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Intramedullary nailing versus external ring fixator for treatment of tibial fractures – a study protocol for a randomised clinical trial

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ABSTRACT

INTRODUCTION. Tibial shaft fractures are among the most common lower extremity fractures. Treatment of tibial shaft fractures with intramedullary nailing has become the treatment of choice in adults. However, commonly reported outcomes include knee pain, limitations in activities of daily living and reduction in quality of life (QOL). The literature lacks high-quality studies to document superiority of intramedullary nailing versus other surgical treatment methods. The present study aims to compare the 12-month Knee Injury and Osteoarthritis Outcome Score (KOOS) – sport and recreation activities (sport/rec) after standard intramedullary nailing with external ring fixation for adult patients with isolated tibial shaft fractures.

METHODS. This study is a multicentre randomised, prospective clinical trial. A total of 67 patients will be included in the study, and the primary outcome will be the KOOS-sport/rec at 12 months after surgery.

CONCLUSIONS. With KOOS-sport/rec as the primary outcome, the findings of the present study are expected to advance our understanding of knee pain, function and QOL, regardless of the treatment option and the outcome of the study.

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TRIAL REGISTRATION. ClinicalTrials.gov ID: NCT-03945669, version 1.1, 21 September 2022.

The incidence of tibial shaft fractures was reported to be 16.9/100,000/year, representing around 40% of all long-bone fractures in adults [1]. Treatment of tibial shaft fractures includes closed reduction and casting, internal fixation with intramedullary nails, plates and screws or external fixation. In the past decade, intramedullary nailing has become the standard method for treating tibial shaft fractures [2]. The operative procedure was reported to have high rates of union and low rates of complications [3].

Knee pain is the most common complication of intramedullary nailing in tibial shaft fractures [4]. The incidence of knee pain was reported to fall in the 10-80% range with varying follow-up times [4-7]. The association between knee pain and poorer patient-reported outcomes was frequently reported [5, 8].

While several reasons for anterior knee pain and a decrease in quality of life have been suggested, the aetiology is not fully understood [4]. Anterior knee pain may be caused by injury to the soft tissues and bones during both

the initial trauma and the following operative procedure [4]. Treatment with external ring fixators is a minimally invasive surgical procedure compared with intramedullary nailing, only requiring stab incisions for passing of half pins or wires. Moreover, external ring fixation does not require access to the tibia through the knee joint. A few studies have tested intramedullary nailing against other surgical procedures, including treatment with external ring fixators in patients with tibial shaft fractures [9, 10]. A randomised control trial by Ramos et al. [10], including 58 diaphyseal tibial fractures, reported that patients treated with intramedullary nailing had more pain and were less satisfied than those treated with an external ring fixator. Frihagen et al. [9] recently reported on 65 adult patients and found that surgery with an external fixation did not differ from surgery with intramedullary nailing in terms of quality of life (QOL) and pain at a two-year follow-up. Potential advances in the treatment of tibial shaft fractures with external fixators in adults are lacking, and further clinical trials are warranted. Compared to the studies by Ramos et al. [10] and Frihagen et al. [9], this study will use a knee-specific questionnaire as its primary outcome. We expect that a knee-specific instrument may be more sensitive to investigating knee complaints between intramedullary nailing and external fixation.

The present study aims to compare the 12-month Knee Injury and Osteoarthritis Outcome Score (KOOS) – sport and recreation activities (sport/rec) after standard intramedullary nailing in adult patients with isolated tibial shaft fractures (Arbeitsgemeinschaft für Osteosynthesefragen Foundation (AO)/Orthopaedic Trauma Association (OTA) fracture types: AO-42-).

We hypothesise that patients treated with external ring fixators report significantly better KOOS-sport/rec than patients undergoing standard surgical treatment with intramedullary nailing 12 months after surgery.

PATIENTS AND METHODS

Study setting

This study is a pragmatic multicentre, randomised and prospective clinical trial in which standard intramedullary nailing is compared with an external ring fixator for patients with isolated tibial shaft fractures. The trial adheres methodologically to the CONSORT guideline. The study has been pre-registered with ClinicalTrials.gov (**NCT03945669)** and has been approved by the Ethics Committee of the North Denmark Region (N-20180075) and the Danish Data Protection Agency (ID 2019-151) based on the present trial protocol using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT statement).

Participants

Patients will be recruited from six Danish hospitals: Aalborg University Hospital, Aarhus University Hospital and regional hospitals in Hjoerring, Thisted, Farsoe and Viborg.

Patients who meet the criteria outlined in **Table 1** will be included by consecutive sampling and randomised (1:1) to the hospitals' standard surgical intramedullary nailing procedure or to external ring fixation.

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria
Fracture of the tibial shaft: AO/OTA classification type: 42-A1-A3, -B1-B3 and -C1-C3
The fracture type is deemed operable with an intramedullary nail
Exclusion criteria
< 18 years of age
Open fracture, excluding the use of intramedullary nails
History of severe systemic diseases or cancer
Bilateral tibial shaft fracture
Multiple fractures
Pregnancy
Patients without gait function prior to fracture
Cognitive impairment

OA = Arbeitsgemeinschaft für Osteosynthesefragen Foundation;
OTA = Orthopaedic Trauma Association.

Surgical procedures

Details of the two surgical procedures are available in the **supplemental materials** (https://content.ugeskriftet.dk/sites/default/files/2023-11/a05230281-supplementary.pdf).

Outcome assessments

The SPIRIT diagram presents the follow-up schedule (**Figure 1**). The full overview of the follow-up is presented in **Table 2.**

FIGURE 1 Draft CONSORT flow diagram.

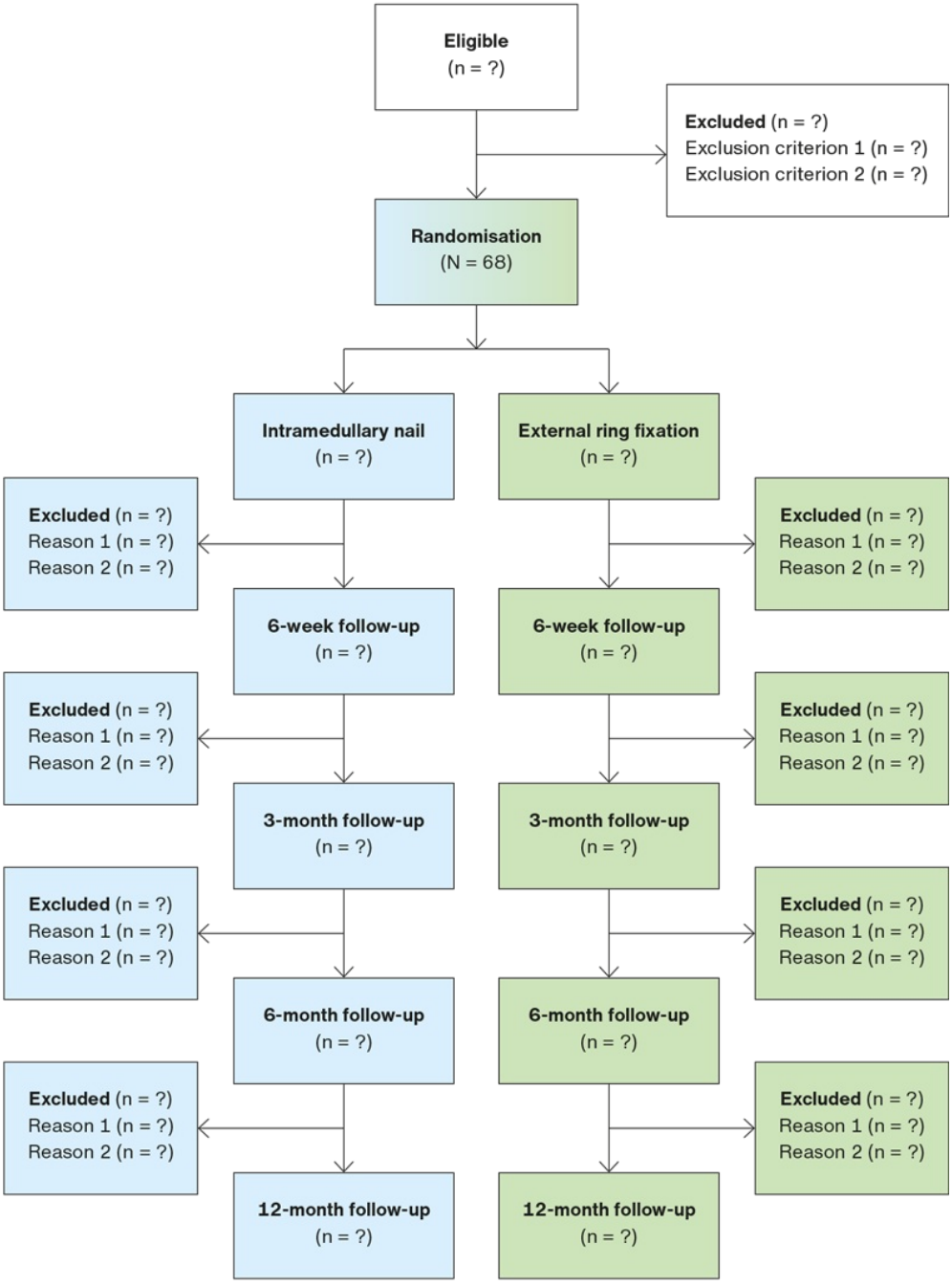

TABLE 2 Follow-up diagram.

	Enrolment	6 weeks	3 months	6 months	12 months
Randomisation	x				
Baseline variables	x				
Intervention	x				
Objective measurements		x	x	x	x
Patient-reported outcomes		x	x	x	x
Pain		x	x	x	x
X-ray	x	x	x	x	x
Complications	x	x	x	x	x

Primary outcome and endpoint

The primary outcome will be measured by the KOOS-sport/rec at a 12-month follow-up [11]. The questionnaire includes five subscales: pain, activity of daily living (ADL), symptoms, sport/rec, and QOL. KOOS scores will be collected at all follow-ups.

Secondary outcomes

The Foot and Ankle Outcome Score (FAOS) is a standardised patient-reported questionnaire developed to evaluate foot and ankle problems [12]. The questionnaire includes five subscales: pain, ADL, symptoms, sport/rec, and QOL. FAOS scores will be collected at all follow-ups.

The EuroQol-5D-5L (EQ-5D) is a standardised questionnaire developed to evaluate generic QOL [13]. It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Furthermore, the EQ-5D contains a self-rated health scale on a 20 cm vertical, visual analogue scale (VAS) with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine.' EQ-5D scores will be collected at all follow-ups. This will also allow for a subsequent cost-effectiveness analysis.

The pain intensity of the injured leg for worst pain during the past 24 hours and pain at rest are measured on a 10 cm VAS with the endpoints "no pain" and "maximal pain." Furthermore, the use of analgesics is collected. Pain intensity and analgesics will be collected at all follow-ups.

Radiological assessment of the injured leg will be performed prior to surgery and post-operatively at six weeks; and three, six, and 12 months; and as deemed necessary by the surgeon. Fracture classification will be performed according to the AO classification and will be conducted on the preoperatively obtained radiographs [14]. Bone union will be assessed by the surgeon in charge of treatment. Bone union is defined as: *i*) visible callus formation on at least three of four cortices on standard X-ray examination, no visible fracture line, no pain from the fracture at weight-bearing and following clinical examination (defined as: union), *ii*) visible callus formation on at least one of four sides, with a visible fracture line (defined as: partial union) and *iii*) visible fracture lines and no visible callus formation (defined as: no union) [15].

Knee and ankle range of motion are measured with the patient supine on an examination table. The full range of passive motion in both knees and ankle joints will be measured using a standard goniometer. Range of motion will be measured at all follow-ups.

The Patient-Acceptable Symptom State (PASS) is included to express the highest level of symptom beyond which patients consider themselves well. PASS will be included by one specific question: "Based on your current

symptoms, would you seek professional medical treatment if you were not part of this study?" PASS will be collected at the three-, six- and 12-month follow-up.

All possible adverse events, including (but not limited to) refracture, superficial and deep infection, deep venous thrombosis, reoperations and unscheduled removal of pins and wires will be continuously recorded throughout the study period and registered in an adverse event database.

Furthermore, information regarding time to return to work and time to return to sport will be obtained. Explorative outcomes will include an economic evaluation and a qualitative study investigating patients' experience between groups.

Sample-size calculation

Due to the lack of previous studies utilising the primary outcome measure KOOS-sport/rec for tibial fractures, an interim analysis is preplanned following the 12-month follow-up of the first 20 patients to calculate the final sample size. The interim analysis will be blinded to the treatment arm and only the mean difference in the two groups will be extracted. With an observed mean difference of 20 points on the KOOS-sport/rec and a standard deviation of 25.5, the sample size calculation showed that inclusion of 28 patients in each group ($n_1 = n_2 = 28$) will allow for detection of a statistically significant difference in KOOS-sport/rec with a power of 80% and a significance level at 0.05 (two-sided). We aim to include a total of 67 participants to account for missing data and an estimated drop-out rate of 20%.

Recruitment

One senior on-call orthopaedic traumatologist will assess the patient, radiographs and, if available, computed tomographies (CT). When the patient's treatment involves intramedullary nailing, they become eligible for participation in the study. Upon acceptance of participation and signing of the consent form, patients will be enrolled in the study. Following acceptance to enter the study, the surgeon requests a digital randomisation key whereby the treatment option is revealed. Theoretically, cross-over between the groups could occur in case that treatment allocation were revealed to the patient before the surgery or in case of serious adverse events such as deep infection, making it necessary to change the treatment strategy. The patient enrolment flow is presented in Figure 1.

Randomisation and blinding

Block randomisation (block-size 3) and stratification will be used to ensure an equal distribution of procedures at each recruitment site and an equal distribution by age groups (18-30 years, 31-50 years, 51+ years). Because of the nature of the surgery, blinding of the surgeon and clinical accessor is not possible. The patient will be blinded to the surgical method until after surgery. The data assessor is a physiotherapist/nurse not involved in treating the patient. An independent statistician blinded to group allocation will perform the analysis based on a predefined analysis plan.

Data collection

All patients presenting with a tibial shaft fracture (AO 42-) [14] admitted to one of the participating hospitals will be registered in the intramedullary nailing versus external ring fixation (IMVEX) database. Following the initial assessment of inclusion and exclusion criteria (Table 1), patients eligible for inclusion in the study will be presented with both written and oral information regarding the study.

Data management

Good clinical practice guidelines will be followed throughout every aspect of the study. Accordingly, all data will be kept in a password-protected electronic database with logging of data activities, and data will be kept

confidential throughout and after the study.

Statistics

Statistical principles

All statistical tests conducted to explore between-group effects will consist of two-sided tests with a 5% significance level ($p \leq 0.05$). Confidence intervals will be reported two-sided at 95%.

The primary analysis will follow the intention-to-treat principle. A secondary per-protocol analysis will be performed, excluding patients not attending the 12-month follow-up. Notably, crossovers are unlikely in the study design as explained above.

In case of missing follow-up data, no imputation will be performed.

Thresholds on the minimal clinical difference on the KOOS vary between subscale scores and studies [16,17]. A difference of nine points on the KOOS-sport/rec score is our predefined threshold for clinically important differences on conclusion of the study.

Descriptive statistics

Between-group baseline characteristics will be presented as mean or frequencies with standard deviation (SD) or as percentages in a table. Baseline demographic such as age, gender, Body Mass Index, smoking status, mode of injury, energy of injury, employment, fracture classification (AO) and comorbidity will be reported.

Primary analysis

The primary analysis will be calculated for the KOOS-sport/rec at the 12-month follow-up. A linear mixed regression model will be used to estimate the mean difference in KOOS-sport/rec scores between the two treatment arms. Patients will be considered in regard to random effects and at follow-up (at six weeks and three, six, and 12 months); treatment arm and interaction will be treated as fixed effect variables. Mean scores, standard deviations, mean differences, 95% confidence intervals and p-values will be reported. Conclusions will be drawn only based on differences or the lack hereof at the primary endpoint at 12 months.

Secondary analyses

Secondary analyses at the six-week, three-, six- and 12-month endpoints will be calculated for the KOOS subscales (pain, symptoms, ADL, sport/rec, and QOL), FAOS subscales (pain, symptoms, ADL, sport and QOL, EQ-5D index and subscales (mobility, self-care, usual activity, pain, anxiety) EQ-VAS, knee and ankle ROM, self-reported pain reactions and PASS. The difference between the two treatment arms will be estimated by a mixed-model regression model as described above. Mean scores, SD, mean differences, 95% confidence intervals and p-values will be reported in a table.

Furthermore, a mixed-model repeated measure will be used to take the repeated measurements into account and report the within group development/recovery for the KOOS subscales (pain, symptoms, ADL, sport/rec and QOL), the FAOS subscales (pain, symptoms, ADL, sport/rec and QOL, the EQ-5D index and subscales (mobility, self-care, usual activity, pain, anxiety), the EQ-VAS, knee and ankle ROM, self-reported pain reactions and PASS at all follow-ups. The following aspects will be incorporated into the model: the effects of the surgery procedure, follow-up time and interaction.

Adverse events and radiology, including bone union and alignment/length, will be reported across treatment arms and presented in a table.

Ethical considerations

Both intramedullary nailing and external ring fixators are valid and commonly used treatment methods for tibial shaft fractures. The choice of method often depends on the complexity of the fracture. Agreement to participate will likely not result in an inferior treatment compared with the current standard treatment of intramedullary nailing.

Trial registration: ClinicalTrials.gov ID: NCT-03945669, version 1.1, 21 September 2022.

DISCUSSION

Based on the findings of the present study, the understanding of knee pain function and QOL following treatment of tibial shaft fractures is expected to improve, regardless of the outcome of the trial. This study may improve the quality of informed consent when counselling tibial shaft fracture patients in the future. The study is likely to contribute to choosing the right treatment for the right patient for one of the most common long-bone fractures worldwide, which often results in disability, pain and decreased QOL.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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Supplementary material **https://content.ugeskriftet.dk/sites/default/files/2023-11/a05230281-supplementary.pdf**

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