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Smoking, Obesity, and Disability Benefits or Litigation Are Not Associated with Clinically Important Reductions in Physical Functioning After Intramedullary Nailing of Tibial Shaft Fractures: A Retrospective Cohort Study

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Abstract

Background Forty percent of long bone fractures involve the tibia. These fractures are associated with prolonged recovery and may adversely affect patients' long-term physical functioning; however, there is limited evidence to inform what factors influence functional recovery in this patient population.

Question/purpose In a secondary analysis of a previous randomized trial, we asked: What fracture-related, demographic, social, or rehabilitative factors were associated with physical function 1 year after reamed intramedullary nailing of open or closed tibial shaft fractures?

Methods This is a secondary (retrospective) analysis of a prior randomized trial (Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures; TRUST trial). In the TRUST trial, 501 patients with unilateral open or closed tibial shaft fractures were randomized to self-administer daily low-intensity pulsed ultrasound or use a sham device, of which 15% (73 of 501) were not followed for 1 year due to early study termination as a result of futility (no difference between active and sham interventions). Of the remaining patients, 70% (299 of 428) provided full data. All fractures were fixed using reamed (298 of 299) or unreamed (1 of 299) intramedullary nailing. Thus, we excluded the sole fracture fixed using unreamed intramedullary nailing. The co-primary study outcomes of the TRUST trial were time to radiographic healing and SF-36 physical component summary (SF-36

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PCS) scores at 1-year. SF-36 PCS scores range from 0 to 100, with higher scores being better, and the minimum clinically important difference (MCID) is 5 points. In this secondary analysis, based on clinical and biological rationale, we selected factors that may be associated with physical functioning as measured by SF-36 PCS scores. All selected factors were inserted simultaneously into a multivariate linear regression analysis.

Results After adjusting for potentially confounding factors, such as age, gender, and injury severity, we found that no factor showed an association that exceeded the MCID for physical functioning 1 year after intramedullary nailing for tibial shaft fractures. The independent variables associated with lower physical functioning were current smoking status (mean difference -3.0 [95% confidence interval -5 to -0.5]; p = 0.02), BMI > 30 kg/m^2 (mean difference -3.0 [95% CI -5.0 to -0.3]; p = 0.03), and receipt of disability benefits or involvement in litigation, or plans to be (mean difference -3.0 [95% CI -5.0 to -1]; p = 0.007). Patients who were employed (mean difference 4.6 [95% CI 2.0 to 7]; p < 0.001) and those who were advised by their surgeon to partially or fully bear weight postoperatively (mean difference 2.0 [95% CI 0.1 to 4.0]; p = 0.04) were associated with higher physical functioning. Age, gender, fracture severity, and receipt of early physical therapy were not associated with physical functioning at 1-year following surgical fixation.

Conclusion Among patients with tibial fractures, none of the factors we analyzed, including smoking status, receipt of disability benefits or involvement in litigation, or BMI, showed an association with physical functioning that exceeded the MCID.

Level of Evidence Level III, therapeutic study.

Introduction

Forty percent of long-bone fractures in adults involve the tibia [7], with an estimated incidence of 17 per 100,000 per year in the developed world [17, 41]. The incidence of tibial fractures is expected to rise in countries with developing economies because of the growth of loosely regulated and unsafe public transportation [42]. Patients undergoing tibial fracture fixation may experience adverse events such as prolonged knee pain [19, 31], muscle weakness [35], reoperation [28], and angular malalignment [37].

Several studies have disagreed in terms of how patients achieve (or do not achieve) functional recovery after tibial fractures [18, 30, 37]. For example, a cross-sectional study of 49 patients with tibial fractures found substantial limitations in activities and restrictions in quality of life at 1 year after injury compared with a reference population [18]. Another investigation of 1319 patients with surgically managed tibial fractures found that functional outcome scores at 1 year, as measured by the SF-36 physical component summary (PCS) score, were much lower than preinjury scores [20]. However, there are limited data with regard to which factors are associated with functional recovery post–tibial fracture fixation. Identifying such factors could allow health care providers tailor their management plan to maximize function in this patient population.

Therefore, we performed a secondary analysis of a previous randomized trial [33] to ask: What fracture-related, demographic, social, or rehabilitative factors were associated with physical function 1 year after reamed intramedullary nailing of open or closed tibial shaft fractures?

*Members of the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) are listed in an Appendix at the end of this article.

The Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) was an investigator-initiated trial, supported by grants from the Canadian Institutes of Health Research (CIHR) (MCT 67815, Co-PIs: GH Guyatt, MB) and an industry grant in an amount of USD more than USD 1,000,001 from Smith & Nephew (funds provided between the period of April 2007 and April 2011). The funders had no role in the design and conduct of the current study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Smith & Nephew personnel reviewed initial drafts of the trial protocol and raised many issues about alternative approaches to study design. Issues regarding the protocol were resolved through negotiation between Smith & Nephew and the trial steering committee. Final decisions regarding the protocol and issues that arose during the conduct of the trial were the purview of the trial steering committee. The investigators had full access to all trial data. Smith & Nephew had no role the initial preparation of the current study manuscript but had the right to review the manuscript and make non-binding comments and suggestions.

Each author certifies that neither he nor she, nor any member of his or her immediate family, has funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

This work was performed at McMaster University, Hamilton, ON, Canada, and the University of Western Ontario, London, ON, Canada.

Patients and Methods

Study Design

This study used data from the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) [33]. In the TRUST trial, 501 patients with unilateral open or closed tibial shaft fractures were randomized postoperatively to self-administer daily low-intensity pulsed ultrasound (LIPUS) (n = 250). The TRUST trial protocol was approved by the McMaster University research ethics board (REB#08-171) and local boards at 42 participating trauma centers in Canada and the United States. This trial was registered at www.clinicaltrials.gov with the identifier NCT00667849. Skeletally mature patients with an open (Gustilo Types I to IIIB) or closed (Tscherene Grade 0 to 3) tibial fracture amenable to intramedullary nail fixation were eligible for enrollment in the TRUST trial. The exclusion criteria were pilon fractures, tibial shaft fractures extending into the knee or ankle indicating reduction, pathologic fractures, bilateral tibial fractures, segmental fractures, spiral fractures longer than 7.5 cm, concomitant injuries that were likely to impair function, tibial fractures that showed less than 25% cortical contact and more than a 1-cm gap after intramedullary nail fixation, likely problems with maintaining follow-up, cognitive impairment or language difficulties, women who were pregnant or nursing or planned to become pregnant during the enrollment period, patients with osteobiologics or implants at the site of their tibial fracture, and those with active implanted devices such as cardiac pacemakers.

Of the 501 participants enrolled, only two patients received unreamed nails. The primary study endpoints of the original trial were time to radiographic healing within 1 year of fixation and SF-36 PCS scores. The industry sponsor conducted an unplanned interim analysis of blinded data from 237 TRUST participants with 1-year follow-up. The results showed no difference in radiographic healing or physical function between treatment groups, and the sponsor declined to continue funding the trial. The final results showed no impact on SF-36 PCS scores between patients treated with LIPUS and the control group (mean difference 0.55 [95% confidence interval -0.75 to 1.84]; p = 0.41) or for the interaction between time and treatment (p = 0.30). Moreover, there was no difference in time to radiographic healing between the groups (hazard ratio 1.07 [95% CI 0.86 to 1.34]; p = 0.55). In this secondary analysis, we explored factors associated with physical functioning in this patient population.

Measuring Physical Functioning

We measured physical function via SF-36 PCS scores at 1 year after intramedullary nail fixation. The SF-36 is a widely accepted, well-validated [11, 22, 40] instrument that measures quality of life across eight domains, including physical functioning, role limitations because of physical health, role limitations because of emotional problems, energy level and fatigue, emotional well-being, social functioning, pain, and general health. These scores can be aggregated into physical and mental summary scores. SF-36 PCS scores range from 0 (worst possible function) to 100 (best possible function). The minimum clinically important difference (MCID) in SF-36 PCS scores has been estimated to be 5 points [1, 39].

Selection of Prognostic Factors

We identified 10 factors potentially associated with PCS scores at 1 year using data collected as part of the TRUST trial, based on biologic and clinical rationales and reference to previous studies [3, 5, 16, 24]: (1) age, by decade as a continuous variable; (2) gender (men or women); (3) current smoker (yes or no); (4) employment status at the time of injury (employed or not); (5) BMI (18-25 kg/m^2, 25-30 kg/m^2, or > 30 kg/m^2); (6) fracture severity (open or closed); (7) receipt of disability benefits or involved with a lawyer/ongoing litigation as a result of this injury (yes or likely I will versus no or it's possible I will); (8) receipt of physiotherapy by 6 weeks (yes or no); (9) interventions administered in the TRUST study: LIPUS and sham therapy [29]; and (10) surgeon's advice to bear weight on the limb soon after surgery (partial or full weightbearing versus nonweightbearing). The decision to recommend weightbearing was based on surgeons' discretion; however, it was often influenced by the degree of cortical contact.

Patients

Of 501 eligible patients enrolled in the TRUST trial, 73 patients were followed for fewer than 12 months because of the industry sponsor's decision to stop the study early (Fig. 1). As a result, we consider these data to be missing at random, and as such, they are unlikely to bias the study's results, as the reason for discontinuation (stoppage by the sponsor) would not introduce systematic differences in patients before and after the trial was stopped [21]. Of the remaining patients, 70% (299 of 428) provided complete baseline data and completed the SF-36 questionnaire at 1 year of follow-up. All fractures were fixed using reamed (298 of 299) or unreamed (1 of 299) intramedullary nailing; however, we excluded the patient who underwent unreamed nailing for homogeneity, and 298 participants were included in our analysis. Baseline characteristics were similar between patients eligible for our study and all patients enrolled in the TRUST trial (Table 1).

The mean age of study participants was 39 ± 14 years, and participants were predominantly male (65% [195 of 298]). The

Table 1. Patient characteristics

Characteristic	Current cohort (n = 298)	All TRUST patients (n = 501)
Baseline patient characteristics		
Age in years, mean ± SD	39 ± 14	38 ± 14
Men, % (n)	65 (195)	69 (345)
Current smoker, % (n)	29 (87)	33 (165)
Diabetes, % (n)	5 (14)	6 (30)
Employed, % (n)	76 (226)	74 (368)
BMI in kg/m^2, % (n)		
18-25	38 (111)	39 (197)
25-30	36 (106)	34 (170)
> 30	27 (81)	26 (129)
Fracture characteristics, % (n)		
Open fracture	20 (61)	23 (114)
AO classification		
Class A	67 (201)	67 (337)
Class B	30 (89)	30 (148)
Class C	3 (8)	3 (15)
Gustilo-Anderson classification		
Type I	11 (34)	10 (51)
Type II	5 (14)	7 (34)
Types IIIA and IIIB	4 (13)	6 (29)
Tscherne classification		
0	26 (77)	25 (126)
1	46 (137)	44 (220)
2	7 (22)	7 (37)
3	1 (2)	1 (5)
Treatment characteristics, % (n)		
Randomization group		
LIPUS	51 (152)	50 (250)
Sham	49 (146)	50 (251)
Postoperative weightbearing status		
weightbearing Non	47 (141)	44 (220)
Partial or full weightbearing	52 (157)	56 (281)
Receiving physiotherapy at 6 weeks	30 (88)	28 (141)
Benefits, % (n)		
Receiving disability benefit or lawyer/litigation involvement		
No or it is possible I will	62 (185)	60 (299)
Yes or likely I will	38 (113)	35 (175)

LIPUS = low-intensity pulsed ultrasound.

mean PCS score at 1-year postsurgery, among respondents, was 50 ± 8. The proportion of the study sample who were current smokers was 29% (87 of 299), and the incidence of diabetes was 5% (14 of 299). Most of the included patients were employed (76% [226 of 298]). About 1 in 5 tibial fractures were open (20% [61 of 298]), and 13 patients had Gustilo-Anderson Types IIIA and IIIB fractures (Table 1).

Statistical Analysis and Model Validation

Given that the TRUST trial was a no-difference study, we pooled patients into a single group for the current study. We did, however, include treatment (LIPUS or sham) as a variable in our adjusted analysis. We report the mean and SD of continuous variables and the frequency of occurrences and

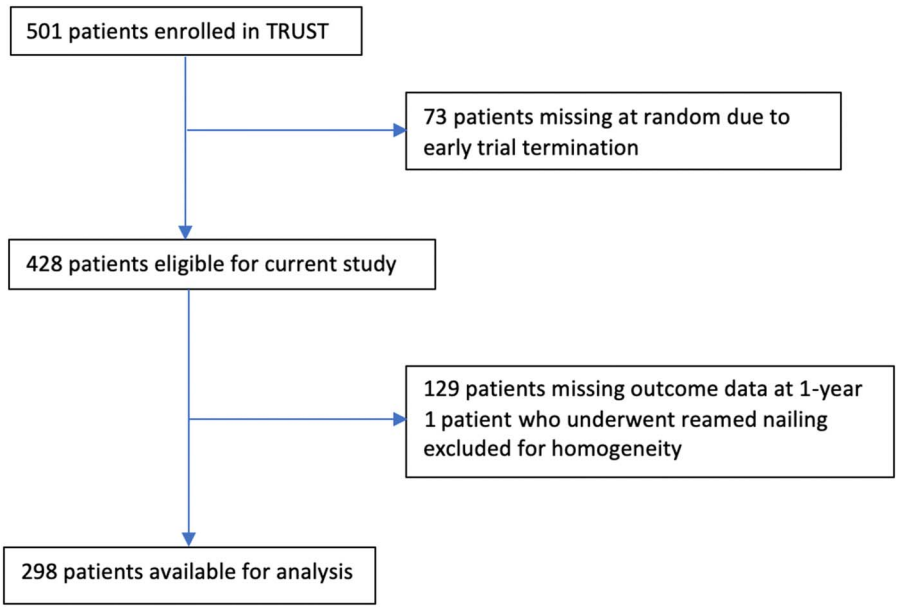

Fig. 1 Flowchart of patient selection process for this study.

percentages for categorical variables. We constructed a linear regression model to explore the association between our independent factors and SF-36 PCS scores at 1 year after intramedullary nailing of tibial fractures. All participants with incomplete data were excluded from the analysis, and all potential prognostic factors were entered simultaneously into the model. We calculated that we would require at least 100 patients with complete data to avoid overfitting our regression model (10 respondents for each level of independent variable considered) [24]. We excluded independent variables with fewer than 50 observations, unless we were able to collapse them with other related variables to exceed this threshold.

We tested for multicollinearity between included variables using the variance inflation factor statistic and excluded variables with a variance inflation factor ≥ 5. We report mean differences with associated 95% CIs and p values for all independent variables in our adjusted regression analysis. We calculated the r^2 value, which reflects the amount of variance in the dependent variable that is explained by the factors in the model. In addition, we performed an F-test to determine the overall significance of the model. All analyses were performed using IBM SPSS Statistics for Macintosh, version 25 (IBM Corp, Armonk, NY, USA), using two-tailed tests with a significance level of alpha less than or equal to 0.05.

Standardized residual plots showed no violation of model assumptions. The variance inflation factor was less than 5 for each independent variable, suggesting no problems with multicollinearity. Our model explained 15% of the variation (adjusted $r^2 = 0.15$) in SF-36 PCS scores at 1 year after intramedullary nail fixation. The F-test showed that the model was significant ($p < 0.001$); thus, our model provides a better fit than the intercept-only model.

Results

In our adjusted analysis, no single factor showed an association with physical functioning that exceeded the MCID of 5 points. Independent variables associated with lower physical functioning were current smoking status (mean difference -3 [95% CI -5 to -0.5]; p = 0.02), BMI > 30 kg/m^2 (mean difference -3 [95% CI -5 to -0.3]; p = 0.03), and receipt of disability benefits or involvement in litigation, or plans to be (mean difference -3 [95% CI -5 to -1]; p = 0.007). Employment at the time of injury (mean difference 4.6 [95% CI 2 to 7]; p < 0.001) and advice by surgeons to partially or fully bear weight postoperatively (mean difference 2 [95% CI 0.1 to 4]; p = 0.04) were associated with higher physical functioning. Age, gender, fracture severity, and receipt of early physical therapy were not associated with 1-year physical functioning. (Table 2).

Discussion

Tibial shaft fractures may result in sustained functional limitations for patients. Therefore, efforts should be made to improve and tailor management to maximize function. We used data collected prospectively as part of a randomized controlled trial to perform our study. None of the factors we studied showed an association with physical function at 1 year that met the MCID.

Limitations

Our study does have limitations. Firstly, the TRUST trial was prematurely terminated because of perceived futility by its industry sponsor. Early trial termination by the

Table 2. Multivariable linear regression with SF36 PCS scores as the dependent variable

Independent variable	Adjusted mean difference (95% CI)	p value
Baseline patient characteristics		
Age (per 10-year increase)	-0.4 (-1.0 to 0.1)	0.29
Gender		
Women	Reference category	
Men	-0.40 (-2.0 to 1.6)	0.68
Smoking status		
Non-smoker or prior smoker	Reference category	
Current smoker	-3.0 (-5.0 to -0.5)	0.02
Employment status		
Unemployed	Reference category	
Employed	4.6 (2.0 to 7.0)	< 0.001
BMI (kg/m^2)		
18-25	Reference category	
25-30	-2.0 (-4.0 to 0.4)	0.11
> 30	-3.0 (-5.0 to -0.3)	0.03
Fracture characteristics		
Fracture type		
Open fracture	Reference category	
Closed fracture	2.0 (-0.20 to 4.0)	0.08
Treatment characteristics		
Randomization group		
Sham	Reference category	
LIPUS	1.0 (-1.0 to 3.0)	0.18
Postoperative weightbearing status		
Nonweightbearing		
Partial or full weightbearing	Reference category	
Receiving physiotherapy at 6 weeks	2.0 (0.1 to 4.0) -1.0 (-3.0 to 1.0)	0.04 0.25
Benefits		
Receiving disability benefit or lawyer/litigation involvement		
No or it is possible I will	Reference category	
Yes or likely I will	-3.0 (-5.0 to -1.0)	0.007

LIPUS = low-intensity pulsed ultrasound.

industry sponsor based on unplanned interim analyses may be regarded as inappropriate and sometimes ethically problematic; however, missing patient outcome data due to early stoppage of the TRUST trial may reasonably be considered to be missing at random, and therefore do not introduce bias into our results. Secondly, our cohort study had a 30% loss to follow-up; however, baseline characteristics of patients with missing outcome data were not different from included patients in terms of age, gender, smoking status, diabetes, and fracture severity, and so study attrition seems unlikely to have exerted any strong bias on our main findings. Thirdly, the results of this study are limited to the variables that were collected as part of the TRUST trial and do not include all potential prognostic factors (such as anxiety or socioeconomic status). This was reflected in our analysis, as the 10 variables included in our model explained only 15% of the variability of 1-year SF-36 PCS scores. Fourthly, the SF-36 PCS is a generic health-related quality of life questionnaire and some may question its sensitivity to change in fracture patients. Our decision to use the SF-36 over other available instruments was based on its widespread use in orthopaedics and evidence of its validity in a previous study evaluating ankle fracture outcomes [2]. Moreover, we have compared the Short Musculoskeletal Function Assessment Dysfunction Index (SMFA DI) and SF-36 PCS scores among 1319 patients

undergoing operative management of tibial fractures. The SMFA DI and SF-36 PCS scores were highly correlated at 3, 6, and 12 months postsurgical fixation, and there was no difference in the mean standardized change scores for SMFA DI and SF-36 PCS, from 3 to 12 months post–surgical fixation [4]. Lastly, 1-year SF-36 PCS scores were not adjusted with scores at baseline, as baseline scores were not collected as part of the main TRUST trial, and thus, differences found in our results could be attributable to differences present at baseline.

Factors Associated with Functional Recovery

Our participants' characteristics are comparable to those of patients with tibial shaft fractures in other studies in terms of age, gender distribution, and smoking status [32, 36]. However, in contrast to many other studies [8, 9, 10, 12, 13, 23, 27, 29, 34, 38], none of the point estimates of fracture-related, demographic, social, or rehabilitative factors were associated with clinically important differences in physical function 1 year after intramedullary nailing of open or closed tibial shaft fractures. Nonetheless, point estimates could be far removed from the true (mean) value of the population, whereas estimate of precision details the range of the where the true value might plausibly lie. Moreover, given that the 1-year PCS measures in this study were derived from an adjusted model, patients who have combined factors associated with lower physical functioning can have lower physical function. For example, a patient who currently smokes, receives disability benefit or is involved in a litigation/lawyer, and has a BMI of > 30 kg/m^2 can have a PCS score lower by 9 points compared with the mean. However, only 3% (9 of 298) of study participants had a combination of these factors.

Studies have found that smoking negatively affects orthopaedic patients due to impaired wound healing [10], higher rates of surgical site wound infection [29], and increased risk of nonunion [13]. Moreover, smoking was found to be associated with lower health-related quality of life in patients with other diseases [23, 27] and in the general population [9, 38]. However, we found no clinically important association between smoking and lower levels of physical functioning, but the magnitude of association was below the MCID. Likewise, although previous studies have found that patients with higher BMI reported lower physical functioning after surgery [8, 12, 34], we found that the decreases in scores for physical function observed among patients with high BMI (>30) were not of a clinically important magnitude in our study. A study by Houben et al. [15] concluded that delayed weightbearing increases the impaired healing risk in patients with tibial shaft fractures. We found that patients who were advised to fully or partially bear weight postoperatively by their surgeon reported higher physical function at 1 year compared with those who were advised to avoid bearing weight, but again, the magnitude of the association fell below the MCID.

We found that being employed at the time of injury was associated with higher 1-year SF-36 PCS scores, the magnitude of which approximated the MCID. The reasons for this are not clear; however, many TRUST patients were recruited from US trauma centers, and most US workers have access to healthcare insurance through their employer [6]. Most personal bankruptcies in the United States are the result of medical expenses [14], and fear of losing health insurance is likely a powerful incentive to pursue recovery and return to work. We found that receipt of disability benefits or involvement in litigation (or plans to be) was associated with a small reduction in physical functioning at 1 year that fell below the MCID. However, a separate analysis of the TRUST trial found disability benefits or litigation was associated with a 29% increased risk of prolonged unemployment [25], suggesting that return to work after injury is not simply a measure of physical capacity.

In keeping with our findings, neither age nor gender have been shown to have an association with functional outcomes in previous studies of patients with tibial fractures [3, 5, 16]. Our finding that fracture severity is not associated with functional recovery is not consistent with prior studies that have found worse function at 1 year with open fractures than with closed fractures [3, 16]. This no-difference finding may have been a function of the limited number of patients with open fractures, specifically high-grade fractures, who were available for analysis (n = 13).

Conclusion

In summary, we found no factors that were associated with clinically important differences in physical functioning 1 year after tibial fracture repair. Our findings highlight the importance of contextualizing prognostic factors and reading other studies' results carefully with respect to effect sizes; not all "statistically significant" differences are likely to be important to patients, and statistical findings should not be conflated with clinical importance.

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