPO vs. Intra-Medullary Nailing for Extra-Articular Distal Tibia Fractures and the Efficacy of Intra-Operative Alignment Control: A Retrospective Cohort of 135 Patients		
Resident Symposium Dutch Society for Trauma Surgery, Amsterdam, the Netherlands	2020	0.5
German Congress of Orthopedics and Traumatology	2021	0.1
Poster presentations		
Incidence of Rotational Malalignment after Intramedullary Nailing of Tibial Shaft Fractures		
Symposium Experimenteel Onderzoek Heelkundige Specialismen (SEOHS)	2019	0.5
Other		
Grand Rounds Department of Orthopedic Surgery, Flinders Medical Centre, Adelaide, Australia	2017	4

PUBLICATIONS

Intraoperative Fluoroscopic Protocol to Avoid Rotational Malalignment after Nailing of Tibia Shaft Fractures: Introduction of the 'C-Arm Rotational View (CARV)'
(April 2022, accepted European Journal of Trauma and Emergency Surgery)
N.J. Bleeker, *J.N. Doornberg, K.ten Duis, M. El. Moumni, I.H.F. Reininga, R.L. Jaarsma, F.F.A. IJpma and the Traumaplatform 3D Consortium.*

Clinical Validation of the 'C-Arm Rotational View (CARV)': Study Protocol of a Prospective Multi-Center Randomized Controlled Trial (April 2022, submitted BMJ Open)
N.J. Bleeker, *J.N. Doornberg, K. ten Duis, M. El. Moumni, R.L. Jaarsma, F.F.A IJpma.*

The Value of Fibular Fixation in Patients with Stabilized Distal Tibia Fractures (September 2021, published European Journal of Trauma and Emergency Surgery)
N.M. van Veelen, B.J.M. van de Wall, ***N.J. Bleeker****, I.R. Buenter, B.-C. Link, F. Migliorini, R. Babst, M. Knobe, F.J.P. Beeres.*

MIPO vs. Intra-Medullary Nailing for Extra-Articular Distal Tibia Fractures and the Efficacy of Intra-Operative Alignment Control: A Retrospective Cohort of 135 Patients (Published European Journal of Trauma and Emergency Surgery, November 2021)
N.J. Bleeker*, N.M. van Veelen, B.J.M. v.d. Wall, I.N. Sierevelt, B.C. Link, Professor R. Babst, Professor M. Knobe, F.J.P. Beeres.*

Difference in Pain, Complication Rates and Clinical Outcomes after Suprapatellar vs. Infrapatellar Nailing for Tibia Fractures? A Systematic Review of 1447 Patients (Published Journal of Orthopaedic Trauma, August 2021)

N.J. Bleeker, *I.H.F. Reininga, B.J.M. van de Wall, L.A.M. Hendrickx, F.J.P. Beeres, K. ten Duis MD, J.N. Doornberg, R.L. Jaarsma, G.M.M.J. Kerkhoffs, F.F.A. IJpma.*

Plate vs. Nail for Extra-Articular Distal Tibia Fractures: How Should We Personalize Surgical Treatment? A Meta-Analysis of 1332 patients (Published Injury, March 2021)
N.J. Bleeker, *B.J.M. v.d. Wall, F.F.A. IJpma, J.N. Doornberg, G.M.M.J. Kerkhoffs, R.L. Jaarsma, M. Knobe, R. Babst, F.J.P. Beeres.*

Incidence of Rotational Malalignment after Intramedullary Nailing of Tibial Shaft Fractures: Can we Reliably Use the Contralateral Uninjured Side as the Reference Standard? (Published JBJS, April 2020).
Cain M, Hendrickx R, ***Bleeker NJ,*** *Lambers K, Doornberg JN, Jaarsma RL.*

Bilateral Low-Dose Computed Tomography Assessment for Post-Operative Rotational Malalignment after Intra Medullary Nailing of Tibial Shaft Fractures: Reliability of Practical Imaging Technique (Published Injury, July 2018).
Bleeker NJ, *Cain M, Rego M, Saarig A, Chan A, Sierevelt I, Doornberg JN, Jaarsma RL.*

PARAMETERS OF ESTEEM

2020 – Van Walree Grant of the Royal Netherlands Academy of Arts and Sciences.

2020 – Professor Marti-Keuning Eckardt Foundation Research Scholarship.

2019 – Traumaplatform Research Grant.

2019 – Van Walree Grant of the Royal Netherlands Academy of Arts and Sciences.

2019 – de Fundatie van de Vrijevrouwe van Renswoude te Delft Research Scholarship

2017 – Van Walree Grant of the Royal Netherlands Academy of Arts and Sciences.

CURRICULUM VITAE

N.J. Bleeker was born at the 22th of august 1994 in Rotterdam, the Netherlands. He moved at the age of 9 together with his family (father, mother, one brother and two younger brothers) to a small village named Suawoude in Friesland. He finished first HAVO in 2011 and second VWO in 2013 at Comenius Achter de Hoven, Leeuwarden. Starting as a Medicine-student at the University of Groningen, Nils Jan moved to Groningen in 2013. During his bachelor's degree, he participated in multiple – both national and international – clinical internships and he started focusing on the field of orthopaedic trauma at an early stage. In 2017, Nils Jan wished to pursue a scientific career and therefore he crossed the Pacific for a research fellowship mentored by prof. dr. R.L. Jaarsma and prof. dr. J.N. Doornberg. He has been contributing to a successful research collective with Amsterdam (prof. dr. G.M.M.J. Kerkhoffs) and Adelaide (prof. dr. R.L. Jaarsma). It turned out to be the basis of current thesis. After his time in Australia, Nils Jan travelled through Asia. Back in the Netherlands, he went on with his Master's degree and got accepted by prof. dr. G.M.M.J. Kerkhoffs for a clinical internship at the department of orthopedic surgery. Parallel to his Master's degree, Nils Jan continued his PhD and performed a research fellowship under supervision of Dr. F.J.P. Beeres at the Cantonal Hospital of Lucerne, Switzerland and at the University Medical Centers Groningen under supervision of Dr. F.F.A. IJpma. He was also part of the organization committee of the 4th biennial Traumaplatform Symposium ''Challenges in Trauma'' and ''Triathlon for Trauma'' 2019. Nils Jan graduated in 2021 and started to work as a general surgery resident-not-in-training at the in the North West Clinics Alkmaar (Dr. K.J. Ponsen) and as orthopaedic surgery resident-not-in-training at the University Medical Centers Groningen (Prof. Dr. P.C. Jutte). He aims to start his resident training program in 2022.

DANKWOORD

Geachte lezer,

Zoals u misschien al had vernomen refereert de coverpagina naar *La Mezquita-Catedral de Córdoba*. Niet alleen een historisch- en architectonisch hoogstaand kunstwerk, maar ook één van de favoriete plekken van mijn vader. De oneindige zuilen met dubbele bogen creëren een gevoel van gewichtsloosheid en het spectrum van kleuren dat door de diverse bogen naar binnen treedt is magisch en onnavolgbaar. Echter dient het ook een functioneel doel waarin de zuilen als draagelement van de kathedraal fungeren. U zult misschien erkennen dat hierin ook de symboliek schuilt met mijn proefschrift, waarin *de tibia* een vergelijkbaar doel dient.

De totstandkoming van dit proefschrift is het resultaat van een diepgaande samenwerking met diverse personen, zowel op professioneel- als persoonlijk vlak. Het heeft geleid tot onvergetelijke buitenlandse avonturen, professionele- en persoonlijke ontwikkeling, hechte vriendschappen en bovenal nieuwe wetenschappelijke inzichten. Ik zou graag, naast alle patiënten die hebben deelgenomen aan de onderzoeken, een aantal personen in het bijzonder willen bedanken:

Promotor Prof. Dr. R.L. Jaarsma

Beste Ruurd, onze eerste mailcorrespondentie dateert uit 2016, waarin ik als jonge bachelor-student naarstig op zoek was naar een buitenlandse onderzoekservaring. Je bood mij deze kans waarin ik onder jouw vleugels de eerste stappen heb gezet in het wetenschappelijke veld. Jouw steun, begeleiding en altijd waardevolle en nuchtere advies hebben mede tot dit resultaat geleid en daar ben ik je ontzettend dankbaar voor. Ik zal de momenten in Las Vegas in de Ford Mustang Cabrio niet vergeten, ondanks dat het regende op *de Strip*.

Promotor Prof. Dr. G.M.M.J. Kerkhoffs

Beste Gino, via de destijds net opgezette transoceanische connectie tussen Adelaide en Amsterdam ben ik ook onder jouw vleugels terecht gekomen, iets wat mij op zowel klinisch- als wetenschappelijk vlak veel gebracht heeft. Als oudste coassistent uit Groningen kwam ik op jouw afdeling in het Amsterdam UMC terecht, een ervaring waar ik met een goed gevoel op terugkijk. Naast de begeleiding op het wetenschappelijk gebied wilde ik je ook bedanken voor je begeleiding op het professionele vlak.

Copromotor Prof. Dr. J.N. Doornberg

Beste Job, waar moet ik beginnen? Je loopt als rode draad door mijn onderzoeksperiode heen. Allereerst de begeleiding in Adelaide, waar ik onder jouw begeleiding samen met prof. Jaarsma de basis heb gelegd voor dit proefschrift. Je hebt mij naast veel kansen en mogelijkheden bovenal veel vertrouwen gegeven om mij te ontwikkelen. Van de diverse buitenlandse congressen waar ik op de grote podia ons verhaal mocht vertellen tot aan het organiseren van het *Symposium Challenges in Trauma and Triathlon for Trauma 2019*. Jouw aanstelling in het UMCG heeft zeker bijgedragen aan de keuzes die ik tot nu toe gemaakt hebt. Ik ben je daar erg dankbaar voor en kijk er naar uit om nu ook klinisch veel van je te leren.

Copromotor Dr. F.J.P. Beeres

Beste Frank, als Nederlands traumachirurg in Zwitserland heb je mij de kans geboden om een stage te volgen in Luzern. Ondanks de verkorte periode hebben we in deze tijd drie papers geschreven waarvan er twee een belangrijke bijdrage hebben geleverd aan dit proefschrift. Ik heb veel gehad aan jouw wetenschappelijke begeleiding, scherpe revisies en nieuwe ideeën voor onderzoek waarvoor ik je erg dankbaar ben. Ik hoop in de toekomst in Luzern te mogen terugkeren om te leren van je chirurgische vaardigheden.

Dr. F.F.A. IJpma

Beste Frank, door onze samenwerking heb ik er een goede vriend bij gekregen. Het begon op een onderzoeksmeeting in Amsterdam, waarin we spraken over een manier om tibia rotatie te voorkomen. Dit hebben we uitgewerkt en tegelijkertijd hebben we nog een aantal andere artikelen geschreven en gepubliceerd. Dankzij jouw supervisie, laagdrempelige begeleiding en enthousiasme heeft dit proefschrift een erg mooi einde gekregen. De momenten op de fiets, diverse etentjes, borrels en aanwezigheid op jouw bruiloft heb ik als waardevol ervaren. Je bent op zowel wetenschappelijk- als chirurgisch gebied een ware inspirator voor me. Ik kijk uit naar de klinische implementatie van de CARV en de verdere onderzoeken die gaan komen.

Coauteurs

Beste coauteurs, ik dank jullie voor de bijdrage aan dit proefschrift. Ik wil in het bijzonder Bryan van de Wall bedanken voor je aanstekelijke enthousiasme voor het vak en de momenten dat we in een relatief korte tijd meerdere papers hebben geschreven. De dagelijkse contactmomenten en dagelijkse revisies hebben gemaakt dat we in korte tijd iets heel erg moois hebben neergezet. Ik dank je voor je positiviteit, inspiratie, begeleiding en al het statistische advies. Ik hoop dat we de wetenschappelijke samenwerking kunnen continueren.

Overige leden van de promotiecommissie: prof. dr. F. Nollet, prof. dr. R.J. Oostra, prof. dr. M. Maas, prof. dr. F.W. Bloemers, dr. K.J. Ponsen, prof. dr. M.H.J. Verhofstad

Geachte leden van de promotiecommissie, ik dank jullie voor de tijd, kritische vragen en bovenal interesse in dit proefschrift.

Paranimf Martijn Tuinte

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Paranimf Geerben Bleeker

Beste Geerben, als jongste van het Bleeker-telg en niet-dokter vervul je een belangrijke rol aan mijn zijde tijdens de verdediging van het proefschrift. In de geest van pap doet het mij veel dat je deze rol wilt vervullen. Ik ben trots op jouw groei en potentie in het ondernemerschap.

Vrienden

Beste Martijn Diekmann, Chris, Jeroen, Max en Sam en overige leden van JC Braga, veel dank dat jullie de tijd in Groningen onvergetelijk hebben gemaakt. Beste Martijn Tuinte, Rob en Jesse. Dank voor jullie vriendschap en altijd luisterend oor als het om dit proefschrift ging! Op nog vele mooie momenten samen. Beste Gysbert, Robbin, Tom, Daniël en Mart. Al tijdens de middelbare school een hechte groep waarbij ik elk jaar weer uitkijk naar ons jaarlijkse vaarweekend in Friesland en weekje zon in het najaar. Dat er nog vele mogen volgen!

Benthe Spruijt

Lieve Bennie, veel dank voor jouw creativiteit en inspiratie voor het ontwerp van de cover!

Afdeling Chirurgie NWZ en Afdeling Orthopedie UMCG

Beste collega's van de afdeling Chirurgie in het NWZ, in het bijzonder Dr. K.J. Ponsen, en afdeling Orthopedie in het UMCG, in het bijzonder prof. dr. P.C. Jutte en Dr. J.J.W. Ploegmakers, veel dank voor jullie bijdrage, ruimte en tijd die jullie mij gegund hebben om deze promotie af te maken.

Jate en Riekus Bleeker

Beste Jate en Riek, als het overgebleven Bleeker-telg kunnen jullie niet achterblijven in mijn dankwoord. Jate, dankzij jouw creativiteit heeft de *'C-Arm Rotational View'* een gezicht gekregen en zijn we samen in PubMed te vinden. Dat had pap vast prachtig gevonden. Riek, pap is ontzettend trots op je en ik ben blij dat je mijn broertje bent!

Rozemarijn Flisijn

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Mam

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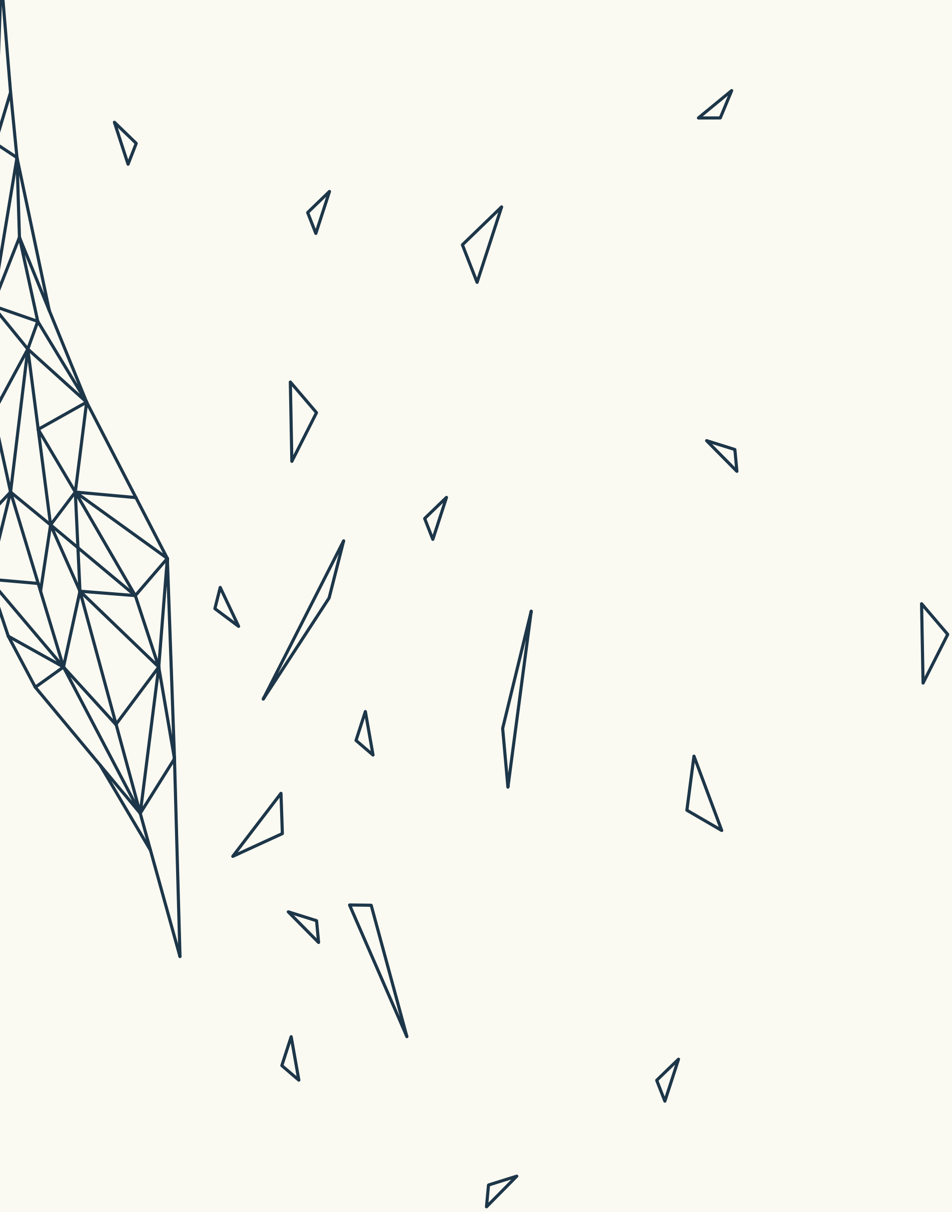
Pap

Lieve pap, het proefschrift begint en eindigt bij jou. Ik mis je gulle lach, betrokkenheid en onvoorwaardelijke liefde. Ik mis onze gedeelde passie in de wetenschap, want als enige van de familie had je ook een PhD-titel. Het doet mij pijn dat je hier fysiek niet bij kan zijn, maar tegelijkertijd weet ik dat je erbij bent. Je bent mijn inspirator en mijn rots in de branding. Deze is voor jou!



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