Initial Surgical Treatment of Humeral Shaft Fracture Predicts Difficulty Healing when Humeral Shaft Nonunion Occurs

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Abstract *Background:* Although most humeral nonunions are successfully treated with a single procedure, some humeral nonunions are more difficult to heal and require multiple procedures. Current literature does not provide evidence describing how the prognosis for surgical repair in patients who develop humeral diaphyseal nonunions may be affected by initial operative versus nonoperative treatment. *Questions/Purposes:* The purpose of this study was to assess whether operative versus nonoperative treatment of acute humeral shaft fractures impacts outcome of subsequent repairs of humeral nonunions (NU) including the need for additional surgery and a comparison of pain relief (Visual Analogue Scale for pain) and functional outcome (Short Musculoskeletal Functional Assessment). *Methods:* Thirty-four patients with humeral shaft nonunion were evaluated of which 15 patients had been treated operatively (OF), and 19 patients had been treated nonoperatively (NO) for their initial humerus shaft fracture. All patients underwent plating with autogenous bone graft or allograft ± bone morphogenetic protein (BMP) 2 or 7 as their final NU repair surgery prior to healing. We compared functional outcome and pain for both cohorts and determined risk factors for requiring more than 1 nonunion repair surgery. *Results:* The mean time of final follow-up was 14.7±10.4 months. Thirty-three of 34 NUs (97.1%) healed. Patients who underwent OF of their original fracture were more likely to require more than 1 NU repair surgery (66.7 vs. 0%, $p<0.01$). Of the 15 patients who underwent initial OF,

33.0% required 1 NU surgery, 33.0% required 2 NU surgeries, and 33.0% required 3 NU surgeries. Patients who underwent initial OF were more likely to require >6 months to achieve union (40.0 vs. 10.5%, $p=0.04$). At final follow-up, there was no difference in functional outcome or pain scores. Initial OF was the only independent predictor of needing more than 1 NU repair surgery (OR 70.1 CI 2.8–1762.3) to achieve healing. *Conclusion:* Humeral shaft nonunions following initial operative fixation of the index fracture is more resistant to achieving union when compared to nonunions forming after initial nonoperative treatment. When final healing is achieved, there is no difference in function or pain.

Keywords humerus shaft · humerus nonunion · functional outcome · recalcitrant nonunion · delayed union · revision nonunion surgery

Introduction

Fractures of the humerus comprise approximately 5 to 8% of all extremity fractures [8]. Nonunion rates for diaphyseal humerus fractures treated nonoperatively range from 0 to 13%, with the incidence increasing to 15 to 30% for operatively treated fractures [8]. Numerous techniques and fixation constructs have been described to treat humeral diaphyseal nonunions with mostly good to excellent rates of fracture healing. Although most of these humeral nonunions are successfully treated with a single procedure, some humeral nonunions are more difficult to heal and require multiple procedures.

The purpose of this study was to assess whether operative versus nonoperative treatment of acute humeral shaft fractures impacts outcome of subsequent repairs of humeral nonunions (NU). Our hypothesis is that, when compared to initial nonoperative treatment of acute diaphyseal fractures, operative treatment is an independent predictor of a recalcitrant nonunion requiring multiple procedures to achieve bone healing. The specific aims of this study included assessment of the need for additional surgery following

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Level of Evidence: Prognostic Study, Level II.

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treatment of humeral nonunions as a function of the prior surgical treatment. We also assessed the time to healing as a function of any prior surgery and measured functional outcome and pain after healing, and finally, we assessed risk factors for requiring more than 1 nonunion surgery.

Patients and Methods

A consecutive series of 36 patients who were referred to our institution between September 2004 to September 2012 with the diagnosis of a humeral diaphyseal nonunion were identified within our IRB-approved fracture nonunion database. Nonunion was defined as a lack of evidence of continued fracture healing on consecutive plain radiographic images at a minimum of 6 months from initiation of treatment and/or clinical evidence of instability and pain at the fracture site. All 36 patients with humeral shaft nonunion underwent operative repair. Inclusion criteria for this study was age ≥ 18 and a minimum follow-up of ≥ 6 months after the final nonunion repair surgery. Two patients were excluded from study analysis for failing to meet the inclusion criteria (both patients have < 6 month follow-up) resulting in 34 patients available for analysis. Patients were divided into 2 cohorts for analysis: initial operative fixation (OF) of humeral fracture and initial nonoperative treatment of humeral fracture (NO).

Patient demographics were recorded and included the following: age, sex, body mass index (BMI), level of education, alcohol and cigarette use. Fracture characteristics recorded into this database included the following: nonunion classification according system of Weber and Cech modified by Brinker [2], presence of gross infection, mechanism of initial injury, pre-existing nerve injury, initial treatment (operative versus nonoperative) and whether the initial fracture was open or closed. Surgical data was also collected and included use of autologous bone graft, bone morphogenic protein (BMP) and implantable electronic bone stimulator. Validated outcome measurements that included the Short Musculoskeletal Functional Assessment (SMFA) and pain scores as measured by the 10-point Visual Analogue Scale (VAS) were obtained at baseline and then at 3, 6 and 12 months (and longer if possible). All data was collected via direct patient contact by a research associate blinded to the healing status of the nonunion.

All patients were treated by open reduction and internal fixation (ORIF) with compression plating or bridge plating depending on amount of bone contact and the use of supplemental bone grafting and/or BMP. Bone graft was either autogenous iliac crest bone graft (ICBG) or iliac crest aspirate with allograft cancellous bone chips. If BMP was used, it was either BMP-2 (Infuse®) or BMP-7 (OP-1®). No strict protocol for adjunctive graft type was utilized. Choice of bone graft and/or BMP use was based upon several factors including nonunion type, surgeon preference, patient preference, implant availability and number of previous surgeries. The use of an external bone stimulator was also at the discretion of the surgeon and typically utilized prior to surgical intervention as a means of avoiding an operation.

If prescribed prior, its use was continued post-operatively. Patient compliance with this device was measured by verbal response only.

Radiographic confirmation of nonunion and eventual healing was performed on all patients by evaluating anterior-posterior (AP) and lateral plain radiographs of the affected humerus. When the diagnosis was unclear, a CT scan of the region was obtained to confirm. Radiographic union was defined as bridging of three of four cortices on orthogonal radiographic views at a particular follow-up. Radiographic healing was reported as occurring by 3, 6, 12, 18, or 24 months, or not healed and was determined by both the treating surgeon and a radiologist. Clinical diagnosis of healing was established by absence of gross motion and tenderness to palpation at the fracture site and was determined by the treating surgeon.

All patients undergoing revision surgery underwent standard laboratory serologies and intraoperative cultures to evaluate for the presence of infection. All positive cultures were treated with organism-specific antibiotics for a minimum of 6 weeks under the care of an infectious disease specialist. Patients were followed with weekly ESR, CRP, and leukocyte counts until these values normalized as a measure of response to antibiotic treatment.

Statistical Analysis

Student's *t* test was used to calculate differences in age, BMI, follow-up time, union time, and final VAS (pain) and SMFA (function and bothersome) scores. Chi-square test was used to calculate differences in gender, marital status, alcohol and cigarette use, schooling, graft type, bone stimulator use, nonunion type, rate of healing by 6 months, initial open versus closed injury, number of nonunion procedures to achieve healing, mechanism of injury (high versus low), presence of infection at nonunion repair surgery and nerve injury. A multivariate logistic regression analysis was used to determine risk factors for requiring more than 1 nonunion repair surgery to achieve healing. All calculations were performed using Microsoft Excel 2012/ XLSTAT (Addinsoft, New York, NY).

Results

A total of 34 patients with 34 humeral nonunions met inclusion criteria for study analysis. The mean time of final follow-up for all patients was 14.7 ± 10.4 months. Thirty-three of 34 nonunions (97.1%) eventually healed. Fifteen (44.1%) patients underwent initial operative fixation of their humeral fracture whereas the remaining 19 (55.9%) patients underwent initial nonoperative management and subsequently developed a nonunion. There was no difference in demographic or bone healing augmentation characteristics between cohorts (see Table 1).

There were significantly more patients in the OF versus NO cohort who required more than 1 NU surgery to achieve healing (11 (73.3%) patients vs. 0 (0.0%) patients, $p < 0.01$). Several patients in the OF cohort had unsuccessful NU

Table 1 Comparison of demographic, injury, and bone healing augmentation characteristics for initial operative versus nonoperative treatment of humeral diaphyseal fractures that subsequently developed a nonunion and underwent surgical repair

	Initial operative treatment (N=15)	Initial nonoperative treatment (N=19)	p value
Demographic characteristics			
Age	47.7±17.6	53.8±18.5	0.34
Gender (M:F)	4:11	4:15	0.70
BMI	28.8±6.1	28.3±6.3	0.83
Married	8 (53.3)	8 (42.1)	0.51
Schooling≥college	5 (33.3)	8 (42.1)	0.83
ETOH	4 (26.7)	1 (5.3)	0.08
Smoking	4 (26.7)	4 (21.1)	0.70
Follow-up time (months)	14.2±8.7	15.1±11.8	0.80
Injury Characteristics			
Union time (months)	8.4±7.6	4.6±1.5	0.04*
Union ≥6 months	6 (40.0)	2 (10.5)	0.04*
Open fracture	2 (13.3)	0 (0.0)	0.10
>1 NU surgery	10 (66.7)	0 (0.0)	<0.01*
High mechanism of injury	8 (53.3)	5 (26.3)	0.11
Infected NU	3 (20.0)	0 (0.0)	0.04*
Hypertrophic NU (vs. atrophic/oligotrophic)	2 (10.5)	7 (36.8)	0.12
Nerve injury	2 (13.3)	4 (21.1)	0.56
Bone healing augmentation			
Autologous ICBG	7 (46.7)	9 (47.4)	0.97
Iliac crest aspirate	4 (26.7)	9 (42.1)	0.34
BMP-7	5 (33.3)	11 (57.9)	0.15
BMP-2	5 (33.3)	4 (21.1)	0.42
BMP+cancellous allograft	2 (13.3)	8 (42.1)	0.07
Bone stimulator	3 (20.0)	8 (42.1)	0.17

M male, F female, BMI body mass index, ETOH alcohol, NU nonunion, ICBG iliac crest bone graft, BMP bone morphogenic protein

*significant difference between groups

repair surgery prior to presenting to our institution. Four (26.7%) patients had 0 NU surgeries prior to presenting to our institution, 6 (40.0%) patients had 1 failed NU surgery and 5 (33.3%) patients had 2 failed NU surgeries. Once reaching our institution and undergoing NU repair surgery, 14/15 (93.3%) patients achieved union after 1 NU repair surgery. Ultimately, in the OF cohort, 5 (33.3%) patients required only 1 NU surgery to achieve healing, 4 (26.7%) patients required 2 NU surgery to achieve healing and 5 (33.3%) required 3 NU surgeries to achieve healing. One (6.7%) OF patient did not achieve healing. In contrast, all 19 patients (100.0%) in the NO cohort required only 1 NU surgery to achieve healing (100.0 % union rate). We found that there were significantly more patients with infected nonunion in the OF cohort compared to the NO cohort (3 (20.0% patients vs. 0 (0.0%) patients, $p=0.04$).

Time to final union was significantly longer for the OF cohort (8.4±7.6 vs. 4.6±1.5 months, $p=0.04$). Additionally, the number of patients who required ≥6 months to achieve healing was significantly greater for the OF cohort (6 (40.0%) patients vs. 2 (10.5%) patients, $p=0.04$).

At final follow-up, there was no difference between OF and NO cohorts in mean SMFA function (15.8±16.5 vs. 14.9±14.7, $p=0.84$), SMFA bothersome (22.9±22.3 vs. 22.5±21.1, $p=0.77$) or VAS pain scores (1.1±2.0 vs. 2.2±2.0, $p=0.14$) (see Table 2).

Univariate analysis revealed that age (OR 0.95 CI 0.90–0.99, $p=0.04$), high-energy mechanism of injury (OR 10.50 CI 1.70–65.00, $p=0.01$) and initial operative fixation (OR: 74.50 CI: 3.45–1605.20, $p<0.01$) were all

risk factors for requiring more than 1 NU repair surgery to achieve healing (see Table 3). Multivariate analysis found that only initial operative fixation was an independent risk factor for requiring more than 1 NU repair surgery (OR 70.10 CI 2.79–1762.3).

Discussion

Operative fixation of diaphyseal humeral fractures is associated with a nonunion rate ranging from 15 to 30% compared to a nonunion rate of 0 to 13% for nonoperatively treated diaphyseal humeral fractures [8]. Lacking from current literature is the prognosis of patients who develop humeral diaphyseal nonunions in the setting of initial operative versus nonoperative treatment. Our data suggests that, when compared to initial nonoperative treatment of acute diaphyseal fractures, operative treatment is an independent predictor of a more recalcitrant nonunion requiring multiple procedures to achieve bone healing.

The limitations of this study include its retrospective design. We were not powered to detect many of the differences in demographic, injury and bone healing augmentation characteristics that we evaluated. However, nonunions of the humeral diaphysis are not common and despite the small sample size, we were able to detect significant differences between the OF and NO cohorts that provide valuable information regarding prognosis.

To date, only 1 study has evaluated the impact of initial operative versus nonoperative treatment on the final outcome

Table 2 Comparison of visual analogue scale (pain) and short musculoskeletal functional assessment function and bothersome scores at final follow-up for initial operative and nonoperative treatment of humeral diaphyseal fractures that subsequently developed a nonunion and underwent surgical repair

	Initial operative treatment (<i>N</i> =15)	Initial Nonoperative treatment (<i>N</i> =19)	<i>p</i> value
VAS (pain)	1.1±2.0	2.2±2.0	0.14
SMFA (function)	15.8±16.5	14.9±14.7	0.84
SMFA (bothersome)	22.9±22.3	22.5±21.1	0.77

VAS Visual Analogue Scale, SMFA Short Musculoskeletal Functional Assessment

(healing time and functional outcome). Atalar et al. evaluated the treatment of 81 nonunions involving the proximal, diaphyseal and distal humerus with 3 different fixation constructs (Ilizarov fixator, monorail external fixator, and plate/screw fixation) [1]. Of the 21 nonunions treated with plate fixation and autogenous iliac crest bone graft, they reported a union rate of 95.2% (1 nonunion). Interestingly, their results were similar to ours as they found that patients who had initially been treated operatively (11 patients) had a significantly longer union time than those treated nonoperatively (10 patients) (6.6±3.0 vs. 4.6±1.3 months vs, $p<0.01$). The authors also found that there was no difference in DASH scores at final union between initial operative versus nonoperatively treated humerus fractures; however, it is difficult to interpret this data given that there was a mix of proximal, diaphyseal and distal humerus nonunion, whereas our study focused specifically on diaphyseal humeral nonunions.

There was no difference in functional outcome or pain scores at final follow-up between OF and NO cohorts. Besides Atalar et al., no other authors have compared functional outcomes between these 2 cohorts. We are unaware of any other studies evaluating humeral diaphyseal nonunions that have used the SMFA to assess functional outcome. Only 1 author has used the VAS to assess pain. Patel et al. used the VAS for pain to evaluate repair of 16 diaphyseal humeral nonunions using an Ilizarov circular external fixator and reported a final VAS score of 2.5 at the end of treatment [4]. This is comparable to results we achieved in this study using plate and screw constructs.

The key finding in our study was the fact that in the OF cohort 2/3 of patients required more than 1 nonunion repair surgery to achieve final union. This was in stark contrast to the NO cohort in which 100% healed after 1 nonunion repair surgery. Ring et al. reported similarly high rates of successful healing (90.7%) after 1 nonunion repair surgery of diaphyseal humeral fractures treated nonoperatively in a functional brace [6]. In our study, patients who underwent OF had a 75× increased risk of requiring a second nonunion repair surgery. This finding is significant because it provides valuable prognostic information regarding the expected

length of treatment to achieve union in the setting of a previously operatively treated humerus fracture. Univariate analysis revealed that high-energy mechanisms of injury, decreasing age and initial operative intervention were predictive of requiring more than 1 nonunion repair surgery. However, a multivariate analysis revealed that the only independent predictor of requiring more than 1 surgery was initial operative treatment of the fracture.

Initial operative treatment tends to occur in the setting of high-energy diaphyseal humerus fractures. These fractures inherently have more significant disruption of the soft-tissue envelope surrounding the fracture and are more likely to have devitalized bone fragments, large bone gaps and open wounds [3]. In this setting, operative fixation via an open approach with plates and screws may cause additional insult to the soft-tissue envelope resulting in a poor biological environment for fracture repair to occur [5]. In this study, we had nearly 2× as many high-energy mechanisms of injury in the OF cohort as the NO cohort; however, this difference was not significant. Our data suggests that operative fixation is skewed towards those patients already at higher risk for developing a nonunion.

Decreasing age was found to be predictive of requiring more than 1 nonunion repair surgery in our univariate analysis, and it is likely due to its association with higher-energy fractures (which in-turn are more likely to undergo operative fixation) [7]. In both cohorts, no patients ≥65 years had a high-energy mechanism of injury suggesting that a correlation between younger age and higher mechanisms of injury. Every 1 year decrease in age was found to increase the risk of developing a nonunion by 5.0%.

Ultimately, this study gives the physician information regarding the prognosis of patients with humeral diaphyseal nonunions who have previously been treated operatively or nonoperatively. In the setting of prior nonoperative treatment, patients have a high likelihood of achieving successful union after 1 surgery (100% in this series) using plate and screw fixation and autogenous or allograft bone±BMP and achieve union at mean of 4.6 months. In the setting of prior operative treatment, union is more difficult to achieve and may require multiple surgeries. However, plate and screw fixation with bone graft is a reliable technique to achieve healing even in these recalcitrant cases that have undergone multiple prior surgeries. Patients requiring multiple surgeries to achieve union have functional outcomes and pain that is comparable to that of patients who were treated nonoperatively initially. These findings can help guide management of patients with this debilitating injury.

Table 3 Factors that predict the need for more than 1 nonunion repair surgery to achieve ultimate union of diaphyseal humeral nonunions

	Odds ratio (CI)	<i>p</i> value
Age	0.95 (0.90–0.99)	0.04
High-energy mechanism	10.50 (1.70–65.00)	0.01
Initial operative fixation	74.50 (3.45–1605.20)	<0.01

CI confidence interval

Disclosures

Conflict of Interest: Sanjit R. Konda, MD and Roy I. Davidovitch, MD have declared that they have no conflict of interest. Kenneth A. Egol, MD is a consultant for Exactech; receives royalties from Slack Inc. and Lippincott; other from OTA Board of Directors, outside the work.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

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