Tibial Shaft Fractures

incidence, costs and outcome after intramedullary nailing

Mandala Şenay Leliveld

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Fracturen van de tibiaschacht

incidentie, kosten en uitkomsten na mergpenosteosynthese van de tibia

Tibial Shaft Fractures

incidence, costs and outcome after intramedullary nailing

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Chapter 1

General introduction

Epidemiology and burden to society

Lower extremity fractures account for 6.2% of all emergency department visits in the Netherlands during 2001-2002.[1] In 1.9% the tibial diaphysis is affected as shown by an analysis of all individuals presenting with a fracture at the emergency department of the Royal Infirmary of Edinburgh (United Kingdom) in the year 2000.[2] Tibia shaft fractures have a bimodal distribution with a high peak in young males and a small peak in older females.[3] Over the past decades the incidence rate of tibia shaft fractures has declined from 18.7/100,000 person years in 1998 to 16.1/100,000 in Sweden in 2004.[3] The incidence rate in the elderly (65 years or older) showed even further decline from 27.0/100,000 in 1990 to 14.0/100,000 in 2004 in the United Kingdom.[4]

Although the incidence rate of lower leg fractures is low compared to, e.g., hip and wrist fractures, the impact of these injuries is high. With 26.6%, lower leg fractures contributed most to the global years lived with disability of injuries in 2013.[5] After two years of follow-up, the self-reported health status of patients that sustained a lower extremity fracture is still impaired.[1] And even five years after injury of the tibia shaft function does not improve to baseline.[6] Due to the high proportion of patients with lifelong disabilities in combination with the patients' relatively young age the societal burden associated with these injuries is eminent.

Clinical presentation

In younger patients fractures of tibial diaphysis are mostly caused by a sports accident. Elderly often sustain such a fracture after a simple fall. High-energy tibia fractures are usually the result of traffic accidents, such as motor vehicle, pedestrian versus car bumper, or cycling collisions.[3] Patients present with pain, swelling, and hematoma at the fracture site. Moreover, there is an inability to use the leg. Muscle compartment syndrome occurs relatively common. In a conscious and alert patient, there will be unrelenting, worsening pain, greater than expected for the particular injury, and not related to limb position. Compartment syndrome is a true surgical emergency and needs urgent treatment by decompression to prevent major limb disability.

The AO/OTA fracture classification divides the diaphyseal tibia fractures into simple fractures (42A1-3), wedge fractures (42B1-3), and complex fractures (42C1-3). In 2018 this classification was simplified and the 42B1 and 42C1 fracture types were removed.[7]

The status of the soft-tissue surrounding the tibia is a crucial determinant of the outcome. Closed and open fractures of the tibia both have their own classification system. For closed fractures the Tscherne classification can be applied (Table 1.1).[8] An alternative is the AO classification which provides a grading system for injuries of the skin, muscles and tendons and neurovascular injuries, each of which is divided into five degrees of severity.[9] However, the complexity of this system hampers its use in daily practice. For open fractures the Gustilo-Anderson classification is most commonly used.[10] The Gustilo-Anderson classification divides soft-tissue injury of open fractures into three grades – I, II, and III (Table

1.2). The III grade is further subdivided into types IIIA, IIIB, and IIIC.[11] A systematic literature review and meta-analysis identified infection rates of over 31% in patients with Gustilo-Anderson grade IIIB or IIIC open tibial fractures treated with an implant versus infection rates below 3% occurring in less severe open tibial fractures.[12] Every effort should be made to reduce the risk of infection by using *e.g.*, aseptic technique, peri-operative antibiotics, and soft-tissue care (including debridement, stabilization of the fracture and tension free wound closure). Innovations to reduce this risk also include antibiotic-coated implants.

Treatment

Intramedullary fixation is the treatment of choice for the majority of tibial shaft fractures due to high union rates and low infection and deformity rates.[13-15] The infrapatellar approach is most commonly used. With the knee in 90 degrees flexion, an incision is made between the apex of the patella and the tibial tuberosity. The entry point to the medullary canal is reached through a transpatellar or parapatellar approach. After reaching the nail entry site the medullary canal is opened and if necessary, the shaft is reamed. The nail is then inserted during or after proper fracture reduction and proximal and distal locking screws are inserted. An end cap can be used in order to prevent ingrowth of bony tissue. The wound is closed in layers and a soft dressing is applied. After surgery the focus lies on pain control, mobilization, prophylaxis of infection and deep venous thrombosis, and early recognition of complications (including development of a compartment syndrome).

Table 1.1. Tscherne classification for closed fractures.

Grade	Description
0	No or minor soft-tissue injury from a simple fracture due to indirect trauma
I	Superficial contusion or abrasion to the skin
II	Deep contaminated abrasions with skin or muscle contusion from direct trauma
III	Extensive skin contusion with destruction of subcutaneous tissue avulsion or muscle destruction

Table 1.2. Gustilo-Anderson classification for open fractures.

Grade	Description
I	Skin wound less than 1 cm, clean, simple fracture pattern
II	Skin wound more than 1 cm, soft tissue damage not extensive, no flaps or avulsions, simple fracture pattern
IIIA	Adequate soft-tissue coverage of a fractured bone despite extensive soft-tissue laceration or flaps, or high energy trauma irrespective of the size of the wound
IIIB	Extensive soft-tissue injury loss with periosteal stripping and bone exposure. This is usually associated with massive contamination
IIIC	Open fracture associated with arterial injury requiring repair.

Hyperflexion of the knee during tibial nailing is associated with an increased risk of valgus and procurvatum deformities, especially in nailing proximal third tibial shaft fractures. In an attempt to address this problem, a semi-extended technique has been developed.[16,17] For the same reasons, the suprapatellar approach has been introduced.[18-20] For this approach, an incision is made just proximal to the superior pole of the patella and the nail is inserted through the patellofemoral joint. Although all techniques for nail insertion have been proven feasible, a comparison of their rates of anterior knee pain and functional outcome is lacking.

Patient-reported outcome

Patient-reported outcome measures (PROMs) are becoming increasingly important instruments to evaluate clinical outcome and functional recovery from the patient's perspective.[21] PROMs measure patient perceptions of specified aspects of their own health that either cannot be directly observed (*e.g.*, pain), or that are not practical or feasible to directly observe (*e.g.*, performance of daily activities).[22] An advantage of generic quality of life PROMs, like the EuroQol-5D (EQ-5D), is that they allow comparison across populations with different medical conditions. Region-specific instruments give insight in disabilities, pain, and problems caused by a specific condition. Effects of treatment can be monitored over time with these instruments, and they can be used to compare different treatment strategies. Instruments should only be used if proven reliable and valid for the patient population that is studied.

Anterior knee pain

Anterior knee pain is one of the most reported complaints after tibial nailing.[23] This post nailing pain can last for years.[14,24] Removal of the intramedullary nail relieves anterior knee pain in the majority of patients.[25] In the remaining patients pain persists after nail removal, aggravates, or even develops in previously asymptomatic patients.[26,27] The most painful daily activities are kneeling and squatting.[28] The etiology of this phenomenon is not elucidated.

Infrapatellar nerve injury

Among the structures at risk for injury during nail insertion through an infrapatellar approach is the infrapatellar branch of the saphenous nerve. It is a sensory nerve innervating the anterior aspect of the knee, the anterolateral aspect of the proximal part of the lower leg, and the anteroinferior part of the knee joint capsule.[29,30] The infrapatellar branch of the saphenous nerve originates from the saphenous nerve and arises distal to the adductor canal.[31] It pierces the sartorius muscle, after which it runs a superficial course and generally forms two branches.[32,33] Both branches cross the patellar tendon in a transverse way to form the infrapatellar plexus.[29,34] These branches are at risk for transection, especially when longitudinal surgical incisions are made at the anteromedial side of the knee.

Injury to the infrapatellar branch of the saphenous nerve usually results in numbness on the anterior aspect of the knee and the proximal lateral part of the lower leg. This complication has been reported after several other surgical procedures around the knee, such as knee total knee arthroplasty,[35,36] arthroscopy,[34] anterior cruciate ligament reconstruction,[37] and tibial nailing.[14] Also, post-procedural neuropathic pain and symptomatic neuroma can develop.[38,39] Studies to examine a relation between infrapatellar nerve injury and anterior knee pain after tibial nailing have not yet been conducted.

Although the infrapatellar branch of the saphenous nerve is a known anatomic structure, its relevance in daily clinical practice is underestimated as of yet, since longitudinal incisions in the anteromedial region of the knee are still commonly used. A safe zone for incisions at the anterior aspect of the knee can give surgeons guidance to minimize iatrogenic injury to the infrapatellar nerve and possibly reduce the risk of chronic anterior knee pain.

Aims of this thesis

- To give insight into the changes in incidence rate and treatment-associated costs of patients admitted with an isolated tibial shaft fracture;
- To describe the outcome of different treatment strategies for tibial nail insertion;
- To validate instruments used to measure outcome of treatment in patients with a tibial shaft fracture;
- To determine the rate of infrapatellar nerve injury and anterior knee pain after tibial nailing;
- To determine an anatomical safe zone at the anterior aspect of the knee in order to minimize the risk of injury of the infrapatellar nerve;
- To compare the effect on anterior knee pain of a potentially infrapatellar nerve sparing (transverse) incision versus a longitudinal incision for tibial nail insertion.

Outline of the thesis

This thesis is divided in three parts. The first part describes long-term population-based trends in the incidence rate of patients with an isolated tibia shaft fracture admitted to a hospital between 1991 and 2012 in the Netherlands (**Chapter 2**) and gives a detailed overview of the associated costs for health care and lost productivity (**Chapter 3**). In **Chapter 4** the cost-effectiveness of the use of antibiotic coated intramedullary nails in open tibia fractures in Europe is analyzed.

The second part focuses on patient reported outcomes after tibial nailing. **Chapter 5** describes the rates of anterior knee pain and functional outcome following different surgical techniques for tibial nailing, for which a systematic review and pooled analysis of all available literature was performed. The validity, reliability, responsiveness and Minimal Important Change (MIC) of the Short Musculoskeletal Functional Assessment (SMFA) and Lower Extremity Functional Scale (LEFS) for patients with a tibia shaft fracture are described in **Chapter 6**.

The third part centers around anterior knee pain after tibial nailing, focusing on the infrapatellar nerve as a possible source for this problem. In **Chapter 7** the rate of anterior knee pain and infrapatellar nerve injury after tibial nailing is retrospectively examined. The effect of an infrapatellar nerve block on chronic anterior knee pain after tibial nailing is investigated by means of the randomized controlled trial described in **Chapter 8**. **Chapter 9** examines the surgical anatomy of the infrapatellar nerve in relation to incisions on the anteromedial aspect of the knee and provides a safe zone for incisions to minimize the risk of infrapatellar nerve injury. Finally, the effect of the theoretically infrapatellar nerve sparing transverse incision versus the longitudinal incision for insertion of a tibial nail in a multicenter randomized trial described in **Chapter 10**.

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PART I

Incidence and costs of tibia shaft fractures

Chapter 2

Epidemiologic trends for isolated tibia shaft fracture admissions in the Netherlands between 1991 and 2012

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Abstract

Introduction

Population-based knowledge on the occurrence of specific injuries is essential for the allocation of health care services, optimization of preventive measures, and research purposes. Therefore, the aim of this study was to examine longterm nation-based trends in the incidence rate, trauma mechanism, hospital length of stay (HLOS), treatment, and outcome of hospital-admitted patients with an isolated tibia shaft fracture between 1991 and 2012 in the Netherlands.

Methods

All hospital-admitted patients in the Netherlands between 1991 and 2012 with an isolated tibia shaft fracture were included. Age and gender-standardized incidence rates were calculated for each year. Data were extracted from the National Medical Registration.

Results

The incidence rate for men decreased to 13.8/100,000 person years (py). For women the incidence rate remained stable with 7.2/100,000 py. Incidence showed a peak for adolescent men (15–19 years), and increased in both genders from 65 years onwards. Since 1993 the mean HLOS for isolated tibia fractures reduced from 10.8 to 5.4 days. Mean HLOS increased with age. Mean years lived with disability (YLD) was 4.5 years, declined linearly with age, and showed no gender effect.

Conclusions

In 22 years, the incidence rate of hospital admitted patients with an isolated tibia shaft fracture in the Netherlands dropped with 12%, which was mainly attributable to a 15% decline among men. Incidence rate, trauma mechanism, and HLOS were age and gender related. HLOS also reduced over time. Operation rate and YLD were only age related.

Introduction

Trauma is among the leading causes of (temporary) disability, dependence, and absence from work. Whereas the incidence rate of long bone fractures in the upper extremities (including humeral fractures) have increased over time,[1] the opposite seems the case for long bone fractures in the lower extremities. Literature data for tibia shaft fractures suggest that the incidence rate has declined over the past decades. Weiss et al. performed a nationwide study in Sweden and showed a decrease from 18.7/100,000 person years in 1998 to 16.1/100,000 in 2004.[2] Prospectively gathered data by Clement et al. from the Royal Infirmary of Edinburgh (United Kingdom) showed the incidence rate in the elderly (65 years or older) declined from 27.0/100,000 in 1990 to 14.0/100,000 in 2004.[3]

Tibia shaft fractures have a bimodal distribution with a peak in young males and in older females.[2,4,5] Elderly often sustain such a fracture after a simple fall, in younger patients they are mostly caused by a sports accident. High energy tibia fractures are usually the result of traffic accidents, such as motor vehicle, pedestrian versus car bumper or cycling collisions.[2,4]

Whether or not the decline in tibia shaft fractures incidence rates and the age and gender relatedness also apply to the Netherlands has not been published. Population-based knowledge on the occurrence of specific injuries is essential for the allocation of health care services, optimization of preventive measures, and research purposes; it may also provide a forecast for the future. Therefore, the aim of this study was to examine long-term population-based trends in the incidence rate, trauma mechanism, hospital length of stay, treatment, and outcome of patients with a tibia shaft fracture (with or without fibula fracture) admitted to a hospital in the Netherlands between 1991 and 2012.

Methods

Data source

For this retrospective epidemiological study data were collected for patients admitted to a hospital in the Netherlands with a tibia shaft fracture with or without a concomitant fibula fracture in the period 1991–2012. The methods are essentially the same as published before.[1,6,7] In 2012 the Netherlands had 16.7 million inhabitants.[8] Injury cases were extracted from the National Medical Registration (LMR) of the Dutch Hospital Database (DHD), Utrecht, the Netherlands. The DHD collects hospital data of all hospitals in the Netherlands with a uniform classification system and has an almost complete national coverage (missing values <5%, except in 2007 12%). These figures were extrapolated by the Consumer and Safety Institute to full national coverage for each year. The extrapolation factor was estimated by comparing the adherence population of the participating hospitals with the total Dutch population in each year using the population data obtained from Statistics Netherlands.[9] Patients are included in the LMR for their main diagnosis at hospital discharge, defined by the International Classification of Diseases (ICD) 9th and (since 2010) 10th revision.[10] Codes for tibia shaft fractures are presented in Table 2.1. Both patients with and without concomitant fibula (shaft) fracture were included in this study.

The study was exempted by the local Medical Research Ethics Committee Erasmus MC (no. MEC-2015-218).

Calculation of incidence rates

Age- and gender-specific incidence rates were calculated in 5-year age groups for each year of the study. In order to adjust for differences in the demographic composition over time, incidence rates were standardized for age (in 5-year age groups) and gender using a direct standardization method, as previously described.[1] In short, the age- and sex-specific incidence rates per 100,000 person years were calculated based upon the Dutch mid-year standard population.

Trauma mechanism, surgical intervention and hospital length of stay

Data regarding trauma mechanism, operation rate and hospital length of stay (HLOS), were extracted from the LMR database for 10-year age categories and for males and females separately. Percentage of trauma mechanisms and mean HLOS were averaged over 5-year intervals from 1993 to 2012 to assess trends over time. For operation rates, data were averaged over a 5-year interval 2007–2012, as earlier data were not available. For HLOS, the total HLOS was calculated by multiplying the mean HLOS per patient with the total number in each age category.

Years lived with disability

YLD was obtained by linking the incidence data (subdivided into injury diagnosis groupings) with disability information, that is the proportion of injury cases with lifelong consequences, and injury-specific disability weights of temporary and lifelong consequences. The number of years lived with disability (YLD) was calculated from a patient follow-up survey on health care use and functional outcome.[11,12] The disability weights were derived from empirical follow-up data on the health-related quality of life of individual trauma patients,[11] and adjusted for population norms, age and gender.[13] A random sample of patients was invited to complete a survey at 2.5, 5, 9, and 24 months after injury. YLDs were calculated in three steps.[13] First, data were gathered on the incidence rate, age, and gender distribution of patients hospitalized due to a tibia shaft fracture. Second, the incidence data were divided into the injury categories of the EUROCOST classification system.[14] Finally, the grouped incidence data were combined with the disability weights and durations developed within the framework of the European INTEGRIS (Integration of European Injury Statistics) study.[13] The disability weight reflects the impact of a health condition in terms of health-related quality of life; it has a value ranging from 1, indicating worst imaginable health state, to 0, indicating full health.[13]

Registered cases were multiplied with the 1-year disability weight, the proportion of lifelong consequences, and the duration (life expectancy at age of injury, by gender). The mean 1-year disability weights included the temporary and lifelong consequences for

Table 2.1. Tibia shaft fractures classified in ICD-9 and ICD-10.

ICD	Group	Subgroup	Description
ICD-9	823.2		Fracture of shaft of tibia and fibula closed
		823.20	Closed fracture of shaft of tibia alone
		823.21	Closed fracture of shaft of fibula alone
		823.22	Closed fracture of shaft of fibula with tibia
	823.3		Fracture of shaft of tibia and fibula open
		823.30	Open fracture of shaft of tibia alone
		823.31	Open fracture of shaft of fibula alone
		823.32	Open fracture of shaft of fibula with tibia
ICD-10	S82.2		Fracture of shaft of tibia
		S82.20	Unspecified fracture of shaft of tibia
		S82.22	Transverse fracture of shaft of tibia
		S82.23	Oblique fracture of shaft of tibia
		S82.24	Spiral fracture of shaft of tibia
		S82.25	Comminuted fracture of shaft of tibia
		S82.26	Segmental fracture of shaft of tibia
		S82.29	Other fractures of shaft of tibia

ICD International Statistical Classification of Diseases and Related Health Problems

2

cases seen in EDs and those recorded in hospital discharge registers. Data gathered during the 5-year interval 2007–2012 were used for this study.

Results

Incidence rates

Between 1991 and 2012, 32,350 patients required admission for an isolated tibia shaft fracture in the Netherlands. During this period the overall crude number of patients (male and female combined) per year decreased with 12%; from 1860 in 1991 to 1640 in 2012. This decline in crude numbers was most apparent between 1991 and 2006 (−36%). From 2007 onwards numbers seem to rise again (Figure 2.1a).

Figure 2.1b shows the annual incidence rate of isolated tibia shaft fractures per 100,000 person years (py). For men, the mean incidence rate between 1991 and 2012 was 13.3/100,000 py. The incidence rate decreased with 15% (from 16.3/100,000 py in 1991 to 13.8/100,000 py in 2012). The incidence rate for women remained constant over time: 7.5 per 100,000 py in 1991 and 7.2 per 100,000 in 2012 (mean incidence rate 5.6/100,000 py). The male:female ratio remained 2.4:1 during the study period (Figure 2.1a, b).

The age-specific incidence rates showed a bimodal distribution as can be seen in Figure 2.1c, d. The incidence shows a first peak among adolescent men (15–19 years). This peak has decreased with 53% during the study period (from 47.5/100,000 py in 1991 to 22.2/100,000 py in 2012). In women, the first peak in incidence is lower than in men. Moreover, it occurred at a younger age (10–14 years) and decreased less than in men (−38%; from 16.2/100,000 py

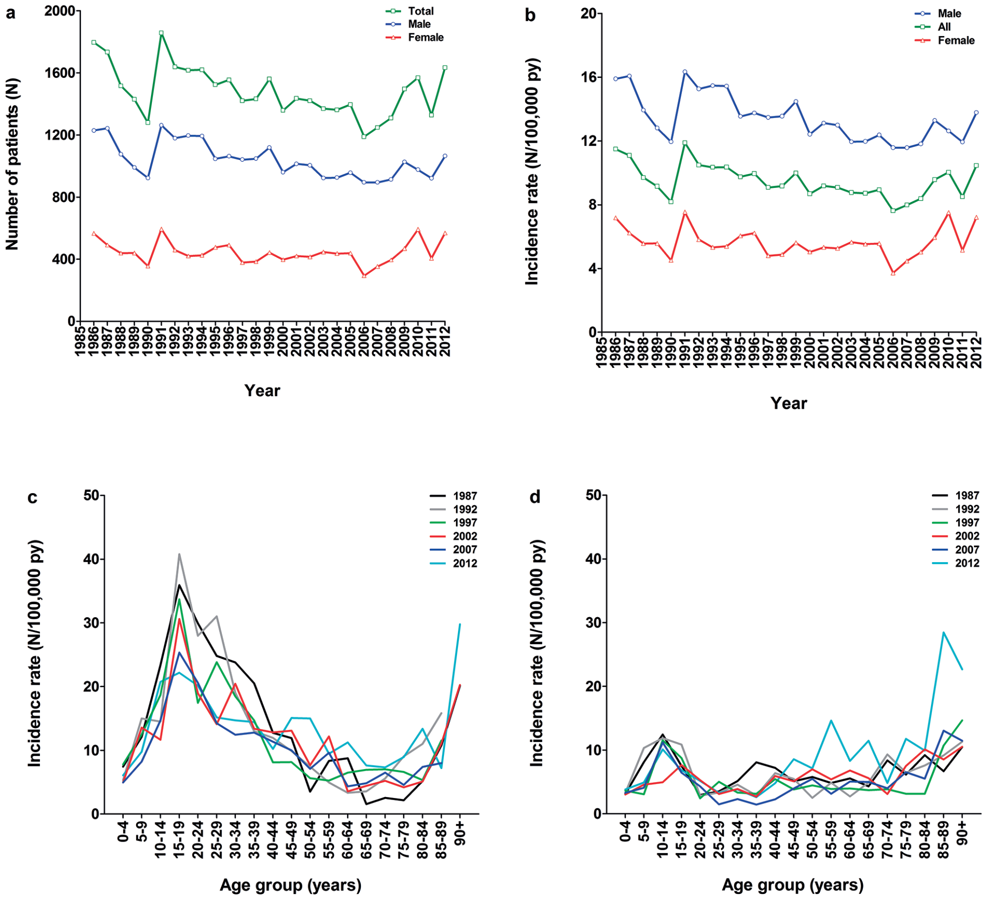

Figure 2.1. Case numbers (**a**), incidence rates (per 100,000 person years) of isolated tibia shaft fractures annually since 1991 (**b**), and age relation in males (**c**) and females (**d**). **a, b** The crude numbers of patients and the incidence rate per year from 1991 to 2012, respectively. The age-dependency of the incidence rate for every fifth year during the study period in males (**c**) and females (**d**).

in 1991 to 10.1/100,000 py in 2012). The gradual increase in incidence rates as seen from 65 years onwards seems unrelated to gender.

Table 2.2 shows that the incidence rates in the overall population in 2012 was hardly related to age. However, incidence rate showed a clear decrease with age in males (from 15.3 to 8.9/100,000 py) and a noticeable increase with age in females (from 6.5 to 11.7/100,000 py).

Trauma mechanism

Figure 2.2a shows the trauma mechanisms causing isolated tibia shaft fractures in men and women in four consecutive 5-year periods. Throughout the years the majority of fractures in women were caused by a fall. In men traffic accidents and falls contributed almost equally.

Table 2.2. Incidence rates (per 100,000 person years) of isolated tibia shaft fractures in 2012 for different age groups in males and females.

Age group	Males	Females	Total (males + females)
0–19 years	15.3	6.5	11.0
20–49 years	15.0	4.7	9.9
50–64 years	12.0	10.0	11.0
≥ 65 years	8.9	11.7	10.5
All ages combined	13.8	7.2	10.5

Sport accidents were seen more in men. During the displayed years, all mechanisms showed fairly steady patterns. The age and gender dependency of trauma mechanisms for 2012 are presented in Figure 2.2b, c. In males, the dominant trauma mechanism was a traffic accident until 20 years of age (36%). From 60 years onward, falls predominated (Figure 2.2b). Women showed a similar pattern; the dominant trauma mechanism was a traffic accident in the age group <40 years (50%) and falls in the age group >40 years (72%; Figure 2.2c). Direct contact and sports particularly contributed at the age of 20–29 years, especially in men (27%).

Operative treatment

In 2012, 57.9% of patients (all ages combined) were treated surgically for their sustained isolated tibia shaft fracture (Table 2.3). The highest operation rate was 70.7% for patients between the age of 30 and 39 years (Figure 2.3). The lowest rates were seen in children (19.7% between 0 and 9 years) and elderly (31.7% in 90+). Operation rate seemed unaffected by gender (Figure 2.3).

Hospital length of stay

Hospital length of stay (HLOS) per case increased with age. Mean HLOS was 1.6 (SD 4.0) days for patients aged 0–9 years and 12.7 (SD 12.4) days for patients aged 80–89 years in 2012. The mean HLOS per case declined from 10.8 (SD 13.2) days in 1997 to 5.4 (SD 8.6) days in 2012 (Figure 2.4a, b). HLOS per case seemed unrelated to gender (Table 2.4).

Table 2.3. Age-related percentage of patients undergoing surgical treatment in males and females in 2012.

Age group	Males	Females	Total (males + females)
0–19 years	43.1	40.8	42.4
20–39 years	66.0	72.1	67.3
40–59 years	71.0	62.4	68.2
≥ 60 years	61.0	47.2	53.1
All ages combined	59.9	53.8	57.9

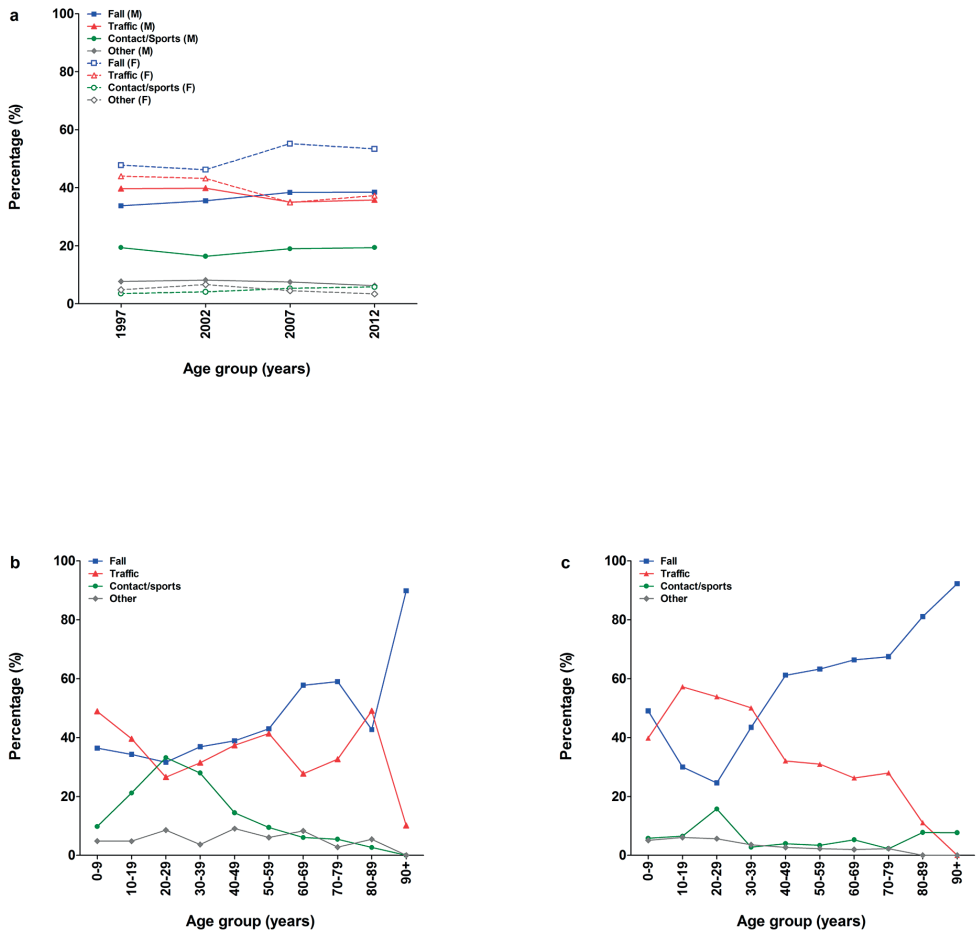

Figure 2.2. Trauma mechanisms causing isolated tibia shaft fractures. **a** The relative occurrence of trauma mechanisms in four time periods in males and females. The age-dependency of trauma mechanisms in 2012 for males (**b**) and females (**c**).

Table 2.4. Age-related hospital length of stay due to an isolated tibia shaft fracture in males and females in 2012.

Age group	Males	Females	Total (males + females)
0–19 years	2.8	2.4	2.7
20–39 years	4.6	4.6	4.6
40–59 years	6.0	5.3	5.7
≥ 60 years	9.9	9.7	9.8
All ages combined	5.1	6.0	5.4

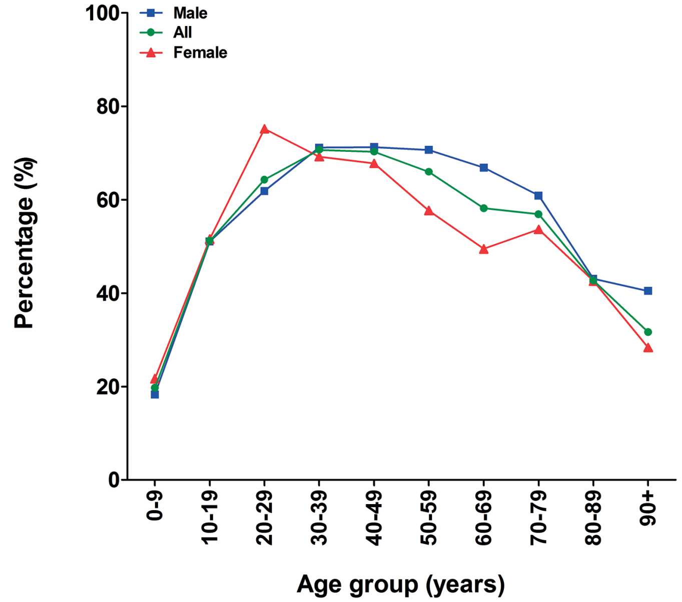

Figure 2.3. Age-related percentage of patients undergoing surgical treatment in males and females in 2012.

Due to a higher incidence rate of isolated tibia shaft fractures, the total HLOS was higher in men than in women until 60 years of age. A decline in total HLOS throughout the years was seen in men aged ≤60 years (Figure 2.4c). The greatest decrease was seen in men aged 10–19 years (–69%, from 2320 days in 1997 to 725 days in 2012). In women total HLOS was similar for all ages over the consecutive years (Figure 2.4d).

Years lived with disability

Years lived with disability (YLD) per case declined almost linearly with age, but seemed unrelated to gender (Figure 2.5). In 2012, the mean YLD per case declined from 7.8 YLD in patients aged 0–10 years to 0.6 YLD in the very elderly (90+ years). The overall YLD for all age groups and both genders combined was 4.5 YLD.

Discussion

From 1991 to 2012 the incidence rate of hospital admitted patients with isolated tibia shaft fractures dropped with 12% in the Netherlands. This study reports on age- and genderspecific trends in incidence rate, trauma mechanism, hospital length of stay and treatment for patients admitted with these fractures in the Netherlands between 1991 and 2012. Furthermore, this study is the first to describe the age- and gender-specific outcome (YLD) after a sustained tibia shaft fracture.

With 13.3/100,000 py for men and 5.6/100,000 py for women, the overall incidence rate of hospital admissions for isolated tibia shaft fractures in the Netherlands in both genders

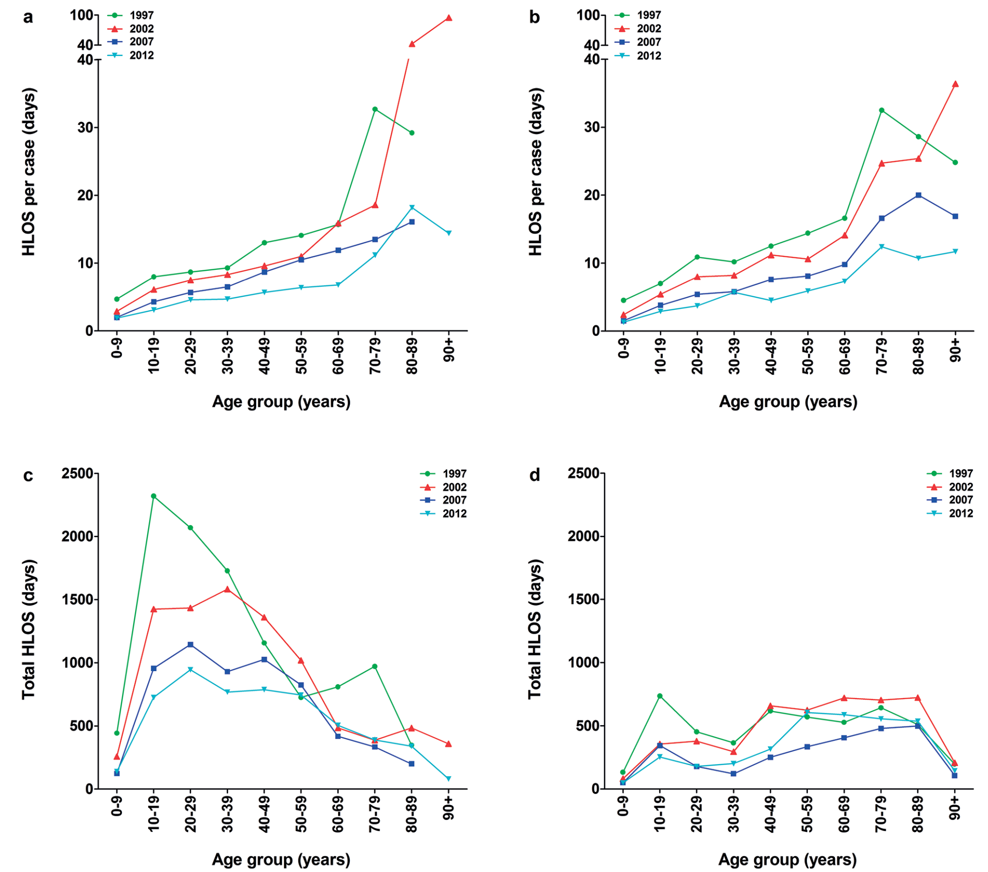

Figure 2.4. Hospital length of stay due to an isolated tibia shaft fracture. HLOS per patient for four different time periods in males (**a**) and females (**b**). The total HLOS for males (**c**) and females (**d**) for four different time periods.

is lower than the incidence rate of hospital admissions in Sweden reported by Weiss et al. (21/100,0000 py in men and 13/100,000 py in women).[2] In the National Medical Registration database only the most serious injury of the patient admitted to the hospital is registered. The numbers reported in the current paper therefore represent the actual number of patients admitted for an isolated tibia shaft fracture. The overall decline in incidence rate between 1991 and 2012 in the current study was mainly attributable to a 15% fall in incidence rate in men (to 13.8/100,000 py in 2012). Especially in adolescent men (15–19 years) the incidence rate dropped substantially with 53% during this period. A reduction of 12% in the number of hospital admissions between 1998 and 2004 is also described for the Swedish population,[2] but age-dependent incidence trends are not reported by Weiss et al.

The mean hospital length of stay per case decreased by half between 1993 and 2012 both in men and women, whereas the total admission duration decreased only in men.

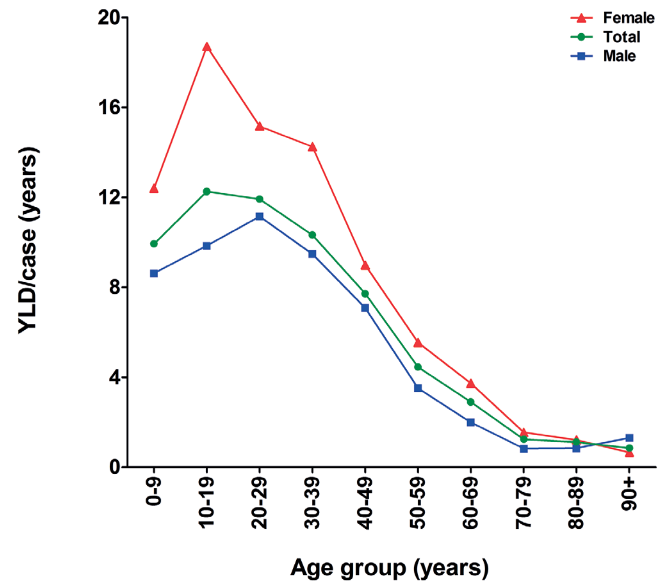

Figure 2.5. Age-related effect of isolated tibia shaft fractures on the years lived with disability in 2012.

The latter reflecting the fall in incidence rate for men only. Only the most serious injury on admission is listed in The National Medical Registration database. When, for example, a patient is admitted with traumatic brain injury and a tibia shaft fracture, only the brain injury will be registered. Since at least 32.7% of patients with a tibia fracture is multiply injured,[15] these injuries will consequently have influenced reporting on the hospital length of stay in other studies.[2] The hospital length of stay in our study thus represents admission days for an isolated tibia shaft fracture only.

The current study is the first to report age- and gender specific outcome of YLD after isolated tibia shaft fractures. With 26.6%, nature-of-injury categories fracture of patella, tibia, fibula or ankle contributed most to the global YLDs of injury in 2013.[16] With regard to serious road injuries in the Netherlands during 2000–2009, the total burden of injury was highest for fractures in knee and lower legs (22%).[17] These findings emphasize that although the incidence of lower leg fractures is low compared with, e.g., hip and wrist fractures, the (lifelong) impact of this injury is high. The high average burden is due to the high disability weights and proportions of lifelong disabilities of some lower leg injuries in combination with the casualties' relatively young age.

Treatment of individual fractures is not specifically improved by epidemiological studies, but surgeons should have knowledge of the spectrum of fractures which they treat; not only for educational purposes, but also to allow resources to be allocated. A limitation of this study is that data from the National Medical Registration did not provide a subdivision of open and closed tibia fractures. Since the start of the registration, the treatment concept of tibia shaft fractures has changed radically, especially in the last two decades. As reflected in several international guidelines, the fracture itself is more and more seen as a part of a lower leg injury. The prognosis and therapeutic choices are merely depending on the concomitant soft tissue injury. In addition, the provided data concerning the treatment of tibia fractures were only divided in operative versus nonoperative treatment. It does not provide information on trends in the use of different surgical devices (i.e., intramedullary nails, plates or external fixators). Allocation of parameters on the severity of soft tissue injury and implants used are helpful to predict future requirements for equipment and resources such as plastic reconstructive surgery and rehabilitation medicine. A detailed registration of both diagnosis and treatment at the beginning, combined with technical solutions to guarantee the privacy of individual patients, would make a detailed nationwide survey feasible. the Netherlands is currently working on such improvements.

Data registered by The National Medical Registration has an almost complete national coverage and was extrapolated to full national coverage, making it a reliable source for an epidemiological study. However, the database has some limitations. Nonoperatively treated patients, who were not admitted, are not taken into account. This implies that both patients treated in an outpatient clinic only and patients sustaining at least one more severe injury than a tibia shaft fracture are missing. Furthermore, patients are included in the LMR for their main diagnosis at hospital discharge. If the tibia fracture coincides with a more severe trauma or the postoperative course is complicated by, for example, a pulmonary embolism, this additional, more severe diagnose will be registered in the LMR at discharge. This accounts for an underestimation of isolated tibia fractures of less than 10%. Finally, bilateral tibia shaft fractures are included in the database, but not separately listed. If and how these shortcomings influence ratios between men and women and/or the young and elderly, cannot be appraised. On the other hand, since the registration rules have been consistent over time, it is likely that trends during the years are reliable.

Conclusion

From 1991 to 2012 a total of at least 32,350 patients were admitted for a tibia shaft fracture with or without concomitant fibula shaft fracture to a hospital in the Netherlands. During this period the incidence rate of hospital admitted patients dropped with 12%, which was mainly attributable to a 15% decline in incidence rate in men. Throughout the years the majority of tibia shaft fractures in women were caused by a fall. In men traffic accidents and falls contributed almost equally. No historical trends were visible for the different trauma mechanisms. In both men and women hospital length of stay (HLOS) per case increased with age and the mean HLOS per case declined to 5.4 days in 2012. Operation rate was only age related. The mean YLD was 4.5 years, declined linearly with age and showed no gender effect.

2

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Chapter 3

Health care and productivity costs for isolated tibia shaft fracture admissions in the Netherlands

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Abstract

The aim of this study was to provide a detailed overview of age and gender specific health care costs and costs due to lost productivity for hospital admitted patients with an isolated tibia shaft fracture in the Netherlands between 2008 and 2012. Injury cases and length of hospital stay were extracted from the National Medical Registration. Information on extramural health care and work absence were retrieved from a patient follow-up survey on health care use. Medical costs included ambulance care, in hospital care, general practitioner care, home care, physical therapy, and rehabilitation/nursing care. An incidence-based cost model was applied to calculate direct health care costs and lost productivity in 2012. Total direct health care costs for all patients admitted with a tibia shaft fracture (n=1,635) were € 13.6 million. Costs for productivity loss were € 23.0 million. Total costs (direct health care and lost productivity) per patient were highest for men aged 40-49 years mainly due to lost productivity, and for women aged >80 years, due to high direct medical costs.

Introduction

Fractures of the lower leg are one of the leading injuries that come with high health care costs.[1-6] As a consequence, these injuries may impose a considerable economic burden to society. Several studies assessed the costs of direct health care,[1-3,5-7] short-term disability[1] and absenteeism[1] for lower leg fractures, including tibia shaft fractures. However, most studies do not focus on tibia shaft fractures as separate entity,[2,6,7] and if they do, only specific age groups are accounted for.[3,5] Furthermore, health care consumption and lost productivity are age and gender dependent[8-10] and detailed evaluations of direct health care costs for tibia shaft fractures are lacking.

Population based information about parameters that contribute most to the overall costs of tibia shaft fractures – such as costs for hospital stay, physical therapy, rehabilitation, nursing care, and economic production losses – are relevant for policy making. Therefore, the aim of this nationwide study was to provide an age and gender specified overview of the associated costs for health care use and lost productivity for patients admitted with a tibia shaft fracture.

Patients and methods

Data were collected for patients with a tibia shaft fracture who were admitted to a hospital in the Netherlands in the period 2008-2012 (population of 16.7 million in 2012[11]). The methods are essentially the same as published before.[8-10] Injury cases were extracted from the National Medical Registration (LMR) of the Dutch Hospital Database (DHD, Utrecht, the Netherlands). The DHD collects its data in all hospitals nationwide with a uniform classification system (missing values <5%). Extrapolations were made to the national level by the Consumer and Safety Institute to full national coverage for each year. An extrapolation factor was estimated by comparing the adherence population of the participating hospitals with the total Dutch population in each year using the population data obtained from Statistics Netherlands.[11,12] Patients are included in the LMR for their main diagnosis at discharge, which is generally the most severe injury, defined by the International Classification of Diseases (ICD) 9th and (since 2010) 10th revision.[13] Tibia shaft fractures are encoded in ICD-9 as 823.2 ('Fracture of shaft of tibia and fibula closed') and 823.3 ('Fracture of shaft of tibia and fibula open'), and in ICD-10 as S82.2 ('Fracture of shaft of tibia').

The study was exempted by the local Medical Research Ethics Committee Erasmus MC (No. MEC-205-218).

Data regarding hospital length of stay (HLOS) were extracted from the LMR database for 10- year age categories. In order to estimate the direct health care costs of injury and productivity costs due to work absenteeism the incidence-based Dutch Burden of Injury Model was used.[2,6,7,10] Patient numbers, health care consumption, and related costs were calculated using the LMR database and a patient follow-up survey on health care use.[14] Medical costs included ambulance care, in-hospital care, general practitioner (G.P.) care, home care, physical therapy, and rehabilitation/nursing care. Patients were followed until two years after trauma. Health care costs were calculated by multiplying incidence and health care volumes with unit costs (e.g., costs per day in hospital). National guidelines for health care costing were used in order to estimate unit costs.[15] Data for were averaged over the 5-year interval (2008-2012).

Productivity costs were determined as described elsewhere.[2] Costs for lost productivity were defined as the costs associated with production loss and replacement due to illness, disability, and premature death.[16] Data were retrieved from the LMR database and a patient follow-up survey with questions relating to work absence, absence duration, and return to work.[4] The absenteeism model was used in order to estimate costs for productivity loss for all patients aged 15-65 years. The friction cost method was used because healthcare needs are most substantial in the first year after injury for the majority of injuries.[17]

Results

HLOS for patients with a tibia shaft fracture increased with age similarly for men and women (Figure 3.1). Mean HLOS for men was 5.1 (± 8.9) days, for women 6.0 (± 8.0) days.

The mean cost per case for direct health care costs were higher for women (€ 10,687) than for men (€ 7,073; Table 3.1). Cost per case in men increased with age, which was mainly attributable to the rise in costs for revalidation and nursing care (Figure 3.2A). Hospital related costs predominated in younger ages. Cost per case in women also increased with age (Figure 3.2B). From the age of 70 years and older, costs for rehabilitation and nursing

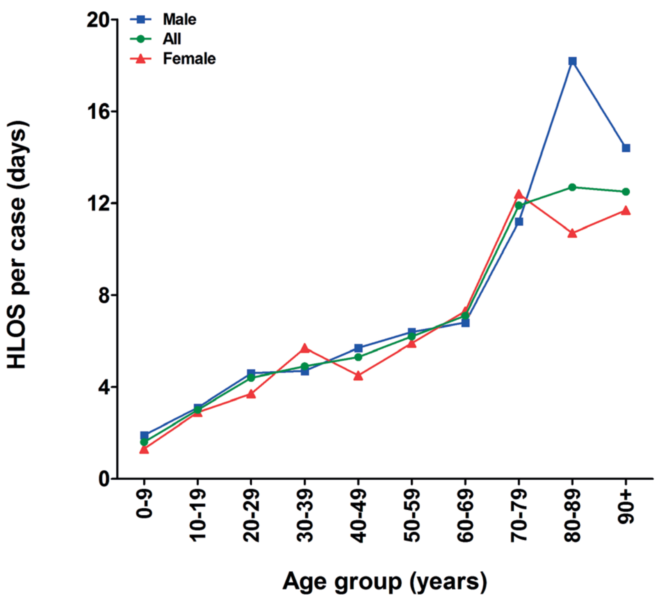

Figure 3.1. Age and gender related hospital length of stay due to a tibia shaft fracture. Hospital length of stay increased with age for both genders equally.

Table 3.1. Direct and indirect costs per case and total costs by gender.

	Cost determinant	Male (n=1,066)	Female (n=569)	Total (n=1,635)
Direct costs	Ambulance care			
	Cost/case (€)	264	277	268
	Total cost (€)	280,941	157,553	438,493
	Hospital care			
	Cost/case (€)	5,142	5,788	5,367
	Total cost (€)	5,478,606	3,295,916	8,774,522
	Rehabilitation/Nursing care			
	Cost/case (€)	940	2,944	1,638
	Total cost (€)	1,001,444	1,676,696	2,678,140
	Home care			
	Cost/case (€)	187	932	446
	Total cost (€)	199,224	530,602	729,826
	G.P. care			
	Cost/case (€)	97	116	104
	Total cost (€)	103,759	66,061	169,82
	Physical therapy			
	Cost/case (€)	443	630	508
	Total cost (€)	472,537	358,667	831,204
	Subtotal direct costs			
	Cost/case (€)	7,073	10,687	8,332
	Total cost (€)	7,536,511	6,085,495	13,622,006
Indirect costs	Productivity loss			
	Cost/case (€)	16,523	9,326	14,017
	Total cost (€)	17,605,893	5,310,662	22,916,555
Total costs	Total costs			
	Cost/case (€)	23,596	20,013	22,348
	Total cost (€)	25,142,404	11,396,157	36,538,561

care were higher than for hospitalization in women. For men, the annual direct health care costs (calculated by multiplying cost per case with incidence) were € 7.5 million (Table 3.1). These costs were lowest in the youngest age group (0-9 years; € 309,311) and in the highest age group (€ 134,258; Figure 3.2C). Costs were highest between the age of 10 and 19 years (€ 1.25 million) and gradually decreased with age.

For women, the annual direct health care costs were € 6.0 million (Table 3.1). The lowest costs were seen in the youngest age group (0-9 years; € 149,065). Annual costs were not as age dependent in women as in men, which is attributable to the incidence peak in elderly women. Highest costs were seen for women aged 80-89 years (€ 1.45 million; Figure 3.2D).

Between the age of 15 and 65 years 73% was unable to work due to their sustained tibia fracture. Mean work absence was 89±5 days, which was unrelated to gender and age (Figure 3.3A). Mean costs per case due to productivity loss were € 16,523 for men and € 9,326 for women and showed a comparable increase in both genders until the age of 40 years.

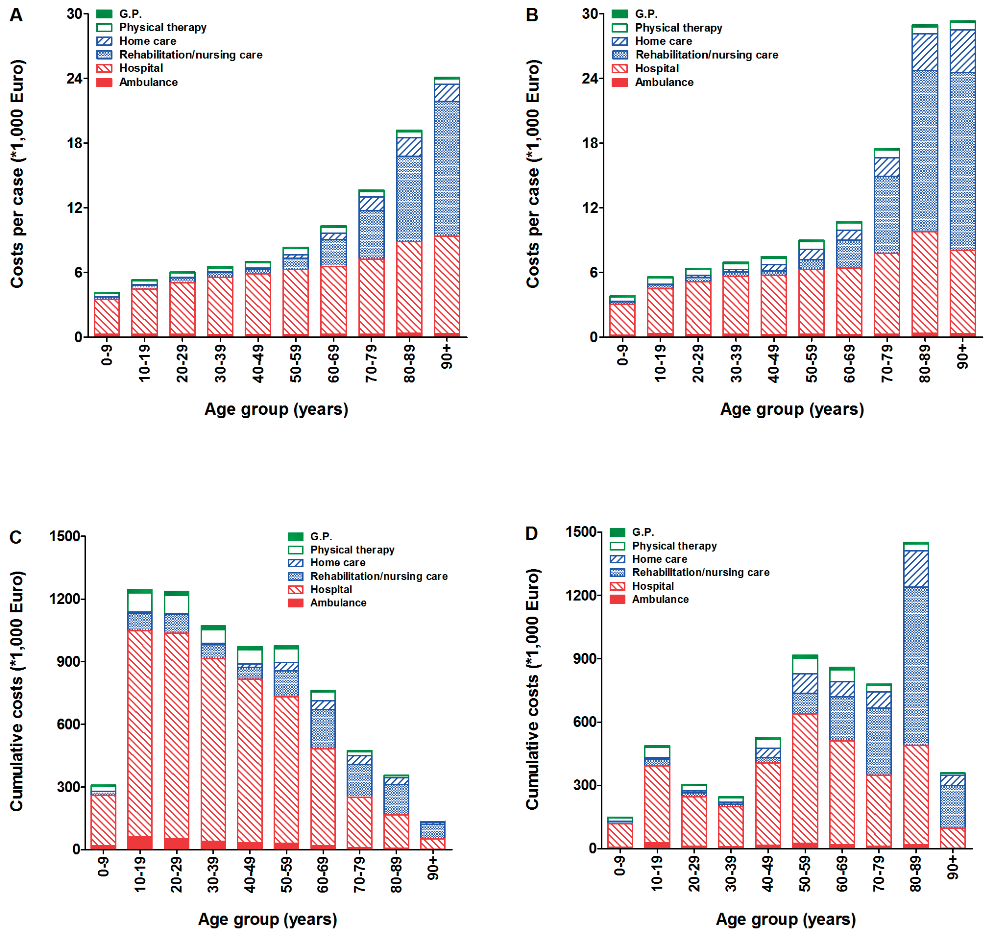

Figure 3.2. Age-related cost per case (A, B) and total costs (C, D) due to tibia shaft fractures in males (A, C) and females (B, D). A: Cost per case in men increased with age, which was mainly attributable to the rise in costs for revalidation and nursing care. Hospital related costs predominated in younger ages. B: Cost per case in women also increased with age. From the age of 70 years and older, costs for revalidation and nursing care out were higher than for hospitalization. C: Total costs (cost per case*incidence) in men were lowest in the youngest age group (0-9 years). From the age of 10 years and onwards total costs gradually decreased. Hospital related costs were the major component of the overall total costs in men. D: Total costs (cost per case*incidence) in women were lowest in the youngest age group (0-9 years). Although not as apparent as in men, costs seem to increase with age in women too.

Hereafter these costs only increased in men (Figure 3.3B). Total costs due to productivity loss were € 17.6 million for men and € 5.3 million for women (Table 3.1).

Annual direct health care costs for all patients admitted with a tibia shaft fracture in the Netherlands were € 13.6 million. Costs due to lost productivity for men and women were € 22.9 million. For men (all ages combined), mean costs per case for combined direct health care costs and costs due to lost productivity, were € 23,596. Of these costs, 70% was due

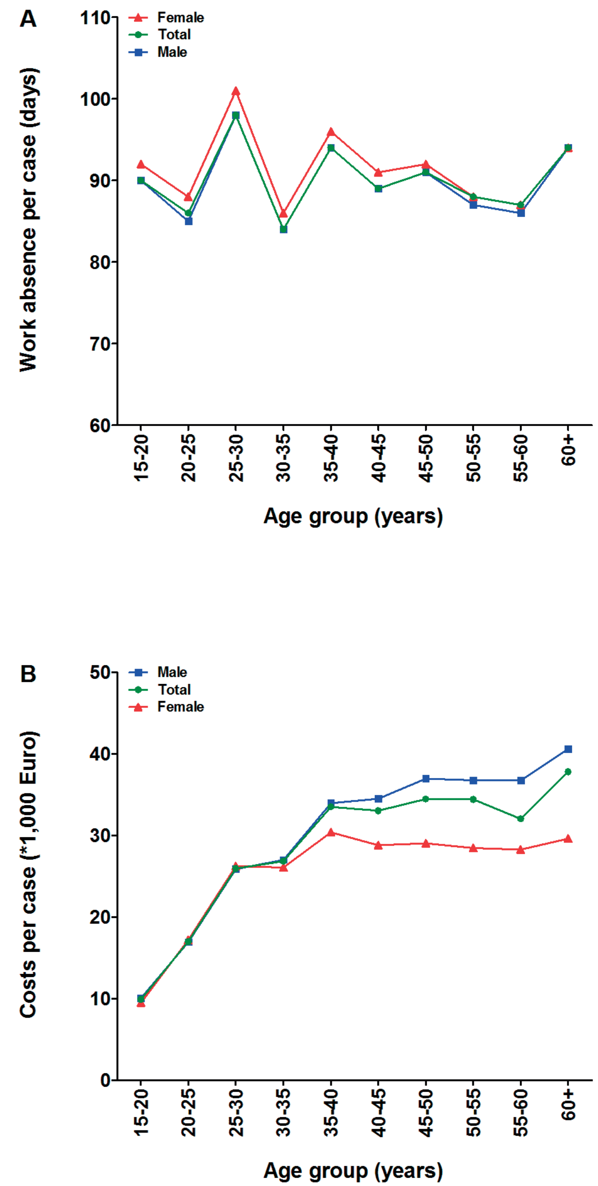

Figure 3.3. Age-related work absence (A) and associated costs (B) for lost productivity in males and females. A: Work absence per case showed no evident correlation with age or gender. B: Costs per case for associated costs increased in men and women until the age of 40 years. Hereafter costs only increase for men.

to productivity loss (Table 3.1). The highest costs per case were for men between the age of 40 and 49 years (€ 38,569; Figure 3.4A). In women, the highest costs per case were seen between the ages 30 and 39 years (€ 28,473; mean € 20,013 for all ages combined) and 47% were due to lost productivity (Figure 3.4B). Noteworthy is that direct health care costs per

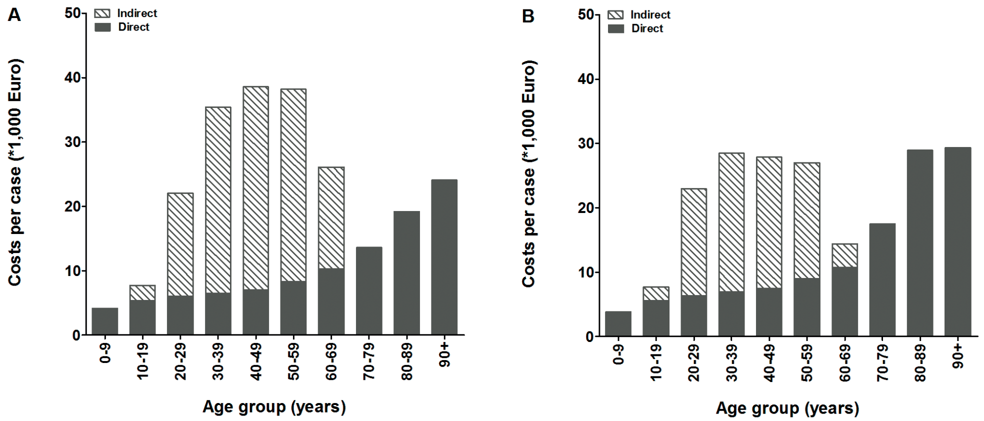

Figure 3.4. Age-related direct and indirect costs in males (A) and females (B). A: Direct and indirect costs per case combined were highest for men aged 40-49 years. B: Direct and indirect costs per case combined were highest for women aged 30-39 years.

case in women in the oldest age categories (80+ years) exceed the highest combined direct health care and lost productivity costs.

Discussion

The aim of this study was to provide a detailed overview of age and gender related health care costs and costs due to lost productivity for patients with a tibia shaft fracture admitted to a hospital in the Netherlands. Productivity loss in middle aged men and health care consumption in elderly women accounted for a substantial share of health care costs for tibia shaft fracture admissions. These high costs are either due to a high incidence (men) or high costs per patient (women).

Previous studies showed that productivity costs due to work absenteeism generally are larger than health care costs,[18] as is the case in the current study. Mean costs per case due to productivity loss were € 16,523 versus € 7,073 for health care consumption in men. In women mean lost productivity costs were € 10,687 and mean health care costs € 9,326. A large American claims-based study analyzed both direct medical costs and utilization, as well as work absenteeism and short-term disability in patients with long bone fractures between 2001 and 2008[1]. The costs per case presented for absenteeism and short-term disability were $ 5,166 (~ € 4,000),[1] which is more than half of the amount we report. This discrepancy can be explained by the fact that the study by Bonafede et al. did not include presentism (i.e., the degree to which employees are present at work but not fully engaged or productive). They only captured lost productivity from absenteeism or short-term disability, resulting in a lower cost burden. Furthermore, the analysis in the American study was limited to 6 months post-fracture, whereas the population-based study from Meerding et al. showed that hospitalized patients with a lower extremity fracture (excluding hip fracture) had a return-to-work rate of 64% at 5 months.[4] Lost productivity costs were therefore

underestimated in the study from Bonafede et al. Finally, sociodemographic characteristics and educational level might differ from the Dutch study population.

The costs per case for direct health care for patients admitted with a tibia shaft fracture were € 8,332 in our study. These expenditures were comparable to the direct health care costs found by Bonafede et al. ($ 10,070 [~ € 7,750]). Likewise, health care consumption in the claims-based study from Ohsfeldt et al. in patients aged 45 years and older was valued $ 10,224 (~ (€ 7,900).

A major strength of the present study is that it is based on population-based data on the costs of tibia shaft fractures. Health care resources that are most important for these fractures, such as hospital inpatient care and rehabilitation/nursing home care are analyzed. Also, it provides age and gender specific costs which is important for potential allocation of health care resources. Furthermore, this study presents a comprehensive incidence- based cost model in which both health care and productivity costs were included.[6,17]

An inherent limitation of a population-based survey is the lack of available clinical details of the patient and the injury – for example, comorbidities, the severity of the fracture or whether the fracture was open or closed. Overall, patients with tibia shaft fractures are relatively healthy[1] and therefore no major variation is expected in the current study population.

Patients are included in the LMR for their main diagnosis at discharge only, which is generally the most severe injury. This implies that both patients that sustained at least one more severe injury than a tibia shaft fracture and those treated in an outpatient clinic only, are missing. It cannot be appraised whether this shortcoming influences ratios between men and women and/or the young and elderly.

Clinical research on surgical and rehabilitation interventions for tibia shaft fractures that aim to lower the time off from work, such as minimally invasive surgical techniques or early active mobilization therapy, may have large economic potential, especially in middle aged men and women. For the elderly, where costs for rehabilitation and nursing care are highest, focus should be on (fall) prevention. Quicker discharge from hospital or nursing home will lower costs for those facilities, but likely put increased pressure on other health care sectors (and their costs). Due to a shift in health care use and associated costs, the efficiency of the health care system may not improve for the elderly.

Conclusion

In 2012, direct health care costs were € 13.6 million euro and costs due to lost productivity were € 22.9 million euro for patients admitted with a tibia shaft fracture. Both expenditures were age and gender dependent. Costs per patient were highest for women aged >80 years, due to high direct medical costs and for men aged 40-49 years mainly due to lost productivity. Further research should focus on interventions to lower costs due to lost productivity in middle aged men and women and (fall) prevention in the elderly, thus reducing the costs of this injury both to the health care system and society.

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Chapter 4

Use of antibiotic coated intramedullary nails in open tibia fractures: A European medical resource use and cost-effectiveness analysis

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Abstract

Purpose

In patients with open tibial fractures, bone and wound infections are associated with an increased hospital length of stay and higher costs. The infection risk increases with the use of implants. Innovations to reduce this risk include antibiotic-coated implants. This study models whether the use of a gentamicin-coated intramedullary tibial nail is cost-effective for trauma centers managing patients with a high risk of infection.

Efficacy

Absolute infection risk and relative risk reduction, by fracture grade, for antibiotic-coated nails compared to standard nails for patients with open tibial fractures were estimated based on the results of a meta-analysis, which assessed the additional benefit of locally-administered prophylactic antibiotics in open tibia fractures treated with implants. The observed efficacy of antibiotic-coated nails in reducing infections was applied in an economic model.

Methods

The model compared infection rates, inpatient days, theatre usage and costs in high risk patients, with a Gustilo-Anderson (GA) grade III open fracture, for two patient cohorts from a trauma center perspective, with a 1-year time horizon. In one cohort all GAIII patients received a gentamicin-coated nail whilst GAI and GAII patients received a standard nail. All patients in the comparator cohort received a standard nail. Four European trauma centers provided patient-level data (n=193) on inpatient days, procedures and related costs for patients with and without infections.

Results

Using the gentamicin-coated nail in patients at high risk of infection (GAIII) was associated with 75% lower rate of infection and cost savings (€477 - €3.263) for all included centers; the higher cost of the implant was offset by savings from fewer infections, inpatient days (-26%) and re-operations (-10%). This result was confirmed by extensive sensitivity analyses.

Conclusions

Analyses demonstrated that infection rates and total costs for in-hospital treatment could be potentially reduced by 75% and up to 15% respectively, by using a gentamicin-coated nail in patients at high risk of infection. Fewer infections, reduced inpatient days and re-operations may be potentially associated with use of antibiotic-coated implants. Results are sensitive to the underlying infection risk, with greatest efficacy and cost-savings when the coated implant is used in high risk patients.

Introduction

Health care-associated infections (HAI) are the most frequent adverse events affecting patient safety worldwide. Surgical site infections (SSI) are the second most common form of HAI in Europe and the United States of America.[1] Such infections are challenging to treat, requiring prolonged antibiotic treatment and often repeated surgical operations.[2,3] A major risk factor for an SSI is the presence of an indwelling device.[4] Bacteria can adhere to the surfaces of invasive devices such as implants by forming a biofilm. This causes difficulties in treating infections as the biofilm significantly reduces the impact of systemic antibiotics. Eradication of the bacterial biofilm requires up to 1000 times higher antibiotic concentrations than those required for “free-floating”bacteria.[7] Implant coatings have gained attention due to their potential to prevent implant-related infections by delivering high local concentrations.[8] Ongoing research is aimed at identifying new prevention options such as novel antibiotic delivery systems and using antibacterial agents to coat foreign materials such as implants and sutures.[9–11] Recently, the World Health Organisation recommended that antimicrobial-coated sutures should be used for all surgical procedures to prevent SSIs.[1] Other risks for SSI include patients with systemic illnesses giving rise to immunosuppression, smoking, age and fracture severity.[5] Risk increases in case of open fractures with extensive soft-tissue injury and contamination. A systematic literature review and meta-analysis[6] identified infection rates of over 31% in patients with Gustilo-Anderson (GA) grade IIIB or IIIC open tibial fractures receiving an implant compared to infection rates below 3% with less severe open tibial fractures. It also compared the incidence of infections in patients with open tibia fractures, treated with intramedullary nails, receiving locally-delivered antibiotics plus standard care vs. standard care (n=1819).[6] Most studies delivered antibiotics to the local site using polymethylmethacrylate (PMMA) bead chains impregnated with vancomycin or tobramycin. Beads were placed directly on the fracture site during the peri-operative period and removed as healing progressed. Two studies included in the review used the gentamicin coated intramedullary nail (UTN).[6] These contributed outcomes for 20 out of 209 fractures (9.6%). Findings from this meta-analysis[6] included that the absolute risk of infection was lower for all GA grades when local antibiotics (PMMA bead chains impregnated with vancomycin or tobramycin or coated nails) were administered as adjunctive prophylactic therapy to standard of care. For the more severe GA III fractures, adding local antibiotics or antibiotic coated nails in addition to the systemic antibiotic prophylaxis reduced the infection rate from 14.4% to 2.4%. For the most severe cases (GA IIIB/C), the incidence of infections was reduced from over 31% for patients who received systemic antibiotics only to below 9% when local antibiotics or coated nails were added to standard of care.[6] One novel implant, the Expert Tibial Nail (ETN) PROtect®nail (Synthes GmbH, Oberdorf, Switzerland), is coated with a 10 µm thin layer of gentamicin designed to impede bacteria from adhering to the implant surface and thereby prevent biofilm formation. The implant releases high doses of gentamicin to a localised area around the implant at the moment of implantation with 80% released within 48 h after implantation.[24] Postoperative monitoring of renal function

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was not seen necessary as it was not possible to determine the release of gentamicin into the systemic circulation above the lowest detectable level of 0.2 mg/dL.[25] The gentamicin-coated nail is indicated for fractures in the tibial shaft and could be of benefit to patients with an increased risk of local bone infection such as polytraumatised or immunosuppressed patients and patients with severe closed and open soft tissue injuries.[9] Contraindications are established or suspected intolerance or allergy to gentamicin or other aminoglycosides or to polylactides.[12] The gentamicin coating has been applied to ETN PROtect and its predecessor the Unreamed Tibial Nail (UTN) PROtect (Synthes GmbH, Oberdorf, Switzerland). Limited clinical experience has demonstrated the performance and safety of the two intramedullary nails featuring the gentamicin coating.[8,13-15] In the four studies, two single center case series studies (n=35) and two case studies (n=2), none of the patients developed a deep wound infection whilst one patient developed a superficial infection. Currently, there are insufficient high-quality clinical studies to demonstrate the effectiveness of gentamicin-coated nails in reducing infection rates. To estimate the impact in the clinical setting, this study models whether the use of a gentamicin-coated nail is cost-effective for trauma centers managing patients with a high risk of infection.

Materials and methods

A cost-consequences analysis (CCA) of the clinical pathway was undertaken to establish cost-effectiveness for hospitals that adopt the gentamicin-coated nail for tibial shaft fractures compared to standard nails. The pathway includes the first admission, re-admissions and all operations associated with the initial episode of care within 12 months of the initial admission. Long term sequalae are not captured in the follow up. The CCA used the change in infection rates comparing the gentamicin-coated nail and a standard nail as reported by a systematic review and meta-analysis.[6] This meta-analysis compared the rate of deep wound infections in patients with open tibia fractures, treated with intramedullary nails, receiving additional locally-delivered antibiotics to reduce the risk of infection vs. patients that received the standard care of systemic antibiotics, only. Four of the seven included studies of locally-delivered antibiotics used polymethylmethacrylate bead chains impregnated with vancomycin or tobramycin. These were placed directly on the fracture site during the peri-operative period and removed as healing progressed. Two studies used a gentamicin-loaded coating on an intramedullary nail and one study used vancomycin-loaded calcium sulphate.

The meta-analysis was used in preference to the data from the four clinical studies on the gentamicin coated nail as it included 1819 open tibial fractures and was considered of higher quality evidence. The epidemiology of fracture type is based on the systematic review of Papakostidis et al.[18] The CCA adopted the perspective of healthcare providers in tertiary trauma centers.

Resource use and cost data for the pathway were collected from four European trauma centers. The pathway included the initial admission, re-admissions, all antibiotics and other medication, laboratory, radiology and other diagnostic tests, theatre and day case

procedures, associated with the initial episode of care for a patient with an open tibial fracture. In all cases the pathway was less than 1 year in duration. The authors judged this pathway duration as sufficient to capture the differences in resource use between patients with and without infections. All patients who entered the model had an open tibia fracture that required treatment with a nail. Each patient was identified by fracture severity using the GA classification for open fractures. Patients moved through the model and either developed an infection or did not develop an infection, depending on the nail deployed and the associated risk of infection. There are 8 health states: GA I, GA II, GA IIIA and GA IIIB/C with or without infection. Each health state is associated with the number of inpatient days, including re-admissions related to the index event, surgical operations and costs. These values are derived from the aggregate data of the trauma centers. Change in length of stay (LoS), number of surgical operations and total hospital-related costs were calculated and reported in the model.

Patient recruitment and characteristics

The four trauma centers that participated in this study are: Department of Trauma Surgery, University Hospitals Leuven, Belgium; Department of Trauma, Hand and Reconstructive Surgery, University Hospital Muenster, (UKM), Germany; Department of Trauma and Orthopaedic Surgery, General Infirmary University Hospital of Leeds, England; Department of Trauma Surgery, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands. Clinicians at each center provided anonymised patient level data, oversaw model inputs and assisted with interpreting results. Clinicians at (UKM) piloted and refined the questionnaire which comprised:

a) A retrospective review of bone and wound infection rates in patients with tibia fractures.
b) A resource survey to identify healthcare resources and costs to manage bone and deep wound infections in patients with tibia fractures.

Inclusion criteria were consecutive patients undergoing a surgical operation because of a primary tibia fracture, associated with soft tissue and skin injury and any subsequent infection. Patients were excluded, if their primary clinical presentation related to reasons other than the tibia fracture including:

- Severe multiple injuries to different parts of the body (polytrauma)
- A fracture due to a disorder such as a primary or metastatic tumour (pathological fractures)
- Multiple operations arising from disorders unrelated to the tibia fracture
- Patients treated with a surgical debridement and external or internal fixation in another hospital before referral to the study center.

Bone and deep wound infections were defined using the Centers for Disease Control and Prevention (CDC) criteria,[16] consistent with the definitions used in the meta-analysis.[6]

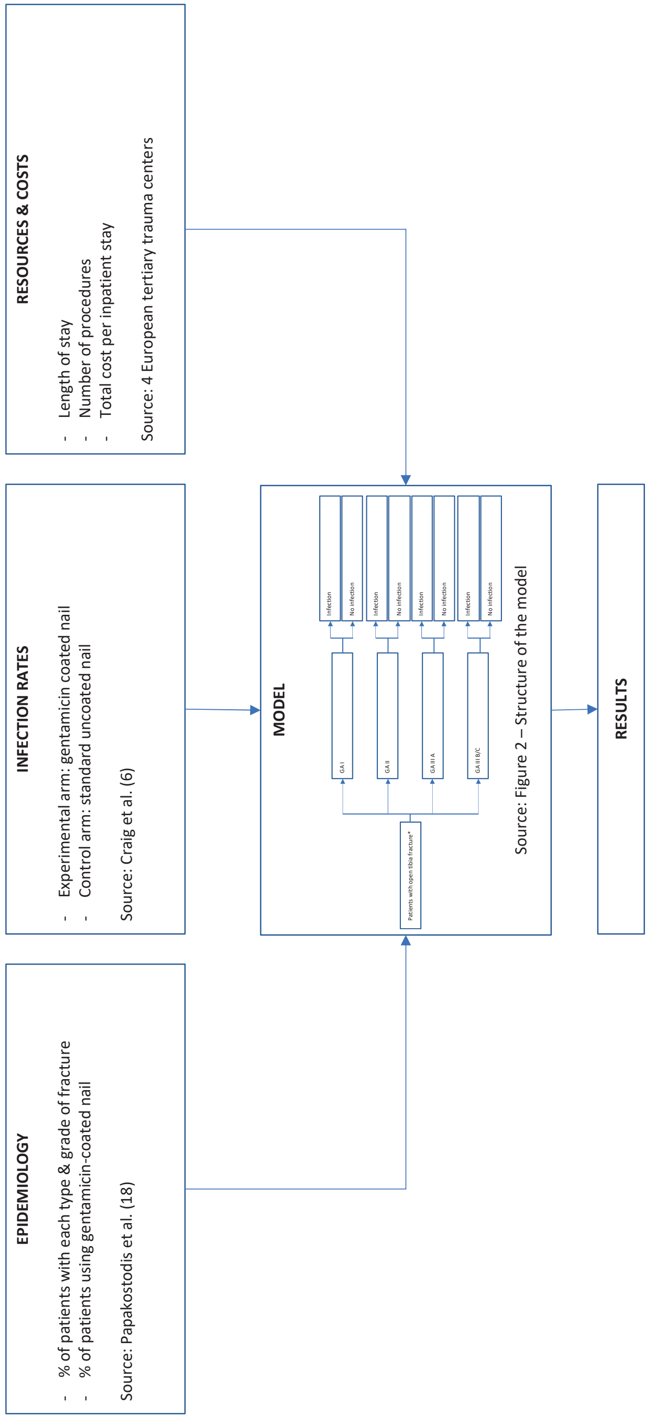

Figure 4.1. Overview of cost-consequences analysis model.

Bone infection was recorded separately as the resources required to manage a bone infection were usually higher than for a deep wound infection.[17] Patients with both types, were classified as having the more severe bone infection only.

Medical resource use and cost inputs

Each center submitted patient-level data for number of operations, admissions and readmissions, LoS on general wards and intensive care units (ICU), and associated costs (admissions, readmissions, operations and total). These were quality assured by York Health Economics Consortium. Patient level data on LoS and operations was aggregated across the four centers. All costs were expressed in Euros, with the UK center applying an average conversion rate of £1 = €1.17. Given the short time horizon of the model, no discounting was applied. For the implant costs the local list prices were provided by the manufacturer. Results are presented aggregated across the four centres and also separately for each centre, to reflect local costs.

Model structure

An overview of the model is provided in Figure 4.1. The model combined fracture and infection characteristics of the meta-analysis with the costs they caused during the acute phase of primary hospital treatment based on results of the four trauma centers. Two cohorts of 100 patients each with open tibial fractures were modelled.

Overall, 17% of patients were assumed to have GA I fractures, 26% GA II fractures, and 57% GA III fractures. GA III fractures were further split into IIIA (38%) and IIIB/C (62%), based on epidemiology data from Papakostidis et al.[18] In one arm, patients with a GA III grade fracture received a gentamicin-coated nail whilst GAI and GAII patients received the standard of care with an uncoated nail. In the second arm all 100 patients received the standard of care with an uncoated nail indicated for the same fracture type. All patients were assumed to have the same characteristics in terms of wound severity, risk of infection, age and sex as the patients with open tibial fractures reported from the four trauma centers and to receive systemically administered antibiotics as part of standard prophylactic care. Results are presented as the absolute cost per patient to manage all patients in the gentamicin-coated nail arm and standard of care arm with the uncoated nail, with the difference being the incremental cost or saving from using the gentamicin-coated nail. The detailed model, shown in Figure 4.2, also reports the number of infections, LoS and operations for each arm, together with the differences between them. The assumption that only patients with GA III fractures, which have the highest risk of infection, receive the gentamicin-coated nail was adopted, recognising the requirement for optimal patient treatment decisions within today ´s very cost constraint healthcare environment. In GA III fracture patients, the infection risk is 14.4%. GA IIIA and GAIII B/C fractures have infection risks of 11.2% and 31.2% respectively, compared to 3% or under in GA II and GA I fractures.[6]

Clinical effectiveness

The primary measurement of effectiveness was the reduction in the rate of infection associated with the gentamicin-coated nail. In the absence of directly observed evidence of the impact of gentamicin-coated nails on infection rates, the parameters adopted in the economic model use the absolute risk of infection and relative risk reduction from the meta-analysis.[6] The numbers of fractures informing each arm of the meta-analysis are substantially higher than those reported from the centers. To avoid the risk of selection and reporting biases, the results from the meta-analysis have been assumed to be valid surrogate measures of the effectiveness of the gentamicin-coated nail implant.[6]

Table 4.1 presents the infection rates reported in the meta-analysis, by GA grade, for patients receiving systematic antibiotics only (n=1681) and for those also receiving local antibiotics delivered at the tissue/implant interface plus systemic antibiotics (n=138). A comparison of these rates to the infection rates in the 4 centers (n=60) is provided in the supplementary material.

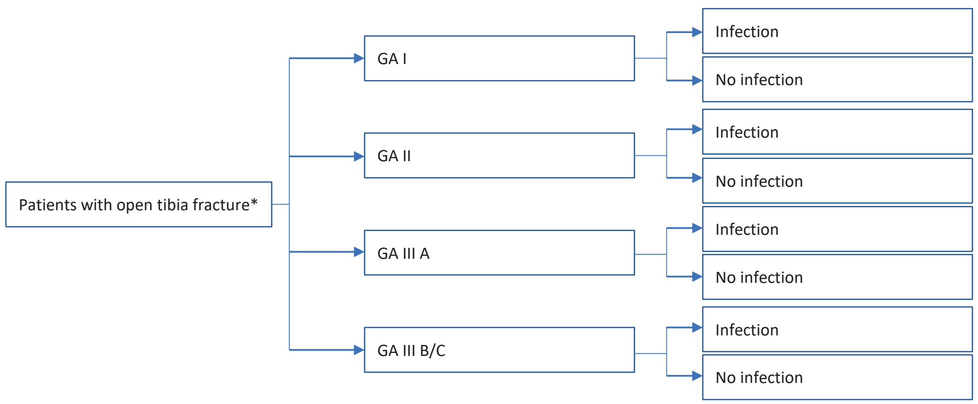

Figure 4.2. Structure of the Model. *All patients required a nail. All GAI and GAII fractures received a standard nail. In the gentamicin-coated nail arm GA III fractures received gentamicin-coated nails.

Table 4.1. Description of results from meta-analysis for different open tibial fractures.

	Meta-analysis: Infection rate with systemic antibiotics*	
GA Classification	Plus local antibiotics (nail or beads)	With no additional local antibiotics
GAI	0.0% (n=17)	1.6% (n-469)
GAII	2.2% (n=46)	3.0% (n=510)
GAIII	2.4% (n=75)	14.4% (n=702)
of which GAIIIA	0.0% (n=43)	11.2% (n=186)
and GAIIIB/C	8.8% (n=28)	31.2% (n=109)

*n = number of fractures (Note percentages may not sum due to rounding).

Results

In total 193 patients were included across the 4 centers. Most patients were male (127/193, 66%) and almost half (94/193, 49%) were aged between 31 and 60, with 25% (49/193) aged between 21 and 30 (data not shown). The age and sex profiles were broadly equivalent across centers. Most fractures were closed (133/193, 69%) and only 4% of the fractures were GA III B/C (7/193). Information on number and type of fractures and infection rates, by severity, are provided in supplementary materials. They were not used for the efficacy assumptions in the cost-effectiveness analysis.

Resource use by infection status, type and severity of fracture

Local costs for each inpatient day on a general ward ranged from €166 to €292 and from €562 to €1,096 for ICU across the centers. One center used an average inpatient cost of €594 per day (see Table 4.2). A full list of the parameters and their sources used in the base case is provided in the supplementary material. Aggregated patient level information across the centers showed consistent trends and are presented in Table 4.3:

- Resource use and costs increased by fracture severity
- The key cost driver was LoS on general wards

Table 4.2. Unit costs per general ward and ICU for each center.

Centers	Cost per day general ward	Cost per day ICU
Center 1	€ 197	€ 899
Center 2	€ 166	€ 562
Center 3	€ 292	€ 1096
Center 4	€ 594	

Table 4.3. Mean length of stay on general and ICU wards by infection status, by fracture severity of the four centers.

	General ward (days)		ICU (days)		Total costs (Euro)*	
Fracture type	No infection	Infection	No infection	Infection	No infection	Infection
GA I	6.8[a]	5.8	0.1	0.0	5,336	4,121
GA II	9.0	30.3	0.0	2.3	7,703	18,143
GA IIIA	10.4	17.5	0.1	0.0	7,604	9,593
GA IIIB/C	27.8	99.0	0.0	7.7	15,418	43,249

*The model used local list prices for the gentamicin-coated nail which ranged from €2,500 to €2,840 and for a similar uncoated nail, the Expert Tibial Nail, which ranged from €417 to €702. a The mean length of stay for GA type I no infection arm includes one patient who was an outlier, with a hospital stay of 16 days.

In some fracture types there are small numbers of patients. Different sites had different mixes of fracture grades, duration of stay and costs. Many of the patients with GA I fractures, and no infections were from a center with the highest average LoS and costs. This resulted in the LoS and costs for GA I with no infection exceeding the LoS and cost of those with infection (Table 4.4).

Model results

Reflecting the approach whereby clinical benefit and the resources required to manage patients with and without infections have been averaged across all centers, the clinical and resource benefits were the same for each center. Thus, for 400 patients with open tibial fractures, using the gentamicin-coated nail for GA III fractures rather than the standard of care with an uncoated nail, led to 43 avoided infections (a reduction of over 70%), 128 avoided operations (10% fewer), saving over 2,500 inpatient days (26% fewer). The different cost savings across centers reflect the different relative costs for the nails and the different cost per inpatient day. Thus, Center 4, which has the highest cost per inpatient day, has the greatest saving (€3,263 per patient receiving the gentamicin-coated nail) whilst Center 2, with the lowest cost per inpatient day, has the lowest savings per patient (€477). At all centers the increased implant costs are offset by savings from shorter LoS and theatre costs for patients with a GA III fracture. The average cost savings across the four centres was €1,705 per patient, an 11% saving on the cost of standard care.

Sensitivity analyses

To address first-order uncertainty around the input parameter values, one-way deterministic sensitivity analyses (DSA) were undertaken by varying the values of key parameters by + /- 20%. Probability sensitivity analyses (PSA) explored joint uncertainty in the modelled parameters. The DSA and PSA inputs are described in the supplementary material. The findings are consistent across the centers. The coated nail was cost saving for changes in all parameters except for a 20% reduction in the probability of infection with standard care with an uncoated nail at Center 2. This resulted in a cost increase of €69. Key parameters which had a significant impact on results, in descending order of impact were:

- Probability of infection with a standard nail
- LoS on a general ward with an infection
- General ward cost per day
- Theatre costs with an infection.

The PSA reported gentamicin-coated nail used in patients with GA III fractures was cost saving in 88%, 63%, 90% and 92% of the 1,000 model iterations at Centers 1, 2, 3 and 4 respectively. Results of DSA are not presented and available on request to the lead author.

Scenario analysis

Results from a scenario analysis assuming all patients in the gentamicin-coated nail arm receive the coated nail compared to the base case which assumed only those with a GA III fracture received gentamicin-coated nail are presented in Table 4.5. In all centers except Center 2 using the gentamicin-coated nail for all patients and not just for those with high-risk fractures using the gentamicin-coated nail was cost saving. The savings from avoided infections exceeded the higher cost of using the gentamicin-coated nail.

Table 4.4. Presents the base case results in total and at each center.

Assuming each center manages 100 patients (n=400)	Gentamicin-coated Nail	Uncoated Nail	Incremental change from standard implant
Total number of infections	15	58	-43 (-75%)
Total number of operations	1,100	1,228	-128 (-10%)
Total length of stay	7,308	9,904	-2,596 (-26%)
Total costs per patient (Euro)*	13,121	14,826	-1,705 (-11%)
Center 1 (n=100)			
Total costs per patient (Euro)*	10,937	12,163	-1,226 (-10%)
Center 2 (n=100)			
Total costs per patient (Euro)*	10,832	11,309	-477 (-4%)
Center 3 (n=100)			
Total costs per patient (Euro)*	12,662	14,514	-1,852 (-13%)
Center 4 (n=100)			
Total costs per patient (Euro)*	18,053	21,316	-3,263 (-15%)

*Total costs sum all admission, readmission, operation and device costs for all 100 patients in each cohort. The costs per patient are these costs expressed as a per patient cost. (Note percentages and numbers may not sum due to rounding).

Table 4.5. Scenario 1 All patients receive gentamicin-coated nail.

Assuming each center manages 100 patients (n=400)	Gentamicin-coated Nail	Uncoated Nail	Incremental change from standard implant
Total number of infections	15	58	-43 (-75%)
Total number of operations	1,100	1,228	-128 (-10%)
Total length of stay	7,288	9,904	-2616 (-26%)
Total costs per patient (Euro)*	14,051	14,826	-775 (-5%)
Center 1 (n=100)			
Total costs per patient (Euro)*	11,772	12,163	-391 (-3%)
Center 2 (n=100)			
Total costs per patient (Euro)*	11,939	11,309	629 (6%)
Center 3 (n=100)			
Total costs per patient (Euro)*	13,532	14,514	-981 (-7%)
Center 4 (n=100)			
Total costs per patient (Euro)*	18,961	21,316	-2,355 (-11%)

*Total costs sum all admission, readmission, operation and device costs for all 100 patients in each cohort. The costs per patient are these costs expressed as a per patient cost. (Note percentages and numbers may not sum due to rounding).

At Center 2, the additional cost of the coated nail marginally exceeded the savings from managing avoided infections (by €629 or 6%). The average saving across the four centers was €775, equivalent to 5% of the cost of managing a patient under standard care.

Discussion

The epidemiological data reported from the four trauma centers confirmed findings from the meta-analysis[6] that patients with severe GA III open fractures are prone to infection. The infection rates reported by the four trauma centers were higher than the rates reported in the meta-analysis for all fracture grades, however a much smaller sample size was evaluated in the centers (n=60) vs. the metanalysis (n=1,681).[19] Although the GA fracture classification is universally accepted, it has limitations including variable accuracy, dependent on the experience of the surgeon, and moderate-to-poor interobserver agreement plus underestimation of damage to muscles and bone.[6] Results from the model showed that the usage of the gentamicin-coated nail in patients with severe open fractures (GA III) which have high risk of infection, can potentially lead to substantial cost savings from avoided infections due to savings in inpatient days and procedures. These findings may be valid to other patient subgroups at higher risk of infection, for example immunocompromised patients, polytrauma, those with chronic disease, obese or smokers.[6]

It is also important to note that compared to beads, by using a gentamicin-coated nail a second operation to remove the beads is not required. Although the use of gentamicin-loaded PMMA beads is accepted in clinical practice, the beads themselves can act as a biomaterial surface that microorganisms preferentially adhere to and grow on, and potentially develop antibiotic resistance.[20] There are limitations of this medical resource use and CCA. The first limitation is the absence of comparative studies using gentamicin-coated nails. Therefore, only pooled results from a meta-analysis could be used as the best surrogate measure of the benefits.[6] The meta-analysis itself had limitations including that several of the studies were graded low, with a risk of bias in the results' precision. Only one study was randomised. Moreover, it was not possible to adjust for differences in case-mix or study treatments. These factors may have impacted infection rates. In addition, the literature review informing the meta-analysis was conducted in 2012. If the risk of infection or treatment pathways have changed over time, then the results may not generalise to current tertiary centers. However, the findings from the four centres suggest the rate of infection may be higher in clinical practice than that reported in the review, suggesting the results are conservative. Secondly, at the time of the review and therefore in this study, surgical site infections were defined following criteria from the CDC. As recently stated in a consensus definition,[23] these criteria do not focus on musculoskeletal trauma patients and were initially introduced as surveillance guidelines. Thirdly, the meta-analysis was limited to patients with open and isolated fractures only. There is no evidence on the impact of using local antibiotics for patients with closed fractures or other high-risk factors such as a compromised autoimmune system. The literature review conducted to identify papers to inform the meta-analysis identified low numbers of fractures and infections in some GA classifications and no studies were randomised. The PSA has explored the uncertainty inherent in the model and parameter values used but cannot overcome the limitation arising from the limited number of patients reported in studies of the ETN Protect nail. It is clear that many high energy injuries result in polytrauma. However, to avoid heterogeneity in study data only patients with isolated fractures were recruited. The decision to exclude multiple injured patients - to reduce the number of confounders - decreases the number of inclusions substantially. Fourthly, it was only possible to aggregate theatre costs across the centers because the number and duration of operations varied widely, making it impossible to define 'standard operations' and to aggregate these. Finally, important patient benefits have not been captured as infections lead to increased morbidity, loss of quality of life and mortality and their negative impact can be lifelong.[21] Also, this study has only included infections identified during the inpatient hospital stay, but evidence shows that the majority of surgical site infections are identified after discharge.[22] Further research could establish the relative risk reduction for infection with gentamicin-coated nails directly.

Conclusion

The base case results, sensitivity analyses and scenario analysis of the model demonstrate the potential for substantial benefits from adopting the gentamicin-coated nail rather than the standard of care with an uncoated nail in patients with a GA III fracture and hence at high risk of infection. The main patient benefit would be a reduced infection risk, which reduces patients' morbidity, mortality and improves quality of life. It thereby could also save cost by reducing LoS and theatre time. Thus, hospital providers could, based on the model, observe potential cost savings of up to 15% per patient, that would offset the higher cost of the nail. The greatest efficacy and savings to be expected when the device is used in patients at high-risk of infection. The generalisability of the results is sensitive to the assumptions informing the model, particularly the underlying infection risk and mean length of stay.

4

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4

PART II

Outcome after tibial nailing

Chapter 5

Anterior knee pain and functional outcome following different surgical techniques for tibial nailing: a systematic review

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Abstract

Purpose

The aim of this systematic review was to compare knee pain and function after tibial nail insertion through an infrapatellar, semi-extended and suprapatellar technique.

Methods

A search was carried out to identify articles with an exact description of the method used for insertion of the tibial nail and description of the outcome parameters (knee pain or function). Data on study design, population, rate and severity of anterior knee pain and function scores were extracted. Pooled rates and scores were calculated.

Results

67 studies with 3,499 patients were included. The pooled rate of patients with anterior knee pain was 38% (95% CI 32–44) after nail insertion through an infrapatellar approach and 10% (95% CI 1–26) after insertion through a suprapatellar approach. Pooled analysis was not possible for the semi-extended technique. Knee pain scores as measured by visual analogue score (0–10) ranged from 0.2 (95% CI – 0.1–0.5) for general knee pain to 3.7 (95% CI 1.3–6.1) for pain during kneeling. Pooled estimates for the Lysholm score were 87 points (range 77–97) for the infrapatellar technique and 85 points (range 82-85) for the suprapatellar technique. Iowa Knee scores were 94 (range 86–96) and Anterior Knee Pain Scale scores were 76 (range 75–80) after infrapatellar nail insertion.

Discussion

Depending on the technique used, the proportion of patients with knee pain after tibial nailing varied between 10 and 38%. The actual measured knee pain scores were, however, surprisingly low. Knee function was good for both the infra- and suprapatellar technique.

Introduction

Diaphyseal fractures of the tibia are commonly treated with an intramedullary nail. The infrapatellar approach is most commonly used. However, hyperflexion of the knee during this procedure is associated with an increased risk of valgus and procurvatum deformities in proximal third tibial shaft fractures. In an attempt to address this problem, a semiextended technique has been developed,[1,2] of which also a subcutaneous variant exists.[3] For the same reasons, the suprapatellar approach has been introduced.[4–6] For this approach, an incision is made just proximal to the superior pole of the patella and the nail is inserted through the patellofemoral joint. The first clinical studies have suggested favorable outcomes associated with a suprapatellar approach.[4,5,7–9] The concern of potential damage to the cartilage of the patellofemoral joint remains a significant drawback, although rates of anterior knee pain after this procedure seem lower than seen after the infrapatellar approach.[5,7,9]

Although all techniques for nail insertion have been proven feasible, a comparison of their rates of anterior knee pain and functional outcome is lacking. The aim of this systematic review and pooled analysis was, therefore, to compare these parameters between different techniques for tibial nail insertion. This information gives perspective to the patient's rehabilitation after tibial nailing and can aid surgeons in their decision to choose between these surgical techniques.

Patients and methods

The following databases were searched on December 19, 2018: Embase, Medline (OvidSP), Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. Searched items consisted of terms related to tibia shaft, intramedullary nailing and terms related to pain and function (for full search strategy, see Supplementary data).

Titles and abstracts were screened independently by three reviewers (MSL, JVH, and EAVB). Inconsistencies were resolved by consensus. Studies were included if they met the following inclusion criteria: (1) tibial shaft fracture treated with intramedullary nailing, (2) description of the surgical method used for insertion of the tibial nail (infrapatellar, (subcutaneous) semi-extended or suprapatellar; insertion through patellar tendon, medial or lateral to patellar tendon; use of longitudinal or transverse incision) and (3) primary data for at least one of the outcome parameters (knee pain, function). No limitations on language were considered and only studies from 1990 onwards were included. Studies were excluded if no full-text version was available after contacting corresponding authors. Studies encompassing patients with intraarticular fractures (i.e., tibia plateau or pilon fracture) or only patients with ipsilateral fractures (*i.e.*, patients with a floating knee), studies that described only pathological fractures or those with a population aged <18 years, were excluded. Case reports and letters to or from the editor were also excluded. Reference lists of review articles and eligible studies were examined for additional studies that may have been missed.

Randomized controlled trials (RCTs) and cohort studies were found to be eligible. Patient groups of comparative studies that were treated with the same incision were taken together; the pooled study population was considered one cohort over which knee pain rate, pain and functional scores were calculated.

Two reviewers (MSL and EAVB) independently assessed the methodological quality of the studies using the MINORS (Methodological Index for Non-Randomized Studies) scale[10] (see Supplementary Materials), the global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Data were independently extracted in duplicate by three reviewers (MSL, JVH, and EAVB) using a standardized data sheet. Discrepancies were resolved by consensus. The following data were extracted for each publication: name of first author, publication year, population size and age, percentage of polytrauma patients and patients with ipsilateral fractures, the approach used, the rate of anterior knee pain, the pain scores, functional outcome scores, and the moment at which these measurements were done. When measurements were done at different time points, the scores at 12 months were used for calculation.

Analyses were performed using MedCalc Statistical Software (version 17.6; MedCalc Software bvba, Ostend, Belgium; https ://www.medca lc.org;2017). The rates of anterior knee pain were computed for each study and expressed as percentage. Visual Analog Scales (VAS) with a scale 0–100 were divided by 10 to compare them with 10 cm VAS and 10-point Numeric Rating Scales (NRS). Heterogeneity of the data was assessed using the Cochrane χ^2 *Q*-test (significance set at $p<0.10$) and I^2 statistic. Outcomes for cohorts with the same surgical approach were pooled if data were available for at least two groups. A random effects model was used if the I^2 statistic was >40%; a fixed-effect model was used if it was <40%. For comparative studies, the relative risk ($RR_{transpatellar/parapatellar\ medial}$ and $RR_{infrapatellar/\ suprapatellar}$) was determined for binomial variables and a mean difference for continuous variables. Pooled estimates and relative risks are reported with their 95% confidence interval.

Results

The literature search identified 5,322 potentially eligible studies. After removal of the duplicates (2,365 studies) and applying the inclusion and exclusion criteria, 67 studies remained for analysis (Figure 5.1).

Anterior knee pain

Pain rate

The pooled percentage of patients with anterior knee pain after intramedullary nailing was 38% (95% CI 32–44) after use of the infrapatellar approach and 10% (95% CI 1–26) after the suprapatellar approach (Table 5.1). The relative risk of anterior knee pain after tibial nailing was 1.3 (95% CI 0.9–2.0) when comparing the infrapatellar and suprapatellar techniques.[4,7,9,81]

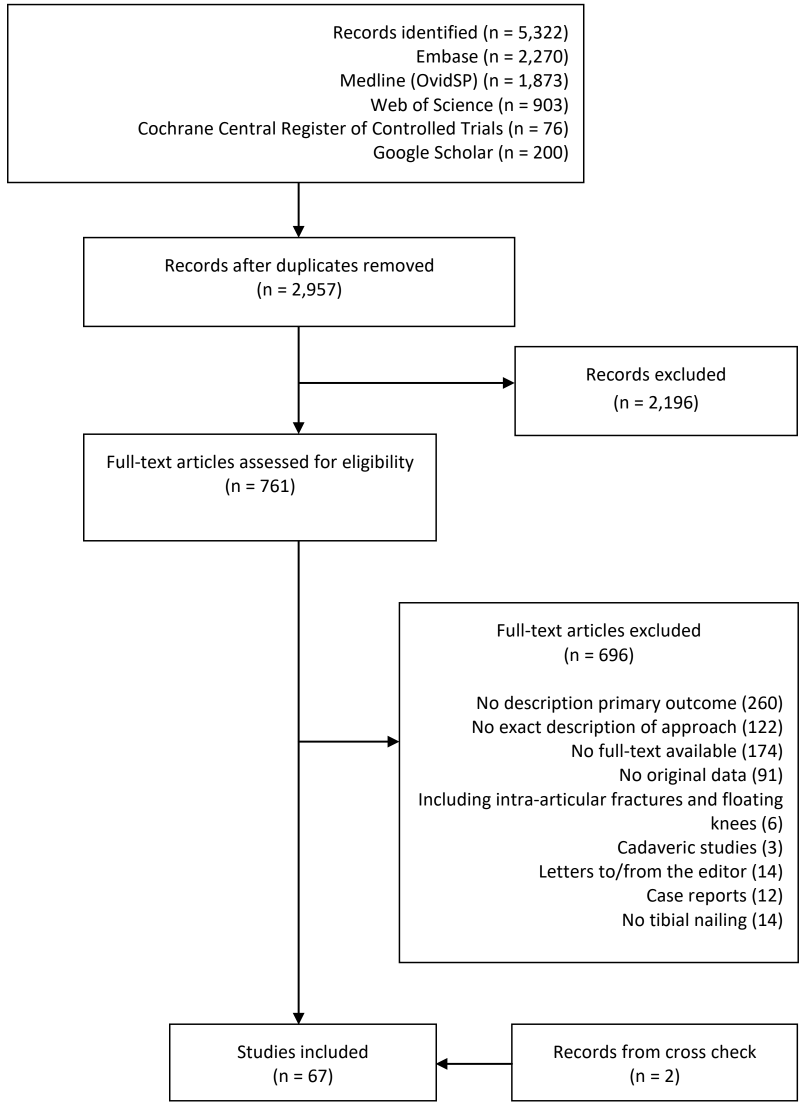

Figure 5.1. Study flowchart.

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In the majority of the studies, the infrapatellar approach was described.[4,7–9,11–78] Six studies reported on the suprapatellar approach[4,5,7–9,79–83] and one on the semi-extended technique.[66] There were 17 randomized trials[7,9,19,23,26,30,48,49,52,54,57,59–61,64,68,71] of which five compared different methods for tibial nailing[7,9,26,49,71], 14 prospective studies [5,11,14,28,31,34,37,39,46,55,70,72,73,83] and 45 retrospective studies.[4,8,12,13,15–18,20–22,24,25,27,29,32,33,35,36,38,40–45,47,50,51,53,56,58,62,63,66,67,69,74,76,78–82,84] The mean follow-up ranged from 8[63] to 94[28] months. In the majority of the papers, it was clearly stated that the study population did not comprise any polytrauma patients.[7–9,22–26,28,32,33,36,43,44,48,51,53,55,60,63,64,66,68,71,74,79,81,84] However, 23 studies included multiple injured patients in their population.[5,11–14,16,18,19,27,30,34,35,37–39,41,52,54,62,65,72,80,82] ranging from 4%[38] to 100%.[80] In those articles that included patients with ipsilateral fractures,[5,12,19,30,32,34,35,46,52,54,62,67,80,82] the proportion of ipsilateral fractures was between 3%[19] and 56%.[80] These patients were excluded in 29 studies.[7–9,22–26,28,33,36,38,43–45,48,51,53,55,60,64,66,68,71–73,77,79,81] The moment at which data on anterior knee pain or function were conveyed, was documented in 28 studies[4,5,7,9,18–20,25,26,28,30,42,45,49,51,53,54,56,58,60,66,70–73,81,83] and ranged from 3 months[71] to 94 months.[28]

Pain scores

Six different scales were used for measuring the severity of anterior knee pain (Table 5.2). For the majority of the studies, it was not documented on how data on knee pain were retrieved. Pooled estimates for knee pain (VAS 0–10) were 2.2 (95% CI 1.5–2.9) for the infrapatellar technique and 0.2 (95% CI -0.1-0.5) for the suprapatellar technique (Figure 5.2a, b). Pain scores for specific (daily) activities could only be pooled for the infrapatellar technique. Kneeling was reported as most painful (VAS 3.7; 95% CI 1.3–6.1).[26,53,58] Pain scores for other activities were described in two studies[26,53]: 0.3 (95% CI – 0.1–0.7) in rest, 0.6 (95% CI – 0.0–1.1) for prolonged sitting with knees bend, 0.5 (95% CI 0.01–1.0) during walking, 1.0 (95% CI 0.0–2.1) for running, 1.6 (95% CI 0.5–2.7) while squatting, 1.1 (95% CI 0.2–2.1) for ascending stairs and 0.9 (95% CI – 0.1–1.9) for descending stairs.

Table 5.1. Pooled pain rates per (sub)group.

Parameter	(Sub)group	Studies (N)	Population (N)	Q (p-value)	I^2 (95% CI)	Pooled estimate (95% CI)
Pain (%)	Infrapatellar technique	51	2,853	612.3 (<0.0001)	92 (90-93)	38 (32-44)
	Suprapatellar technique	5	174	29.2 (<0.0001)	86 (70-94)	10 (1-26)

Table 5.2. Different instruments used for measuring knee pain.

Instrument used to measure knee pain	N studies
Unspecified[11-16,19-23,25,27,29,30,32,34-37,40, 41,44,47,50,52,59,62,64,65,69,71]	32
VAS 0-10[5,7,9,24,38,46,49,55,56,63,70]	11
VAS 0-100[26,33,53,58,60]	5
Direct questioning[20,28,45,51,54]	5
NRS 0-10[17,42,67]	3
Oxford Knee Score (pain component)[8]	1
Lysholm Knee Score (pain component)[72]	1
Kujala or Anterior Knee Pain Scale (pain component)[4]	1

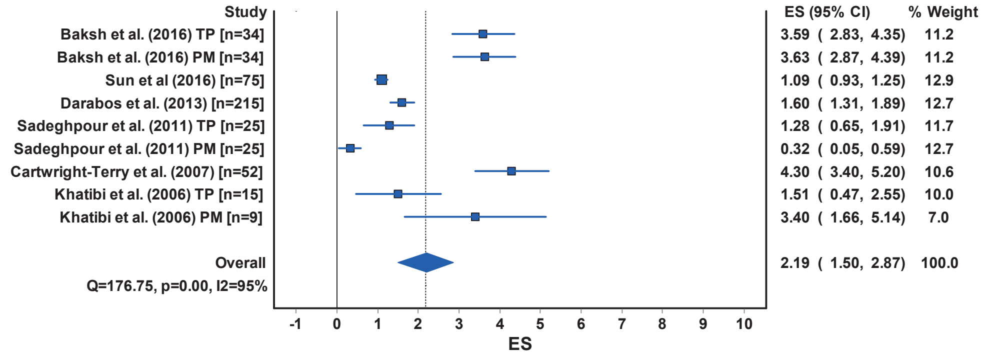

Figure 5.2a. Pooled estimates for knee pain scores for the infrapatellar approach. ES, effect size (pooled estimate for Visual Analogue Score); 95% CI, 95% Confidence Interval; Q, Cochran's Q-statistic for study heterogeneity; I2, statistic for study heterogeneity; numbers indicate the number of patients in each study or subgroup; TP, transpatellar approach; PM, parapatellar medial approach.

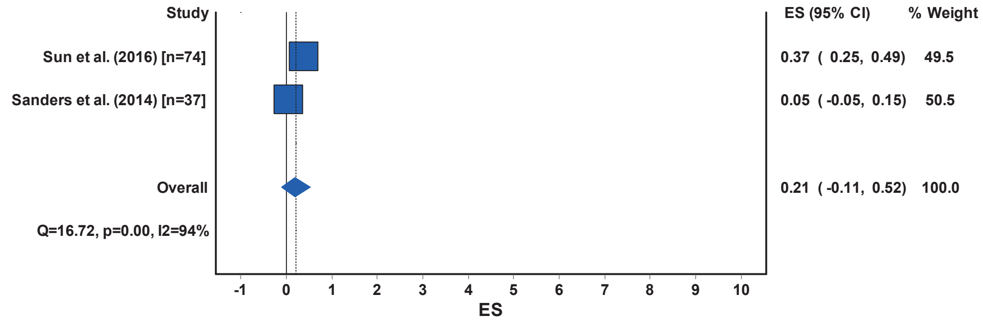

Figure 5.2b. Pooled estimates for knee pain scores for the suprapatellar approach.

Function

General function lower extremity

To measure the lower extremity function in general, the Tegner Activity Score,[14,23,26,53,77] Lower Extremity Functional Score,[35] and Musculoskeletal Function Assessment[54] were used. The pooled analysis for the Tegner Activity score was 3.9 (95% C.I. 3.6–4.2) for the infrapatellar technique.[53]

Knee function

The Lysholm Scale,[5,9,26,45,53,56,66,73,75,77,79–81,83,84] Iowa Knee Score,[24,26,33,48] (Kujala) Anterior Knee Pain Scale (AKPS),[4,51,80,81] Functional Anterior Knee Pain Score,[38,75,80] Oxford Knee Score[8,80] and International Knee Documentation Committee (IKDC Questionnaire)[80] were used for measuring the knee function after tibial nailing. Pooled estimates for the Lysholm Scale were 87 points (95% CI 81–94) for the infrapatellar technique and 85 points (95% CI

83–87) for the suprapatellar technique (Figure 5.3a, b). Pooled analysis for the Iowa Knee Score (Figure 5.4) was only possible for the infrapatellar technique and was 94 points (95% CI 91–97) (Figure 5.4). Pooled estimates for the Anterior Knee Pain Scale (or Kujala) were

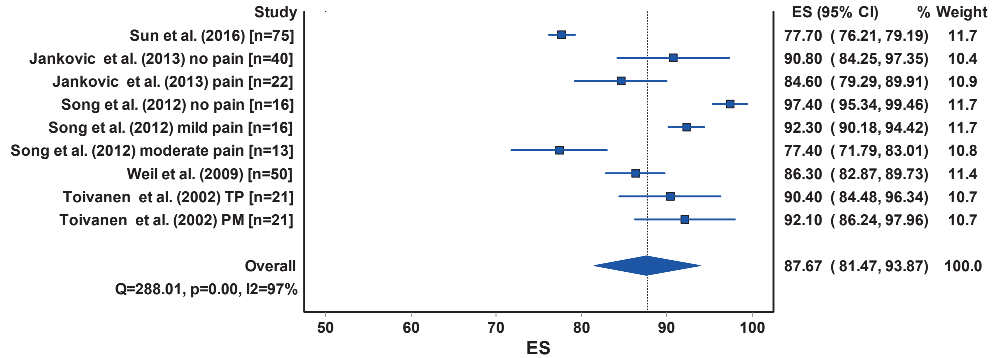

Figure 5.3a. Pooled estimates for Lysholm score for the infrapatellar approach.

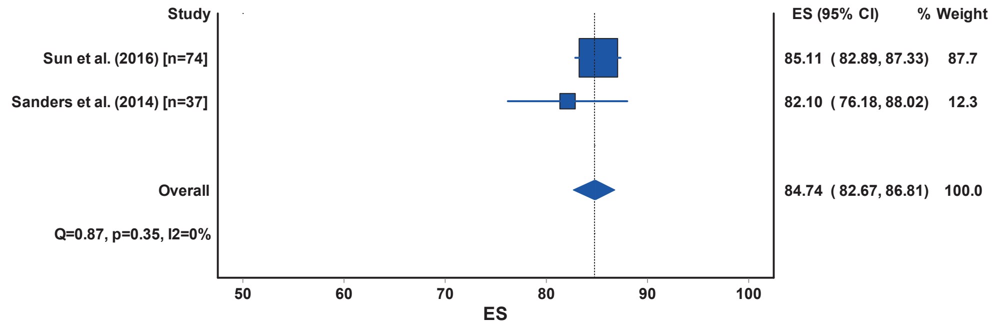

Figure 5.3b. Pooled estimates for Lysholm score for the suprapatellar approach.

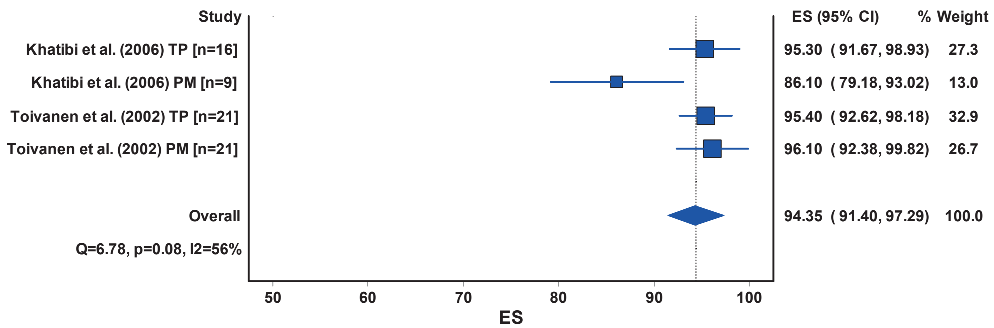

Figure 5.4. Pooled estimates for Iowa knee score for the infrapatellar approach.

79 points (95% CI 76–83) for the infrapatellar technique and 79 points (95% CI 71–86) for the suprapatellar technique.

Ankle function

To measure ankle function, the following instruments were used: AOFAS ankle–hindfoot scoring system,[67,77,78,82] Iowa Ankle Score (also known as Merchant and Dietz Ankle Function Score),[24,31,33,36,48] Olerud and Molander Ankle Score,[36,76,82] Mazur Ankle Score,[59] and Foot Function Index.[54] Pooled estimates for the AOFAS ankle–hindfoot scoring system and Iowa Ankle Score were 91 (95% CI 87–93) and 92 (95% CI 89–96) for the infrapatellar and suprapatellar technique, respectively.

Quality of life

The Short Form-36 (SF-36),[5,7,9,24,43,48,51,61,67,80,83] SF-12,[4] EQ5D,[60] and the Nottingham Health Profile[23,60] were used to measure quality of life after tibial nailing. The pooled estimates could only be calculated for the physical and mental component score (PCS and MCS) of

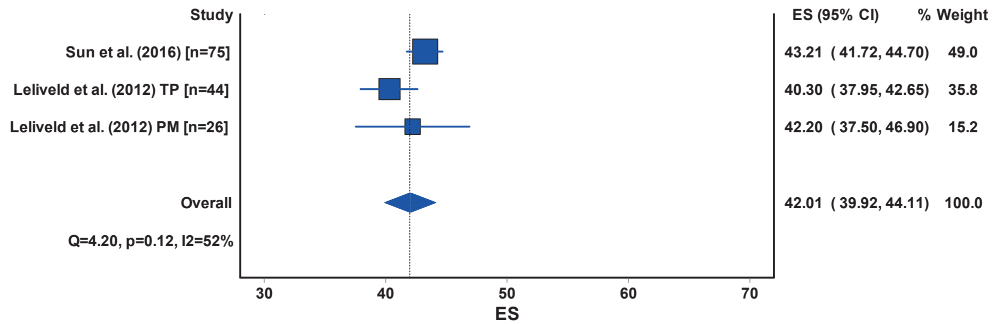

Figure 5.6a. Pooled estimates for SF-36 PCS for the infrapatellar approach.

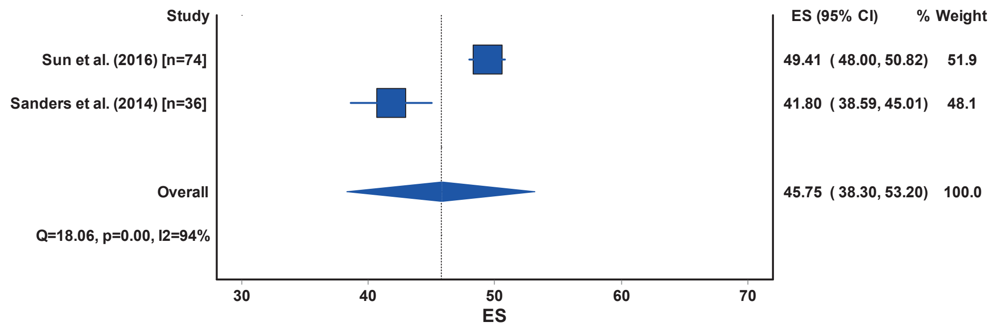

Figure 5.6b. Pooled estimates for SF-36 PCS for the suprapatellar approach.

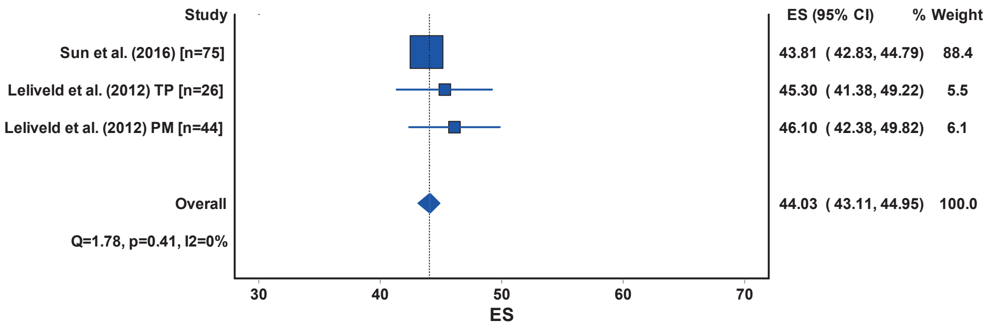

Figure 5.7a. Pooled score for SF-36 MCS for the infrapatellar approach.

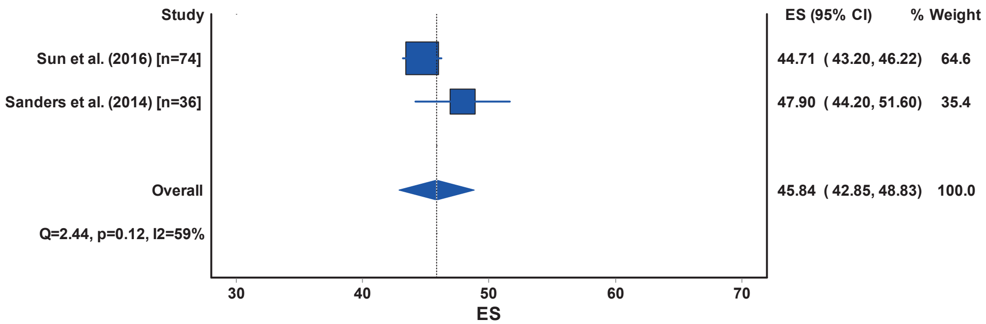

Figure 5.7b. Pooled score for SF-36 MCS for the suprapatellar approach.

the SF-36. The PCS was 42 (95% CI 40–44) for the infrapatellar technique and 46 (95% CI 41–51) for the suprapatellar technique (Figure 5.6a, b). The pooled estimate for the MCS was 44 (95% CI 43–45) for the infrapatellar technique and 48 (95% CI 44–52) for the suprapatellar technique (Figure 5.7a, b).

Discussion

The aim of this systematic review was to compare knee pain and function after tibial nail insertion through different surgical methods. For the infrapatellar approach, the proportion of patients with anterior knee pain in the current review was 38%. The percentage found for the suprapatellar technique was 10%. The documented general knee pain scores (VAS/NRS 0–10) were, however, surprisingly low for both techniques (2.2 for the infrapatellar technique and 0.2 for the suprapatellar technique). For the infrapatellar technique, pain scores during common daily activities were also low, except for kneeling (range 3.2–4.7). Knee function was good for both the infra- and suprapatellar techniques.

The pooled proportion of 38% of patients with knee pain is lower than the much-quoted percentage of 47.4% from the systematic review by Katsoulis et al.,[85] but it is still

a substantial percentage. Although many patients report pain, pooled estimates were high for the Lysholm score, Iowa Knee score and AKPS. The scope of most knee function scores is limited to patients with osteoarthritis or those receiving total knee replacements. For fractures around the knee, there is currently no validated, reliable, and reproducible outcome measure. For patients with tibia fractures only, the disease-specific Short Musculoskeletal Function Assessment (SMFA) and the generic measure SF-36 have been demonstrated responsive and valid.[86] Both assess the general functional status of patients and how bothered they are by functional problems without focus on knee function and knee pain. Since outcome scoring is vital in the accurate evaluation and comparison of interventions, what knee scoring system should we use to measure knee pain and/or function after tibial nailing? The Lysholm Score and Iowa Knee Score[24,26,33,48] are the most commonly used for this cause, but neither is validated for this specific patient population. Validation of (at least one of) these questionnaires in a patient population that include tibial fractures is, therefore, needed.

One limitation of this systematic review is the lack of randomized controlled trials (RCT) comparing different methods in tibial nailing. Only two RCTs compared nail insertion through the patellar tendon with insertion medial to the patellar tendon[26,49] and two other RCTs compared an infrapatellar and suprapatellar technique.[7,9] Furthermore, most studies lack information on how pain as an outcome parameter was acquired, as did information at the point of time at which the parameter was measured. The proportion of patients with knee pain might well be higher within the first months after surgery than years later. This should be taken into account when interpreting such percentages. Pain scores and functional outcome measurements can additionally be affected by the presence of other injuries. Therefore, outcome measures from studies that included multiple injured patients or patients with ipsilateral fractures must also be interpreted with caution.

Overall, adequate reporting of outcome measures was poor. Besides, the previously mentioned lack of how and when measurements were taken, the standard deviation for mean pain or functional scores was not always provided. Furthermore, some authors chose to report scores only in terms of excellent, good, fair etc., without mentioning an overall score. The quality of a systematic review, such as the current review, depends on the quality of the underlying studies and although it is the authors' responsibility to report their data adequate and complete, it would be helpful if journal reviewers and editors would ask for any missing information.

Conclusion

The question whether one surgical approach for tibial nailing is superior to another cannot be answered due to limited availability of adequate data. One can conclude though that in terms of anterior knee pain, the suprapatellar technique has the lowest proportion (10.0%) of patients with this complaint. Overall, general knee pain scores are low (range 0.2–3.7). Knee function was good for both the infra- and suprapatellar techniques.

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Appendix search strategy

Embase.com (Embase plus Medline): 2270

('tibia shaft fracture'/de OR 'tibia fracture'/de OR 'distal tibia fracture'/de OR 'proximal tibia fracture'/de OR (tibia* AND fractur*):ab,ti) AND ('Bone nail'/de OR 'intramedullary nail'/exp OR 'intramedullary nailing'/de OR (((intramedullar* OR IM OR medullar* OR tibial OR ender) NEAR/4 (nail* OR rod* OR pin* OR fixation* OR osteosynth*)) OR (bone NEAR/3 (nail* OR pin* OR rod*)) OR Micronail* OR Olecranail* OR Targon* OR Fixion* OR Trigen):ab,ti) AND ('treatment outcome'/exp OR 'pain'/exp OR 'musculoskeletal function'/exp OR (outcome* OR pain* OR function*):ab,ti)

Medline Epub (OvidSP): 1873

("Tibial Fractures"/ OR (tibia* AND fractur*).ab,ti.) AND ("Bone Nails"/ OR "Fracture Fixation, Intramedullary"/ OR (((intramedullar* OR IM OR medullar* OR tibia* OR ender) ADJ4 (nail* OR rod* OR pin* OR fixation* OR osteosynth*)) OR (bone ADJ3 (nail* OR pin* OR rod*)) OR Micronail* OR Olecranail* OR Targon* OR Fixion* OR Trigen).ab,ti.) AND (exp "treatment outcome"/ OR exp "pain"/ OR "recovery of function"/ OR (outcome* OR pain* OR function*).ab,ti.)

Cochrane Central (trials): 76

((tibia* AND fractur*):ab,ti) AND ((((intramedullar* OR IM OR medullar* OR tibial OR ender) NEAR/4 (nail* OR rod* OR pin* OR fixation* OR osteosynth*)) OR (bone NEAR/3 (nail* OR pin* OR rod*)) OR Micronail* OR Olecranail* OR Targon* OR Fixion* OR Trigen):ab,ti) AND ((outcome* OR pain* OR function*):ab,ti)

Web of Science: 903

TS=((tibia* AND fractur*) AND (((intramedullar* OR IM OR medullar* OR tibial OR ender) NEAR/3 (nail* OR rod* OR pin* OR fixation* OR osteosynth*)) OR (bone NEAR/2 (nail* OR pin* OR rod*)) OR Micronail* OR Olecranail* OR Targon* OR Fixion* OR Trigen) AND (outcome* OR pain* OR function*))

Google Scholar: 200 (sorted on relevance)

"tibia fracture" "intramedullary|IM|medullary|tibial|ender nail|rod|pin|fixation"|"bone nail|pin|rod"|Micronail|Olecranail|Targon|Fixion|Trigen outcome|pain|functioning

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Chapter 6

Measurement properties of Patient-Reported Outcome Measures in patients with a tibial shaft fracture; validation study alongside the multicenter TRAVEL study

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Injury 2021;52(4):1002-1010

Abstract

The aim of this study was to evaluate the measurement properties of the Short Musculoskeletal Function Assessment (SMFA) and Lower Extremity Functional Scale (LEFS) in patients who sustained a tibial shaft fracture, by comparing them with the scores of a general health-related quality of life instrument scale (i.e., EuroQoL-5D).

Data of 136 patients participating in a multicenter randomized controlled trial comparing incisions for intramedullary nail entry in adults with a tibial shaft fracture were used. Patients completed the SMFA, LEFS, EQ-5D and an anchor question at 2 and 6 weeks, and at 3, 6 and 12 months. Reliability (internal consistency), construct validity, responsiveness (longitudinal validity), floor and ceiling effects, minimal important change (MIC), and smallest detectable change (SDC) were determined.

The SMFA and LEFS (sub)scales showed adequate internal consistency ($0.84<\alpha<0.94$). Construct and longitudinal validity were also adequate (correctly predicted hypotheses between 83%-100%). Floor effects were not present. Ceiling effects were present at 12 months for the SMFA lower extremity dysfunction and bother subscales (22% and 19%, respectively) and the LEFS (19%). MICs could not be determined with the available data. The SDC was 13.84 points for the SMFA and 38.74 points for the LEFS.

This study confirms that the SMFA and LEFS are reliable, valid, and responsive instruments for monitoring functional limitation in patients after sustaining a tibia shaft fracture during at least the first six months post-injury. An anchor-based MIC for the SMFA remains to be determined.

Introduction

Compared with, e.g., hip fractures the incidence rate of lower leg fractures is low, but the average burden of these fractures is high for patients. This is due to the high proportion of patients with lifelong disabilities of some lower leg injuries in combination with the patients' relatively young age.[1,2]

In order to monitor outcome, functional recovery, and quality of life after lower-limb injury or (surgical) treatment, patient-reported outcome measures (PROMs) are becoming increasingly important instruments. For this purpose numerous disease-specific and region-specific PROMs are being used.[3-5]

The SMFA is a patient-reported questionnaire, designed to detect differences in functional status of patients who have a broad range of musculoskeletal disorders. In its original language version the SMFA is proven to be a valid, reliable, and responsive questionnaire.[3] Psychometric properties of the SMFA were tested in a variety of populations of patients: patients with ankle arthritis,[6] hip/knee osteoarthritis,[7] rheumatoid arthritis,[7] severely injured patients (ISS>15),[8] and patients with various musculoskeletal disorders.[3,9,10] Van Son et al. translated and culturally adapted the Dutch version of the SMFA.[11] They additionally adapted some items in order to avoid double-barrelled items.[11]

Whereas the SMFA is developed for patients with any musculoskeletal disorder, the Lower Extremity Functional Scale (LEFS) is a region-specific PROM. The measurement properties of LEFS indicate that it is a reliable, valid, and responsive tool for assessing functional status in several populations with lower extremity musculoskeletal conditions.[12] Furthermore, the LEFS was found to be responsive in patients with total hip or knee replacement,[13] general lower extremity dysfunction,[14] osteoarthritis,[15] and ankle fractures.[16] The LEFS was translated into Dutch from its original language by Hoogeboom et al.[15]

Patient reported outcome measures are useful for measuring the trajectory of functional recovery after sustaining a tibial shaft fracture. For this specific population of patients the measurement properties of the SMFA and LEFS are not fully known. The aim of this study was to evaluate the measurement properties of the SMFA and LEFS (sub)scores in patients that sustained a tibial shaft fracture by comparing them with the scores of a general health-related quality of life instrument scale (*i.e.*, EuroQoL-5D). This study is registered at the Netherlands Trial Register (NTR5091).

The study was approved by the Medical Research Ethics Committees Erasmus MC (Ref. No. MEC-2014-335 and NL49144.078.14) and Local Ethics Boards of all participating centers.

Materials and methods

Study data

All 136 patients who were included in a multicenter randomized controlled trial comparing two incisions for intramedullary nail entry in adult patients with a tibial shaft fracture were used.

Study population

Patients were recruited from September 6, 2015 until June 12, 2018. Patients aged between 16 years and 65 years presenting with a tibial shaft fracture (AO type 42) to the Emergency Department of one of 13 participating hospitals in the Netherlands were eligible for inclusion. Exclusion criteria were 1) polytraumatized patients; 2) concurring injury affecting treatment and recovery; 3) bilateral tibial fractures; 4) pathological or recurrent fracture of the tibia; 5) Gustilo Anderson type IIIC open fractures or open wound on knee; 6) pre-existing knee pathology (e.g., menisci or cruciate ligament); 7) pre-existing functional impairment influencing rehabilitation (e.g., wheelchair-bound); 8) rheumatoid arthritis; 9) bone disease resulting in delayed union (except osteoporosis); 10) problems ensuring follow-up (e.g., no fixed address or cognitive impairment); and 11) insufficient comprehension of the Dutch language.

Questionnaires

Patients were asked to complete Dutch versions of the SMFA,[11] LEFS,[15] and EuroQoL-5D (EQ-5D-3L)[17] questionnaires at two and six weeks, and at three, six, and 12 months after tibial nailing.

The Dutch SMFA consists of 53 items, each scored using a 5 points Likert scale. It is divided in three subscales: a 23-item Dysfunction lower extremity (LE) scale, a 9-item Dysfunction upper extremity (UE) scale and a 15-item Bother scale. The SMFA score is calculated for each subscale using the formula: ((sum of all items/number of items)-1) *maximum score). The overall score as well as the subscale scores range from 0 to 100 points. Higher scores refer to greater disability.

The LEFS is developed to measure function in patients with a wide range of lower-extremity orthopedic conditions.[4] It is a self-reported measure and consists of 20 items, each with a maximum score of 4. The total possible score of 80 indicates a high functional level. The total score is calculated using the formula: ((sum of all items/number of items)/80). The EQ-5D-3L is a validated instrument for measuring health-related quality of life.[5]

The EQ-5D utility score (EQ-US) ranges from 0 to 1 and is determined from five 1-item domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item has three possible answers. In addition, the individual's rating of his/her quality of life state is recorded by means of a standard Visual Analog Scale (EQ-VAS), which ranges from 0 to 100. Higher scores represent better health-related quality of life.

Baseline characteristics collected were age, gender, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) classification, and smoking. Fracture details collected were affected side, AO classification, and presence of a fibula fracture and additional injuries.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 (SPSS, Chicago, Ill., USA). The Receiver Operating Characteristic (ROC) curve and Youden Index were analyzed using MedCalc version 14.10.2 (MedCalc Software, Ostend, Belgium). Measurement properties of the (sub)scales were determined in compliance with the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines.[18] Data are reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE).[19] Since raw data for individual items were analyzed, missing responses to the questionnaires were not imputed.

Descriptive statistics were used in order to describe the main characteristics of the study participants. Measurement properties of the SMFA, LEFS, and EQ-5D (sub)scores were determined by comparing them with those of the general health-related quality of life instrument EQ-5D.

Reliability was determined by evaluating internal consistency. Internal consistency is a measure of the extent to which items in a (sub)scale are correlated (homogeneous), thus measuring the same concept.[20] For each (sub)scale, correlation between the items was calculated using Cronbach's alpha. Internal consistency can be considered sufficient if the Cronbach's alpha value is between 0.70 and 0.95, provided that the scale is unidimensional.[20] This analysis requires a sample size of 10 per item in the instrument, with a minimum of 100 patients.[20] The six weeks data were used, since the largest heterogeneity in the degree of recovery and consequently the largest variability in scores were expected at that time.

Validity is the degree to which a questionnaire measures the construct it is supposed to measure. As there was no gold standard in the current study, the validity of the instruments was expressed in terms of the construct validity. Construct validity represents the extent to which scores on a specific questionnaire relate to other measures in a way that is in agreement with prior theoretically derived hypotheses concerning the concepts that are being measured.[20] The six weeks data were used. Continuous data were tested for normality using the Shapiro-Wilk test. As not all of the (sub)scales were normally distributed, Spearman rank correlations between the (sub)scales of the SMFA, LEFS, and EQ-5D were determined in order to assess the construct validity. Strengths of correlation were categorized as high ($r>0.6$), moderate ($0.3<r<0.6$), or low ($r<0.3$).[21] Construct validity was considered sufficient if at least 75% of the results were in accordance with predefined hypotheses in a (sub)sample of at least 50 patients.[20] The hypothesized correlations between the (sub)scale scores are shown in Supplemental Table S6.1A and were made in consensus between two authors (MSL and EMMVL).

Responsiveness refers to the ability of a questionnaire to detect clinically important changes over time.[20] In addition, the effect size (ES) and standardized response mean (SRM) were determined as measures of the magnitude of change over time. Longitudinal validity can be considered as a measure of responsiveness. Longitudinal validity refers to the extent to which change in one measurement instrument relates to corresponding change in a reference measure.[22] Analogous to construct validity, longitudinal validity was assessed by testing predefined hypotheses about expected correlations between changes in SMFA, LEFS, and EQ-5D (sub)scale scores. Change scores were calculated as the difference in score from six weeks follow-up to the final measurement at 12 months. Normality was tested using the Shapiro-Wilk test. Since all change scores deviated from a Normal deviation, Spearman correlation coefficients were calculated.

Longitudinal validity was considered sufficient if at least 75% of the results were in accordance with predefined hypotheses in a (sub)sample of at least 50 patients.[20] The hypothesized correlations are shown in Supplemental Table S6.1B and were made in consensus between two authors (MSL and EMMVL).

The Effect Size (ES) and Standardized Response Mean (SRM) were determined as measures of the magnitude over time. The ES was calculated as the mean change in score between two time points (*i.e.*, score at 12 months–score at six weeks) divided by the standard deviation of the first measurement.[23] The SRM was calculated as the mean change in score between two time points (*i.e.*, score at 12 months–score at six weeks) divided by the standard deviation of this change.[23] A value of 0.2-0.4 is considered a small, 0.5-0.7 a moderate, and ≥0.8 a large effect.[21] Large effect sizes were expected a priori, since at six weeks most patients were expected to have functional limitations, whereas at 12 months large improvement or even full recovery was expected for most patients.

Floor and ceiling effects are present if more than 15% of the study population rates the worst (floor effect) or best (ceiling effect) possible score on any questionnaire (sub) scale.[24] In the presence of floor and ceiling effects, items might be missing from the upper or lower ends of the scale, reducing content validity. Likewise, patients with the highest or lowest scores cannot be distinguished from one another, indicating limited reliability.[20] Floor and ceiling effect were determined for each follow-up moment separately.

The Minimal Important Change (MIC) is defined as the smallest measurable change in outcome score that is perceived as significant by patients.[25] An anchor-based method was used as this gives a better indication of the importance of the observed change to the patient.[20] In addition to the questionnaires, patients were asked to complete an transition item (anchor question) at six weeks and at three, six, and 12 months evaluating their perception of change in the general condition of the affected leg. The question was: 'How would you judge the condition of your affected leg at this point, compared with the last time you completed this questionnaire?' The item scored from 1 'much better' through 2 'slightly better', 3 'no change', 4 'slightly worse', or 5 'much worse'.

The anchor or transition item was judged as adequate if a Spearman's rank correlation between the anchor and the change score of the questionnaire was >0.29.[26] The corresponding change score (*i.e.*, score at time of completion of the transition item minus the score at the previous follow-up moment) of patients who answered the transition item as 'slightly better' can be considered the MIC.[27]

As an alternative, the MIC was also calculated for the (sub)scores by plotting the Receiver Operating Characteristics (ROC) curve of the change in score for patients who scored 'slightly better' on the transition item versus patients who scored 'no change'.

The area under the ROC curve is provided as measure of discriminatory power. The ROC cutoffpoint (*i.e.*, the associated criterion of the Youden index) reflects the MIC. This MIC is shown with its 95% confidence interval (CI) after bootstrapping (10 0 0 replicates and 900 random-number seeds).

In addition to the MIC, the Smallest Detectable Change (SDC) was determined. SDC is defined as the smallest intra-personal change in score that represents (with p<0.05) a 'real' difference above measurement error.[28] As patients need to be assumed to be stable in the interim period, this was based on the change scores of patients who answered 'no change' on the transition item. First, the standard error of measurement (SEM) was calculated by dividing the standard deviation of the mean difference between both measurements (SD_{change}) by the square root of two.[29] SEM can be considered as a measure of absolute measurement error.[20] For the individual patient, the SDC was calculated as 1.96 x square root of 2 x SEM (herein, SEM=SD_{change} / square root of 2).[20] Ideally, for evaluative purposes, the SDC should be smaller than the MIC.[20]

Results

Patient demographics

A total of 136 patients was enrolled. They had a median age of 35 (P_{25}-P_{75} 24-53) years and a BMI of 24.5 (P_{25}-P_{75} 21.8-26.9) kg/m^2. The majority of the patients was male (n=99; 73%) and had an American Society of Anesthesiologists (ASA) classification of I (*n*=108; 81%). A total of 40 (29%) patients smoked at the age of trauma. The right side was affected in 74 (54%) patients. Most fractures were closed (*n*=109; 80%), AO type 42A (*n*=92; 68%) and also had a fibula fracture (*n*=114; 89%). A minority of 27 (20%) patients had additional injuries (not affecting their recovery from the sustained tibial shaft fracture).

Changes in outcomes scores over time

During the one-year follow-up, all outcome scores consistently improved over time. The median SMFA total score decreased from 43 (P_{25}-P_{75} 33-51) at two weeks to 6 (P_{25}-P_{75} 1-14) at 12 months (Figure 6.1). Decreases were noted for both the SMFA Dysfunction lower extremity subscale (from 63 (P_{25}-P_{75} 19-74)) to 4 (P_{25}-P_{75} 1-14) and the SMFA Bother subscale (from 32 (P_{25}-P_{75} 23-47)) to 8 (P_{25}-P_{75} 2-7)). The SMFA Dysfunction upper extremity subscale showed no change in outcome scores over time. The LEFS score increased from 26 (P_{25}-P_{75} 16-39) at two weeks to 89 (P_{25}-P_{75} 74-98) at 12 months. Finally, the health-related quality of life improved from 2 weeks to 12 months, with EQ-US scores increasing from 0.43 (P_{25}-P_{75} 0.31-0.69) to 0.93 (P_{25}-P_{75} 0.81-0.93), EQ-VAS score increasing from 70 (P_{25}-P_{75} 60-80) to 80 (P_{25}-P_{75} 74-90).

Reliability

The internal consistency for the SMFA and all subscales was adequate (Cronbach's alpha between 0.84 and 0.94). Internal consistency was also adequate for the LEFS (alpha=0.93) but inadequate for the EQ-5D (alpha=0.66). Cronbach's alpha could not be determined for the EQ-5D-VAS because internal consistency does not apply to a single-item domain (Table 6.1).

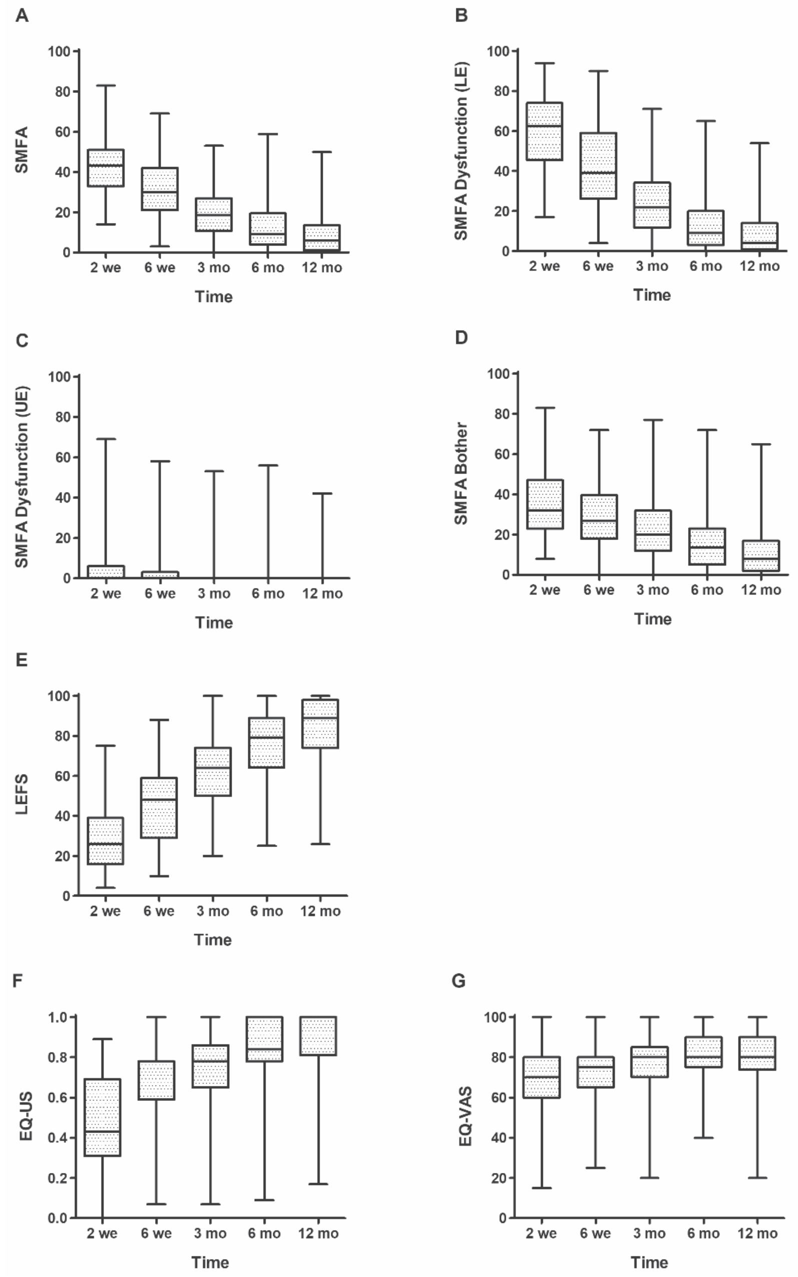

Figure 6.1. SMFA (A-D), LEFS (E), and EQ-5D (F-G) (sub)scales at each follow-up visit in patients with a tibial shaft fracture.

Table 6.1. Internal consistency of the instruments in patients with a tibial shaft fracture.

(Sub)scale	N	N items	Cronbach's alpha
SMFA (total)	99	53	0.94[a]
Lower extremity dysfunction	112	23	0.94
Upper extremity dysfunction	112	9	0.84
Bother	108	15	0.90
LEFS (total)	113	20	0.93
EQ-5D EQ-US	116	5	0.66
EQ-VAS	115	1	N.D.[b]

Data are shown for the six weeks follow-up. The maximum number of patients was 136. [a] Value should be interpreted carefully, since the total scale is not unidimensional. [b] The EQ-VAS consists of a single item. Internal consistency does not apply to a single-item domain. EQ-5D, EuroQoL-5D; EQ-US, EuroQoL-5D Utility Score; EQ-VAS, EuroQoL-5D Visual Analog Scale; LEFS, Lower Extremity Functional Scale; N.D., not determined; SMFA, Short Musculoskeletal Functional Assessment.

Construct validity

Construct validity is shown in Table 6.2. Construct validity was adequate for all questionnaires. The Spearman's rank correlation coefficients of the SMFA were consistent with 16 of the 18 (89%) theoretically derived hypotheses. The hypotheses of the SMFA lower and upper extremity dysfunction scales were confirmed in 5 of the 6 (83%) values. All correlations were correctly predicted for the SMFA bother scale (6/6), as were the correlations of the LEFS (6/6). For the EQ-US and EQ-VAS 5 out of 6 (83%) correlations were as hypothesized.

Responsiveness

Longitudinal validity

Spearman's rank correlation coefficients for longitudinal validity are shown in Table 6.3. For the SMFA the correlations were in line with the predefined hypotheses in 16 out of the 18 (89%) values, indicating sufficient longitudinal validity. For all three SMFA sub- scales 83% (5/6) hypotheses were predicted correctly. Longitudinal validity was also sufficient for the LEFS, EQ-US and EQ-VAS with 100% (6/6), 83% (5/6) and 100% (6/6) correlations as hypothesized, respectively.

Standardized Response Mean (SRM) and Effect Size (ES)

The SRM and the ES of the SMFA, LEFS, and EQ-5D and their subscales are reported in Table 6.4. For the SMFA and the lower extremity dysfunction and bother subscales, the magnitude of change over time was large (SRM between -2,25 and -1.45; ES between -1.58 and -1.00). For the SMFA upper extremity dysfunction subscale the magnitude of change over time was small (SRM -0.32; ES -0.25). The magnitude of the change of the LEFS was large with a SRM of 2.18 and an ES of 2.01. The EQ-US and EQ-VAS showed a large (SRM 1.04; ES 0.93) and small (SRM 0.41; ES 0.45) magnitude of change over time, respectively.

Table 6.2. Construct validity of the instruments in patients with a tibial shaft fracture

	SMFA			LEFS		EQ-5D	
(Sub)scale	Total	UE dysfunction	LE dysfunction	Bother	Total	EQ-US	EQ-VAS
SMFA (total)	1	0.95 [99]	0.61 [99]	0.82 [99]	-0.89 [98]	-0.64 [96]	-0.59 [95]
LE dysfunction	0.95 [99]	1	0.48 [112]	0.64 [108]	-0.89 [111]	**-0.56 [108]**	-0.53 [107]
UE dysfunction	0.61 [99]	0.48 [112]	1	0.43[108]	-0.49 [111]	-0.37 [108]	**-0.27 [107]**
Bother	0.82 [99]	0.64 [108]	0.43 [108]	1	-0.64 [107]	-0.67 [105]	-0.54 [103]
LEFS (total)	-0.89 [98]	-0.89 [111]	-0.49 [111]	-0.64 [107]	1	0.59 [109]	0.43 [108]
EQ-5D EQ-US	-0.64 [96]	**-0.56 [108]**	-0.37 [108]	-0.67 [105]	0.59 [109]	1	0.48 [111]
EQ-VAS	-0.59 [95]	-0.53 [107]	**-0.27 [107]**	-0.54 [103]	0.43 [108]	0.48 [111]	1

Data are shown for the six weeks follow-up. The maximum number of patients was 136. Construct validity is shown as Spearman's rank correlation coefficients (r) with the number of patients included in the correlation between square brackets. r > 0.6 represents high correlation, 0.3 < r < 0.6 moderate correlation, and r < 0.3 low correlation. Bold and underlined correlations were not hypothesized correctly.EQ-5D, EuroQoL-5D; EQ-USUS, EuroQoL-5D Utility Score; EQ-VAS, EuroQoL-5D Visual Analog Scale; LE, Lower Extremity; LEFS, Lower Extremity Functional Scale; N.D., not determined; SMFA, Short Musculoskeletal Functional Assessment; UE, Upper Extremity.

Table 6.3. Longitudinal validity of the instruments in patients with a tibial shaft fracture

	SMFA			LEFS		EQ-5D	
(Sub)scale	Total	UE dysfunction	LE dysfunction	Bother	Total	EQ-US	EQ-VAS
SMFA (total)	1	0.93 [88]	0.302 [88]	0.65 [88]	-0.77 [87]	-0.30 [85]	-0.15 [81]
LE dysfunction	0.93 [88]	1	0.25 [103]	**0.44 [97]**	-0.78 [102]	-0.30 [99]	-0.15 [94]
UE dysfunction	0.302 [88]	0.25 [103]	1	0.19 [97]	-0.12 [102]	**-0.21 [99]**	0.05 [94]
Bother	0.65 [88]	**0.44 [97]**	0.19 [97]	1	-0.47 [96]	-0.34 [94]	-0.26 [89]
LEFS (total)	-0.77 [87]	-0.78 [102]	-0.12 [102]	-0.47 [96]	1	0.35 [100]	0.24 [95]
EQ-5D EQ-US	-0.30 [85]	-0.30 [99]	**-0.21 [99]**	-0.34 [94]	0.35 [100]	1	0.19 [98]
EQ-VAS	-0.15 [81]	-0.15 [94]	0.05 [94]	-0.26 [89]	0.24 [95]	0.19 [98]	1

Responsiveness is shown as Spearman's rank correlation coefficients (r) of change in scores between six weeks and 12 months with the number of patients included in the correlation between square brackets. The maximum number of patients was 136. r > 0.6 indicates high correlation, 0.3 < r < 0.6 moderate correlation, and r < 0.3 low correlation. Bold and underlined correlations were not hypothesized correctly. EQ-5D, EuroQoL-5D; EQ-USUS, EuroQoL-5D Utility Score; EQ-VAS, EuroQoL-5D Visual Analog Scale; LE, Lower Extremity; LEFS, Lower Extremity Functional Scale; N.D., not determined; SMFA, Short Musculoskeletal Functional Assessment; UE, Upper Extremity.

Table 6.4. Responsiveness: standardized response mean (SRM) and Effect Size (ES) of the instruments in patients with a tibial shaft fracture.

(Sub)scale	N	Mean change	SD_{change}	SRM	$SD_{6\ weeks}$	ES	
SMFA (total)	88	-23.54	10.45	-2.25	14.89	-1.58	large
LE dysfunction	103	-33.28	16.88	-1.97	19.83	-1.68	large
UE dysfunction	103	-2.31	7.31	-0.32	9.12	-0.25	small
Bother	97	-16.90	11.69	-1.45	16.89	-1.00	large
LEFS (total)	104	38.25	17.55	2.18	19.00	2.01	large
EQ-5D US	107	0.20	0.20	1.04	0.22	0.93	large
VAS	102	6.38	15.51	0.41	14.03	0.45	small

Change scores were calculated from six weeks to 12 months. The maximum number of patients was 136. EQ-5D, EuroQoL-5D; EQ-US, EQ-5D Utility Score; EQ-VAS, EQ-5D Visual Analog Scale; LE, Lower Extremity; LEFS, Lower Extremity Functional Scale; N.D., not determined; SD, Standard deviation of mean change; SRM, standardized response mean; SMFA, Short Musculoskeletal Functional Assessment; UE, Upper Extremity.

Floor and ceiling effects

Floor and ceiling effects for all instruments are shown in Figure 6.2. None of the questionnaires and their subscales showed a floor effect at any point in time. All the measures can therefore be used to accurately interpret the change in status in patients with poor function and health-related quality of life. The SMFA total score showed no ceiling effect. However, for the SMFA lower extremity dysfunction and bother subscales 22% and 19% of all patients, respectively, reported the best score at 12 months follow-up. The SMFA upper extremity dysfunction subscale shows a ceiling effect at each follow-up, increasing from 51% at two weeks to 90% at 12 months follow-up. A ceiling effect of the LEFS is present at 12 months (19%). The EQ-VAS has no ceiling effect, but a ceiling effect of the EQ-US is seen from 3 months (15%) onwards.

Minimal Important Change (MIC) and Smallest Detectable Change (SDC)

The number of patients per transition item for the different time intervals is shown in Supplemental Table S6.2. Anchor-based MIC and distribution-based SDC values are shown in Table 6.5. Overall, 146 transition items were reported as 'slightly better' and 103 as 'no change'. None of the transition items were judged as adequate since the Spearman's rank correlation between the anchor and the change scores of the questionnaires were all <0.3. There- fore the MICs for the evaluated instruments are potentially unreliable and should be interpreted with care (*r* between -0.14 [EQ-US] and 0.24 [SMFA total]; data not shown). The SDC was 13.84 points (SEM 4.99) for the SMFA total score and 38.74 points (SEM 13.97) for the LEFS, 0.51 (SEM 0.19) for the EQ-US and 22.99 (SEM 8.29) for the EQ-VAS.

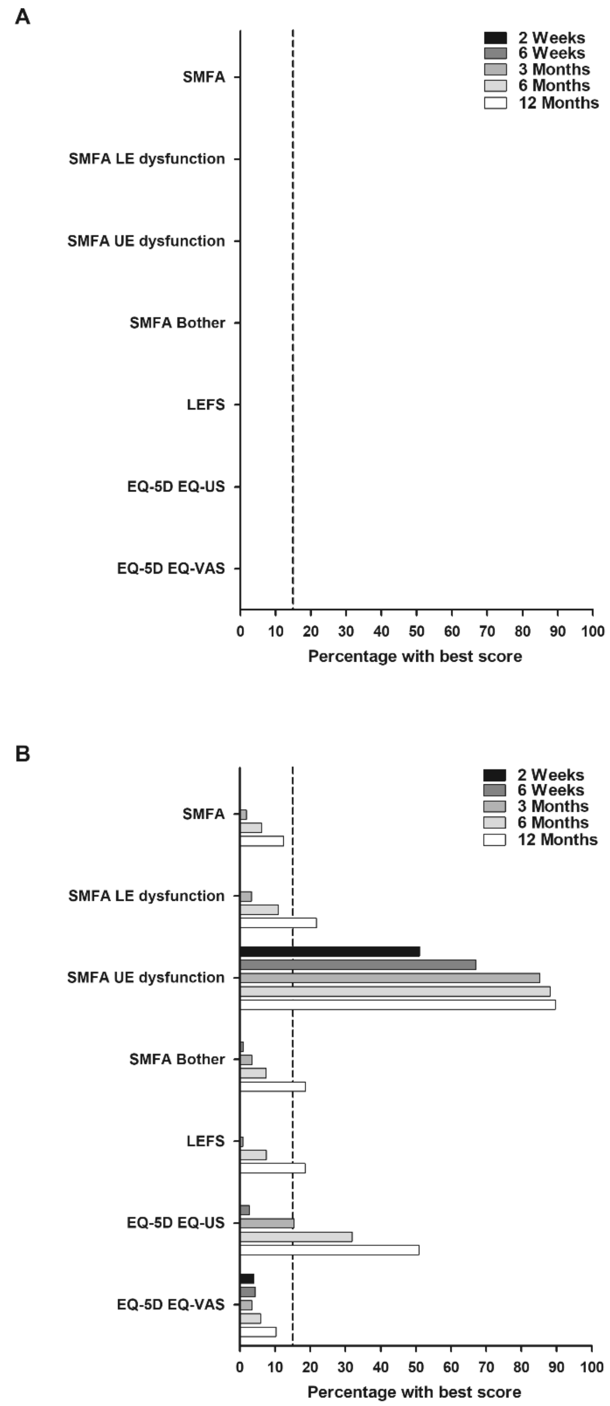

Figure 6.2. Floor (A) and ceiling (B) effects of the instruments at each follow-up visit in patients with a tibial shaft fracture.

Table 6.5. Minimal Important Change and Smallest Detectable Change values of the instruments in patients with a tibial shaft fracture

(Sub)scale	Scoring range	Anchor-based approach						Distribution-based approach			
		N	MIC^A	AUC	MIC^B	Sensitivity (%)	Specificity (%)	N	SD_{change}	SEM	SDC
SMFA (total)	0;100	116	8.12 [6.36;9.88]	0.55 [0.47;0.62]	0.92 [-2.89;3.77]	85.3	25.7	74	7.06	4.99	13.84
LE dysfunction	0;100	127	11.62 [9.13;14.10]	0.54 [0.47;0.61]	7.6 [1.09;29.36]	59.8	53.5	86	12.00	8.48	23.52
UE dysfunction	0;100	127	1.29 [0.23;2.35]	0.53 [0.47;0.60]	2.8 [-2.7;11.1]	83.5	22.1	86	7.23	5.11	14.16
Bother	0;100	124	6.08 [4.29;7.87]	0.53 [0.46;0.60]	10.0 [0.3;20.0]	39.5	74.7	83	2.87	6.02	16.68
LEFS (total)	0;100	127	7.32 [3.65;10.99]	0.54 [0.47;0.61]	12.5 [-13.8;31.3]	38.6	76.1	88	19.76	13.97	38.74
EQ-5D US	-0.329;1.000	122	0.09 [0.05;0.14]	0.55 [0.48;0.62]	0.1 [-0.3;0.1]	47.5	65.5	87	0.26	0.19	0.51
VAS	0;100	128	3.64 [1.60;5.68]	0.55 [0.48;0.62]	0.0 [-14.9;10.0]	55.5	57.3	89	11.73	8.29	22.99

Anchor-based and distribution-based methods for Minimal Important Change (MIC) and Smallest Detectable Change (SDC) values, respectively. The MIC and the Area under the Receiver Operating Curve (AUC) are shown with 95% confidence intervals between brackets. MIC is calculated as mean change score for all respondents reporting "slightly better" on the transition question (MIC^A) and as criterion in the Receiver Operating Curve (MIC^B). AUC, Area under the Receiver Operating Curve; EQ-5D, EuroQoL-5D Assessment; EQ-US, EuroQoL-5D Utility Score; EQ-VAS, EuroQoL-5D Visual Analog Scale; LE, Lower Extremity; LEFS, Lower Extremity Functional Scale; MIC, Minimal Important Change; N.D., not determined; SD_{change}, Standard deviation of mean change; SDC, Smallest Detectable Change; SEM, standard error of measurement; SMFA, Short Musculoskeletal Functional; UE, Upper Extremity.

Discussion

Clinimetric properties of the SMFA and LEFS have previously been tested in a heterogeneous population of patients with lower-limb conditions and some homogeneous populations of patients with lower-limb conditions. For evaluation of patients with tibial shaft fractures, measurement properties of these questionnaires were not fully known. Data of the current study confirm that the SMFA and LEFS are reliable, valid, and responsive in the study population. The MIC of these questionnaires should be interpreted with care. Both questionnaires are useful for monitoring patients' functional limitation after sustaining a tibia shaft fracture for at least the first six months.

Reliability of the SMFA and LEFS was supported by adequate internal consistency. The Cronbach's alpha values of the SMFA and its subscales are comparable with published values of the original language version and translated versions.[3,7,9-11,30] The Cronbach's alpha value for the LEFS was also high (0.93) and in concordance with literature.[12] The SMFA and LEFS showed adequate construct validity.

The SMFA total score and SMFA bother scale were highly correlated with the EQ-US (*r* -0.64 and *r* -0.67, respectively). The SMFA and its subscales showed a moderate to low correlation with the EQ- VAS ($-0.27<r<0.54$). These observations are new and suggest that sustaining a tibial shaft fracture does not necessarily affect a patient's general health perception.

The LEFS scores correlated highly with the SMFA total score (*r* - 0.89). This confirms the correlation between these two instruments found by Pinsker et al. in a population of pre- and postoperative ankle arthrodesis and arthroplasty patients.[6] The moderate level of correlation between the LEFS and EQ-US (*r* 0.59) differs from a published study in patients with an ankle fracture (*r* 0.73).[31] In the latter study questionnaires were sent three years after surgery, which may explain the higher correlation between the LEFS and the EQ-US.

Longitudinal validity was adequate for the SMFA total score and LEFS as reflected by the percentage of correctly predicted hypotheses (both 100%). The correlations of the LEFS with the SMFA subscales indicate that changes in lower extremity function have a moderate effect on the bother scale (*r* -0.47) and little effect on up- per extremity dysfunction (*r* -0.12). The latter correlation has also been found by De Graaf et al.[32] The large SRM and ES for the SMFA and LEFS indicate that both instruments can excellently detect clinical change over time.

The large SRM value for the SMFA lower extremity dysfunction scale (-1.97) is similar to values found by Busse et al. in tibial shaft fractures,[33] tibial plateau fractures,[34] and ankle fractures.[10] The SRM of the SMFA bother scale was also comparable to values found in patients who sustained an ankle fracture.[10] In groups with various musculoskeletal disorders and nonoperatively treated patients the responsiveness of the SMFA is much lower.[35] The excellent ability of the LEFS to detect change over time has been shown before in patients with various lower limb injuries.[12] The EQ-US and EQ-VAS showed a moderate and low ES, respectively. This implies that sustaining a tibial shaft fracture has only limited effect on health-related quality over time.

None of the questionnaires showed a floor effect, which is in line with other studies.[12,35] The SMFA total score showed no ceiling effect, however, the SMFA lower extremity dysfunction and bother scale did so at 12 months. The presence of ceiling effects can be expected when instruments are used in time points when participants have much disability and improve over time after an injury or treatment. Treatment effects in this patient population can therefore be measured with the SMFA within the first 6 months after surgery, but effects can be missed later in the follow- up.[10,33,34] Likewise, the LEFS can detect functional improvement during the six months post-surgery (ceiling effect reached at 12 months (19%)). The latter finding is new, since earlier studies on the measurement properties of the LEFS had a follow-up period of 26 weeks or less.[15,16,36] Whereas a ceiling effect of the EQ-US was present at three months and onwards, the EQ-VAS did not have a ceiling effect at all in the current study. The EQ-VAS can thus be used to measure health-related quality of life on the long term in patients that sustained a tibial shaft fracture.

The SDC is a measure of the variation in a scale due to measurement error. Thus, a change score can only be considered to represent a real change if it is larger than the SDC. The SDC values of the SMFA total scale have been reported in three studies.[6,9,32] In patients with stable ankle arthritis the SDC was 9.60[6] which is lower than the SDC found in the current study (SDC 13.84). In addition to the stable condition of the patients, the average follow-up time ranged from 7 months to 2.5 years after surgery, which may explain the lower SDC. The SDC's reported by Reininga et al. and De Graaf et al. were higher, but the difference in factor structure of the SMFA hampers a comparison with our results.[9,32] The reported SDC values of the LEFS show much variation (ranging from 2.18 for Spanish LEFS scores in patients diagnosed with lower extremity musculoskeletal conditions[37] to 18.1 in patients with knee osteoarthritis,[38] as displayed in the systematic review by Mehta et al.[12] All values are much lower than the SDC found in the current study (SDC 38.74). Explanations for this difference include more heterogeneity of the patient population,[36,37] shorter follow-up time,[36,37,39] and smaller sample size.[40]

The most important clinimetric property for interpreting change over time is the minimum important change (MIC). For the SMFA no studies have evaluated this measurement property using an anchor-based method. Due to the inadequate correlation between the transition item "slightly better" and change scores, the true MIC remains undetermined. The sample size of 136 patients in this study should have been adequate to determine the MIC. In addition, there were enough (n=146) transition items reported as "slightly better". The time between 2 subsequent follow-up moments varied from 4 weeks to 6 months. The drawback of the anchor-based approach is that it is based on retrospective judgement of change and is susceptible to recall biases.[41]

This study shows that when taking into account the SDC and MIC, the change score should exceed 13.8 points for the SMFA (total score) and 38.7 points for the LEFS to have a clinically relevant change on the questionnaire in patients that sustained a tibial shaft

fracture. The MIC for the SMFA remains to be determined. The known anchor-based MIC value of the LEFS (9[4,42]) only exceeds the SDC found in two studies (2.18 points for the Spanish LEFS[37] and 8.0 points in patients with anterior knee pain.[40] If the SDC is smaller than the MIC, it is possible to distinguish a clinically important change from measurement error with a large amount of certainty. However, this is much more difficult if the SDC is larger than the MIC, since there is a considerable chance that the observed change is caused by measurement error. This study has some limitations. The relatively long interval between two subsequent follow-up moments (four weeks to six months) hindered an adequate test-retest analysis. It may also have led to recall bias with regard to the transition item and thus affected correct anchor-based MIC and SDC calculations. For future studies that aim to determine the MIC for the SMFA in patients that sustained a tibial shaft fracture we recommend to shorten the intervals between the questionnaires (in combination with the anchor-based questions).

In order to monitor outcome, functional recovery, and quality of life after lower-limb injury or (surgical) treatment, PROMs are becoming increasingly important instruments. By using these instruments different treatment strategies and their outcome can be compared. The SMFA and LEFS are useful instruments for monitoring functional limitation in patients after sustaining a tibia shaft fracture during at least the first 6 months post-injury. Both instruments are reliable, valid, and responsive. The MIC could not be determined reliably.

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Supplementary Data

Supplemental Table S6.1. Hypothesized correlations between the instruments for (A) construct validity and (B) Longitudinal validity in patients with a tibial shaft fracture

	SMFA			LEFS		EQ-5D	
(Sub)scale	Total	UE dysfunction	LE dysfunction	Bother	Total	EQ-US	EQ-VAS
A. Construct validity							
SMFA (total)	N.A.	High	High	High	High	High	Moderate
LE dysfunction	High	N.A.	Moderate	High	High	High	Moderate
UE dysfunction	High	Moderate	N.A.	Moderate	Moderate	Moderate	Moderate
Bother	High	High	Moderate	N.A.	High	High	Moderate
LEFS (total)	High	High	Moderate	High	N.A.	Moderate	Moderate
EQ-5D EQ-US	High	High	Moderate	High	Moderate	N.A.	Moderate
EQ-VAS	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	N.A.
B. Longitudinal validity							
SMFA (total)	N.A.	High	Moderate	High	High	Moderate	Low
LE dysfunction	High	N.A.	Low	High	High	Moderate	Low
UE dysfunction	Moderate	Low	N.A.	Low	Low	Moderate	Low
Bother	High	High	Low	N.A.	Moderate	Moderate	Low
LEFS (total)	High	High	Low	Moderate	N.A.	Moderate	Low
EQ-5D EQ-US	Moderate	Moderate	Moderate	Moderate	Moderate	N.A.	Low
EQ-VAS	Low	Low	Low	Low	Low	Low	N.A.

Expected strength of correlation or all possible combinations; r>0.6 indicates high correlation, 0.3<r>0.6 moderate correlation, and r> 0.6 low correlation. * Correlations between brackets are self-correlations and are not included in the calculation of the percentage correlations predicted correctly. For the SMFA, the overall number of correlations is 42 (the correlations given above the self-correlation that are marked with an asterisk are also mentioned in the columns to the left as reversed correlation, and are thus superfluous). EQ-5D, EuroQoL-5D; EQ-US, EQ-5D Utility Score; EQ-VAS, EQ-5D Visual Analog Scale; LE, Lower Extremity; LEFS, Lower Extremity Functional Scale; N.A., not applicable; SMFA, Short Musculoskeletal Functional Assessment; UE, Upper Extremity

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Supplemental Table S6.2. Answers to the transition item at four different time windows in patients with a tibial shaft fracture

		Time window			
Transition item	Total (N=527)	2 to 6 weeks (N=134)	6 weeks to 3 months (N=133)	3 to 6 months (N=132)	6 to 12 months (N=128)
1 'much better'	202 (38%)	60 (45%)	59 (44%)	48 (36%)	35 (27%)
2 'slightly better'	146 (28%)	29 (22%)	43 (32%)	40 (30%)	34 (27%)
3 'no change'	103 (20%)	11 (8%)	23 (17%)	25 (19%)	44 (34%)
4 'slightly worse'	23 (4%)	5 (4%)	4 (3%)	9 (7%)	5 (4%)
5 'much worse'	5 (1%)	1 (1%)	1 (1%)	1 (1%)	2 (2%)
Missing data	48 (9%)	28 (21%)	3 (2%)	9 (7%)	8 (6%)

Data are shown as number with valid percentage.

PART III

Anterior knee pain after tibial nailing

Chapter 7

Injury to the infrapatellar branch of the saphenous nerve, a possible cause for anterior knee pain after tibial nailing?

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Abstract

The purpose of this study was to determine the long-term incidence of infrapatellar nerve damage after tibial nailing and its relation to anterior knee pain. We retrospectively evaluated 71 patients in whom 72 isolated tibial shaft fractures were treated with an intramedullary nail. The mean follow-up time was 84 months. Twenty-seven patients (38%) complained of chronic anterior knee pain. Infrapatellar nerve damage was found in 43 patients (60%). Of the 27 patients with knee pain, 21 (78%) had sensory deficits in the distribution area of the infrapatellar nerve, compared to 22 of the 45 patients (49%) without knee pain (p=0.025). Patient and fracture characteristics showed no significant differences between the two groups. At time of follow-up a total of 33 nails were removed of which twelve were taken out because of knee pain. The pain persisted in seven of these twelve patients (58%).

The incidence of iatrogenic damage to the infrapatellar nerve after tibial nailing is high and lasting. Injury to this nerve appears to be associated with anterior knee pain after tibial nailing.

Introduction

Intramedullary nailing is considered to be the treatment of choice for tibia shaft fractures due to the high union rates, good functional and predictable results, low infection and deformity rates.[1–3] Nevertheless, postoperative pain and discomfort at the anterior aspect of the knee is one of the most frequent complications after tibial nailing. In a meta-analysis Katsoulis et al. report a mean incidence of anterior knee pain after tibial nailing of 47.4%.[4] It has been attributed to multiple factors such as injury to cartilage,[5] the retropatellar fat pad,[6] the patellar tendon,[7] and nail protrusion.[8] No publication has yet provided conclusive data regarding the aetiology of anterior knee pain after tibial nailing and it remains a complex problem.

Several anatomic structures around the knee are prone to injury during nail insertion, including the infrapatellar branch of the saphenous nerve. The infrapatellar nerve arises from the saphenous nerve distal to the adductor canal. It then courses laterally to cross the patellar tendon in a transverse way[9,10]. Cutaneous sensation of the anterior aspect of the knee and the anterior inferior knee capsule is supplied by the infrapatellar nerve.[11] Iatrogenic injury to the nerve will result in predictable sensory loss lateral or downstream to the incision. Additionally, in some individuals neuropathic pain can develop (hypalgesia, dysesthesia or allodynia).[12] This neuropathic component of the pain may even persist in the absence of any peripheral noxious stimuli or ongoing peripheral inflammation.[12] Infrapatellar nerve injury can be caused by surgical trauma. Sensory disturbances have been reported following arthroscopic and open knee surgery in the (medial) knee region.[10,13–15] Also neuroma formation and reflex sympathetic dystrophy following infrapatellar nerve injury have been reported.[12,15]

Injury to the infrapatellar nerve is not widely recognised after tibial nailing. Only few authors mention infrapatellar nerve injury after this procedure.[3,16] Our primary goal was to determine the long-term incidence of infrapatellar nerve injury after tibial nailing. Additionally, the incidence of infrapatellar nerve injury after intramedullary nailing of the tibia was compared between patients with and without anterior knee pain.

Patients and methods

Study group

After approval of the study design by the local ethics committee, all adult patients (age 18–65 years) admitted to our institution for an isolated, traumatic tibial shaft fracture between June 1998 and June 2008 were identified by the ICD-10 codes S82, S82.1, S82.2, S82.3, S82.8, S82.9 as put down in the hospital's electronic patient data management system and medical record. One-hundred-thirtyfour patients (136 fractures) were treated with an intramedullary nail during that time frame. Exclusion criteria for the current study were: fracture lines extending into the knee or ankle joint (n=3), soft tissue lacerations in the knee area (n=7), pretraumatic knee pain (n=4), Gustilo–Anderson grade III-C[17] open fractures (n=1) and loss to follow-up due to relocation to another hospital or death (n=22). One patient was diagnosed with gonarthrosis of both knees several years after tibial nailing and one patient had recently been treated for a meniscal lesion in the fractured leg. Both were additionally excluded.

This left 97 patients with 99 fractures eligible. All patients were contacted by mail, followed subsequently by telephone. Twelve patients were untraceable. Thirteen patients refused to participate mainly because of interference with work, lack of time or relocation. No compensation in any kind was provided for participation in this study. Seventy-one patients with 72 fractures could be enrolled in the study, which resembles a recall rate of 73%. All participants gave written informed consent. Both the case notes and radiographs were evaluated retrospectively.

Questionnaires

Each patient was asked to fill out three questionnaires: a validated Dutch translation of the Short Form-36 (SF-36),[18] the Anterior Knee Pain Scale (AKPS)[19] and a study-specific questionnaire. The latter questionnaire counted for limitations on work related and leisure activities and overall function of the operated leg. If applicable, the effect of nail removal was evaluated. Patients were directly asked if they experienced anterior knee pain. For the purpose of further analysis, this group of patients was designated as the 'pain' group. The remaining patients were designated as the 'no pain' group. Both groups were compared to determine whether the existence of any significant differences could help explain the presence or absence of knee pain. The SF-36 questionnaire measures the generic health status and is divided into eight components: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health status. Each component is given a score ranging from 0 to 100 points, with high scores indicating better function. The categories are combined to a physical component score (PCS) and a mental component score (MCS). These data were normalised to a population mean of 50. The AKPS is a validated questionnaire that consists of 13 items evaluating subjective symptoms and functional limitations. Items included are: limp, support, walking, stair climbing, squatting, running, jumping, prolonged sitting with knees flexed, pain, swelling, subluxations, atrophy of thigh and flexion deficiency. The minimum score is 0 points (poor function), the maximum score is 100 (best function).

Physical evaluation

For all patients, location, direction and length of the skin incision used for nail insertion was noted. Sensory function in the distribution area of the infrapatellar nerve was tested using a cotton swab and compared with sensation on the contralateral leg and dermatoma's surrounding the infrapatellar nerve. Deficits were defined as numbness or neuropathic pain (hypalgesia, dysesthesia or allodynia) or a combination of these deficits. Sensory function of other peripheral nerves in the affected lower leg and foot was also tested. Both knees were

tested for range of motion, collateral and cruciate ligamentous insufficiency and meniscal pathology. Finally, to evaluate kneeling pain patients were asked to kneel and tell whether the affected leg was more painful than the unaffected contralateral one.

Statistical analysis

To compare normally distributed continuous variables of patients with and without knee pain, two-tailed t-tests were used. Non-parametrical tests were used for not normally distributed variables. A Chi-square test was applied for comparison of categorical variables between the two groups. A p-value of <0.05 was considered statistically significant. Statistical tests were performed using SPSS for Windows software (version 16; SPSS Inc., Chicago, IL).

Results

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The mean follow-up was 84-37 months (SD). Evaluated patients were predominantly male and fractures were mainly caused by a fall (Table 7.1). At the time of follow-up, the average age of male patients was 43.0-12.7 years and of female patients was 50.6-10.9 years. Fracture characteristics are demonstrated in Table 7.2. All fractures were treated with an Unreamed Tibial Nail (UTN; Synthes, Bettlach, Swiss). The intramedullary canal was reamed in three patients. Fourty-six approaches of the intramedullary canal were performed medial to the patellar tendon, 26 approaches were transtendinous. Fourty-nine nails were statically locked, eighteen were dynamically locked and five nails were left unlocked.

Five patients required an immediate fasciotomy. There were four cases of malunion and malalignment occurred three times. Three patients were diagnosed with a superficial infection, one patient had a deep infection. One patient developed a neuroma at the nail

Table 7.1. Patient characteristics (n=72).

	38.6 ± 12.6	
Mean age at time of operation (year ± SD)	**n**	**%**
Gender		
Male	47	65
Female	25	35
Mechanism of injury	27	38
Fall	17	23
Pedestrian-motor-vehicle accident	15	21
Direct trauma (blunt)	6	8
Twisted	5	7
Motorcylce accident	1	1
Crush injury	1	1
Side of fracture		
Left	39	54
Right	33	46

Table 7.2. Fracture characteristics.

Type of fracture	n	%
Closed		
Tscherne 0-1	39	54
Tscherne 2-3	10	14
Open		
Gustilo I	8	11
Gustilo II	8	11
Gustilo IIIA	4	6
Gustilo IIIB	3	4
Location in shaft		
Proximal	2	3
Midshaft	38	53
Distal	32	44
AO classification		
A1	15	21
A2	14	19
A3	11	15
B1	5	7
B2	13	18
B3	5	7
C1	1	1
C2	4	6
C3	4	6

entry site which has been resected. Eight locking screws were removed of which three to accomplish dynamisation, the remaining five were removed for they caused pain or discomfort to the patient. Nail exchange occurred three times and four nails were exchanged for a different implant. Bone grafting had been used in three cases.

At follow-up 33 of the 72 nails had been removed. Fourteen nails were taken out for they caused general discomfort and twelve nails because of knee pain. A deep infection required nail removal in one patient. Another nail was found to be too short postoperatively and was exchanged. The remaining nails were removed to correct malunion or to achieve union using various implants. Of the 39 nails that were in situ, nineteen were found to be prominent on the lateral radiographs.

All incisions were vertical, except one oblique. Fourty-six incisions were placed medial to the patellar tendon, 26 incisions were located right on the patellar tendon. The mean length of the incision was 69±2 mm. Sensory deficits related to the infrapatellar nerve were detected in 43 patients (60%). At the time of follow-up normal sensation at the anterior aspect of the knee had returned in four patients. Numbness in the dermatome of the infrapatellar nerve lateral or caudolateral to the incision as an isolated symptom was found in 31 patients. Isolated neuropathic pain in the same area was found in seven patients. A combination of both was detected in five cases.

Decreased sensation on the medial side of the calf (distribution area of the sartorial branch of the saphenous nerve) was found in one patient. Another patient suffered from hyperesthesia of the superficial peroneal nerve. Finally, one patient complained of numbness in his first web space without additional symptoms.

A side-to-side difference in range of motion in the knees was detected in four patients (range 5–158). None of the patients showed clinical signs of ligamentous, meniscal or other pathology related to the knee joint. Fourty-four patients (61%) reported pain when kneeling. Patients with altered sensation (n=32) complained significantly more of kneeling pain than those in which no deficits were detected (n=12) (p=0.007).

Seven patients stated they felt restricted in work-related activities due to their knee pain and thirteen patients experienced limitations on leisure activities. Overall, 27 of the 72 patients (38%) complained of chronic anterior knee pain as judged by direct questioning. This group of patients was designated as the pain group. The remaining 45 patients were designated as the no pain group. Mean score of the AKPS was 75.4±15.7 for patients with anterior knee pain and 86.6±15.5 for those without anterior knee pain (p=0.004). There were no significant differences found for the mean PCS and MCS of the two groups, nor did the scores significantly differ from the population mean of 50. Comparative analysis of the pain and no pain groups of patients was undertaken. All patient and fracture characteristics were evenly distributed between the two groups. Complication rate and number of re-operations also failed to show significant differences between the two groups. However, of the 27 patients with knee pain, 21 (78%) had sensory deficits in the distribution area of the infrapatellar nerve, compared to 22 of the 45 patients (49%) without knee pain (p=0.025). The odds ratio was 3.7 (95% CI 1.2–10.8). The kind of sensory deficit detected (numbness, neuropathic pain or a combination) did not differ between patients with and those without knee pain. In the knee pain group nails were more often removed (p=0.002), but no difference was found between the two groups in the existence of a prominent nail (p=0.408) (Table 7.3).

At time of follow-up a total of 33 nails were removed of which twelve were taken out because of knee pain. The pain persisted in seven of these twelve patients (58%).

Discussion

Anterior knee pain is a common complaint after intramedullary nailing of tibial shaft fractures. The aetiology of this complication has not yet been elucidated and it presumably is multifactorial in origin. The course of the infrapatellar nerve makes it susceptible to iatrogenic injury during nail insertion, especially when medial and midline incisions are being used.[9,10] After a mean follow-up of seven years after tibial nailing the incidence of sensory deficits related to the infrapatellar nerve was 60% in our study population. The incidence of postoperative anterior knee pain was found to be 38%. Sensory deficits related to infrapatellar nerve injury were significantly more detected in patients with anterior knee pain, irrespective of the type of deficit (numbness or neuropathic pain).

Table 7.3. Comparative analysis of patients with and without chronic anterior knee pain.

	Chronic anterior knee pain			
Clinical characteristics	Yes (n=27)		No (n=45)	
Mean AKPS score	75.41 ± 15.67		86.56 ± 15.46	
	n	%	n	%
Patellar tendon approach				
Medial parapatellar	10	37	16	36
Transpatellar	17	63	29	64
Nail prominence	9	33	10	26
Nail removal	19	70	14	31
Kneeling pain	23	85	21	47

Although the mechanism of knee pain following injury to this nerve is not fully understood, it is described as a source of pain following arthroplasty,[20] open meniscectomy,[21] arthroscopy[10] and blunt trauma to the knee.[15] The nerve can be transected, entrapped during skin closure or during wound healing in scar tissue. Only few studies report sensory deficits related to the infrapatellar nerve after intramedullary fixation of the tibia. Lefaivre et al. revealed that a quarter of 33 patients experienced tenderness at the anterior side of the knee 14 years after tibial nailing.[3] Karladani et al. report dysesthesia at the anterior aspect of the knee in 44% of patients after removal of the intramedullary nail.[16] Unfortunately, both authors do not mention the type of skin incision that was used for nail insertion. In our study all but one tibial nails were inserted through a longitudinal skin incision. This incision has been rejected by some surgeons because of concern to damage the cutaneous nerve and keloid formation. Court-Brown et al. used a transverse incision for either a transtendinous or medial parapatellar approach of the proximal tibia. Nevertheless, they reported an incidence of anterior knee pain of 41%[22] and 56%.[23] This is within range of the incidence of anterior knee pain after use of a longitudinal incision.

The intramedullary canal can be reached through a medial parapatellar approach, a transtendinous approach or a lateral parapatellar approach. There is no consensus regarding the safest approach of the intramedullary canal and a vast intersurgeon variety exists. A survey of Orthopedic Trauma Association (OTA) members by Althausen et al. revealed that a medial parapatellar approach is used most commonly, followed by a transpatellar approach.[24] The lateral parapatellar approach is less used. Independent of the technique used, injury to the tendon and soft tissues is unavoidable. Both the patellar tendon splitting and medial parapatellar approaches are associated with high rates of anterior knee pain.[4] In a prospective, randomised comparison of the paratendinous or transtendinous technique, Vaisto et al. failed to show any difference between the two approaches. About 70% of patients reported knee pain.[25] Similarly, we found no correlation between knee pain and the type of approach. However, Weil et al. used a lateral parapatellar approach for intramedullary tibial nailing and reported an 18% incidence of knee pain after an average follow-up of thirteen months.[26] Studies comparing a lateral parapatellar approach with a transtendinous or medial parapatellar approach have yet to be conducted.

The lateral incision as described by Weil et al. avoids the contact area of the knee with the ground during kneeling, as opposed to medial and anterior incisions. We found that significantly more patients with sensory deficits reported kneeling pain, irrespective of the kind of sensational disturbance (numbness, neuropathic pain or a combination). Direct pressure is applied to the anterior knee when kneeling, which should under normal conditions be painless. Pain in response to a non-noxious stimulus (allodynia) is not uncommon after nerve injury. This could explain why patients perceive pain when kneeling, despite the fact that in many of them numbness was detected. Of course, this is one of many explanations and only a diagnostic nerve block of the infrapatellar nerve could confirm this hypothesis.[12]

Three patients experienced altered sensation in areas other than the anterior aspect of the knee. Nerves that were involved were the sartorial branch of the saphenous nerve, the superficial and the deep peroneal nerve. The first two nerve injuries are likely to be caused by the locking bolts. The incision for insertion of the most proximal locking screws can also transect infrapatellar nerves with an aberrant course. Although unlikely, we cannot prove that proximal locking screws do not.

The presence of a prominent nail has been suggested as causative factor for knee pain.[8] But, like other authors,[3,27] we could not confirm this. Anterior knee pain is the main reason for removal of the nail.[16] However, the outcome after nail removal to alleviate pain is unpredictable and this procedure may even initiate anterior knee pain.[16,28] Our comparative analysis between patients with and without anterior knee pain showed that significantly more nails were removed in the knee pain group. However, the pain did not improve or disappear in all cases. The pain persisted in 58% of the patients in which the nail was removed because of knee pain. Removal of the hardware puts the soft tissues around the knee at a second risk for iatrogenic injury and should therefore only be done in patients of whom a positive outcome can be expected. This raises the question whether the conventional lateral and/or anteroposterior radiographs of the knee are sensitive enough to detect nail prominence. Only a slight deviation of the leg can hide a prominent nail. A CT-scan of the knee might be more sensitive to determine nail protrusion.

In a meta-analysis Katsoulis et al. report a mean incidence of anterior knee pain after tibial nailing of 47.4%. Thirty-eight percent of the patients in this study complained of postoperative knee pain. These patients scored significantly less on the AKPS. Despite the lower functional outcome and the fact that twenty patients stated they felt limitations in work-related and/or leisure activities, the generic health status did not differ between both groups, nor did it differ from the normal population data.

Although in our series one patient had developed a proven neuroma at the nail entry site, we cannot prove the others had not. No cases of reflex sympathetic dystrophy were detected. Infrapatellar nerve damage appears to be long-lasting. Thirty years ago Hunter et al. studied 75 patients who underwent open meniscectomy through a medial parapatellar incision. Sixty-nine percent of the patients reported significant altered sensation, especially when kneeling. Only seven of 67 patients reported that the abnormal area of sensation had decreased after one year.[21] In our study group, normal sensation had returned in only four patients. Sensory function in the distribution area of the infrapatellar nerve has been evaluated using a cotton swab. Although it is assumed that reliability and reproducibility of monofilament testing devices to our knowledge have not been established yet, these devices have been developed to produce a constant test quality, e.g., in time or between patients. However, the reliability of a cotton swab to test sensory function is not bad at all since patients served as their immediate internal controls since not only the unaffected contralateral leg, but also sensory function in dermatomas surrounding the infrapatellar nerve was assessed.

Other limitations of this study include its retrospective design and the relatively small number of patients. Despite the low numbers statistical differences were found. Moreover, pain is a complex symptom, often multifactorial in origin with other related symptoms. However, several functional outcome scores that incorporate pain as a symptom exist to evaluate anterior knee pain after tibial nailing or even an aspecific visual analogue pain (VAS) scores can be used. We chose to use the AKPS, which differentiated well between patients with and those without knee pain. On the other hand this choice hampers direct comparison with studies using other scoring systems, e.g., the Short Musculoskeletal Functional Assessment score, Lysholm knee function questionnaire, Tegner's knee score, the Iowa knee score and a VAS score for several activities.

In summary, the incidence of anterior knee pain after tibial nailing is high and we provide arguments for the hypothesis that iatrogenic injury to the infrapatellar nerve is an important cause. The sensory deficits are long-lasting and therefore emphasis in future research should be put to avoid this complication. Although we show that direct iatrogenic injury to the infrapatellar nerve is associated to postoperative chronic anterior knee pain, we cannot prove a causal relationship from the current results. To give conclusive data on this topic a randomised trial comparing different incision types is currently being conducted.

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Chapter 8

An infrapatellar nerve block reduces knee pain in patients with chronic anterior knee pain after tibial nailing: a randomized, placebo-controlled trial in 34 patients

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Abstract

Background and purpose

Anterior knee pain is common after tibial nailing. Its origin is poorly understood. Injury of the infrapatellar nerve is a possible cause. In this randomized controlled trial we compared changes in knee pain after an infrapatellar nerve block with lidocaine or placebo in patients with persistent knee pain after tibial nailing.

Patients and methods

Patients with chronic knee pain after tibial nailing were randomized to an infrapatellar nerve block with 5 ml 2% lidocaine or placebo (sodium chloride 0.9%), after which they performed 8 daily activities. Before and after these activities, pain was recorded using a numeric rating scale (NRS; 0–10). Primary endpoint was the change in pain during kneeling after the infrapatellar nerve block. Secondary outcomes were changes in pain after the nerve block during the other activities.

Results

34 patients (age 18–62 years) were equally randomized. A significant reduction of the NRS for kneeling pain with an infrapatellar nerve block with lidocaine was found compared with placebo (–4.5 [range −10 to −1] versus −1 [–9 to 2]; p=0.002). There were no differences between the treatments for the NRS values for pain during other activities.

Interpretation

Compared with placebo, an infrapatellar nerve block with lidocaine was more effective in reducing pain during kneeling in patients with chronic knee pain after tibial nailing. Our findings support the contention that kneeling pain after tibial nailing is a peripheral nerve-related problem.

Introduction

The common treatment for tibial shaft fractures is intramedullary nailing. A drawback of this procedure is anterior knee pain.[1] Persisting knee pain after more than 8 years post-nailing is reported with restrictions in daily and leisure activities.[2-4] Removal of the nail does not alleviate pain in all patients and can even initiate anterior knee pain in some.[5] The cause of this phenomenon is unknown. Among the structures at risk for injury during tibial nailing through an infrapatellar approach is the infrapatellar branch of the saphenous nerve. Injury to this nerve usually results in numbness on the anterior aspect of the knee and the proximal lateral part of the lower leg. This complication has been reported after several other surgical procedures around the knee, such as knee arthroscopy[6] and anterior cruciate ligament reconstruction.[7] In addition, development of postprocedural neuropathic pain has been described.[8] Since the infrapatellar nerve runs perpendicular to the patellar tendon, the nerve is at risk for transection during tibial nailing.[6,9] Injury to the infrapatellar nerve after tibial nailing has been reported,[2,3] and sensory deficits of the infrapatellar nerve have been associated with chronic anterior knee pain after tibial nailing.[3] However, studies to examine a causative relation between infrapatellar nerve injury and anterior knee pain after tibial nailing have not yet been conducted.

We hypothesized that if knee pain after tibial nailing is indeed caused by neuropathic pain due to injury or entrapment of the infrapatellar nerve, an anesthetic block of this nerve with lidocaine will reduce knee pain in these patients.

Patients and methods

Patients

From the medical record systems and charting database patients between 18 and 65 years old, treated with an intramedullary nail for an isolated traumatic unilateral tibial shaft fracture (AO/OTA 42 A–C) between June 2000 and December 2016, were selected from St Elisabeth Hospital (Tilburg, The Netherlands, level 1 trauma center and teaching hospital), Gelderse Vallei Hospital (Ede, The Netherlands, level 2 trauma center and teaching hospital), and Erasmus Medical Center (University Medical Center Rotterdam, The Netherlands, level 1 trauma center and teaching hospital). Nailing or nail removal had to be more than 6 months ago. 601 patients with a tibial shaft fracture were treated with an intramedullary nail introduced through a longitudinal infrapatellar incision during the specified period (Figure 8.1). After application of the exclusion criteria, 407 patients were potentially eligible for trial participation. These patients were sent a numeric rating scale (NRS) to rate knee anterior pain during 8 different daily activities (kneeling, squatting, prolonged sitting with bent knees, jumping, walking on stairs, running, walking, and rest). If the patient did not reply, telephone calls were attempted. Pain scores were returned by 233 patients. Criteria for inclusion in the trial were an NRS of 4–6 (moderate pain) during at least 3 out of 8 activities or an NRS of 7 or higher (severe pain) during 1 or more activities. 79 patients met these criteria, of whom 34 agreed to participate in the study.

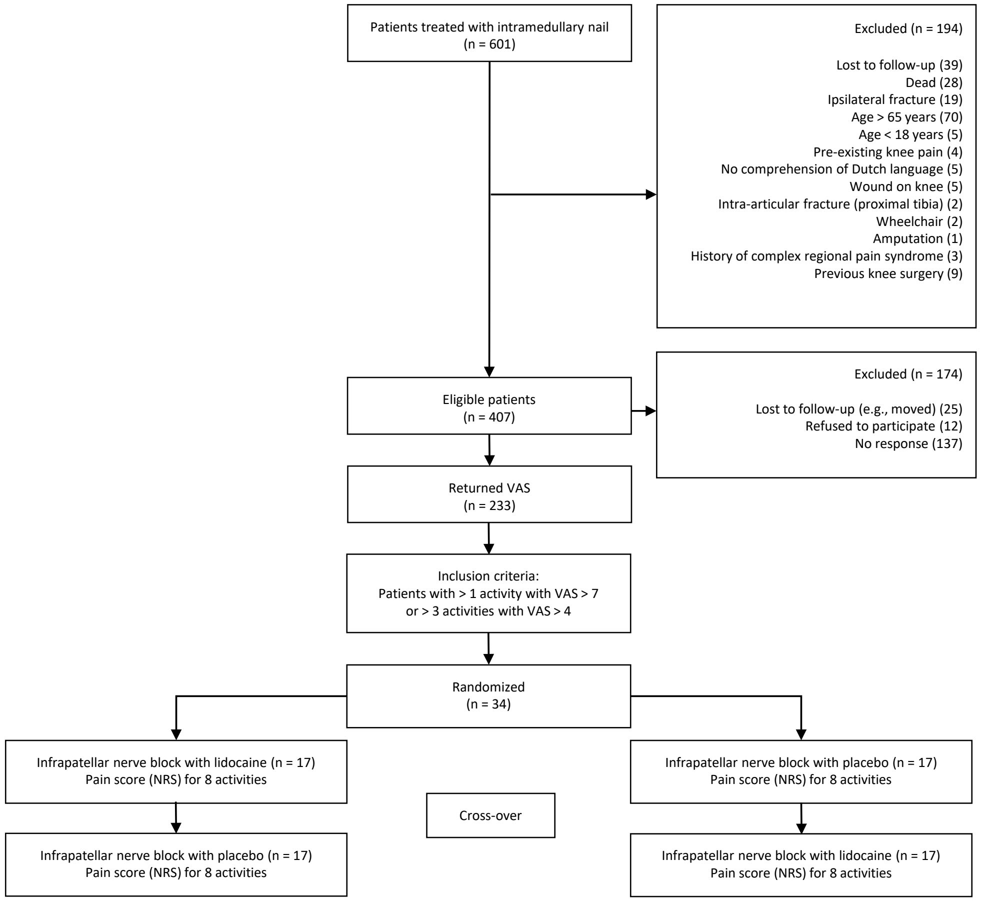

Figure 8.1. Patient selection, allocation and study design.

Study design and assessment

Eligible patients who agreed to participate in this study were seen at the outpatient clinics of the participating hospitals. Trauma characteristics, data concerning the initial procedure and nail removal were gathered retrospectively.

Length of the longitudinal incision was measured on a flexed knee in mm using a tape measure and localization of the incision was noted (on patellar tendon or medial to patellar tendon). Sensory disturbances (numbness, hypesthesia, allodynia) in the area of the infrapatellar nerve (anterior and lateral aspect of the knee) were tested using a cotton swab, comparing the non-operated leg with the operated leg and the surrounding dermatomas. Baseline pain (T0) was scored using an NRS during 8 activities, which were all supervised by an examiner (SJMK or MSL). The NRS measures pain severity by asking the patient to select a number (from 0 to 10) to represent how severe the pain is, where 0 represents "no pain" and 10 represents "worst pain possible." This rating scale has shown to

be valid, reliable, and appropriate for use in clinical practice,[10,11] is responsive in patients with chronic nociceptive or neurogenic pain,[12] and the minimally clinical important change has been determined in patients with chronic musculoskeletal pain.[13,14] If a patient was not able or willing to perform an activity it was noted as a missing value.

Equal randomization of the treatment sequence was performed with use of a random-number generator. The allocated sequence was kept in sealed envelopes. Randomization and preparation of the envelopes by a secretary who had no involvement in the trial. Upon each patient's enrollment into the study, the next consecutively numbered envelope was opened by an outpatient nurse. Lidocaine 2% and sodium chloride 0.9% (saline) were used for the nerve blocks. 2 syringes were prepared, marked with number 1 or 2 according to the allocation, and checked by a doctor not involved in the trial. The name and date of birth of the participant were written on the envelope. As both fluids were colorless and odorless, both patient and examiner remained unaware of which treatment was administered.

An infrapatellar nerve block was performed freehand by depositing 5 mL of the solution in a fan-like manner subcutaneously between the medial surface of the medial femoral condyle and the medial aspect of the patellar tendon, including the incision. After 5 minutes patients completed the 8 activities under supervision and NRS scores were subsequently obtained (T1). Thereafter, each patient crossed over and was injected with the alternate treatment (T2). Time between injections (wash-out period) was approximately 30 minutes. Kneeling is the most frequently and painful activity reported after tibial nailing.[15-18] Therefore, the primary endpoint was the change in pain intensity during kneeling after infrapatellar nerve block with lidocaine and placebo, measured using an NRS. Secondary outcomes were changes in pain intensity after each nerve block as measured using an NRS during the 8 activities.

Sample-size calculation

A mean NRS of 7 for kneeling pain in patients with chronic anterior knee pain after tibial nailing was used for sample-size calculation.[14] A change in pain intensity of >30% was considered clinically meaningful.[13,14] Using a 2-sided test, an α level of 0.05, and a power of 80%, 34 patients were needed to be enrolled.

Statistics

Normally distributed continuous data are presented as mean (SD). Skewed data are presented as median (range). Differences between the 2 groups were tested using Student's t-test (normal distribution) or Mann–Whitney U test (skewed distribution) for continuous variables. The method described by Hills and Armitage for two-period cross-over clinical trials was applied.[19] Treatment effect was calculated with (T1–T0) – (T2–T1) for the lidocaine–placebo sequence group and (T2–T1) – (T1–T0) for the placebo–lidocaine sequence group. Period effect (the response to a treatment during the second period is not influenced by the treatment which was given during the first period) was calculated with (T1–T0) – (T2–T1) for both groups. Both treatment effect and period effect were analyzed using Mann–Whitney U test (Hills and Armitage 2004). In cases where a period effect was present, the results from the first nerve block only were analyzed. $p<0.05$ was considered statistically significant. Data analysis was performed using SPSS version 25.0 for Windows (IBM Corp, Armonk, NY, USA).

Ethics, registration, funding, and potential conflicts of interest

Approval was obtained from the central medical research ethics committee and the institutional board of all participating hospitals (NL34510.008.11/P1142 2016/07/20). The study was registered with the Dutch trial registry (NTR4628; Nederlands Trial Register; http://www.trialregister.nl). Written informed consent was obtained from all patients. Participants did not receive compensation of any kind. The study was not funded by any source. The authors have no competing interests to declare.

Results

Patient characteristics

Baseline demographics, length of the incision, placement of the incision, and sensory disturbances of the infrapatellar nerve are displayed in Table 8.1. Median age was 46 years (18–62). Median follow-up was 86 months (6–168). 85% of the patients showed signs of injury to the infrapatellar nerve (numbness, hypesthesia, or allodynia).

Pain scores

All patients received the infrapatellar nerve block according to group allocation. Pain scores at baseline (T0), after the first nerve block (T1), and after the second nerve block (T2) are

Table 8.1. Baseline characteristics.

Factor	Lidocaine group (n=17)	Placebo group (n=17)
Male	9	10
Age, median (range)	40 (22-62)	38 (18-60)
AO/OTA fracture classification type		
A	7	8
B	9	7
C	1	2
Months after tibial nailing, median (range)	80 (6-168)	67 (11-168)
Tibia nail removed	9	12
Length of longitudinal infapatellar incision (mm), mean (SD)	58 (17)	58 (12)
Placement of incision		
medial to patellar tendon	2	2
midbundle of patallar tendon	15	15
Sensory disturbances infrapatellar nerve	15	14

displayed in Table 8.2. Kneeling was the most painful activity, followed by squatting. Some participants were not able or willing to perform all 8 activities.

Treatment effects (decline in median pain scores) were significant for kneeling ($p=0.02$), squatting ($p=0.03$) and sitting with bent knees ($p=0.001$). However, a period effect was present for the primary endpoint kneeling (Table 8.2), meaning the intervention exerted a different effect in the first period (T1–T0) than in the second period (T2–T1). We therefore chose to additionally analyze the results from the first nerve block (T1–T0), like a randomized trial comparing 2 groups.

For kneeling a significant decline in median pain scores remained after a nerve block with lidocaine compared with placebo (–4.5 [–10 to –1] versus –1 [–9 to 2]; $p=0.002$). There was no statistically difference between the groups during squatting, sitting with bent knees, jumping, walking stairs, running, walking, and rest (data not shown).

Discussion

The purpose of this study was to compare changes in knee pain after a subcutaneous lidocaine block of the infrapatellar nerve or placebo in patients with chronic anterior knee pain after tibial nailing. For kneeling a significant reduction in pain scores was found after an infrapatellar nerve block with lidocaine.

The effect of lidocaine usually lasts about 1–2 hours and with a wash-out period of about 30 minutes one can presume that the effect of the lidocaine injection persists during the second treatment period. We expected that pain scores in the lidocaine-first group would reach their utmost lowest levels after injection and only minimal changes would occur after the second injection with saline. Pain scores in the placebo first group were expected to decline only minimally after the first injection and decline further after lidocaine injection; a difference in change scores would then still be observed. However, data analysis showed a period effect for the primary endpoint, meaning the effect of

Table 8.2. Change in pain score after nerve block with lidocaine and placebo. Values are presented as median (range).

Activity	n[a]	Lidocaine	Placebo	n[a]	Placebo	Lidocaine	Treatment effect[b]	Period effect[b]
Kneeling	14	-4.5 (-10 to -1)	0 (-4 to 1)	16	-1 (-9 to 2)	-1.5 (-8 to 2)	0.02	0.004
Squatting	14	-3 (-9 to 1)	0 (-4 to 9)	15	-1 (-9 to 1)	0 (-7 to 2)	0.03	0.09
Sitting with bent knees	15	-3 (-7 to 0)	0 (-1 to 1)	17	-2 (-6 to 0)	0 (-7 to 9)	0.001	1.0
Jumping	11	-1 (-6 to 2)	0 (-1 to 1)	12	-1 (-3 to 1)	-1 (-3 to 1)	0.09	0.3
Walking on stairs	17	0 (-6 to 2)	0 (-1 to 1)	17	0 (-5 to 2)	0 (-4 to 3)	0.4	0.4
Running	11	0 (-5 to 2)	0 (-3 to 8)	11	0 (-3 to 1)	0 (-5 to 0)	0.6	0.8
Rest	17	0 (-1 to 1)	0 (-1 to 1)	17	0 (-1 to 6)	0 (-3 to 1)	0.2	0.1
Walking	17	0 (-5 to 1)	0 (-1 to 2)	17	0 (-4 to 4)	0 (-5 to 3)	0.5	0.4

[a] not all patients performed all activities; [b] Mann-Whitney U.

the treatment was different in the first period (T1–T0) from the effect in the second period (T2–T1). This can easily be explained by the short wash-out period. Also, both the patient and the examiner were blinded to the treatment given. Due to the local effect lidocaine has on the skin, patients may recognize this effect. This affects true blinding and might also have affected the pain scores.

Although pain during kneeling was reduced in both groups, pain was not totally diminished and no statistically significant reduction was seen for pain during the other activities (squatting, sitting with bent knees, jumping, running, walking on stairs, walking, and at rest). A possible explanation is that not all patients were able or willing to do these activities, which affected the statistical power. Moreover, the starting pain level was lower than in other activities, thus a smaller effect size can be expected. The study could be underpowered for these activities; however, they were not the primary outcome. In some patients, pain can be multi-modal and might as well have originated from intra-articular injury[20] or irritation of Hoffa's fat pad.[21]

Knee pain is a common complaint after intramedullary nailing for tibial shaft fractures. In this study 79 of 233 patients (34%) who returned their NRS indicated they had either moderate or severe knee pain during several activities after a median follow-up of 7.1 years (0.5–14). Although there might be some selection bias due to selective response to the initial questionnaire, this percentage is in concordance with the long-term results of Lefaivre et al.[2] and Leliveld and Verhofstad[3,] who respectively reported 29% and 38% of chronic knee pain after tibial nailing after a median follow-up of 14 and 7 years.

Kneeling pain is frequently mentioned to be the most painful activity.[15-18] In a randomized trial comparing 2 different incisions from Toivanen et al.[16] 62% of the patients stated kneeling pain as being most painful. The mean visual analogue score (0–100 mm) for kneeling pain in these patients was 31 mm (transtendinous approach) and 44 mm (paratendinous approach). In a retrospective study Court-Brown et al.[15] even reported kneeling pain as the most painful activity in 92% of their patients, followed by squatting (61%). The average scores for these activities on a 10-point analogue scale were respectively 3.1 and 3.3. The fact that kneeling pain scores in our study are higher (median NRS of 8.0) is due to the fact that patients were selected based on their pain scores (scores of 4 or higher for at least 3 activities or 7 and higher for at least one activity).

We detected sensory disturbances in the area of the infrapatellar nerve (anterior and lateral aspect of the knee) in 29/34 of the patients. Iatrogenic injury to the infrapatellar nerve is one of many concepts regarding the origin of anterior knee pain after tibial nailing. The course of the infrapatellar nerve makes it susceptible to iatrogenic injury during nail insertion, especially when longitudinal infrapatellar medial and midline incisions are used.[9] Long-lasting sensory deficits at the anterior aspect of the knee are described after tibial nailing[2,3,22] and a correlation was found with anterior knee pain after tibial nailing.[3] Nahabedian and Johnson[23] performed a selective infrapatellar nerve denervation in 9 patients with chronic knee pain after blunt trauma to the knee and total knee replacement. Median pain scores (NRS 0–10) reduced from 8.0 (range 7–10) at baseline to 3.0 (range 0–6)

after the denervation and they conclude that selective denervation is a beneficial procedure in selected patients with neuromatous knee pain. An infrapatellar nerve block with lidocaine in our study showed a significant difference in change of pain intensity during kneeling in patients treated with an intramedullary nail, compared with a nerve block with placebo. Because the infrapatellar nerve solely provides sensation of the skin at the antero-lateral aspect of the knee, an anesthetic block with lidocaine can diminish cutaneous neuropathic pain in this region[23,24] but not pain related to intraarticular injury.

Although pain scores declined for all activities at the end of the study, actual function and effect on function were not assessed. Sudden improvement of functional outcome was, however, not expected in patients who sustained knee pain for several years. Long-term improvement in function after infrapatellar nerve block has been reported though,[24] as has long-term pain relief after denervation of the infrapatellar nerve.[8,23]

The incidence of persisting anterior knee pain after tibial nailing is high and we provide arguments for the hypothesis that iatrogenic injury to the infrapatellar nerve contributes to this problem. Patients suffering from this complication who response well to an infrapatellar nerve block with lidocaine might benefit from denervation.[8,23,24] Based on anatomical studies a transverse or oblique incision would yield the least chance of injury to or entrapment of the infrapatellar nerve.[6,9,25] Alternatively, the suprapatellar approach for tibial nailing avoids the risk zone for infrapatellar nerve injury[9] and studies have reported low knee pain scores and good functional results after this approach.[26-28]

In summary, compared with placebo, an infrapatellar nerve block with lidocaine was more effective in reducing pain during kneeling in patients with chronic knee pain after tibial nailing through a longitudinal infrapatellar incision. Our data support the contention that kneeling pain after tibial nailing is a peripheral nerve-related problem.

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Chapter 9

The surgical anatomy of the infrapatellar branch of the saphenous nerve in relation to incisions for anteromedial knee surgery

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Abstract

Background

Iatrogenic injury to the infrapatellar branch of the saphenous nerve is a common complication of surgical approaches to the anteromedial side of the knee. A detailed description of the relative anatomic course of the nerve is important to define clinical guidelines and minimize iatrogenic damage during anterior knee surgery.

Methods

In twenty embalmed knees, the infrapatellar branch of the saphenous nerve was dissected. With use of a computer-assisted surgical anatomy mapping tool, safe and risk zones, as well as the location-dependent direction of the nerve, were calculated.

Results

The location of the infrapatellar branch of the saphenous nerve is highly variable, and no definite safe zone could be identified. The infrapatellar branch runs in neither a purely horizontal nor a vertical course. The course of the branch is location-dependent. Medially, it runs a nearly vertical course; medial to the patellar tendon, it has a –45° distal-lateral course; and on the patella and patellar tendon, it runs a close to horizontal-lateral course. Three low risk zones for iatrogenic nerve injury were identified: one is on the medial side of the knee, at the level of the tibial tuberosity, where a –45° oblique incision is least prone to damage the nerves, and two zones are located medial to the patellar apex (cranial and caudal), where close to horizontal incisions are least prone to damage the nerves.

Conclusions

The infrapatellar branch of the saphenous nerve is at risk for iatrogenic damage in anteromedial knee surgery, especially when longitudinal incisions are made. There are three low risk zones for a safer anterior approach to the knee. The direction of the infrapatellar branch of the saphenous nerve is location-dependent. To minimize iatrogenic damage to the nerve, the direction of incisions should be parallel to the direction of the nerve when technically possible.

Clinical Relevance

These findings suggest that iatrogenic damage of the infrapatellar branch of the saphenous nerve can be minimized in anteromedial knee surgery when both the location and the location-dependent direction of the nerve are considered when making the skin incision.

Introduction

The infrapatellar branch of the saphenous nerve is a sensory nerve innervating the anterior aspect of the knee, the anterolateral aspect of the proximal part of the lower leg, and the anteroinferior part of the knee joint capsule.[1,2] The infrapatellar branch of the saphenous nerve originates from the saphenous nerve and arises distal to the adductor canal.[3] It pierces the sartorius muscle, after which it runs a superficial course and generally forms two branches.[4,5] Both branches cross the patellar tendon in a transverse way to form the infrapatellar plexus.[1,6] These small superficial branches are at risk for transection, especially when longitudinal surgical incisions are made.

Injury to the infrapatellar branch of the saphenous nerve usually results in numbness on the anterior aspect of the knee and the proximal lateral part of the lower leg. Neuropathic pain and symptomatic neuroma can develop even without noxious stimuli.[7,8] A relationship between damage to the infrapatellar branch of the saphenous nerve and reflex sympathetic dystrophy has been described.[9-11] Finally, as the infrapatellar branch of the saphenous nerve innervates the anterior medial ligaments of the knee, it is important for proprioception[12] and thus knee stability and balance. Impaired joint proprioception might in theory contribute toward osteoarthritis.[13-15]

After total knee arthroplasty, numbness due to damage of the infrapatellar branch of the saphenous nerve has been reported in 55% to 100% of patients when a longitudinal incision was used.[16,17] Ojima et al. found significantly fewer subjectively and objectively assessed areas of hypoesthesia when a transverse incision was used. Furthermore, they found significantly more patients who were able to kneel and stated this might partially be due to less pain and numbness as the infrapatellar nerve remained intact.[18]

Damage to the infrapatellar branch of the saphenous nerve has also been reported after surgical meniscectomy (up to 28% of patients report irritating paresthesia[19]), in arthroscopy[6,9,20], after anterior cruciate ligament reconstruction (anesthesia was found in 37% to 86% of patients[21,22]), and even in resections of the prepatellar bursa.[23,24] Although damage to the infrapatellar nerve in tibial nailing has been mentioned by only a few authors[25,26], it can be a causative factor for chronic anterior knee pain[27-29] and a frequent and invalidating complication in tibial nailing (10% to 86%)[30,31] and retrograde femoral nailing (26%).[25]

The clinical importance of damage to the infrapatellar branch of the saphenous nerve is amplified by the fact that recent studies on arthroplasty[32] and tibial nailing[29] have shown that patient satisfaction is inversely correlated to the presence of injury to the infrapatellar nerve.

Although the infrapatellar branch of the saphenous nerve is a known anatomic structure, its relevance in daily clinical practice is underestimated as of yet, since longitudinal incisions in the anteromedial region of the knee are still commonly used. Therefore, the purpose of this study was to further describe and visualize the relative anatomic course of the infrapatellar branch of the saphenous nerve in the flexed knee to provide the surgeon with a safe zone and clinical guidelines to minimize iatrogenic injury during anterior knee surgery.

Materials and methods

Materials

Twenty unpaired embalmed legs (ten left and ten right) from adult donors were dissected in the knee region to study the course of the infrapatellar branch of the saphenous nerve. The specimens had been flushed with AnubiFiX[33] (Department of Neuroscience and Anatomy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands) to regain joint flexibility and were embalmed with a mixture of 6% formaldehyde and 5% phenol. None of the limbs showed macroscopic signs of disease or scarring. The saphenous nerve and the main infrapatellar branch(es) of the nerve were localized by careful dissection and followed peripherally with a magnifying glass (5 dioptre) until branches were too small for further dissection (<1 mm). All knees were then flexed into a 90° angle, simulating the intraoperative position for most anteromedial knee surgical procedures. Osseous landmarks (Figure 9.1) were placed as a reference for measurements and calculations.

Measurements

The distance between the apex of the patella and the tibial tuberosity (the most distal part of the patellar apex and the palpatory center of the tuberosity) was measured. From the apex of the patella, three reference lines (at 90°, 45°, and 0° relative to the line between the apex of the patella and the tibial tuberosity) were projected over the knees for distance measurements to the closest branch of the infrapatellar nerve (Figure 9.2). At the intersection of an infrapatellar branch of the nerve with the projected lines, a pin was placed and the distance to the patellar apex was measured along the circumference of the limb. The position of the nerve was also related to the distance between the apex of the patella and the tibial tuberosity. When the nerve was split into two or more branches, the closest branch to the reference point was used for calculations.

The angle of the nerve related to the midline of the patellar tendon was measured. When more than one branch crossed the patellar tendon, the angles were also noted.

Distances were measured using calipers, and angles were measured using a goniometer. Measurements were repeated, and the mean of both measurements was used for further analysis. Statistical tests were performed using SPSS software (version 17; SPSS, Chicago, Illinois). Nonparametrical tests were used if variables were not normally distributed.

Computer-Assisted Surgical Anatomy Mapping (CASAM)

The novel anatomy-mapping tool CASAM[34-37] was used to visualize and evaluate the complex and variable anatomy of multiple specimens and to visualize the dissected infrapatellar branch of the saphenous nerve in one image of a knee with average dimensions. First, the knees were photographed, using a standardized protocol, with a Canon 350D camera (Canon USA, Lake Success, New York) with a Canon EF-S 18-55-mm lens (Canon USA). Then, nonosseous landmarks were calculated from osseous landmarks to delineate the different shapes of the individual knees (Figure 9.1).

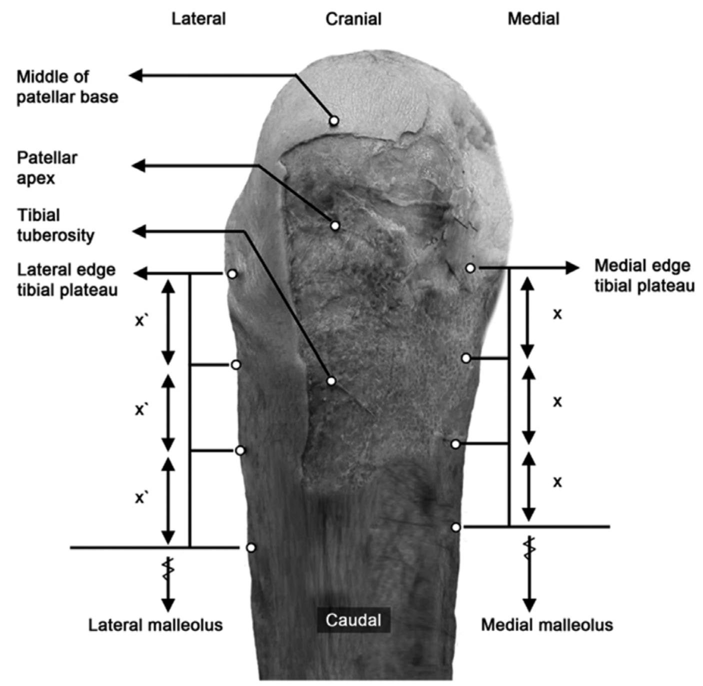

Figure 9.1. Anatomical landmarks. Osseous landmarks include the patellar apex, the highest, most prominent palpable point of the tibial tuberosity; the medial and lateral edge of the tibial plateau; and the medial and lateral malleoli. Nonosseous landmarks are placed at one-tenth of the distance between the tibial plateau and both the medial (X) and lateral (X′) malleoli. The cranial three landmarks on the medial and lateral side are used for CASAM (computer-assisted surgical anatomy mapping) calculations. Test-retest reproducibility of all landmarks was determined by two authors.

The average location of each landmark was calculated from all specimens. Then, with use of Magic Morph 1.9510 software (EffectMatrix Software Studio)[38], each specimen in each original photograph was reshaped (warped) to match the calculated average shape. A thin plate spline was used as a warping algorithm. As the warped specimens had the same calculated average shape, the anatomy of the infrapatellar branch of the saphenous nerve of all specimens could be mapped and visualized in one averagely shaped knee. Photoshop CS4 (Adobe Systems, San Jose, California)[39] was used to highlight relevant anatomy and make renditions. The following four renditions were made:

1. All dissected infrapatellar branches of the saphenous nerve were visualized in one image (Figure 9.3-A).
2. A risk zone of 5 mm was determined and colored in each specimen. All risk zones were then compiled into one image, and a gradient of risk zones was visualized (Figure 9.3-B).
3. Zones were identified in the anteromedial aspect of the knee in which a low density of infrapatellar branches of the saphenous nerve was found (Figure 9.4).

4. A grid of squares was placed over the computerized image depicting all infrapatellar branches of the saphenous nerve (Figure 9.3). Within each individual square, the direction of all branches was measured in relation to a horizontal line. Each square was given a color corresponding to the average direction of the branches within that square. The result is a grid of squares depicting the location-dependent direction of infrapatellar branches of the saphenous nerve (Figure 9.5).

Comparison with published literature

A PubMed/MEDLINE search was performed using the search terms “infrapatellar branch of the saphenous nerve” OR “infrapatellar branches of the saphenous nerve.” This search revealed forty-nine titles. Abstracts were judged for relevance. In case of doubt, full articles were read and checked for cross-references. Three anatomical studies on the course of the infrapatellar branch of the saphenous nerve were selected. The anatomic risk and/or safe zones described by Tifford et al.[20] (twenty flexed fresh-frozen knees), Mochida and Kikuchi[6] (129 extended, embalmed knees), and Ebraheim and Mekhail[1] (twenty-eight flexed knees) were delineated in three new embalmed specimens. The knees were then photographed (flexed in 90°), and data were mapped with CASAM and compared with the location of the dissected infrapatellar branch of the saphenous nerve (Figures 9.3 and 9.6).

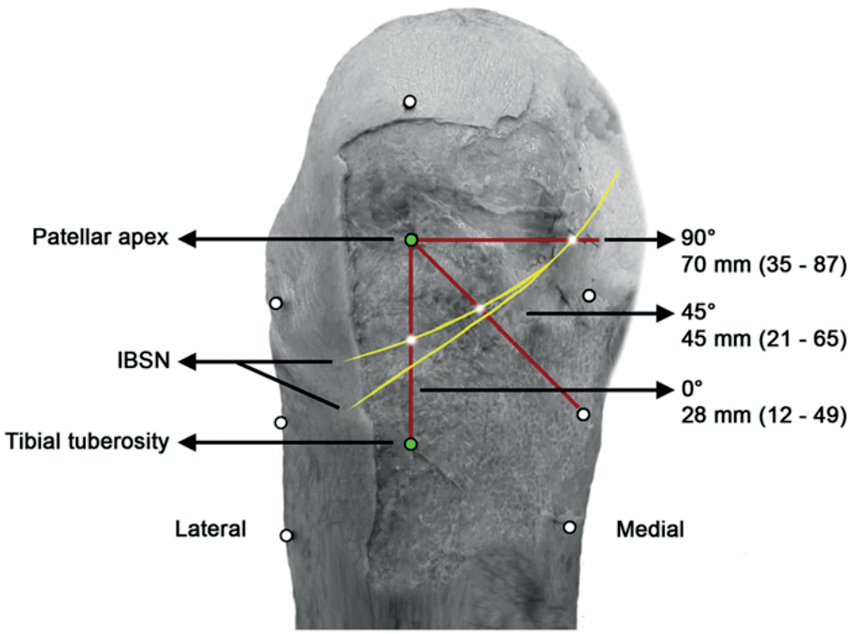

Figure 9.2. Measurements of the distance to the closest infrapatellar branch of the saphenous nerve (IBSN) over three reference lines are shown. The mean distance was 70 mm (range, 35 to 87 mm) over the 90° reference line, 45 mm (range, 21 to 65 mm) over the 45° reference line, and 28 mm (range, 12 to 49 mm) over the 0° reference line.

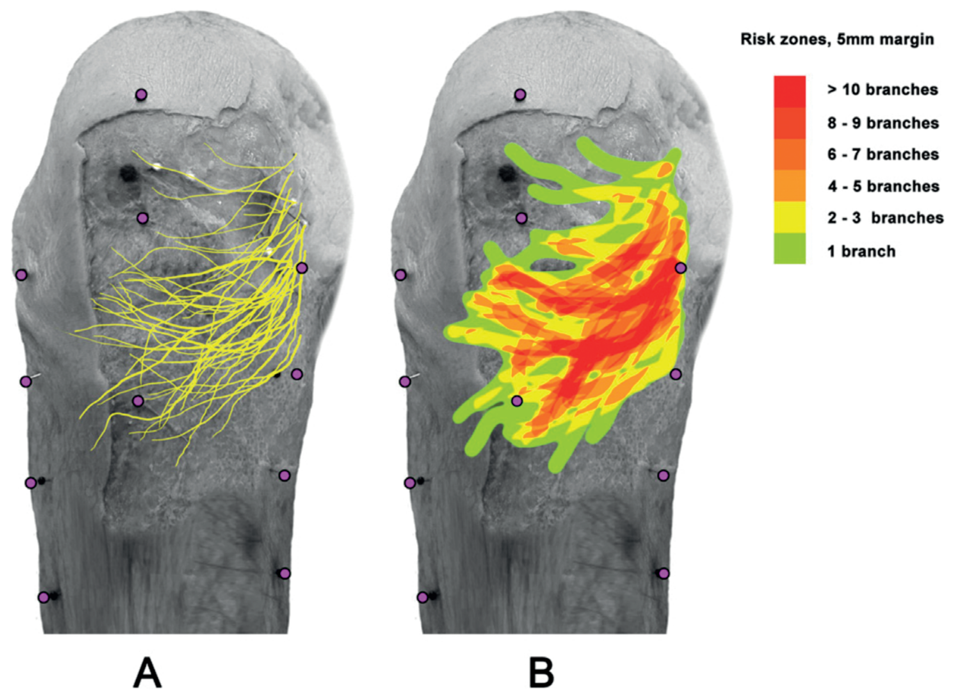

Figure 9.3. The location of the infrapatellar branch of the saphenous nerve with CASAM-generated photographs showing the anatomy of the infrapatellar branch of the saphenous nerve in a knee with average dimensions (n = 20). Fig. 3-A Distribution of the infrapatellar branches. Fig. 3-B A 5-mm margin around each dissected nerve.

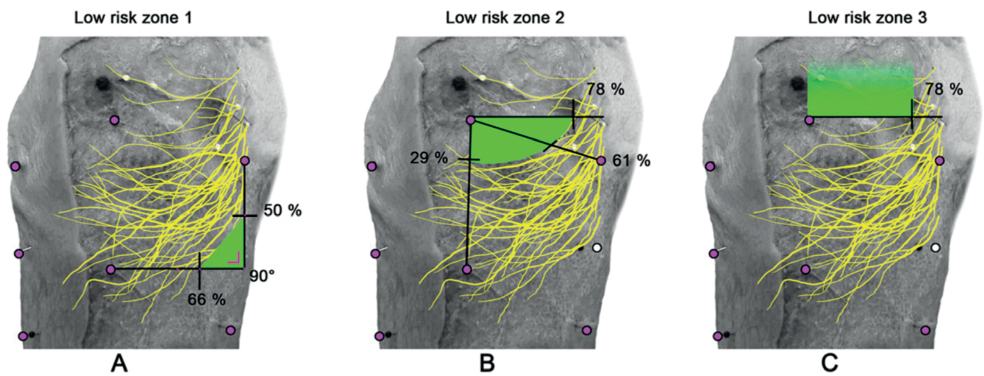

Figure 9.4. Suggested low risk zones. Figure 9.4-A Low risk zone 1. A vertical line is projected downward from the medial edge of the tibial plateau and a horizontal line from the tibial tuberosity to the medial side of the knee. The zone is located distally from 50% of the vertical line and medially from 66% of the horizontal line. Figure 9.4-B Low risk zone 2. The zone extends from the patellar apex up to 29% of the distance to the tibial tuberosity, up to 61% of the distance to the medial edge of the tibial plateau, and up to 78% of the distance to a projected vertical line from the medial edge of the tibial plateau. Figure 9.4-C Low risk zone 3. Medially and cranially, the zone extends over a horizontally projected line to 78% of the distance between the patellar apex and the level of the medial edge of the tibial plateau.

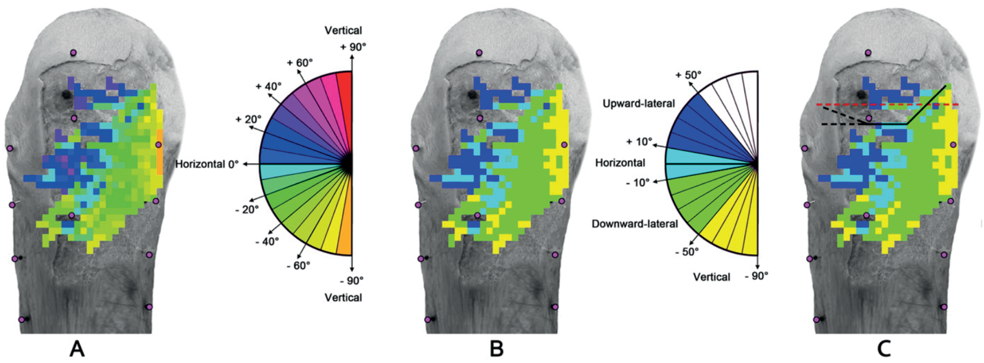

Figure 9.5. The location-dependent direction of the infrapatellar branch of the saphenous nerve. Figure 9.5-A The location-dependent direction of the nerve, divided in 10° increments. Figure 9.5-B The location-dependent direction of the nerve, divided in vertical (–90° to approximately –50°), downward-lateral (–50° to approximately –10°), horizontal (–10° to approximately 110°), and upward-lateral (110° to approximately 150°) directions. Fig. 9.5-C The red dashed line indicates the transverse incision as proposed by Ojima et al.18: "A transverse incision was made at a 90° knee flexion at the level of the lower end of the patella, along the skin crease." The black line shows an adaptation to the incision line proposed by Ojima et al. To make the incision mostly run perpendicular to the infrapatellar branch of the saphenous nerve, the medial part runs in a 45° downward direction. The middle, horizontal part of this incision is located in safe zone 2. The lateral part either runs horizontally or in an upward 20° angle.

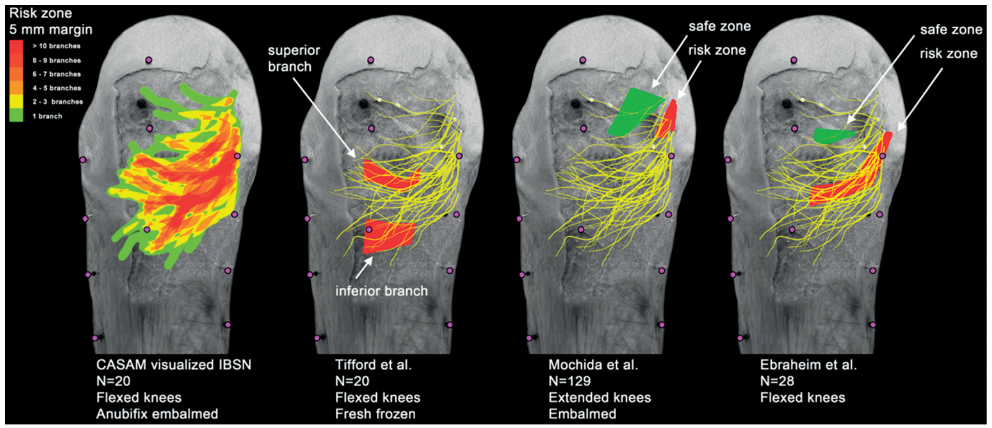

Figure 9.6. Comparison with reports in the literature. The first image of the infrapatellar branch of the saphenous nerve (left) was made with CASAM visualization and a 5-mm margin and shows the gradient of low risk and high risk zones. The second image shows the findings of Tifford et al.[20], with red indicating risk zones for both the superior and inferior branch of the nerve. The third image shows the findings in the study by Mochida and Kikuchi[6], with red indicating the risk zone and green, the safe zone. The fourth image (right) shows the findings of Ebraheim and Mekhail[1], with red indicating the risk zone and green, the safe zone.

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No external source of funding was used for this research.

Results

Topographic anatomy

The median distance between the apex of the patella and the tibial tuberosity was 64 mm (range, 46 to 78 mm). The infrapatellar branch of the saphenous nerve consisted of one branch in two specimens, of two branches in twelve specimens, and of three branches in six specimens. The distance between the apex of the patella and the points along the course of the uppermost infrapatellar branch of the saphenous nerve is demonstrated in Figure 9.2. In all twenty specimens, the infrapatellar branch of the saphenous nerve crossed the 90° reference line at a mean distance of 70 mm (range, 35 to 87 mm). In nineteen specimens, the infrapatellar branch crossed the 45° reference line at a mean distance of 45 mm (range, 21 to 65). In sixteen specimens, the infrapatellar branch crossed the 0° reference line at a mean distance of 28 mm (range, 12 to 49). There was no significant difference between left and right knees for these distances (p=0.256, p=0.870, and p=0.447, respectively). Sixteen proximal branches cross the patellar tendon, and four of them are located on the proximal third; ten, on the middle third; and two, on the distal third of the patellar tendon. A total of twenty-four branches (in sixteen knees) crossed the sagittal plane of the center of the patellar tendon. On average, these branches run a nearly horizontal course in a -4° downward-lateral direction (range, +28° upward-lateral direction and -58° downward-lateral direction). There was no significant difference between left and right knees for these angles (p=0.052).

Computer-assisted surgical anatomy mapping

The dissected infrapatellar branches of the saphenous nerve of all twenty specimens were visualized in a knee with average dimensions (Figure 9.3-A). The location of the branches demonstrates much variation. The main trunks are located at the medial side of the knee, near the medial edge of the tibial plateau. Branching mostly occurs on the medial side of the knee at a midpatellar tendon level. Branches then follow a more horizontal course toward the patellar tendon.

When the 5-mm margins around all twenty dissected infrapatellar branches of the saphenous nerve were combined, possible safe zones as well as risk zones (with a higher density of branches) could be identified (Figure 9.3-B). The location of infrapatellar branches of the saphenous nerve is extremely variable, and there is no definite or unique safe zone in which iatrogenic nerve damage can be prevented completely. However, there are three distinct areas with a low (or lower) density of infrapatellar branches of the saphenous nerve (Figure 9.4).

The first area is located on the medial side of the knee at the level of the tibial tuberosity (Figure 9.4-A). The boundaries are formed by a virtual vertical line downward from the medial edge of the tibial plateau and a horizontal line from the tibial tuberosity to the medial side of the knee. This zone is located distally from 50% of the vertical line and medially from 66% of the horizontal line.

The second zone is located medial and distal to the patellar apex (Figure 9.4-B). Distally, it extends to 29% of the distance between the patellar apex and the tibial tuberosity. Then it extends to 61% of the distance between the patellar apex and the medial edge of the tibial plateau. Medially, it extends over a horizontally projected line to 78% of the distance between the patellar apex and the level of the medial edge of the tibial plateau.

The third zone is located medial and proximal to the patellar apex (Figure 9.4-C). Medially, it extends over a horizontally projected line to 78% of the distance between the patellar apex and the level of the medial edge of the tibial plateau.

The location-dependent direction of the infrapatellar branches of the saphenous nerve is shown in Figure 9.5. At the medial edge of the knee, the main trunks of the infrapatellar branches of the saphenous nerve run a close to vertical course. Most branches then continue to follow a curved course, and medial to the patellar tendon, branches run, on average, in a distal-lateral direction. At the medial edge of the patellar tendon, the branches run a close to horizontal course. Then, over the patellar tendon, infrapatellar branches of the saphenous nerve curve to proximal and mostly run a proximal-lateral course. However, branches located near the tibial tuberosity do not run a curved course and continue to run in a distal-lateral direction. The average direction of the infrapatellar branches was -45° in low risk zone 1, -8° in low risk zone 2, and +8° in low risk zone 3 (Figure 9.4).

Comparison with the literature

Risk and/or safe zones described by Tifford et al.[20], Mochida and Kikuchi[6], and Ebraheim andMekhail[1] are shown in Figure 9.6. The location of the superior branch of the infrapatellar nerve described by Tifford et al. corresponds well to the superior part of the high risk zone depicted in Figure 9.3-B. However, they found the inferior branch to be located more distal than most infrapatellar branches dissected in our study. The safe zones situated medial to the patella, as described by Mochida and Kikuchi and by Ebraheim and Mekhail, mostly overlap the low risk zones 2 and 3, described in Figure 9.4. The high risk zone that Mochida and Kikuchi described is located medial to our low risk zone 3 (Figure 9.4) and overlaps the most cranial medial part of the high risk zone described in Figure 9.3-B. The high risk zone described by Ebraheim and Mekhail overlaps most of the high risk zone depicted in Figure 9.3, but does not extend to the middle of the patellar tendon.

Discussion

In accordance with previous anatomical studies[1,4,6], the present study shows that variation in the topographic anatomy of the infrapatellar branch of the saphenous nerve is high. Therefore, no safe zones were defined, and the nerve is at risk for transection at the initial surgical incision.

However, three low risk zones were identified; in these zones, fewer infrapatellar branches of the saphenous nerve were located, and incorporation of these zones into daily clinical practice may reduce complications related to the nerve. Low risk zones 1 and 3 are relatively rare sites for anteromedial approaches of the knee. Zone 1, however, provides a safer entry site in open meniscectomy and tendon-harvesting. In addition, medial portal placement during arthroscopy might be possible via this area, but the technical feasibility needs further research as it is located distal to the conventional site. Low risk zone 2 can be used as an entry site for a prepatellar bursectomy. Similarly, low risk zones 2 and 3 provide for a safer approach in tibial nailing and retrograde nailing of the femur. In total knee arthroplasty, when the medial edges of low risk zones 2 and 3 are taken into account, the transverse approach described by Ojima et al.[18] may be even more beneficial regarding complications related to the infrapatellar branch of the saphenous nerve. Furthermore, when the location-dependent direction of the infrapatellar branch of the saphenous nerve is taken into account, a cranial deviation of the lateral and medial part of the incision, resulting in a horizontal "smile" incision just distal to the patella, might further reduce iatrogenic damage to the nerve as the incision then mostly runs perpendicular to the infrapatellar nerve (Figure 9.5-C). The proposed incision may be used, if technically feasible, in total knee arthroplasty. The medial and middle part of the proposed incision can be used in retrograde femoral nailing, tibial nailing, bursectomy, and unicompartmental arthroplasty.

The safe and risk zones described in Figures 9.3 and 9.4 correspond with reports in the literature[1,6,20], except for the location of the inferior branch as described by Tifford et al. Apart from the infrapatellar branch of the saphenous nerve, other superficial nerves such as the saphenous nerve, the sartorial branch of the saphenous nerve, the superficial femoral nerve, and the medial retinacular nerve were not dissected.

In accordance with the literature, we hypothesized that horizontal incisions lead to less iatrogenic damage and fewer subsequent postoperative complications than do longitudinal incisions.[1,6,18,20,29,40] Two recent studies have investigated the possibility of transverse or horizontal incisions for various surgical procedures on the anteromedial aspect of the knee.[18,41] A disadvantage of nonlongitudinal incisions in routine surgery on the anteromedial part of the knee is that subsequent total or partial knee replacement is mostly performed using a longitudinal incision, and the patient would have two perpendicular and crossing incisions. However, Ojima et al. showed that total knee arthroplasty using a transverse incision is technically feasible.[18] Conversely, horizontal incisions cannot be extended and are limited in both length and direction. Therefore, when further exposure for additional surgery, such as quadricepsplasty, is needed, horizontal incisions might be restrictive. Also, the medial retinacular nerve and medial cutaneous femoral nerve[42] might be at risk for transection in a horizontal skin incision.

Since no clear safe zone is identified, the direction of the infrapatellar branches of the saphenous nerve becomes more important; incisions parallel to the nerves exert less risk of damage. Although multiple studies have suggested that horizontal incisions should be made in the anteromedial aspect of the knee, the infrapatellar branch only runs a horizontal course just medial to the patellar tendon. Anteromedially, the infrapatellar branch mostly runs in a downward-lateral angle of -30°, favoring oblique over horizontal incisions. At the medial border of the knee, the infrapatellar nerve, on average, runs a close to vertical course, and longitudinal incisions should be favored. However, in this area, there is a high risk of damage to the infrapatellar branch of the saphenous nerve. On the proximal two-thirds of the patellar tendon and on the patella, the infrapatellar branch mostly runs in an upward-lateral direction of +20°.

In low risk zone 1, the infrapatellar branchof the saphenous nerve runs in a -45° downward-lateral direction, and a parallel oblique incision would be optimal in this area. In low risk zones 2 and 3, a close to horizontal incision would minimize the risk of iatrogenic damage to the infrapatellar branch.

In contrast to previous anatomic studies, the complete course of the infrapatellar branch of the saphenous nerve over the anteromedial side of the knee was mapped and measured using CASAM and was also compared with reports in the current literature. Data gathered with CASAM can be made available via a web-based version, potentially allowing the surgeon to upload a photograph and/or radiographs of a patient. Then, the dissected infrapatellar branch of the saphenous nerve, low risk zones, and location-dependent direction can be displayed over the photograph of the patient's knee.

In conclusion, the infrapatellar branch of the saphenous nerve is at risk for iatrogenic damage in any surgery on the anteromedial aspect of the knee, especially when longitudinal incisions are used. Three low risk zones for iatrogenic nerve injury were identified: one is located on the medial side of the knee, at the level of the tibial tuberosity, in which a -45° oblique incision is least prone to damage the infrapatellar branch, and two zones are located medial to the patellar apex (cranial and caudal), in both of which nearly horizontal incisions are least prone to damage the infrapatellar branch. To minimize iatrogenic damage to the infrapatellar branch of the saphenous nerve, the direction of incisions should be parallel to the direction of the nerve when technically possible.

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9

Chapter 10

The effect of transverse versus longitudinal incisions on anterior knee pain after tibial nailing (TRAVEL); a multicenter randomized trial with 1 year follow-up

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Abstract

Introduction

Anterior knee pain is common after tibial nailing and its origin is poorly understood. Literature suggests it may be related to infrapatellar nerve injury. The aim of this study was to compare the effect of a transverse (potentially infrapatellar nerve sparing) incision for insertion of a tibia nail versus a longitudinal incision on anterior knee pain.

Patients and methods

Adult patients with a tibial shaft fracture to be treated with an intramedullary nail were randomized to a transverse (n=68) or longitudinal incision (n=68) in multiple centers. The primary outcome measure was kneeling pain based on a Numeric Rating Scale (NRS). Secondary outcome measures included knee pain during daily activities, functional outcome (Short Musculoskeletal Function Assessment (SMFA) and Lower Extremity Functional Scale (LEFS)), quality of life (Euro-QoL-5D, EQ-5D), activity resumption, complications, reoperations, and direct and indirect costs until one year after trauma.

Results

At 12 months the estimated marginal mean for kneeling pain was 2.4 (95% CI 1.6–3.2) in the transverse incision group and 3.7 (95% CI 3.0–4.5) in the longitudinal group. Regression analysis showed no significant difference between both groups over time (p=0.239 at 12 months). Knee pain scores for daily activities, functional outcome scores, and quality of life were also comparable between the groups. Signs of infrapatellar nerve injury were found less often after a transverse incision (16% versus 53%; p<0.001). The total (direct and indirect) costs per patient were €10,468 in the transverse incision group and €11,066 in the longitudinal incision group. Loss of productivity accounted for 67% and 52% of the total costs, respectively.

Conclusion

After 12 months follow-up, less iatrogenic injury to the infrapatellar nerve was observed after a transverse incision as compared to a longitudinal incision for insertion of a tibial nail. This did not result in less anterior knee pain during daily activities or improved functional outcome, quality of life, activity resumption. Number of complications and reoperations between groups were similar. Loss of productivity was the main cost driver for patients treated with an intramedullary nail.

Introduction

The treatment of choice for tibial shaft fractures is intramedullary nailing. Even after successful union, anterior knee pain remains an issue for many patients.[1] This post nailing pain can last for years.[2] Removal of the intramedullary nail can relieve anterior knee pain[3], but in a substantial number of patients, pain after nail removal persists, aggravates, or even develops in previously asymptomatic patients.[4,5] The most painful daily activities are kneeling and squatting.[6,7]

A possible anatomical source for persisting anterior knee pain after tibial nailing is injury to the infrapatellar branch of the saphenous nerve.[7,8] This subcutaneous sensory nerve innervates the anterolateral skin of the knee and lower leg. Since its branches run along the medial border of the patella and cross the patellar tendon almost perpendicular, it is at risk for iatrogenic injury during tibial nailing.[8,9] The nerve can be transected during nail insertion or it can get entrapped during skin closure and in scar tissue during wound healing. Injury to the infrapatellar nerve causes sensory deficits[7,10] and can result in painful neuroma formation.[9,11] Entrapment of the nerve may result in pain during knee flexion due to a disrupted gliding mechanism of its subcutaneous tissue and skin.[12,13]

Because the infrapatellar nerve courses almost parallel to the articular surface of the tibia, the risk of injury during tibial nailing is high, especially when a longitudinal incision is used. A transverse incision for nail insertion can be used as an alternative. Because a transverse incision is in line with the course of the infrapatellar nerve at the level of the patellar tendon, it has the potential of reducing the risk of iatrogenic injury.[8] Clinical studies comparing longitudinal and transverse incisions for hamstring tendon harvest in anterior cruciate ligament reconstruction confirm this theory.[14] In a recent study we found an infrapatellar nerve block to reduce kneeling pain in patients with chronic anterior knee pain after tibial nailing.[7] We hypothesized that a transverse incision for insertion of an intramedullary tibial nail results in less anterior knee pain compared to the use of a longitudinal incision as a result of less iatrogenic infrapatellar nerve injury. The aim of this study is to compare the effect of a transverse and longitudinal incision on anterior knee pain after tibial nailing.

Patients and methods

Setting and participants

The TRAVEL study was a multicenter, randomized study. Thirteen hospitals in the Netherlands participated. All patients aged between 16 years and 65 years presenting with an isolated tibial shaft fracture (AO/OTA-type 42) to the Emergency Department of one of the participating hospitals were included after written informed consent was obtained. Exclusion criteria were 1) polytraumatized patients; 2) concurring injury affecting treatment and recovery; 3) bilateral tibial fractures; 4) pathological or recurrent fracture of the tibia; 5) Gustilo grade C open fractures grade or open wound on knee; 6) pre-existing knee pathology (*e.g.*, menisci or cruciate ligament); 7) pre-existing functional impairment influencing rehabilitation (*e.g.*, wheelchair-bound); 8) rheumatoid arthritis; 9) bone disease resulting in delayed union (except osteoporosis); 10) problems ensuring follow-up (*e.g.*, no fixed address or cognitive impairment); and 11) insufficient comprehension of the Dutch language. The study was registered at the Netherlands Trial Register (NTR5091). The study was approved by the Medical Research Ethics Committees Erasmus MC (Ref.No. MEC-2014-335 and NL49144.078.14) and Local Boards of all participating centers. The study was supported by a grant from the AO Foundation (S-14-79L) and Osteosynthesis and Trauma Care (OTC) Foundation (2016-MVEL).

Randomization

Eligible patients were informed about the trial prior to surgery. After informed consent was obtained, patients were assigned a longitudinal or transverse incision for tibial nailing by computerized block randomization. In each block both operative techniques were equally represented. Randomization was done per site. Masking participants or investigators to allocated treatment was not possible.

Intervention

With the knee in 90 degrees flexion, a transverse incision was made from the medial to the lateral border of the palpable patellar tendon, one centimeter caudal of the apex of the patella. After mobilization of skin and subcutaneous tissue at the level of the patella tendon, the knee capsule was split longitudinally through a transpatellar or medial parapatellar approach (surgeon's preference).

Except for the direction of the incision, the procedure for the longitudinal incision group was similar. With the knee in 90 degrees flexion, a 4-5 cm longitudinal skin incision was made from the apex of the patella downwards in line with the tibial shaft, ending cranial of the tibial tuberosity.

After reaching the nail entry site the medullary canal is opened and if necessary, the shaft was reamed. The nail is inserted after proper fracture reduction (closed or open). The choice of intramedullary nail (*i.e.*, manufacturer, type of metal (titanium alloy or stainless steel) and size) was at the discretion of the operating surgeon, as well as the number of locking screws, use of an end cap and closure of the wound. The post-operative weight bearing regime was also at the discretion of the treating surgeon.

Assessment and follow-up

Follow-up data were collected during outpatient visits at 2 and 6 weeks, and at 3, 6 and 12 months after surgery. At each visit independent investigators collected clinical data, complications and interventions. Physical assessment included testing sensibility of the infrapatellar nerve and range of motion of the knee. During these visits, patients were asked to complete a set of patient-reported outcome measures (PROMs), and complete a combination of the Medical Consumption Questionnaire and Productivity Cost Questionnaire). Both questionnaires are validated by the institute for Medical Technology Assessment (iMTA) and contained detailed information on health care consumption (*e.g.*, physical therapy) and resumption of work and leisure activities.[15,16] Standard anteroposterior and lateral radiographs of the lower leg were made at the follow-up visits at 6 weeks, and 3-, 6- and 12-months post-nailing.

The primary outcome measure was pain during kneeling on a numeric rating scale (NRS 0-10) at 12 months. Secondary outcome measures were knee pain during eight daily activities (NRS 0-10), functional status (Lower Extremity Functional Scale (LEFS), Short Musculoskeletal Functional Assessment (SMFA)), the EuroQol-5D (EQ-5D), range of motion (ROM) of the knee, and the occurrence of complications with associated secondary interventions.

The Dutch SMFA consists of 53 items, each scored using a 5 points Likert scale. It is divided in three subscales: a 23-item Dysfunction lower extremity (LE) scale, a 9-item Dysfunction upper extremity (UE) scale and a 15-item Bother scale. The scores range from 0 to 100 points. Higher scores refer to greater disability. It has been validated as a measure of patient function. A validated Dutch language version was available.[17] The LEFS is a self-reported measure that consists of 20 items, including ability during walking, stair climbing, squatting, running, prolonged sitting, and hopping/jumping, each with a maximum score of 4. The total possible score of 80 indicates a high functional level. It has a high test-retest reliability and appears to be moderately responsive to clinical change in patients with anterior knee pain. A validated Dutch language version was available.[18] The EQ-5D is a validated questionnaire for measuring health-related quality of life.[19] Its use is recommended for assessing quality of life in trauma patients, especially for economic assessments.[20,21] The EQ-5D descriptive system consists of five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Scores are converted to a utility score ranging from zero to one, with lower scores indicating poorer quality of life. The EQ VAS records the respondent's self-related health status on a vertical (0-100) visual analog scale.

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At baseline, variables such as age, gender, American Society of Anesthesiologists' (ASA) classification, alcohol and tobacco consumption, comorbidities, medication use, and work and sports participation were collected. In addition, injury-related variables and intervention-related variables were collected.

Patient's medical records and a customized questionnaire were used to collect the direct medical and indirect costs and included: (1) in-hospital care costs; (2) out of hospital care costs for rehabilitation; and (3) indirect costs due to productivity loss. Cost prices were determined by bottom-up micro-costing method and all unit prices were indexed with the national consumer price index to 2018. Costs were calculated by multiplying the volumes with the corresponding unit prices (Table S10.1). During follow-up the number of days with absence from work were reported. The friction cost method was used to calculate indirect costs due to productivity loss, which assumes that initial production levels restore after some period of adaption, taking economic circumstances into account.[22]

Sample size and statistical analysis

A sample size calculation based on previous studies indicated that the mean VAS for kneeling after tibial nailing using a longitudinal incision is 44 mm (SD 38).[23] A 33% decrease in pain represents a reasonable standard for determining that a change in pain is meaningful from the patient's perspective.[24] Thus, with a two-sided alpha of 0.05 and a power of 0.80, 54 patients in each group were needed (total 108) to show a difference of at least 33% after 12 months. Assuming a 25% loss to follow-up, 136 patients were included in the study.

Data were analyzed using SPSS version 25 for Windows. Missing data were not imputed. P-values <0.05 were considered statistically significant. Outcomes for transverse incisions and longitudinal incisions were compared. Normality of continuous data was assessed using the Shapiro Wilk test. Parametric data are presented as mean and standard deviation (SD) and were compared using the Student's t test, non-parametric data are presented by median and quartiles and compared using the Mann-Whitney U-test. Results of categorical variables were analyzed using Chi-square test. Results of the regression analyses are reported as an estimated marginal mean with 95% confidence interval (95% CI).

Continuous outcomes that were repeatedly measured over time were compared between treatment groups using linear mixed-effects regression models. These multilevel models included random effects for the intercepts of the regression model and time coefficient of individual patients. The models included fixed effects for treatment group, and other covariates (open fracture, AO classification and fixation of the fibula). The interaction between treatment group and time was included in the model to test for differences between the groups over time. For each follow-up moment, the estimated marginal mean was computed per treatment group and compared post hoc using a Bonferroni test in order to correct for multiple testing. Absence of overlap in the 95% confidence interval around the marginal means was regarded as a significant difference at p<0.05. The models showed that there were no confounding effects of an open fracture, AO classification and fixation of the fibula on (functional) outcome. Therefore, the uncorrected model was used.

Results

From 9 September 2015 until 6 June 2018, 136 patients were included (Figure 10.1). In 68 patients the intramedullary nail was inserted through a transverse incision, and in 68 patients a longitudinal incision was used. After randomization three patients withdrew their consent. There were 31 missed follow-up moments in the transverse incision group, and 32 in the longitudinal incision group. The majority of patients were men (n=99; 73%), median age was 35 years (P_{25}-P_{75} 24–53) and most were classified as ASA 1 (n=109; 80%). Baseline patient and fracture characteristics for both groups are displayed in Table 10.1. With regard to the surgical characteristics, the median time for the surgical procedure was 94 minutes (70–125) in the transverse incision group and 83 (67-109) minutes in the longitudinal incision group (p=0.264). In both groups one patient had a fasciotomy. Median hospital length of stay (HLOS) was 3 days (P_{25}-P_{75} 2–5) in the transverse group and 4 days (P_{25}-P_{75} 3–5) in the longitudinal group (p=0.205). All patients were discharged home, except for two patients in the longitudinal group, who were discharged to an assisted care facility, for 7 and 22 days.

Pain and functional outcome

In both groups, knee pain scores for daily activities reduced during follow-up. At 12 months the estimated marginal mean (EMM) for kneeling pain was 2.4 (95% confidence interval (CI) 1.6–3.2) in the transverse incision group and 3.7 (95% CI 3.0–4.5) in the longitudinal group (p=0.018 in univariate analysis). This difference perished in the linear mixed-effects regression models in which pain scores were similar over time for both groups for all daily activities (Figure 10.2). Functional outcome scores showed comparable recovery over time in both groups (Figure 10.3). At 12 months, the SMFA total score in the transverse and longitudinal groups improved to 8 (95% CI 5–11) and 10 (95% CI 7–14), respectively.

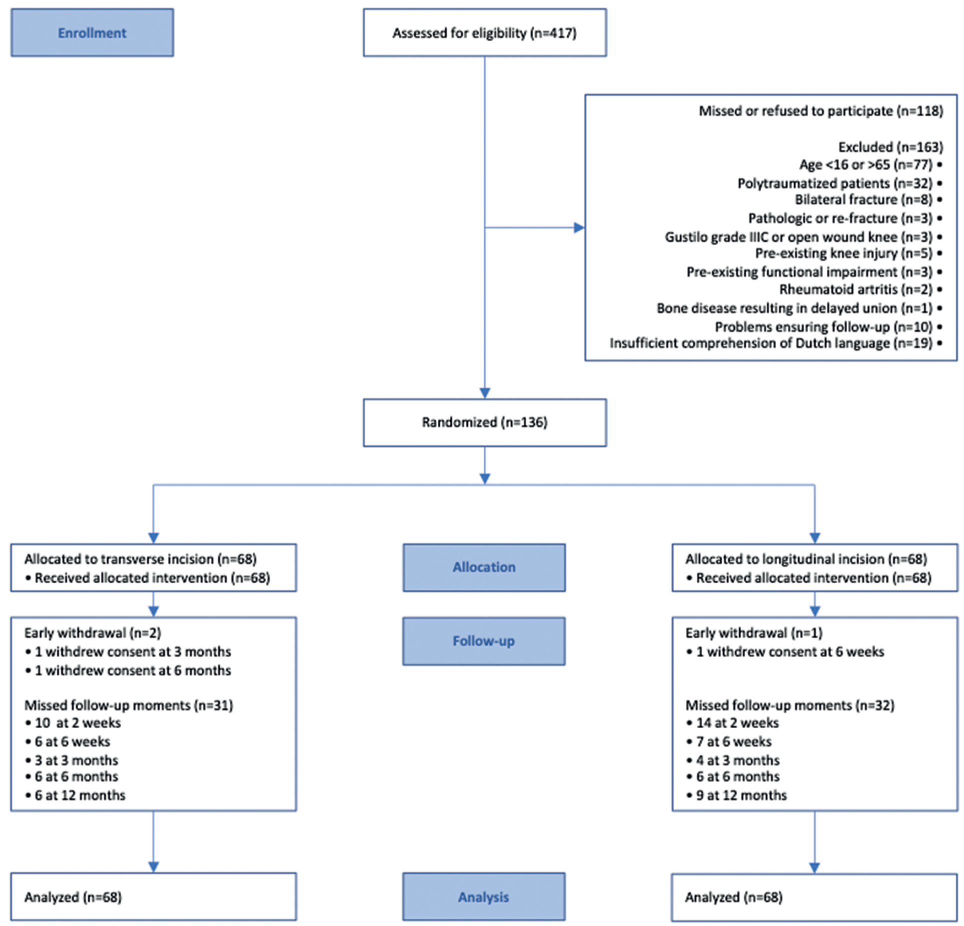

Figure 10.1. Trial flow chart.

The LEFS scores had increased to 85 (95% CI 81–89) and 83 (95% CI 78–87), respectively. Quality of life as measured by the EQ-US and EQ-VAS were 0.87 (95% CI 0.82–0.92) and 81 (95% CI 11–84) in the transverse incision group and 0.82 (95% CI 0.79–0.88) and 80 (95% CI 77–84) in the longitudinal incision group.

Clinical outcome

At 12 months median knee flexion of the operated leg was 133 degrees (P_{25}-P_{75} 130-140) in the transverse group versus 130 degrees (P_{25}-P_{75} 125–140) in the longitudinal group (p=0.594). All patients in both groups reached full extension (0 degrees). Two weeks post-surgery, signs of infrapatellar nerve injury were less often found after a transverse incision (n=11; 19% versus n=38; 70%; p<0.001). At 12 months these symptoms were still present in 11 (16%) and 32 (53%) patients in the transverse and longitudinal incision group, respectively (p<0.001).

Table 10.1. Baseline patient and fracture characteristics

	Transverse incision (n=68)	Longitudinal incision (n=68)	p-value
Men	52 (77)	47 (69)	0.335
Age (year)	38 (25-53)	32 (22-53)	0.341
BMI	25 (22-27)	24 (22-27)	0.834
ASA classification			0.539
1	56 (82)	53 (78)	
2	12 (18)	14 (21)	
3	0 (0.0)	1 (2)	
Current smoker	22 (32)	18 (27)	0.452
Past smoker	11 (16)	13 (19)	0.653
Alcohol consumption	45 (66)	41 (60)	0.477
Trauma mechanism			0.881
Traffic accident	23 (34)	26 (38)	
Fall	19 (28)	15 (22)	
Sports	17 (25)	18 (27)	
Fall from stairs/height	7 (10)	6 (9)	
Direct impact	2 (3)	2 (3)	
Gunshot	0 (0.0)	1 (2)	
AO classification			0.245
42-A	42 (62)	51 (75)	
42-B	19 (28)	13 (19)	
42-C	7 (10)	4 (6)	
Open fracture	16 (24)	11 (16)	0.282
Gustilo-Andersen			0.472
gr I	8 (12)	6 (9)	
gr II	6 (9)	5 (7)	
gr IIIA	2 (3)	2 (3)	

Data are shown as n (%) and median (P_{25}-P_{75})

Radiological outcome

At the final follow-up nail protrusion was seen in six (10.2%) patients in the transverse group and 4 (7.1%) in the longitudinal group. In the transverse group median varus deformity was 5 degrees (P_{25}-P_{75} 5–5) in 5 (7.4%) patients and 5 degrees (P_{25}-P_{75} 5–5) valgus deformity was seen in 2 (2.9%) patients. In the longitudinal group 2 patients (2.9%) had a median varus deformity of 4 degrees and 3 patients (4.4%) had a valgus deformity of 3.0 degrees (3–5). One patient in the transverse incision group had 10 degrees of internal rotation. Three patients (4.4%) in the longitudinal group had an internal rotation of the tibia with a median of 6 degrees (6–10). One patient in the longitudinal group had an external rotation deformity of 7 degrees. None of the radiological findings were significantly different.

Complications and reoperations

All complications and re-operations are displayed in Table 10.2 and Table 10.3, respectively. In one patient the tibial nail could not be inserted into the intramedullary canal due to obstruction of bone fragments and an external fixator was placed. One patient had a rotational deformity which was corrected the day after the initial operation. According to the consensus

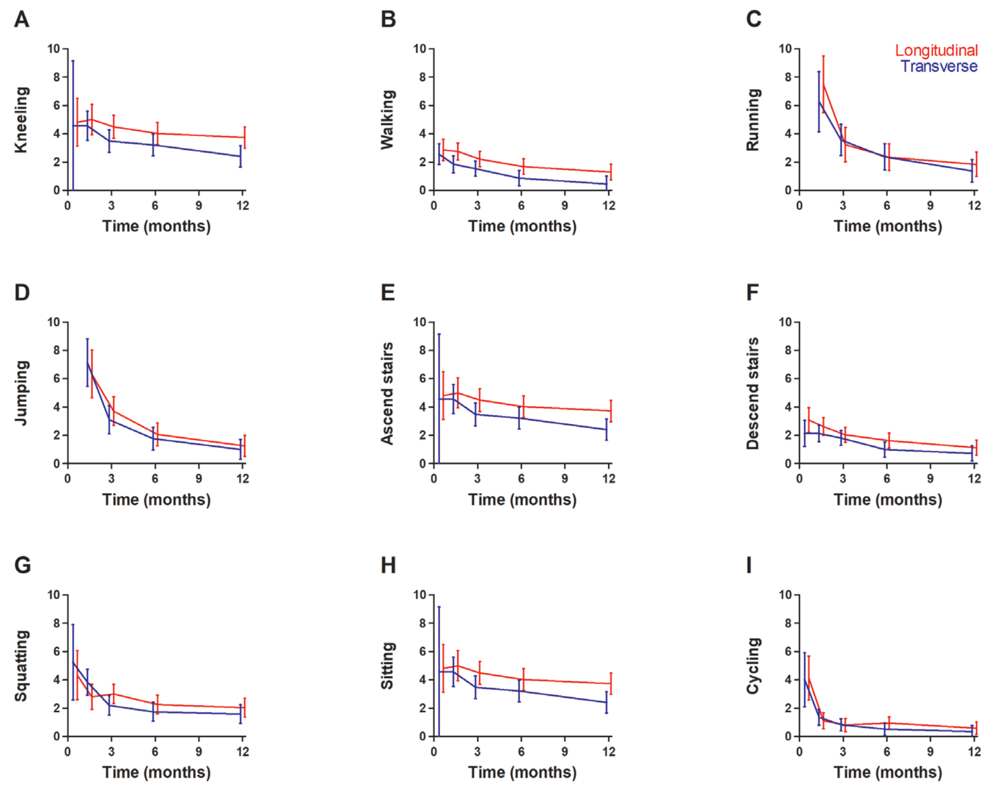

Figure 10.2. Visual analog scores (0 – 10) for knee pain during different daily activities during the 12 months follow-up.

definition of fracture related infections, there were eight patients with suggestive criteria for wound infection in the transverse group and eleven in the longitundinal group. Fracture related infections were confirmed in two and three patients, respectively. One of these patients had need for a free vascularized flap due to pre-tibial wound dehiscence, this flap later needed revision for inadequate vascularity. The other patients underwent wound debridement and were treated with intravenous antibiotics. In five patients in the transverse incision group and in two patients in the longitudinal group a delayed or non-union occurred. One patient with a delayed union refused additional surgery and at the final follow up clinical and radiological fracture healing had been achieved without intervention. Dynamization of the tibial nail was done in the remaining patients without a need for bone grafting.

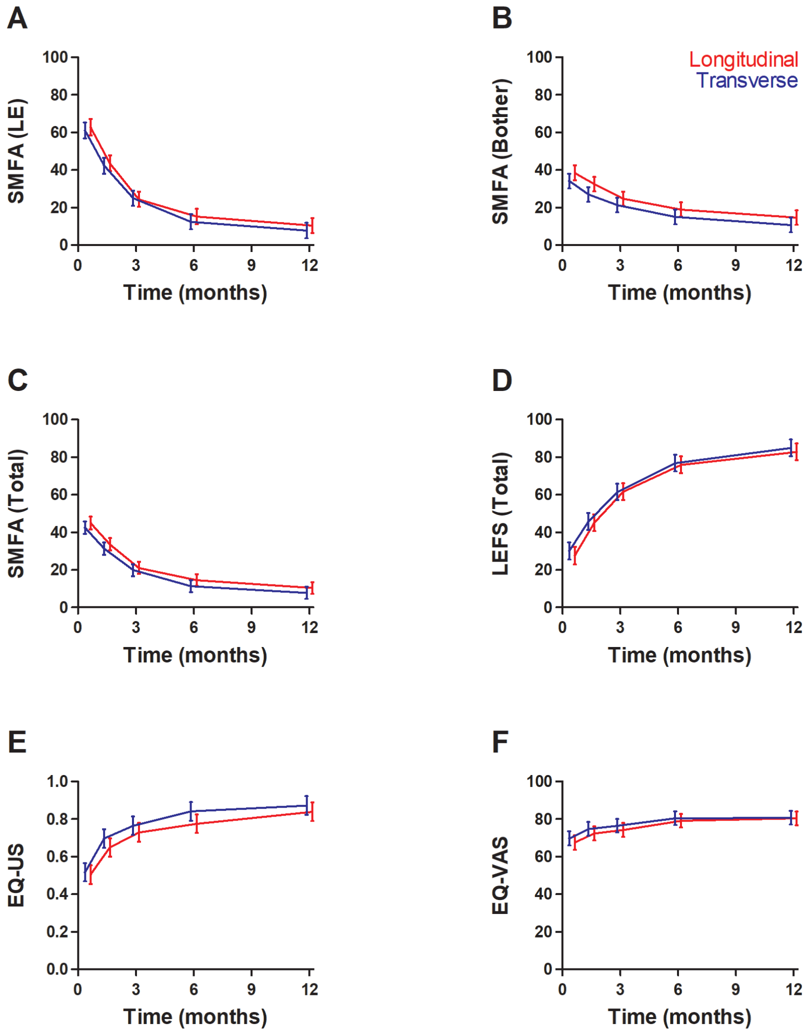

Figure 10.3. Scores of the SMFA, LEFS, EQ-US and EQ-VAS during the 12 months follow-up.

Table 10.2. Complications.

		Transverse incision (n=68)	Longitudinal incision (n=68)
(Intra-)operative complications			
Distal locking screws missing locking holes		1 (2)	0 (0)
Missed posterior malleolus fragment		1 (2)	0 (0)
Inability to insert tibial nail in intramedullary canal (switch to external fixator)		1 (2)	0 (0)
Rotational deformity		0 (0)	1 (2)
Vascular injury		0 (0)	0 (0)
Post-operative complications			
Wound dehiscence		0 (0)	1 (2)
Wounds with suggestive criteria for infection	Incision knee	2 (3)	1 (2)
	Incision locking screws	2 (3)	0 (0)
	Wound open fracture or open reduction	1 (2)	9 (13)
	Incision distal fibula plate	0 (0)	1 (2)
	Pin tracks external fixator	1 (2)	0 (0)
	Other wounds (from trauma)	2 (3)	0 (0)
Wounds with confirmatory criteria for infection	Wound open fracture or open reduction	1 (2)	1 (2)
	Fasciotomy wound	1 (2)	0 (0)
Erysipelas		1 (2)	0 (0)
Septic arthritis knee		0 (0)	0 (0)
Pneumonia		0 (0)	0 (0)
Deep venous thrombosis		0 (0)	1 (2)
Pulmonary embolism		1 (2)	0 (0)
Sural nerve injury		2 (3)	0 (0)
Inability to extend hallux due to extensor tendon injury		1 (2)	0 (0)
Delayed union		5 (7)	2 (3)
Implant failure (broken locking screws)		7 (10)	6 (9)
Pain/discomfort from implant		7 (10)	12 (18)

Data are shown as n (%)

Resumption of daily activities and work

At baseline, 88 patients (65%) were full-time employed and 31 (23%) patients were full time students (some with side jobs). The median work week consisted of 5 (P_{25}-P_{75} 3–5) days with 38 (P_{25}-P_{75} 20–40) hours. The remaining patients were either unemployed (n=9), housewife (n=3), retired (n=4) or partially incapacitated (n=1). Median sick leave was 38 (P_{25}-P_{75} 25–88) (work)days. Resumption of work per follow-up moment is displayed in Table 10.4. At 12 months 86 (91%) patients fully resumed their jobs, 3 patients (3%) resumed work, but in a different function. No differences between the transverse and longitudinal groups for all abovementioned outcomes existed.

Before trauma, a total of 115 (85%) patients reported to spend a median of 5 (P_{25}-P_{75} 3–14) hours per week on sports (63%), hobby (19%), volunteering (7%) and other activities

Table 10.3. Reoperations.

		Transverse incision (n=68)	Longitudinal incision (n=68)
Reoperation (complications)	Wound debridement	2 (3)	0 (0)
	Joint lavage of the knee	0 (0)	0 (0)
	Free vascularized flap	0 (0)	1 (2)
	Revision free vascularized flap	0 (0)	1 (2)
Reoperation (elective)	Closure of fasciotomy wound	1 (2)	1 (2)
	Elective implant removal	11 (16)	16 (24)
Revision of osteosynthesis	Derotation	0 (0)	1 (2)
	Revision distal locking screws	1 (2)	0 (0)
	Additional plate fixation fibula and posterior malleolus	1 (2)	0 (0)
	Dynamization of nail	4 (6)	2 (3)
	Bone graft	0 (0)	0 (0)

Data are shown as n (%)

Table 10.4. Changes over time in ability to perform activities of daily living on pre-trauma level.

	Transverse incision (n=56)*	Longitudinal incision (n=59)*
2 weeks	0	0
6 weeks	0 (0 - 2)	0 (0 - 2)
3 months	3 (0 - 7)	3 (0 - 5)
6 months	6 (3 - 9)	6 (3 - 8)
12 months	9 (6 - 9)	8 (5 - 10)

Data are shown as median (P_{25}-P_{75}). *This represents the number of patients that stated to perform activities at baseline.

(*e.g.*, school; 18%). At 12 months, patients rated their ability to resume these activities with a median of 8 (P_{25}-P_{75} 6–10) points on a NRS 0–10 (Table 10.5). There were no differences over time between the group treated with a transverse incision and longitudinal incision (p=0.496)..

Costs

The costs per patient per cost category are presented in Table 10.6. The median total costs for patients treated with a transverse and longitudinal incision were €10,468 (€7,980 – €17,967) and €11,066 (€8,146 – €16,849), respectively. The associated median indirect costs for loss of productivity were 67% and 52% of the total costs, respectively. Direct and indirect costs were not different for the transverse and longitudinal incision groups.

Table 10.5. Work resumption per follow-up moment

	Transverse incision (n=48)*			Longitudinal incision (n=47)*			
	Partially n (%)	Fully n (%)	Different function n (%)	Partially n (%)	Fully n (%)	Different function n (%)	P value
2 weeks	5 (9)	1 (2)	0 (0)	6 (11)	1 (2)	0 (0)	0.951
6 weeks	15 (28)	9 (17)	0 (0)	10 (19)	6 (11)	0 (0)	0.277
3 months	12 (24)	21 (42)	0 (0)	15 (31)	16 (33)	0 (0)	0.598
6 months	10 (22)	27 (59)	1 (2)	10 (20)	33 (67)	1 (2)	0.753
12 months	3 (7)	40 (89)	0 (0)	1 (2)	46 (94)	1 (2)	0.460

Data are shown as n (%), *This represents the number of patients with a paid job at baseline.

Table 10.6. Total costs per cost category

Costs categories	Total (n=136)	Transverse incision (n=68)	Longitudinal incision (n=68)	P value†
Direct costs	7,353 (6,388 – 8,876)	7,446 (6,456 – 9,019)	7,314 (6,347 – 8,611)	0.607
In-hospital care costs	6,302 (5,454 – 7,180)	6,147 (5,456 – 7,160)	6,491 (5,450 – 7,239)	0.391
Out-of hospital care costs for rehabilitation	843 (397 – 1,585)	942 (461 – 1,663)	685 (330 – 1,507)	0.339
Indirect costs due to productivity loss	6,305 (2,911 – 16,637)	6,980 (3,327 – 17,439)	5,701 (1,750 – 14,731)	0.437
Total costs	10,944 (7,983 – 17,266)	10,468 (7,980 – 17,967)	11,066 (8,146 – 16,849)	0.607

Costs are in euro €, Data are shown as median (P25-P75); not including costs related to complications and reoperations. †Mann-Whitney U.

Discussion

In this multicenter randomized controlled trial with 12 months follow-up, we found that using a transverse incision for insertion of a tibial nail does not result in a significantly lower kneeling pain score than using a longitudinal incision. This is the first published prospective study that compared these incisions.

Repeated assessment of patient's physical function is an important aspect of the treatment of trauma patients. Functional outcome scores of the SMFA and LEFS showed comparable recovery over time in both groups. At 12 months, the SMFA total score in the transverse and longitudinal groups improved to 8 (95% CI 5–11) and 10 (95% CI 7-14), respectively. Ko *et al.* tracked the long-term trajectory of functional recovery after intramedullary nailing using the SMFA dysfunction index and Short Form 36 (SF-36).[25] Patients consistently demonstrated functional improvement between six and twelve months which continued to improve onwards. However, neither functional outcome measure returned to baseline function at five years of follow-up.

When the location-dependent direction of the infrapatellar branch of the saphenous nerve is taken into account, the transverse incision just distal to the patella, might reduce iatrogenic damage to the nerve during tibial nailing as the incision mostly runs perpendicular to the infrapatellar nerve.[26] This theory is confirmed in the study; two weeks post-surgery, signs of infrapatellar nerve injury were less frequently found after a transverse incision (19% versus 70%; p<0.0001). At 12 months these symptoms were still present in 16% and 53% of patients in the transverse and longitudinal incision group (p<0.0001). This observation supports an advice to use a transverse instead of a longitudinal incision, although a reduction of anterior knee pain or better knee function might not be expected. Moreover, it gives support to the hypothesis that anterior knee pain after tibial nailing – or other knee surgery – is presumably multifactorial.

With increasing awareness of anterior knee pain after tibial nailing, new surgical techniques intended to address this issue have been described in recent years. The main focus of these studies is the comparison of a suprapatellar and infrapatellar approach. Regarding surgical aspects such as fluoroscopy exposure and operation time the suprapatellar approach is superior with equivalent risk of developing complications (*i.e.*, infection, malalignment, or retropatellar chondropathy) when compared to the infrapatellar approach.[27-30] The question whether patients benefit from the suprapatellar approach regarding anterior knee pain and functional outcome is still unclear. Meta-analyses by Gao *et al.*[30], Yang *et al.*[29] and Ponugoti *et al.*[27] suggested that the suprapatellar approach was associated with less postoperative knee pain and better function. Although significant, these differences are very small and doubtfully clinically relevant. The weighed mean difference (WMD) on the VAS for post-operative pain score varies between 0.70 (95% CI 0.570-0.83, p=0.000)[29] and 0.75 (95% CI 0.61–0.89[27]). Other meta-analyses and systematic analyses found no significant differences.[31-34]

This study primarily aimed to compare the effect of two surgical incisions on postoperative complaints and knee function. Since no substantial difference was found, it makes sense that direct and indirect costs did not differ either. The direct costs are comparable to those published previously in a paper on health care costs for tibial shaft fractures in the Netherlands (€8,332).[35] the indirect costs are lower. The previous study on health care costs encompassed both operatively and nonoperatively treated tibial shaft fractures. The difference with our study on reported costs can be explained by the fact that nonoperative treatment of tibial shaft fractures comes with a long period of casting (4-6 weeks long leg cast, followed by a patella tendon bearing cast or Sarmiento cast for several weeks) and thus a long(er) period of immobility which can affect the duration of sick leave. Patients in our study were absent from work for a median period of 38 days (the mean period was 62 days) versus 89 (SD 5) days for operatively and nonoperatively treated patients.[35] This also explains the difference in costs for loss of productivity, which was €14,017 in the abovementioned study versus €10,425 in the current study.

Previous studies showed that productivity costs due to work absenteeism generally are larger than health care costs[35,36], as is the case in the current study. With recent advances in technology that enable mobile connections, working as a telecommuter has become increasingly available. The technology for remote working has gained momentum during the COVID-19 pandemic and this might well reduce indirect health care costs, not only for tibial shaft fractures, but for other injuries as well, especially in middle aged office workers.

Strengths of the study include the large cohort size and its generalizability. This cohort also had multiple centers and surgeons involved. Furthermore, the follow-up rate was high (89% at 12 months). The exclusion of polytraumatized patients generated a homogenous cohort. Functional outcome measures are therefore not affected by other injuries and the direct and indirect costs are a good reflection of the expenses in the first year after tibial nailing.

The occurrence of all complications, adverse events, and revision surgeries during the 12 months of follow-up were recorded. A limitation is however that detailed information on the reoperations (*e.g.*, operation time and operation materials) were not registered. Therefore, costs regarding complications, adverse events and revision surgery could not be included in the (direct) costs analysis. Events that occurred after the 12-month follow-up period, such as implant removal, were not recorded and also not taken into account in the costs analysis. The direct costs therefore reflect the initial treatment of a tibial fracture with an intramedullary nail during the first year.

In conclusion, a transverse incision reduces injury to the infrapatellar nerve, but anterior knee pain scores and function are comparable after use of a transverse and longitudinal incision for tibial nail insertion.

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10

Supplementary Data

Table S10.1. Sources and unit costs of health care resources.

Cost categories	Unit	Source of consumption data	Source of value	Unit price (in €)
Medical costs				
Intramural				
Transport and emergency department				
Own transportation	Ride	Study registry (CRF)	Cost manual[a]	4.50
Ambulance	Ride	Study registry (CRF)	Cost manual[a]	702.00
Emergency department	Visit	Hospital registry	Cost manual[a]	269.50
X-ray lower extremity	Per X-ray	Hospital registry	NZa[b]	43.12
CT-scan lower extremity	Per CT-scan	Hospital registry	NZa[b]	145.33
Laboratory tests				
Simple	Per set	Hospital registry	NZa[b]	24.49
Extensive	Per set	Hospital registry	NZa[b]	56.81
Surgery				
Operation room[c]				
Regular hours academic hospital	Hours	Hospital registry	Hospital data	577.06
After hours academic hospital	Hours	Hospital registry	Hospital data	1,671.59
Regular hours general hospital	Hours	Hospital registry	Hospital data	681.22
After hours general hospital	Hours	Hospital registry	Hospital data	1,383.06
Surgeon				
Academic hospital	Hours	Hospital registry	Cost manual[a]	117.58
General hospital	Hours	Hospital registry	Cost manual[a]	120.70
Trays	Per procedure	Hospital registry	Hospital data	153.92
Hardware				
Intramedullary nail	Per piece	Hospital registry	Industry data[e]	622.57
External fixator	Per piece	Hospital registry	Industry data[e]	2,420.00
Fibula plate	Per piece	Hospital registry	Industry data[e]	171.33
Fluoroscopy	Per procedure	Hospital registry	NZa[b]	116.79
Hospital stay				
General hospital	Days	Hospital registry	Cost manual[a]	479.09
Academic hospital	Days	Hospital registry	Cost manual[a]	668.03
Peripheral nerve block	Per procedure	Hospital registry	Hospital data	187.43
Physical therapist	Days	Hospital registry	Cost manual[a]	34.34
Medication	Dose per day	Hospital registry	ZiN[d]	variable
Outpatient clinic visits				
Trauma surgeon	Visit	Hospital registry	Cost manual[a]	75.96
Plaster room	Visit	Hospital registry	Cost manual[a]	33.61
Plastic surgeon	Visit	Hospital registry	Cost manual[a]	94.69
Sports doctor	Visit	Hospital registry	Cost manual[a]	94.69
Rehabilitation doctor	Visit	Hospital registry	Cost manual[a]	94.69
Pain consultant	Visit	Hospital registry	Cost manual[a]	94.69
Rheumatologist	Visit	Hospital registry	Cost manual[a]	94.69
Wound care nurse	Visit	Hospital registry	Cost manual[a]	32.34

Table S10.1. (continued)

Cost categories	Unit	Source of consumption data	Source of value	Unit price (in €)
Extramural				
General practitioner	Visit	Study registry (CRF)	Cost manual[a]	34.34
Assisted care facility	Days	Study registry (CRF)	Industry data[e]	171.58
Home care	Days	Study registry (CRF)	Cost manual[a]	51.10
Paramedic				
Physical therapist	Visit	Study registry (CRF)	Cost manual[a]	34.34
Edema therapist	Visit	Study registry (CRF)	Industry data[e]	40.15
Exercise physiologist	Visit	Study registry (CRF)	Cost manual[a]	35.38
Manual therapist	Visit	Study registry (CRF)	Industry data[e]	44.00
Acupuncturist	Visit	Study registry (CRF)	Industry data[e]	84.75
Chiropractor	Visit	Study registry (CRF)	Industry data[e]	55.32
Psychologist	Visit	Study registry (CRF)	Cost manual[a]	66.59
Care aids				
Crutches	Days	Study registry (CRF)	Industry data[e]	0.53
Wheelchair	Days	Study registry (CRF)	Industry data[e]	2.93
Height adjustable bed	Days	Study registry (CRF)	Industry data[e]	4.39
Walker	Days	Study registry (CRF)	Industry data[e]	0.77
Rollator	Days	Study registry (CRF)	Industry data[e]	1.97
Scooter	Days	Study registry (CRF)	Industry data[e]	4.57
Adjustable toilet seat	Days	Study registry (CRF)	Industry data[e]	1.92
Shower stool	Days	Study registry (CRF)	Industry data[e]	4.81
Bed risers	Days	Study registry (CRF)	Industry data[e]	1.33
Orthopedic shoes	Per set	Study registry (CRF)	Industry data[e]	1226.74
Insoles	Per set	Study registry (CRF)	Industry data[e]	192.43
Medication	Dose per day	Study registry (CRF)	ZiN[d]	variable
Work absence				
Wage	Hour	Study registry (CRF)	CBS[f]	variable

Chapter 11

General discussion, future perspectives and conclusions

General discussion

Studies enclosed in this thesis describe the epidemiology of tibia shaft fractures and the outcome after tibial nailing with special focus on anterior knee pain after this procedure. The main findings are summarized and put into perspective. In addition, suggestions for future research are made.

Part I Incidence rate and costs of tibia shaft fractures

In **Chapter 2** and **Chapter 3** the incidence of tibia shaft fractures and the direct and indirect costs that come with these fractures are addressed.

Tibia shaft fractures have a bimodal distribution with a peak in young males and in older females.[1-4] Between 1991 and 2012 the incidence rate of hospital admitted patients with an isolated tibia shaft fracture in The Netherlands dropped with 12%. A similar reduction of 12% in the number of hospital admissions between 1998 and 2004 is also described by Weiss *et al*. based on Swedish registry data.[2] The overall decline in incidence rate in our study was mainly attributable to a 15% fall in incidence rate in men. Especially in adolescent men the incidence rate dropped substantially with 53% during this period. This pattern is also seen in a nationwide study from Germany between 2002 and 2017.[4] The decrease in incidence, and especially in this age group, cannot be explained by our data since the relative occurrence of trauma mechanisms remained fairly stable, suggesting that there is no decline in one particular trauma mechanism (e.g., less sports accidents or less traffic accidents) between 1991 and 2012.

In women a fall was the main cause of a tibial shaft fracture and this trauma mechanism was even more dominant in elderly women. Tibial shaft fractures increased in incidence for both men and women older than 65 years. Wennergren *et al*. also demonstrated an increase in the incidence of fractures at all tibia locations in women with increasing age based on data from the Swedish fracture registry.[5] Taking into account minor variations, these results are in line with data from our study. Consideration should be given to whether fractures of the tibia should be seen as fragility fractures due to their high incidence in older women (> 65 years) and the concomitant presence of osteoporosis.[1,5]

The mean hospital length of stay (HLOS) per case declined from 10.8 days in 1997 to 5.4 days in 2012. HLOS per case increased with age and the mean HLOS was 12.7 days for patients aged 80–89 years in 2012, which is substantially longer than patients admitted with a hip fracture (8 days).[6]

Mean costs per case for health care consumption in 2012 in men was €7,073 and €9,326 in women, which is comparable to studies from the US.[7,8] Costs per case also increased with age, which was mainly attributable to the rise in costs for rehabilitation and nursing care. Noteworthy is that direct health care costs per case in women in the oldest age categories (80+ years) exceeded the highest combined direct health care and lost productivity costs. For the elderly, where costs for rehabilitation and nursing care are highest, focus should be on (fall) prevention. Quicker discharge from hospital or nursing home will lower costs for those facilities, but likely put increased pressure on other health care sectors (and their costs). Due to a shift in health care use and associated costs, the efficiency of the health care system may not improve for the elderly.

The mean years lived with disability (YLD) after sustaining a tibial shaft fracture was 4.5 years. This burden is attributable to the proportion of disability in combination with the patients' relatively young age.[9] This is also reflected by the fact that productivity costs due to work absenteeism after sustaining such a fracture generally are larger than health care costs.[10] Costs due to productivity loss were €16,523 in men and €10,687 in women in 2012. Between the age of 15 and 65 years 73% was unable to work due to their sustained tibia fracture. Mean work absence was 89 days, which was unrelated to gender and age. Clinical research on surgical and rehabilitation interventions for tibia shaft fractures that aim to lower the time off from work, such as minimally invasive surgical techniques or early active mobilization therapy, may have large economic potential, especially in middle aged men and women.

A limitation of both studies is that data from the National Medical Registration did not provide a subdivision of open and closed tibia fractures. Since the start of the registration, the treatment concept of tibial shaft fractures has changed radically, especially in the last two decades. As reflected in several international guidelines, the fracture itself is more and more seen as a part of a lower leg injury. The prognosis and therapeutic choices are merely depending on the concomitant soft tissue injury. In addition, the provided data concerning the treatment of tibia fractures were only divided in operative versus nonoperative treatment. It does not provide information on trends in the use of different surgical devices (i.e., intramedullary nails, plates or external fixators). Allocation of parameters on the severity of soft tissue injury and implants used are helpful to predict future requirements for equipment and resources such as plastic reconstructive surgery and rehabilitation.

Open tibial fractures with major soft tissue injury (Gustilo-Anderson (GA) grade IIIB or IIIC) are associated with infection rates of over 31% compared to infection rates below 3% in patients with less severe open tibia fractures.[11] Bone and wound infections after tibial nailing are associated with increased HLOS and higher costs. Such infections often require prolonged antibiotic treatment and repeated surgery.[12,13] **Chapter 4** focusses on the reduction of costs for patients at high risk for infection after tibial nailing (GA grade III).[11] In this particular patient group, a gentamicin-coated tibial nail was associated with 75% lower rate of infection and cost savings (€477-€3.263); the higher cost of the implant was offset by savings from fewer infections, inpatient days (-26%) and re-operations (-10%). These findings may be valid to other patient subgroups at higher risk of infection, for example immunocompromised patients, polytrauma, those with chronic disease, obese or smokers.[11] Future studies could demonstrate the relative risk reduction for infection with gentamicin-coated nails in these populations. This requires a large sample size and collaboration of multiple (international) centers, of which the study from Bhandari *et al.* is a good example.[14] Use of a clear definition of fracture-related infection is of paramount importance in such studies.[15]

Part II Outcome after tibial nailing

The infrapatellar approach is most commonly used for insertion of the tibia nail. This technique 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 degrees flexion. The longitudinal incision is made from the distal pole of the patella toward the tibia tubercle. The intramedullary nail is inserted at the anteromedian side of the proximal tibia. In general tibial nailing is associated with high rates of post-operative anterior knee pain[2] and in proximal third tibial shaft fractures this procedure is associated with an increased risk of valgus and procurvatum deformities. In an attempt to address these problems a semi-extended parapatellar technique has been developed.[16-18] Additionally, a suprapatellar approach has been introduced. This approach encompasses two surgical techniques described by Ryan *et al.*[19] and Sanders *et al.*.[20] The technique from Ryan *et al*. describes an incision over the midline of 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.[19] Sanders *et al*. use 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 degrees flexed and a sleeve is used to avoid potential damage to the intra-articular structures of the knee.[20,21] The intramedullary entry point is determined under fluoroscopy.

Trials have compared the above-mentioned approaches to evaluate (surgical) outcomes and complications, resulting in several systematic reviews and meta-analyses.[22-29] Regarding surgical aspects such as fluoroscopy exposure and operation time the suprapatellar approach is superior with equivalent risk of developing complications (i.e., infection, malalignment, retropatellar chondropathy) when compared to the infrapatellar approach.[24-29] The question whether patients benefit from the suprapatellar approach regarding anterior knee pain and functional outcome is addressed in **Chapter 3**. In this systematic review and pooled analysis, the proportion of patients with anterior knee pain was 38% for the infrapatellar approach versus 10% for the suprapatellar approach. The actual documented general knee pain scores were however surprisingly low for both techniques. Overall, the recovery of physical functioning and quality of life following both approaches seemed good.

The accuracy of all systematic reviews and meta-analyses depends on the quality and homogeneity of the trials it includes. This starts with simply reporting outcome measures adequately (i.e., mean values with standard deviations) and providing a clear description of the study population. Since at least 32% of patients with a tibia fracture is multiply injured[14], the presence of other injuries can affect functional outcome scores. Therefore, a proper description of the study population is essential in order to interpret such scores correctly. Although it is the authors' responsibility to report their data adequate and complete, it would be helpful if journal reviewers and editors would ask for any missing information.

Major hurdles in the analysis of the eligible trials for this systematic review were the lack of adequate documentation on how and when pain scores were obtained and the fact that six different scales were used for measuring knee pain. The same number of instruments was used to measure function. This variety in outcome measures makes it difficult to compare study results. For accurate evaluation and comparison of various interventions outcome scoring is vital. Moreover, to achieve sufficient cases to draw conclusions, future research should be performed in a multicenter fashion, preferably in an international collaboration. It is therefore vital to use standardized and valid outcome parameters.

For patients with tibia fractures, the disease-specific Short Musculoskeletal Function Assessment (SMFA) and the generic measure SF-36 have been demonstrated valid and responsive.[30] Both assess the general functional status of patients and how bothered they are by functional problems, but these instruments lack focus on knee function and knee pain and the minimal important change (MIC) is not determined for the SMFA in general and for the SF-36 it is not determined for this specific patient group. The Lower Extremity Functional Scale (LEFS) is a region-specific patient reported outcome measure (PROM), but not yet validated for patients with tibia fractures. The question raises which scoring system should be used to measure knee pain and/or function after tibial nailing? To tackle this question the measurement properties of the Short Musculoskeletal Function Assessment (SMFA) and Lower Extremity Functional Scale (LEFS) in patients who sustained a tibial shaft fracture were evaluated in **Chapter 6**. This study confirmed that both the SMFA and LEFS are reliable, valid, and responsive instruments for monitoring functional recovery in patients after sustaining a tibia shaft fracture. Both instruments can excellently detect clinical change over time, but use of the LEFS should be restricted to the first six months post-injury because effects can be missed later in the follow- up. The EuroQol-5D VAS subscale (EQ-VAS) did not have a ceiling effect and can be used to measure health-related quality of life on the long term in this patient population.

The most important clinimetric property for interpreting change over time is the MIC which is defined as the smallest measurable change in outcome score that is perceived as significant by patients.[31] An anchor-based method was used as this gives a better indication of the importance of the observed change to the patient.[32] In addition to the questionnaires, patients were asked to complete a transition item (anchor question) at six weeks and at three, six, and twelve months evaluating their perception of change in the general condition of the affected leg. The smallest detectable change (SDC) is defined as the smallest intra-personal change in score that represents (with $p<0.05$) a 'real' difference above measurement error.[33] If the SDC is smaller than the MIC, it is possible to distinguish a clinically important change from measurement error with a large amount of certainty. However, this is much more difficult if the SDC is larger than the MIC, since there is a considerable chance that the observed change is caused by measurement error.

Our study shows that the change score should exceed 13.8 points for the SMFA (total score) and 38.7 points for the LEFS to have a clinically relevant change on the questionnaire in patients that sustained a tibial shaft fracture. The MIC for the SMFA (8.12) and LEFS (7.32) were unreliable due to inadequate correlation between the transition item "slightly better" and change scores.

The SDC was based on the change scores of patients who answered 'no change' on the transition item, as patients need to be assumed to be stable in the interim period. The MIC is based on the correlation between the transition item "slightly better" and change scores. The relatively long interval between two subsequent follow-up moments (four weeks to six months) may have introduced a recall bias with regard to the transition item and thus affected correct anchor-based MIC and SDC calculations. Also, these long intervals hindered an adequate test-retest analysis. The previously published anchor-based MIC of the LEFS is 9 points[34,35] for monitoring function in patients with various musculoskeletal disorders. A recent study from de Graaf et al. determined the MIC of the SMFA-NL Lower Extremity Dysfunction subscale to be 14 points.[36] However, the MIC is known to be patient and context dependent. Their population consisted of patients with various injuries of the lower extremity and caution is required with the use of this MIC. For future studies that aim to determine the MIC of the SMFA, LEFS or any other functional outcome measure for a specific injury we recommend to shorten the intervals between the questionnaires (in combination with the anchor-based questions) and to guard the homogeneity of the study population.

Evaluation of existing models and scoring systems for outcome is required to be able to measure what we need to know and to be able to improve the models. The standardization of outcome instrument use in orthopedic research will be a giant leap forward and ideally, a core set of validated patient-reported outcome instruments should be used. For monitoring functional outcome during the first year after injury and/or surgery of the tibial shaft the SMFA is the instrument of choice because in addition to its reliability, validity, and responsiveness it shows no ceiling effect. For measuring health-related quality of life in this patient population the EQ-VAS can be used.

Part III Anterior knee pain after tibial nailing

The etiology of anterior knee pain in patients suffering from a tibial shaft fracture is unknown. Since it is not observed if the fracture is treated with a plate or external fixator, a causal relation with (the introduction of) a nail itself is likely. The prevalence of anterior knee pain after tibial nailing in our retrospective study was 38% (**Chapter 7**), which is in line with the prevalence reported in a meta-analysis by Katsoulis et al..[2] Prevalences described in later studies vary however from 18%[37] to 70%[38]. Scores on the Anterior Knee Pain Scale (AKPS) were lower in patients who reported knee pain, but the generic health status was not affected in these patients. A clear relation with the surgical route (paratendinous or transtendinous) or final position of the nail has not been found in several studies.[39-41] Therefore, an appealing theory is the ability of iatrogenic damage to the sensory nerves around the knee. The rate of sensory deficits related to injury of the infrapatellar nerve was 60% after a mean follow-up of seven years post-nailing. Sensory deficits related to

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infrapatellar nerve injury were significantly more often detected in patients with anterior knee pain. The course of the infrapatellar nerve makes it susceptible to iatrogenic injury during nail insertion.[42,43] The nerve can be transected, entrapped during wound closure, or neuroma formation can occur.[44,45] This theory is tested in **Chapter 8.** We hypothesized that if knee pain after tibial nailing is indeed caused by neuropathic pain due to iatrogenic injury of the infrapatellar nerve, an anesthetic block of this nerve with lidocaine would reduce knee pain in these patients. In this randomized controlled trial, compared with placebo, an infrapatellar nerve block with lidocaine was more effective in reducing pain during kneeling in patients with chronic knee pain after tibial nailing through a longitudinal infrapatellar incision. No differences were found between the groups during squatting, sitting with bent knees, jumping, walking stairs, running, walking, and rest. Signs of infrapatellar nerve injury were found in 85% of the patients.

Data analysis showed a period effect for the primary endpoint. This can be explained by the short wash-out period. Due to this period effect, only the results from the first nerve block were analyzed. Another limitation of the study is that the local effect lidocaine has on the skin could have been recognized by the patients. Although both the patient and the examiner were blinded to the treatment given, the local alteration could have influenced true blinding and might have affected the pain scores. Also, the effect of pain relieve on function was not tested. The baseline pain level was low for all activities (except kneeling); thus, a smaller effect size can be expected and the study could be underpowered to detect differences for these activities.

This study provides arguments for the hypothesis that iatrogenic injury to the infrapatellar nerve contributes to anterior knee pain after tibial nailing. Patients suffering from this complication who respond well to an infrapatellar nerve block with lidocaine might benefit from denervation.[44-46] However, prevention is better than cure and therefore in **Chapter 9** we provide a detailed description of the relative anatomic course of the infrapatellar nerve in order to minimize iatrogenic damage during anterior knee surgery. In accordance with previous anatomical studies[42,47,48], the study shows high variation in the anatomy of the infrapatellar branch of the saphenous nerve. The direction of the infrapatellar branches of the saphenous is location-dependent. Three low risk zones were identified where fewer infrapatellar branches of the saphenous nerve were located. The first area is located on the medial side of the knee at the level of the tibial tuberosity, the second zone is located medial and distal to the patellar apex, the third zone is located medial and proximal to the patellar apex. With minor variations taken into account, the safe and risk zones correspond with reports in literature.[42,47,49] A safe entry site for tibial nailing is through the second or third zone. When the location-dependent direction of the infrapatellar branch of the saphenous nerve is taken into account, a horizontal incision just distal to the patella, might reduce iatrogenic damage to the nerve as the incision mostly runs perpendicular to the infrapatellar nerve.[50,51] Clinical studies comparing longitudinal and transverse incisions for hamstring tendon harvest in anterior cruciate ligament reconstruction confirm this theory.[52] Insertion of a tibial nail through a transverse incision is feasible[53,54] but studies comparing a transverse and longitudinal incision for tibial nailing are lacking. The TRAVEL study described in **Chapter 10** compared these two incisions for tibial nailing. At 12 months there were no significant differences in kneeling pain between the groups. The estimated marginal mean kneeling pain score was 2.4 in the transverse incision group, and 3.7 in the longitudinal group. Pain scores for other daily activities were similar over time for both groups. Functional outcome scores (SMFA and LEFS) and quality of life (EQ-US and EQ-5D) also showed comparable recovery over time. Complications and re-operations were equally spread over both approaches. The total (direct and indirect) costs per patient were €10,468 in the transverse incision group and €11,066 in the longitudinal incision group. Loss of productivity accounted for 67% and 52% of the total costs, respectively. Since no substantial differences were found, it makes sense that direct and indirect costs did not differ either.

Trials like the TRAVEL study come with a high administrative burden and practitioners usually don't have time to complete the case report forms at each follow-up moment. In this trial data collection was done by a dedicated researcher or research assistant, thereby removing almost all administrative activities from the treating surgeon. This resulted in a low percentage of missing data. Patients however completed the questionnaires on paper and the respondent burden of the PROMs was relatively high. Good functioning computer-based versions of these questionnaires might have yielded lower rates of missed follow-up moments.

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The potentially multifactorial nature of anterior knee pain after tibial nailing complicates the search for an obvious explanation or simple solution for this problem. The origin of the pain can be different in each patient presenting with this complaint and potential causes should be ruled out. A straight forward diagnostic test for infrapatellar nerve neuropathy is an injection with lidocaine and in those patients that respond well, a neurectomy can be of relieve. Possible (contributing) factors like nail prominence should be researched in prospective trials with clear research questions and validated outcome measures. The same applies for the effect of nail removal on anterior knee pain after tibial nailing.

In the last three years there was an eruption of systematic reviews and meta-analysis to determine what approach is superior for tibial nail insertion, the infrapatellar or suprapatellar approach.[22-29] Each analysis has somewhat different inclusion criteria but the main conclusion is that the suprapatellar approach can be adopted as a safe and effective option for nailing of tibia shaft fractures. The question whether it is also superior in terms of anterior knee pain and functional outcome remains unclear. Further large scale, randomized studies using validated and appropriate outcome measures are warranted to further support the use of the suprapatellar approach.

Future perspectives

Although treatment of individual fractures is not specifically improved by epidemiological studies, surgeons should have knowledge of the spectrum of fractures which they treat; not only for educational purposes, but also to allow resources to be allocated. A detailed (blinded) registration of both diagnosis and treatment at the beginning would make a comprehensive nationwide survey feasible and evaluation of costs or the impact of implementation of specific guidelines more reliable. An example is the Dutch Hip Fracture Audit (DHFA) by the Dutch Institute for Clinical Auditing (DICA).[6] For tibial fractures the

Arbeitsgemeinschaft für Osteosynthesefragen (AO) initiated the Fracture-related outcome study for operatively treated tibia shaft fractures (F.R.O.S.T.).[55] The development of an integrated system that can safely export selected data with technical solutions to guarantee the privacy of individual patients to such databases would be of much help.

To further improve patient care, practitioners should assess patient outcomes with use of a validated condition-specific instrument and focus on the functional aspects of the disease or injury. Many PROMs have been reported to lack measurement precision and have a relatively high respondent burden.[56] A promising way to overcome these problems with fixed-format PROMs is by computer adaptive testing.[57] A computer adaptive test (CAT) is a computer-based measure that adapts the questions (items) by an algorithm that is based on the patient's response to previous items and their estimated health state within a specific health domain.[57,58] The items in CATs are provided by item banks that are calibrated using Item Response Theory (IRT) analysis, which orders items from an item bank along a measurement continuum, based on their difficulty and discrimination ability.[59] The generic patient-reported outcomes information system (PROMIS) physical function (PF) item bank has shown potential to measure physical function with better precision, interpretability and lower respondent burden compared with traditional patient-reported outcome measures.[60] The first studies into the Dutch–Flemish PROMIS-PF item bank show promising results, with especially high-quality evidence for structural validity and measurement precision in the upper extremity subdomain.[61] However, more studies, and studies with higher methodological quality, are needed to examine the instruments derived from these item banks that are used to actually measure patient outcomes. These studies should also evaluate reliability and responsiveness, content validity, and measurement properties which have not yet been studied (sufficiently). New tools like CATs will advance (trauma) research to a higher level and if used at its full potential patients can, for example, be better informed about expected functional recovery after specific injuries.

Other recent developments with possible high impact on surgical care are 3D printing and augmented reality. Anatomical understanding and pre-operative planning evolved from careful preparation of human anatomical specimen and studying books to integrating the information content of anatomical images (like Computer-Assisted Surgical Anatomy Mapping (CASAM)) either in a 3D virtual environment (desktop application) or in a hybrid simulator, which exploits the potential of the 3D printing and augmented reality functionalities. These gadgets have the potential to guide surgeons in their per-operative decisions, for instance by depicting risk and safe zones for planned incisions for an intramedullary nail and locking screws and of course, by integrating radiological images,

reduction might be simplified in comminutive fractures. One can only start with imagining how these improvements in health-care will impact care, not only for trauma patients, but for all patients we take care of as doctors.

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Chapter 12

Summary and conclusions

Chapter 1 is an introduction of this thesis. It elucidates the epidemiological aspects of tibia shaft fractures. The clinical presentation and treatment of these fractures with an intramedullary nail are described. Furthermore, it gives insight into outcome after tibial nailing, with focus on anterior knee pain.

In **Chapter 2** all patients admitted to a hospital in the Netherlands between 1991-2012 with an isolated tibia shaft fracture were analyzed for age- and gender-specific trends in incidence rate. The incidence rate for men decreased from 16.3/100,000 person years (py) in 1991 to 13.8/100,000 py in 2012. The incidence rate for women remained constant over time: 7.5 per 100,000 py in 1991 and 7.2 per 100,000 in 2012. The age-specific incidence rates showed a bimodal distribution, with a peak among young men (15-19 years) and women (10-14 years) and a gradual increase from 65 years onwards in both genders. The peak in incidence rates in young men and women decreased with 53% and 38% respectively, during the study period.

In males, the dominant trauma mechanism was a traffic accident until 20 years of age (36%). From 60 years onward, falls predominated. Women showed a similar pattern; the dominant trauma mechanism was a traffic accident in the age group <40 years (50%) and falls in the age group >40 years (72%). Direct contact and sports particularly contributed at the age of 20-29 years, especially in men (27%). All mechanisms showed fairly steady patterns during the years. In 2012, 58% of patients were treated surgically for their sustained isolated tibia shaft fracture. The highest operation rate was 71% for patients between the age of 30-39 years. Mean HLOS was 1.6 days for patients aged 0 to 9 years and 12.7 days for patients aged 80 to 89 years in 2012. The mean HLOS per case declined from 10.8 days in 1997 to 5.4 days in 2012. The mean years lived with disability (YLD) per case declined from 7.8 YLD in patients aged 0-10 years to 0.6 YLD in the very elderly (90+ years). The overall YLD for all age groups and both genders combined was 4.5 YLD.

Conclusions:

- The incidence rate of hospital admitted patients with an isolated tibia shaft fracture dropped with 12%, which was mainly attributable to a 15% decline among men.
- The dominant trauma mechanisms were traffic accidents and falls.
- The mean HLOS per case declined from 10.8 days in 1997 to 5.4 days in 2012.
- The overall YLD for all age groups and both genders combined was 4.5 YLD.

Chapter 3 provides a detailed overview of age and gender specific health care costs and costs due to lost productivity for hospital admitted patients with an isolated tibia shaft fracture in the Netherlands between 2008 and 2012. Mean hospital length of stay (HLOS) for men was 5.1 days, for women 6.0 days and increased with age. The mean direct health care costs per case were higher for women (€ 10,687) than for men (€ 7,073). Costs per case in men and women increased with age, which was mainly attributable to the rise in costs for rehabiltation and nursing care. Between the age of 15 and 65 years 73% was unable to work due to their sustained tibia fracture. Mean work absence was 89 days, which was unrelated to gender and age. Mean costs per case due to productivity loss were € 16,523 for men and € 9,326 for women. Total costs due to productivity loss were € 17.6 million for men and € 5.3 million for women.

Annual direct health care costs for all patients admitted with a tibia shaft fracture in the Netherlands were € 13.6 million. Costs due to lost productivity for men and women were € 22.9 million. For men (all ages combined), mean costs per case for combined direct health care costs and costs due to lost productivity, were € 23,596. Of these costs, 70% was due to productivity loss. The highest costs per case were for men between the age of 40 and 49 years. Highest costs per case were seen in women in the oldest age categories (80+ years).

Conclusions

- In 2012, direct health care costs were € 13.6 million and costs due to lost productivity were € 22.9 million.
- Cost per case for direct health care costs in men and women increased with age.
- Mean work absence was 89±5 days, which was unrelated to gender and age.
- Costs per case were highest for men aged 40-49 years mainly due to lost productivity and in women aged > 80 years due to high direct medical costs.

Chapter 4 aimed to determine whether the use of a gentamicin-coated intramedullary tibial nail is cost-effective for trauma centers managing patients with a high risk of infection. Patient-level data were provided by four European trauma centers on inpatient days, procedures, and related costs for patients with and without infections.

The base case results, sensitivity analyses, and scenario analysis of the model demonstrated that the gentamicin-coated tibial nail in patients at high risk of infection (Gustilo Anderson grade III) was associated with 75% lower rate of infection and cost savings (€477- €3,263) for all included centers; the higher costs of the implant was offset by savings from fewer infections, inpatient days (-26%), and re-operations (-10%).

Conclusions

- The use of a gentamicin-coated nail rather than an uncoated nail in patients with a GAIII fracture could potentially reduce infection rates by 75%.
- Reduction of the total costs for in-hospital treatment could potentially be 4%-15%, due to fewer infections, inpatient days, and re-operations in patients at high risk of infection.

Chapter 5 describes a systematic literature review and pooled analysis comparing knee pain and function after tibial nail insertion through an infrapatellar, semi-extended, and suprapatellar technique. A total of 114 studies, describing the results of 3,499 patients, were included. Pooled analysis was not possible for the semi-extended technique. The mean percentage of patients with anterior knee pain was 38% (95% confidence interval (95% CI) 32-44) for the infrapatellar technique and 10% (95% CI 1-26%) for the suprapatellar technique. Visual analogue scores for knee pain (0-10) ranged from 0.2 (95% CI -0.1-0.5) for knee pain in general to 3.7 (95% CI 1.3-6.1) for pain during kneeling. The mean Lysholm scores were 87 points (range 77-97) after nail insertion through an infrapatellar approach and 85 points (range 82-85) after the use of a suprapatellar approach. Iowa knee scores were 94 (range 86-96) and Anterior Knee Pain Scale scores were 76 (range 75-80) after infrapatellar nail insertion. The large variety of outcome measures, differences in data reporting and sometimes missing data (mean value, standard deviation or 95% CI) hampered the meta-analysis.

Conclusions

- The systematic review and pooled analysis showed that the proportion of patients with knee pain after tibial nailing varied between 10 and 38%.
- Pain scores were low and knee function was good after infrapatellar and suprapatellar insertion.
- A more uniform reporting of outcome of treatment helps to compare the results of different studies.

Chapter 6 examines the reliability, validity, responsiveness, floor and ceiling effects, and Minimal Important Change (MIC) of the Short Musculoskeletal Function Assessment (SMFA) and Lower Extremity Functional Scale (LEFS) in patients who sustained a tibial shaft fracture. A total of 136 patients were included. Internal consistency was sufficient for the SMFA and LEFS (sub)scales (Cronbach α 0.84 – 0.94). Construct and longitudinal validity were also adequate for both patient-reported outcome measures (>75% of correlations hypothesized correctly). Floor effects were not present. Ceiling effects were present at 12 months for the SMFA lower extremity dysfunction and bother subscales (22% and 19%, respectively) and the LEFS (19%). The MICs could not be determined with available data.

Conclusions

- The SMFA and LEFS are reliable, valid, and responsive instruments for evaluating outcome in patients with a tibial shaft fracture.
- Both measures are useful instruments for monitoring functional limitations in patients after sustaining a tibia shaft fracture during at least the first 6 months post-injury.

In **Chapter 7** the long-term incidence of infrapatellar nerve damage after tibial nailing was determined and the relation to anterior knee pain was retrospectively examined. A total of 71 patients were included. At a mean follow-up of 84 months, infrapatellar nerve injury was found in 43 patients (60%). Anterior knee pain was reported by 38% of the patients. Patients with anterior knee pain had significantly more sensory deficits than patients without anterior knee pain (p = 0.025). In total 33 nails were removed. Pain persisted in 58% of patients in whom knee pain was the reason for nail removal.

Conclusions

- The majority of patients show signs of infrapatellar nerve injury after tibial nailing, even after long-term follow-up.
- Anterior knee pain occurs in 38% of the patients after tibial nailing and these patients have more sensory deficits of the infrapatellar nerve.
- Knee pain persists after nail removal in the majority of patients.

Chapter 8 describes a randomized controlled trial that compares changes in knee pain after an infrapatellar nerve block with lidocaine or placebo in patients with persistent knee pain after tibial nailing. Thirty-four patients (age 18–62 years) were equally randomized to a nerve block with lidocaine or placebo, after which they performed 8 daily activities (kneeling, squatting, prolonged sitting with bent knees, jumping, walking on stairs, running, walking, and rest). Before and after these activities, pain was recorded using a numeric rating scale (NRS; 0–10). A significant reduction of the NRS for kneeling pain with an infrapatellar nerve block with lidocaine was found compared with placebo (–4.5 [range –10 to –1] versus –1 [–9 to 2]; p = 0.002). There were no differences between treatments for the NRS values for pain during other activities.

Conclusion

- Compared with placebo, an infrapatellar nerve block with lidocaine was more effective in reducing pain during kneeling in patients with chronic knee pain after tibial nailing.

In **Chapter 9** regarding knee surgery, the infrapatellar branch of the saphenous nerve is located and its direction is mapped. The infrapatellar branch was dissected in 20 embalmed knees. With use of a computer-assisted surgical anatomy mapping tool, safe and risk zones, as well as the location-dependent direction of the nerve were calculated. The course of the was location-dependent. On the far medial side of the knee, it runs a nearly vertical course; medial near the patellar tendon, it has a –45° distal-lateral course; and on the patella and patellar tendon, it runs a close to horizontal-lateral course. Three low risk zones for iatrogenic nerve injury were identified: one is on the medial side of the knee, at the level of the tibial tuberosity, where a –45° oblique incision is least prone to damage the nerves, and two zones are located medial to the patellar apex (cranial and caudal), where close to horizontal incisions are least prone to damage the nerves.

Conclusions

- The infrapatellar branch of the saphenous nerve is at risk for iatrogenic damage in anteromedial knee surgery, especially when longitudinal incisions are made.
- There are three low risk zones for a safer anterior approach to the knee.
- The direction of the infrapatellar branch of the saphenous nerve is location-dependent.
- To minimize iatrogenic damage to the nerve, the direction of incisions should be parallel to the direction of the nerve when technically possible.

In **Chapter 10** the effect of a transverse incision and a longitudinal incision for intramedullary nailing of the tibia is described. In this multicenter randomized controlled trial with 12 months follow-up, adult patients with a tibial shaft fracture to be treated with an intramedullary nail were randomized to a transverse (n=68) or longitudinal incision (n=68). Kneeling pain was assessed via Numeric Rating Scale (NRS). Other measurements included knee pain during daily activities, functional outcome (Short Musculoskeletal Function Assessment (SMFA) and Lower Extremity Functional Scale (LEFS)), quality of life (EQ-5D), activity resumption, complications and reoperations and direct and indirect costs until one year after trauma. At 12 months the mean kneeling pain score was 2.4 (SD 3.1) in the transverse incision group and 3.7 (SD 3.0) in the longitudinal group. Regression analysis showed no significant difference between both groups over time (P=0.239 at 12 months). Knee pain scores for daily activities, functional outcome scores and quality of life were also comparable between the groups. Signs of infrapatellar nerve injury were found less after a transverse incision (16,4% versus 53,3%; P<0.0001). The total (direct and indirect) costs per patient were €16,266 of which 58% was due to loss of productivity.

Conclusions

- A transverse incision for insertion of a tibial nail does not result in a significantly lower kneeling pain score than a longitudinal incision.
- Knee pain during other daily activities, functional outcome and quality of life are also comparable between the groups.
- Loss of productivity is the main cost driver for patients treated with an intramedullary nail.

The general discussion and future perspectives are discussed in **Chapter 11.**

Chapter 13

Nederlandse samenvatting en conclusies

Nederlandse samenvatting en conclusies

Hoofdstuk 1 is de introductie van dit proefschrift. Het licht de epidemiologische aspecten van fracturen van de tibiaschacht toe. De klinische presentatie van deze fracturen en de behandeling ervan met een mergpenosteosynthese worden beschreven. Verder geeft het inzicht in de uitkomsten van de behandeling, waarbij de focus ligt op anterieure kniepijn.

Hoofdstuk 2 beschrijft de populatie-gebaseerde trends op de lange termijn in de incidentie van patiënten met een geïsoleerde fractuur van de tibiaschacht die in de periode 1991-2012 in een ziekenhuis in Nederland opgenomen waren. De incidentie voor mannen daalde van 16,3 per 100.000 persoonsjaren in 1991 naar 13,8 per 100.000 persoonsjaren in 2012. Voor vrouwen bleef de incidentie nagenoeg gelijk in deze periode: respectievelijk 7,5 en 7,2 per 100.000 persoonsjaren in 1991 en 2012. Er werd een bimodale verdeling gezien van de incidentie met een piek bij jonge mannen (15-19 jaar) en vrouwen (10-14 jaar) en een geleidelijke toename in incidentie vanaf de leeftijd van 65 jaar voor beide geslachten. Tussen 1991 en 2012 daalde de piekincidentie voor jonge mannen en vrouwen met respectievelijk 53% en 38%. Voor mannen was een verkeersongeval het meest voorkomende traumamechanisme tot de leeftijd van 20 jaar (36%). Vanaf 60 jaar domineerde een val. Bij vrouwen werd een vergelijkbaar patroon gezien: tot 40 jaar was een verkeersongeval de meest voorkomende oorzaak (50%) en na 40 jaar was het een val (72%). Fracturen door direct trauma of sport kwamen vooral voor in de leeftijd 20-29 jaar en dan met name bij mannen (27%). Voor alle traumamechanismen bleek het patroon door de jaren heen stabiel. In 2012 werd 58% van alle patiënten geopereerd in verband met een geïsoleerde tibiaschachtfractuur. Het hoogste percentage operaties was 71% bij patiënten tussen de 30 en 39 jaar. In 2012 was de gemiddelde opnameduur 1,6 dagen voor patiënten tussen de 0 en 9 jaar en 12,7 dagen voor patiënten tussen de 80 en 89 jaar. De gemiddelde opnameduur daalde van 10,8 dagen in 1997 naar 5,4 dagen in 2012. Het gemiddeld aantal ziektejaarequivalenten nam af van 7,8 in de patiëntengroep van 0-10 jaar naar 0,6 in de zeer oude populatie (90+ jaar). Het gecombineerde ziektejaarequivalent voor alle leeftijdsgroepen en beide geslachten samen was 4,5.

Conclusies:

- De incidentie van patiënten die opgenomen werd met een geïsoleerde tibia schachtfractuur daalde met 12%, wat met name kwam door een afname van 15% onder mannen.
- De meest voorkomende traumamechanismes waren verkeersongevallen en een val.
- De gemiddelde opnameduur daalde van 10,8 dagen in 1997 naar 5,4 dagen in 2012.
- Het gecombineerde ziektejaarequivalent was 4,5.

Hoofdstuk 3 geeft een gedetailleerd overzicht van de kosten voor de gezondheidszorg en verloren productiviteit voor patiënten met een geïsoleerde tibia schachtfractuur die in de periode 2008-2012 opgenomen waren in een Nederlands ziekenhuis. De gemiddelde opnameduur voor mannen was 5,1 dagen en voor vrouwen 6,0 dagen. Voor beide groepen gold een toename met het stijgen van de leeftijd. De medische kosten per patiënt waren voor vrouwen gemiddeld hoger (€ 10.687) dan voor mannen (€ 7.073). De kosten per patiënt stegen voor mannen en vrouwen met toename van de leeftijd, wat met name toe te schrijven was aan de stijging in kosten voor revalidatie en verpleegkundige zorg. Tussen de leeftijd van 15 en 65 jaar was 73% tenminste tijdelijk arbeidsongeschikt vanwege een tibiaschacht fractuur. Het gemiddelde werkverzuim was 89 dagen, ongeacht geslacht en leeftijd. De gemiddelde kosten per patiënt voor verloren productiviteit bedroegen € 16.523 voor mannen en € 9.326 voor vrouwen. De cumulatieve kosten als gevolg van verloren productiviteit bedroegen € 17,6 miljoen voor mannen en € 5,3 miljoen voor vrouwen. De jaarlijkse medische kosten voor alle patiënten met een tibiaschacht fractuur in Nederland bedroegen € 13,6 miljoen. De kosten als gevolg van productiviteitsverlies voor mannen en vrouwen bedroegen € 22,9 miljoen. Voor mannen (alle leeftijden samen) bedroegen de gemiddelde kosten per patiënt voor gecombineerde medische kosten en kosten als gevolg van productiviteitsverlies € 23.596. Van deze kosten was 70% te wijten aan productiviteitsverlies. Voor mannen waren de kosten per patiënt het hoogst voor leeftijdscategorie tussen de 40 en 49 jaar. De hoogste kosten per patiënt bij vrouwen werden gevonden in de oudste leeftijdscategorie (80+ jaar).

Conclusies

- In 2012 bedroegen de medische kosten in Nederland € 13,6 miljoen en de kosten als gevolg van productiviteitsverlies € 22,9 miljoen.
- De medische kosten per patiënt namen toe met de leeftijd voor zowel mannen en vrouwen.
- Het gemiddelde werkverzuim was 89 dagen, ongeacht geslacht en leeftijd.
- De kosten per patiënt waren het hoogst voor mannen in de leeftijdscategorie 40-49 jaar, voornamelijk door productiviteitsverlies en voor vrouwen van > 80 jaar ten gevolge van hoge medische kosten.

Hoofdstuk 4 heeft als doel te bepalen of het gebruik van een gentamicine-gecoate intramedullaire tibiapen kosteneffectief is voor traumacentra die patiënten behandelen met een hoog infectierisico. Gegevens werden verstrekt door vier Europese traumacentra over verpleegdagen, procedures en gerelateerde kosten voor patiënten met en zonder infecties.

De resultaten van het basisscenario, gevoeligheidsanalyses en scenarioanalyse van het model toonden aan dat de gentamicine-gecoate tibiapen bij patiënten met een hoog infectierisico (Gustilo Anderson graad III) geassocieerd was met een 75% lager infectiepercentage en kostenbesparing (€ 477- € 3.263) voor alle deelnemende centra; de hogere kosten van het implantaat werden gecompenseerd door besparingen door minder infecties, minder verpleegdagen (-26%) en minder heroperaties (-10%).

Conclusies

- Het gebruik van een gentamicine-gecoate tibiapen in plaats van een niet-gecoate pen bij patiënten met een GAIII-fractuur kan de kans op een infectie met 75% verminderen.
- Vermindering van de totale kosten voor behandeling in het ziekenhuis kan mogelijk 4% -15% bedragen, vanwege minder infecties, verpleegdagen en heroperaties bij patiënten met een hoog infectierisico.

Hoofdstuk 5 beschrijft de resultaten van een systematische analyse van alle literatuur waarin het effect van het inbrengen van een tibiapen door middel van een infrapatellaire, semi-extended en suprapatellaire techniek op kniepijn en -functie is onderzocht en met elkaar is vergeleken. In totaal werden 114 onderzoeken geïncludeerd, waarin de resultaten van 3.499 patiënten werden beschreven. Gepoolde analyse bleek niet mogelijk voor de semi-extended techniek. Het gemiddelde percentage patiënten met anterieure kniepijn was 38% (95% betrouwbaarheidsinterval (95% BI) 32-44) voor de infrapatellaire techniek en 10% (95% BI 1-26%) voor de suprapatellaire techniek. Visueel analoge scores voor kniepijn (0-10) varieerden van 0,2 (95% BI -0,1-0,5) voor kniepijn in het algemeen tot 3,7 (95% BI 1,3-6,1) voor pijn tijdens het knielen. De gemiddelde Lysholm-scores waren 87 punten (bereik 77-97) na het inbrengen van de tibiapen via een infrapatellaire benadering en 85 punten (bereik 82-85) na het gebruik van een suprapatellaire benadering. De Iowa-kniescores waren 94 (bereik 86-96) en de scores op de Anterior Knee Pain Scale waren 76 (bereik 75-80) na een infrapatellaire benadering. De grote verscheidenheid aan uitkomstmaten, verschillen in gegevensrapportage en soms ontbrekende gegevens (gemiddelde waarde, standaarddeviatie of 95% BI) bemoeilijkten de meta-analyse.

Conclusies

- Het systematische review en de gepoolde analyse van de beschikbare literatuur liet zien dat het percentage patiënten met kniepijn na tibiapen plaatsing varieerde tussen de 10 en 38%.
- Pijnscores bleken laag en de kniefunctie was goed na infrapatellaire en suprapatellaire insertie.
- Een meer uniforme rapportage van de uitkomst van de behandeling zou helpen om de resultaten van verschillende onderzoeken met elkaar te vergelijken.

Hoofdstuk 6 onderzoekt de betrouwbaarheid, validiteit, responsiviteit, vloer- en plafondeffecten en Minimal Important Change (MIC) van de Short Musculoskeletal Function Assessment (SMFA) en Lower Extremity Functional Scale (LEFS) bij patiënten met een tibia schachtfractuur. In totaal werden 136 patiënten geïncludeerd. Interne consistentie was voldoende voor de SMFA en LEFS (sub)schalen (Cronbach α 0,84 - 0,94). De construct en longitudinale validiteit waren ook voldoende voor beide instrumenten (> 75% van de voorspelde correlaties bleken correct). Vloereffecten waren niet aanwezig. Plafondeffecten waren aanwezig bij 12 maanden voor de SMFA-subschalen disfunctie van de onderste extremiteit en hinder (respectievelijk 22% en 19%) en de LEFS (19%). De MIC's konden niet worden bepaald met de beschikbare gegevens.

Conclusies

- De SMFA en LEFS zijn betrouwbare en valide instrumenten voor het evalueren van de uitkomst bij patiënten met een tibiaschachtfractuur.
- Beide instrumenten zijn nuttig voor het monitoren van functionele beperkingen bij patiënten die een tibiaschachtfractuur hebben opgelopen gedurende tenminste de eerste 6 maanden na het letsel.

In hoofdstuk 7 werd de langetermijn incidentie van schade aan de nervus infrapatellaris na het inbrengen van een tibiapen bepaald en werd de relatie met anterieure kniepijn retrospectief onderzocht. In totaal werden 71 patiënten geïncludeerd. Na een gemiddelde follow-up van 84 maanden werden bij 43 patiënten (60%) tekenen van schade aan de nervus infrapatellaris gevonden. Kniepijn werd gemeld door 38% van de patiënten. Patiënten met anterieure kniepijn hadden significant meer sensibele stoornissen dan patiënten zonder anterieure kniepijn (p = 0,025). In totaal waren 33 tibiapennen verwijderd. Bij patiënten voor wie kniepijn de reden was voor het verwijderen van de pijn, hield de pijn bij 58% aan.

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Conclusies

- De meerderheid van de patiënten vertoont tekenen van nervus infrapatellaris letsel na behandeling met een tibiapen, zelfs na langdurige follow-up.
- Anterieure kniepijn komt voor bij grofweg 4 van de 10 patiënten na plaatsing van de tibiapen en deze patiënten hebben vaker tekenen van nervus infrapatellaris letsel.
- Na verwijderen van de pen in verband met kniepijn houdt deze pijn bij de meeste patiënten aan.

Hoofdstuk 8 beschrijft een gerandomiseerde studie die veranderingen in kniepijn na een nervus infrapatellaris block vergelijkt met lidocaïne of placebo bij patiënten met aanhoudende kniepijn na tibiapen plaatsing. Vierendertig patiënten (leeftijd 18-62 jaar) werden gerandomiseerd voor een block met lidocaïne of placebo, waarna ze 8 dagelijkse activiteiten uitvoerden (knielen, hurken, langdurig zitten met gebogen knieën, springen, traplopen, rennen, lopen en rust). Voor en na deze activiteiten werd pijn geregistreerd met behulp van een numerieke schaal (NRS; 0-10). Er werd een significante afname van de NRS voor pijn tijdens knielen na een nervus infrapatellaris blok met lidocaïne gevonden

vergeleken met placebo (–4,5 [bereik –10 tot –1] versus –1 [–9 tot 2]; p=0,002). Er waren geen verschillen tussen de beide behandelingen voor de NRS-waarden voor pijn tijdens de andere activiteiten.

Conclusies

- In vergelijking met placebo was een nervus infrapatellaris block met lidocaïne effectiever in het verminderen van pijn tijdens het knielen bij patiënten met chronische kniepijn na tibiapen plaatsing.

In **hoofdstuk 9** werden de locatie en het verloop van de infrapatellaire tak van de nervus saphenus zenuw in kaart gebracht. De infrapatellaire tak werd ontleed in 20 gebalsemde knieën. Met behulp van een computerondersteund hulpmiddel voor het in kaart brengen van chirurgische anatomie werden veilige en risico zones voor een chirurgische toegang bepaald, en werd de locatieafhankelijke richting van de zenuw berekend. Het verloop van de infrapatellaire tak is locatieafhankelijk. Geheel aan de mediale zijde van de knie loopt deze tak bijna verticaal; mediaal van de patellapees is het verloop –45° richting distaal-lateraal en op de patella en patellapees is het verloop vrijwel geheel horizontaal-lateraal. Er werden drie zones met een laag risico voor iatrogene zenuwschade geïdentificeerd: één bevindt zich aan de mediale zijde van de knie, ter hoogte van de tuberositas tibiae, waar een schuine incisie van –45° het minst kans geeft om de zenuwen te beschadigen. De twee andere zones bevinden zich mediaal van de patella (zowel craniaal als caudaal), waar horizontale incisies het minst risico geven op beschadiging van de zenuwtak(ken).

Conclusies

- De infrapatellaire tak van de nervus saphenus loopt risico op iatrogene schade bij anteromediale knieoperaties, vooral wanneer longitudinale incisies worden gemaakt.
- Er zijn drie zones met een laag risico voor een veiligere anterieure benadering van de knie.
- Het verloop van de infrapatellaire tak is locatieafhankelijk.
- Om iatrogene schade aan de zenuw te minimaliseren, moet de richting van de incisie, indien technisch mogelijk, parallel zijn aan de richting van de zenuw.

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In **Hoofdstuk 10** wordt het effect beschreven van een transversale incisie en een longitudinale incisie voor het inbrengen van een intramedullaire tibiapen. In deze multicenter gerandomiseerde gecontroleerde studie met een follow-up van 12 maanden werden volwassen patiënten met een tibia schachtfractuur voor behandeling met een intramedullaire pen gerandomiseerd voor een transversale (n=68) of longitudinale incisie (n=68). Kniepijn werd beoordeeld via Numeric Rating Scale (NRS). Andere uitkomstmaten waren kniepijn tijdens dagelijkse activiteiten, functionele uitkomst (Short Musculoskeletal Function Assessment (SMFA) en Lower Extremity Functional Scale (LEFS)), kwaliteit van leven (EQ-5D), hervatting van werk en activiteiten, complicaties en heroperaties en directe en indirecte kosten tot een jaar na een trauma. Na 12 maanden was de geschatte marginale gemiddelde kniepijnscore 2,4 (95% BI 1.6 – 3.2) in de transversale incisiegroep en 3,7 (95% BI 3.0 – 4.5) in de longitudinale groep. Regressieanalyse toonde geen significant verschil tussen beide groepen in de tijd (p = 0,239 na 12 maanden). Kniepijnscores voor dagelijkse activiteiten, functionele uitkomstscores en kwaliteit van leven waren ook vergelijkbaar tussen de groepen. Tekenen van schade aan de nervus infrapatellaris kwamen minder voor na een transversale incisie (16,4% versus 53,3%; p<0,0001). De totale (directe en indirecte) kosten per patiënt bedroegen € 16.266, waarvan 58% toe te schrijven is aan productiviteitsverlies.

Conclusies

- Een transversale incisie voor het inbrengen van een tibiale pen leidt niet tot een significant lagere kniepijnscore dan een longitudinale incisie.
- Kniepijn tijdens andere dagelijkse activiteiten, functie en kwaliteit van leven zijn ook vergelijkbaar tussen de groepen.
- Productiviteitsverlies is de belangrijkste kostenfactor voor patiënten die worden behandeld met een intramedullaire pen.

Tenslotte zijn de algemene discussie en toekomstperspectieven besproken in **hoofdstuk 11.**

Appendices &

List of publications
Contributing authors
Dankwoord
PhD portfolio
Curriculum Vitae

List of publications

Injury to the infrapatellar branch of the saphenous nerve, a possible cause for anterior knee pain after tibial nailing?
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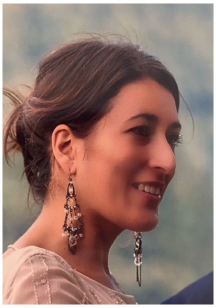
PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student	Mandala S. Leliveld
Erasmus MC Department	Trauma Research Unit, Department of Surgery
PhD period	January 2015 - January 2022
Promotor	Prof. dr. M.H.J. Verhofstad
Co-promotor	Dr. E.M.M. van Lieshout

	Year	Workload (ECTS)
PhD training		
General academic skills		
BROK (Basiscursus Regelgeving en Organisatie van Klinisch Trials (GCP course) Refresher	2019	1.5
Biomedical English Writing and Communication	2017	3.0
Research Integrity	2016	0.3
BROK (Basiscursus Regelgeving en Organisatie van Klinisch Trials (GCP course)	2015	1.5
Research skills		
Master of Science in Epidemiology	2012 - 2015	60.0
Presentations on conferences		
OTA Annual Meeting, National Harbour, USA	2016	1.0
17th European Congress of Trauma & Emergency Surgery, Vienna, Austria	2016	1.0
Symposium Challenges in Trauma, Kuopio, Finland	2015	1.0
14th European Congress of Trauma & Emergency Surgery, Lyon, France	2013	1.0
British Trauma Society Annual Scientific Meeting, Manchester, UK	2010	1.0
11th European Congress of Trauma & Emergency Surgery, Brussels, Belgium	2010	1.0
Chirurgendagen, Veldhoven, The Netherlands	2010	1.0
Traumadagen, Amsterdam, The Netherlands	2010	1.0
Teaching activities		
Supervising practicals and excursions		
Instructor and lecturer Basic Surgical Skills (Edustitch)	2014 - 2020	
Supervising Master's theses		
Jules van Haaren	2015 - 2016	2.0

Curriculum Vitae



Mandala Şenay Leliveld was born on September 26, 1985 in Arnhem, The Netherlands. After graduating high school at the Arentheem College in Arnhem in 2003 she started medical school at the Erasmus University Rotterdam. During her first clinical rotation at the Department of Surgery at the Elisabeth-Tweesteden Hospital in Tilburg, she discovered her love for trauma surgery and she was introduced to the phenomenon "anterior knee pain after tibial nailing". She set her first steps into the field of research, and used this subject for her master thesis. As it turned out, there was much more to explore on the topic, and under supervision of professor M.H.J. Verhofstad she started her PhD which eventually resulted in this doctoral thesis.

After obtaining her medical degree "cum laude" in 2010 she started her clinical career at the department of Surgery at the Elisabeth-Tweesteden Hospital in Tilburg as a resident not in training. In 2012 she started her surgical training at Hospital Gelderse Vallei, Ede, The Netherlands (Dr. R.M.H.G. Mollen) and Radboudumc, Nijmegen, The Netherlands (Dr. B. Verhoeven). The last two years of residency were dedicated to trauma surgery at the Radboudumc and Elisabeth-Tweesteden Hospital (prof. dr. P.W.H.E Vriens). After obtaining her degree as a trauma surgeon she started as a fellow hand and wrist surgery at the Orthopaedic Department at Leuven University Hospital, Belgium (prof. dr. I. Degreef).

She enjoys sports, the highlights of the past years are finishing the Alternatieve Elfstedentocht in 2017 and the Marathon des Sables in 2018. She is living together with her partner Sjaak Schipper and their two sons, Sam and Teun in Leuven.