PREDICTORS OF PATIENT REPORTED PAIN AFTER LOWER EXTREMITY NONUNION SURGERY: THE NICOTINE EFFECT

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ABSTRACT

Background: Nonunion of long bone fractures is a serious complication for many patients leading to considerable morbidity. The purpose of this study is to elucidate factors affecting continued pain following long bone nonunion surgery and offer better pain control advice to patients.

Methods: Patients presenting to our institutions for operative treatment of long bone fracture nonunion were enrolled in a prospective data registry. Enrolled patients were followed at regular intervals for 12 months using the Short Musculoskeletal Function Assessment (SMFA), visual analog scale (VAS), physical examination, and radiographic examination. The registry was reviewed to identify patients with a tibial or femoral nonunion that went on to union with complete follow up. Univariate analyses were conducted to identify patient characteristics associated with postoperative pain. Identified patient factors with univariate p-values <0.1 were included in multivariate linear regression models in order to identify risk factors for pain 3 months, 6 months, and 12 months after nonunion surgery.

Results: Ninety-one patients with tibial or femoral nonunion who went on to union and had complete follow-up were identified. A Friedman test revealed mean pain score decreased significantly by 3 months postoperatively (p<0.0005). Univariate analyses demonstrated age (p=0.016), days from injury to nonunion surgery at our institution (p=0.067), smoking status (p<0.0005), wound status at time of injury (p=0.085), anesthesia (p=0.045), and nonunion location in the bone (p=0.047) were associated with postoperative pain in at least one time point postoperatively. These were included in multivariate models that revealed nonunion location (p=0.035) was predictive of pain 3 months postoperatively, smoking status was predictive of pain 3 months (p=0.012) and 6 months (p<0.0005) postoperatively, and days from injury to nonunion surgery at our institution was predictive of pain 6 months (p=0.024) and 12 months (p=0.004) postoperatively.

Conclusions: Healed patients have improved pain levels after lower extremity nonunion surgery. Orthopedic surgeons should stress smoking cessation programs and minimize delay to nonunion surgery, in order to maximize pain relief in this patient cohort.

INTRODUCTION

Fractures are a common injury in the United States with an estimated 50% of Americans sustaining a fracture by age 65.[1] A possible complication after a fracture is failure to heal and subsequent fracture nonunion. In the United States, an estimated 100,000 fractures fail to heal and progress to nonunion each year.[2] Fracture nonunion leads to physical and psychological morbidity,[3] and pain.[4] Patients with tibial nonunions report physical and mental health outcomes worse than patients that have suffered a myocardial infarction.[5] Nonunions are economically costly leading to increased treatment costs[6] and numbers of days missed from work.[7] With treatment, patients with nonunion can have significant improvement in function and pain relief.[4]

Despite reduction in pain levels following nonunion treatment, some patients may still have residual pain. In a cohort of patients followed after nonunion surgery, Egol et al. showed mean pain level on a visual analog scale (VAS) was 2.8 ± 2.5 12 months postoperatively.[4] Similarly, Taormina et al demonstrated mean 12 month VAS pain levels of 2.6 in patients treated for fracture nonunion.[8] This is consistent with findings by Tay et al., demonstrating that 72% of patients with fracture nonunion report continued pain 12 months after injury.[7] Despite improvements in pain level, some patients have residual pain. Chronic pain can be difficult to treat. This is especially true in patients with fracture nonunion who are more likely to be prescribed

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Table I. Friedman Test comparing pain at 3, 6, and 12 months after nonunion surgery

Comparison	Adjusted p-value
3 months – 6 months	1.000
3 months – 12 months	1.000
6 months – 12 months	0.813

opioids for a prolonged period of time.[6] The purpose of this study was to find patient and treatment specific variables predictive of pain following nonunion surgery.

METHODS

Patients treated operatively at our institution by one of three orthopedic traumatologists for long bone fracture nonunion were enrolled in a prospective registry using an institutional review board approved protocol. Nonunion was defined as lack of progression in radiographic and clinical healing over a three month period.[9,10] Patients provided demographic information, preoperative Short Musculoskeletal Function Assessment (SMFA), VAS,[11,12] and underwent preoperative physical and radiographic examination. Surgical details were obtained from review of patient charts. All patients were treated using a similar algorithm with patients without suspicion of infection undergoing primary or revision open reduction and internal fixation (ORIF). Patients with obvious infection were treated using external fixation or a staged protocol for internal fixation. Seventy-five (82%) patients were treated with ORIF with some type of biologic augmentation. Sixteen (18%) were treated with external fixation. Use of bone graft or bone morphogenetic protein (BMP) was at the discretion of the treating surgeon. Seventy-four percent of patients received iliac crest bone graft (ICBG), with or without BMP. Patients were followed at 3, 6, and 12 months after surgery using the SMFA, VAS, physical and radiographic examination. The registry was reviewed to identify patients with tibial or femoral nonunion that achieved union with complete 3, 6, and 12 month follow-up. Union was defined using a combination of radiographic and clinical factors including bridging callus on at least 3 of 4 cortices, no gross motion at the nonunion site, and pain free weight-bearing and palpation.

Statistical Analysis

A Friedman test was conducted to determine differences in pain level preoperatively, as well as 3, 6, and 12 months postoperatively. Pairwise comparisons were performed using a Bonferroni correction for multiple comparisons.

Univariate analyses were conducted to identify patient and treatment characteristics associated with postoperative pain. Each patient variable was tested for association with pain level 3, 6, and 12 months postoperatively. Mann Whitney U tests were conducted to determine differences in mean postoperative pain level at 3, 6, and 12 months between pairs of dichotomous variables: gender, smoking status, wound status at time of injury (open vs. closed), bone involved (tibia vs. femur), nonunion location in the bone (metaphyseal vs. diaphyseal), energy of causative mechanism, anesthesia, use of ICBG, removal of hardware, addition of hardware, and presence of infection. Energy of causative mechanism was categorized as low or high energy with high energy mechanisms consisting of motor vehicle or motorcycle crash, being struck as a pedestrian, crush injury, or fall from greater than 10 feet. Spearman's rank order correlations were conducted to determine correlation between postoperative pain at 3, 6, and 12 months with continuous variables: age, body mass index (BMI), Charlson comorbidity index (CCI), and days from injury to nonunion surgery at our institution. A monotonic relationship between test variable and pain level was verified. A cut off of $p<0.1$ was used for variables in univariate analyses for inclusion in multivariate models.

Variables associated with pain level at any time point after surgery were included in multivariate linear regression models predicting postoperative pain 3 months, 6 months, and 12 months after surgery. A significance cut off of $p<0.05$ was used for multivariate analyses. The assumptions of linearity, independence of errors, and homoscedasticity were verified. Chi-square tests for association were conducted to determine associations between fracture location and wound at time of injury, and fracture location and energy of causative mechanism. All statistical analyses were conducted using SPSS version 20.0 software (IBM, Armonk, NY).

RESULTS

There were ninety-one patients available for analysis with 57 (63%) tibial nonunions and 34 (37%) femoral nonunions. The cohort consisted of 57 (63%) men and 34 (37%) women. On average, patients were 406 ±433 days from injury at time of nonunion surgery. Mean time to union following nonunion surgery was 6.8 ±4.2 months. Mean preoperative pain was 5.4 ±2.7. Chi-squared tests for association demonstrated no association between nonunion location and wound status at time of injury ($p=0.495$) or nonunion location and energy of causative mechanism ($p=0.062$). Friedman test demonstrated pain levels were statistically different at each of the observed time points. Post hoc analysis revealed significant differences in pain level between baseline and 3 months postoperatively ($p<0.0005$), baseline and 6 months postoperatively ($p<0.0005$), and baseline and 12 months postoperatively ($p<0.0005$). However, there were no significant differences between pain levels when comparing any of the postoperative time points (Table I).

Table II. Results of univariate analyses comparing patient specific variables to postoperative pain

Variable	Mean/Proportion	3 month p-value	6 month p-value	12 month p-value
Age	46.1 years	0.352	0.083	0.016*
BMI	28.6	0.844	0.875	0.504
CCI†	0.5	0.734	0.986	0.247
Days to Surgery	406	0.925	0.143	0.067
Gender	57/91 Male	0.885	0.931	0.920
Smoking	21/91	0.011*	<0.0005*	0.040*
Wound	23/91 Open	0.631	0.356	0.085*
Mechanism	58/91 High energy	0.813	0.970	0.336
Anesthesia	61/91 General	0.144	0.057	0.045*
ICBG‡	67/91	0.276	0.335	0.909
Removal Hardware	55/91	0.818	0.860	0.705
Addition Hardware	58/91	0.904	0.601	0.228
Infection	18/91	0.409	0.537	0.707
Bone	57/91 Tibia	0.849	0.688	0.752
Section	53/91 Diaphysis	0.047*	0.400	0.451

*Denotes statistical significance.†CCI = Charlson Comorbidity Index.‡ICBG = Iliac crest bone graft

Table III. Multivariate Analysis of Patient Variables Associated with Postoperative Pain

Variable	3 month p-value	6 month p-value	12 month p-value
Age	0.294	0.935	0.159
Days to Surgery	0.566	0.024*	0.004*
Smoking	0.012*	<0.0005*	0.179
Wound	0.845	0.365	0.070
Anesthesia	0.219	0.323	0.243
Section	0.035*	0.278	0.898

*Denotes statistical significance.

Results of univariate analyses comparing each patient specific variable to pain at each tested time point are in Table II. BMI, CCI, gender, mechanism of injury, bone involved, ICBG harvest, removal of hardware, addition of new hardware, and presence of infection were not found to be significantly associated with postoperative pain at any tested time point. Age, days from injury to nonunion surgery at our institution, smoking status, wound status at time of injury, anesthesia, and nonunion location in the bone were all found to be significantly associated with postoperative pain for at least one of the tested time points, and were included in multivariate analysis to predict postoperative pain 3 months, 6 months, and 12 months postoperatively. Mean pain plateaued after surgery with patients reporting a mean VAS of 3.2 ±2.7 3 months postoperatively, 3.5 ±3.0 6 months postoperatively, and 2.9 ±2.7 12 months postoperatively. Multiple regressions conducted to predict VAS postoperatively using age, days from injury to nonunion surgery at our institution, smoking status, wound status at time of injury, anesthesia, and nonunion location in the bone demonstrated. active smoking (Odds Ratio [OR] =1.342, 95% Confidence Interval [CI] 0.391 to 3.055, p=0.012) and diaphyseal location in the bone ([OR] =1.342, [CI] 0.095 to 2.590, p=0.035) were predictive of increased pain 3 months postoperatively. . Active smoking ([OR]=2.978, [CI] 1.631 to 4.326, p<0.0005) and greater number of days from injury to nonunion surgery ([OR]=0.002, [CI] 0.0005 to 0.003, p=0.024) were predictive of increased pain 6 months postoperatively. Increased number of days from injury to nonunion surgery ([OR]=0.002, [CI] 0.001 to 0.003, p=0.004) was the only variable found to be significantly predictive of pain 12 months postoperatively. Results from all multivariate regressions are available in Table III.

DISCUSSION

In concordance with previous studies, our results demonstrate a statistically significant improvement in pain after nonunion surgery.[4,8] Pain levels significantly improved compared to baseline by 3 months postoperatively. This occurred despite the cohort healing at a mean time of 6.8 months, over 3 months after the initial drop in pain levels. Interestingly, there was no significant improvement in pain levels between 3 and 12 months postoperatively, during which the patients were finally healed. This suggests that initial healing of the nonunion site in the first

3 postoperatively provides sufficient stabilization to allow for reduction in pain.

An orthopedic surgeon can assist with healing and pain relief after nonunion surgery through treatments aimed at restoring a combination of biologic and mechanical factors. However, patients must be active in their own care as smoking is a known risk factor for development of fracture nonunion[13] and is known to be associated with increased time to union postoperatively.[8] Importantly, there is a greater improvement in pain in patients that achieve union after nonunion surgery.[4] Our data regarding postoperative pain are consistent with these findings. Smoking was positively predictive of pain early after nonunion surgery. We postulate that patients who smoke are less likely to have meaningful healing early after nonunion surgery and are therefore at greater risk of pain than patients that have had a more abundant healing response. This creates a dangerous situation for the smoker in chronic pain. Animal models have begun to illustrate the complex relationship between nicotine and pain, demonstrating the effects of nicotine on the endogenous opioid system.[14] Functional imaging demonstrated the connection between nicotine and the endogenous opioid system showing activation of opioid receptors in nicotine deprived adult smokers who were given nicotine.[15] This connection between nicotine and opioid use becomes clinically important as Hooten et al. previously demonstrated that patients with chronic pain used increased opioid amounts if they were current smokers.[16] In our study, active smokers were at higher risk of postoperative pain, scoring nearly 3 points higher on the VAS pain scale 6 months after surgery. Orthopedic surgeons should counsel patients that, in addition to the negative health effects associated with smoking that they may be more familiar with, active smokers are more likely to have significant pain postoperatively.

The only other early predictor of pain following nonunion surgery was location in the bone of the nonunion, with diaphyseal nonunions being predictive of greater pain early postoperatively. We postulate this is due to the delayed healing associated with diaphyseal fractures. Long bones have varying blood supply depending on the section of the bone. As has been demonstrated in the tibia, blood supply and healing rates of acute fractures are greater in the proximal metaphysis than the diaphysis.[17] Increased metaphyseal blood flow allows for the biologic environment required for bone healing. The improved biologic environment at the metaphysis should allow for earlier healing after nonunion surgery and earlier reduction in postoperative pain. In acute fractures compartment syndrome is associated with worsening soft tissue injury.[18] Park et al. demonstrated that compartment syndrome is more common in fractures of the tibial diaphysis than either metaphysis..[19] Even without the full development of compartment syndrome, subclinical compartment syndrome is a postulated cause of loss of muscle bulk following tibial shaft fractures.[20] Gaston et al. demonstrated that the degree of soft tissue damage measured using the Tscherne classification was predictive of return to activity following tibial shaft fractures.[21] Despite the association between acute diaphyseal fracture and soft tissue injury, in our cohort, there were no associations between energy of causative mechanism or wound status at time of initial injury with nonunion location. It is unlikely that with similar mechanisms and wound status that there were significant differences in soft tissue injuries between diaphyseal nonunions and metaphyseal nonunions in our cohort. Despite the role of soft tissue injury in outcomes after acute fracture, it seems to have less of a role determining pain after nonunion surgery, which is more likely influenced by available blood supply and its effect on postoperative healing.

There continues to be disagreement in the definition of fracture healing[22] and fracture nonunion.[23] This makes it difficult for an orthopedic surgeon to decide the optimal timing of intervention for fracture nonunion. On one hand, the orthopedic surgeon does not want to allow the patient to live with the disability of fracture nonunion. On the other hand, the orthopedic surgeon does not want to put the patient through an unnecessary procedure. It is this balance between alleviating morbidity and avoiding unnecessary procedures and the potential for further complication that guides nonunion care. The United States Food and Drug Administration (FDA) define nonunion as a fracture greater than nine months after injury that has not shown radiographic progression in healing for 3 months.[24] Subsequent research has advocated for intervention prior to the 9 month definition provided by the FDA. The Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT) demonstrated lower nonunion and reoperation rates in tibial shaft fractures when surgeons waited 6 months before operative treatment of nonunion.[25] SPRINT did not advocate delayed treatment based on patient postoperative outcomes including function and pain. Their strategy, while decreasing the number of unnecessary surgeries, still allows for patients with tibial nonunion to live with considerable morbidity for 6 months before nonunion surgery, and based on our data puts patients at higher risk for long term postoperative pain after nonunion repair.

In a retrospective review of 176 tibial fractures, Lack et al. demonstrated the predictive value of radiographs after tibial fracture surgery. They found that tibial fractures showing any cortical bridging 4 months after surgery eventually progressed to bridging of three cortices without further invention.[26] However, there remains further room for improvement in the early identification of lower extremity nonunions. Yang et al. demonstrated the ability of trained orthopedic traumatologists to predict nonunion from case vignettes of patients only 3 months after initial injury.[27] Our data show that there should be another factor in the orthopedic surgeon's consideration for earlier surgical intervention: postoperative pain. Our data demonstrate that delayed operative management of nonunion is predictive of pain 12 months postoperatively. This was the only factor predictive of pain 12 months postoperatively. The orthopedic surgeon and patient must consider and balance preoperative morbidity and postoperative pain with the potential for an unnecessary procedure or complication. Newer methods of determining nonunion not available to the SPRINT investigators are now available to today's orthopedic surgeon. While postoperative pain was statistically significant and should be part of the decision making process, the demonstrated effect size for days from injury to nonunion surgery was small, does not warrant intervention on its own, and may be considered too small to be clinically significant by orthopedic surgeon and patient.

Our study is limited by the disagreement between providers in diagnosing nonunion and postoperative union, which is well illustrated in the orthopedic literature. Through using a multivariate regression, we attempted to control for the individual effect of biologic augmentation. However, there remains the possibility of bias with use of biologic augmentation. The data is the result of investigation at a single institution without the availability of metabolic markers. All surgeons followed a similar postoperative protocol with extended time between study visits. This makes it difficult to assess the exact trends in postoperative pain. We know that pain is significantly improved at the 3 month postoperative time point and plateaus thereafter, but we are unable to comment on changes in pain levels in the early postoperative period, and any factors that may influence those pain levels.

Lower extremity nonunions provide significant diagnostic and therapeutic challenges for the orthopedic surgeon as well as significant morbidity for the patient. Supporting both the biologic environment and mechanical stability of a fracture nonunion allows for faster healing and decreased early postoperative pain. Patients should be advised of their role in the healing process, highlighting correction of metabolic abnormalities,[28] management of medical comorbidities,[29] and smoking cessation. Benefits of early recognition and operative treatment of nonunion, including small reduction in postoperative pain, must be weighed against the risks of unnecessary procedures and become a conversation between the patient and orthopedic surgeon.

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