Abstract

Purpose: Nonunions of the upper and lower extremity have been associated with pain and functional deficits. Recent studies have demonstrated that healing of these nonunions is associated with pain relief and both subjective and objective functional improvement. The purpose of this study was to determine which patient and surgical factors correlated with successful healing of a nonunion following surgical intervention.

Methods: Between September 2004 and February 2008, all patients with a “long bone nonunion” presenting to our academic trauma service were enrolled in a prospective database. Baseline functional, demographic and pain status was obtained. Follow-up was obtained at 3, 6, and 12 months following surgical intervention, with longer follow-up as possible. One hundred and thirty-four patients with a variety of fracture nonunions were operated on by four different fellowship trained trauma surgeons with experience ranging from 2 to 15 years and variable nonunion surgery loads. Patients were stratified into one of three groups: 1. Patients who healed following one surgical intervention, 2. those who healed following multiple surgical intervention, and 3. those who failed to heal (remain ununited or underwent amputation). Healing was determined radiographically and clinically. Complications were recorded. Logistic regression analysis was performed to assess the correlation between specific baseline and surgical characteristics and healing.

Results: A minimum of 1 year follow-up was available for all 134 patients. One hundred and one patients (76%) with a mean age of 50 years healed at a mean of 6 months (range, 3 to 16) after one surgery. Twenty-two patients (16%) with a mean age of 47 years, who required more than one intervention, healed their nonunions at a mean of 11 months (range, 4 to 23). Eleven patients (8%) with a mean age of 50 years failed to heal at an average of 12 months follow-up. Complication rates were 11%, 68%, and 100% respectively for those who healed following one procedure, multiple procedures, and those who never healed. Higher surgeon volume (greater than 10 cases per year) was associated with 85% increased healing rates (OR = 0.15, 0.05-0.47 CI). The presence of a postoperative complication was associated with a 9 times lower likelihood of successful union as well (OR = 9.0, 2.6-31.7 CI). Patient age, sex, BMI, initial injury mechanism, tobacco use, and initial injury characteristics did not correlate with failure to heal.

Conclusion: Our data is similar to other studies assessing outcomes following other complex reconstructive procedures. It appears that more experienced (higher volume) reconstructive surgeons and the development of fewer postoperative complications is associated with greater success following repair of a long bone nonunion. Infection at any point during treatment is associated with failure to achieve successful union.

Nonunion following a fracture is a known complication that has varying incidence, depending on fracture type, location, and certain baseline patient demographics. Motion at the fracture site, avascularity, fracture gap, and presence of infection have all been implicated as causes for development of an ununited fracture. Fracture
nonunions of the upper and lower extremities frequently are associated with functional disturbance and pain. Many patients who have been treated for fracture nonunions have been examined and reported on,1-5 with other series emphasizing specific types of fracture nonunions, treatment success, and functional outcome.1,5-13 These studies have generally had small numbers of patients and used multiple outcome measures to assess the effects of treatment. The purpose of this study was to determine which patient and surgical factors correlated with successful healing of a fracture nonunion following operative intervention. We evaluated patient demographics such as age, gender, infection status, or history of smoking, as well as surgeon volume, as possible predictors of successful union.

Materials and Methods

Between September 2004 and October 2008, we enrolled 145 consecutive patients with established long bone nonunions who presented to our tertiary care center in an IRB approved, prospective database. Baseline functional, demographic, and pain status was obtained at presentation. Follow-up examination and data was obtained at 3, 6, and 12 months following surgical intervention, with longer follow-up as possible. One hundred and thirty-four patients with a variety of fracture nonunions were operated on by one of four fellowship trained trauma surgeons with experience ranging from 2 to 15 years that were categorized into performing less than 5, between 5 and 15, and more than 15 nonunion surgeries per year. Patients were stratified into one of three groups based on final healing status: 1. those who healed following one surgical intervention, 2. those who eventually healed following multiple surgical interventions, and 3. those who failed to heal (remain un-united or underwent amputation). Healing was determined radiographically utilizing plain x-rays and CT scans when available and clinically with physical exam. Radiographic healing was defined by the presence of three out of four healed cortices on plain films. Complications that occurred following intervention were recorded. Logistic regression analysis was performed to assess the correlation between specific baseline and surgical characteristics and healing. Our study consisted of a chart and radiographic review of prospectively collected data. The minimum follow-up was 12 months (mean, 16.8 months; range, 12 to 36 months). We excluded 11 patients overall, 3 who did not return after the index procedure and 8 who had less than 12 month follow-up or incomplete follow-up. Of the remaining 134 (92%), 40 patients (30%) sustained nonunions of upper extremity fractures, and 94 patients (70%) sustained non-unions of lower extremity fractures. There were 66 female (49%) and 68 male (51%) patients. The mean age for these patients was 49 years (range, 18 to 86 years), and the mean body mass index (BMI) of the cohort was 29 kg/m² (range, 19 to 46 kg/m²). Thirty-seven cases were initially open fractures. The entire cohort had a mean of 1.6 surgical procedures (range, 0 to 10) prior to our intervention. A mean of 15 months (range, 2 to 206 months) elapsed from prior surgery to enrollment at our facility. Ninety-nine patients were treated at outside institutions (74 surgically and 25 nonoperatively) before presentation to our institution.

Figure 1 A, 27-year-old female with an established aseptic nonunion of the right humerus shaft with failed hardware. B, Six months s/p removal of hardware and repair of nonunion with iliac crest bone graft reveals solid union.
Thirty-five patients were treated for an index fracture at our institution surgically (30 by a fellowship-trained trauma surgeon and 5 by other staff). Nonunion sites included 63 tibia or fibula (47%), 31 femur (23%), 24 humerus (18%), 9 forearm (7%), and 7 clavicle (5%) fractures. Twenty-four of these cases (17.9%) had positive intraoperative cultures at the time of surgery at our institution.

All patients were followed to determine resolution of their fracture nonunion. We collected: dates and anatomic sites of initial injury; documentation of initial soft tissue injury (open fracture or compartment syndrome); a detailed history of previous surgery, if present; history of previous infection; non-operative modalities used; age; medical comorbidities; smoking status and history; and medications used. The soft tissue envelope was examined for integrity. The suspected nonunion site was palpated for areas of tenderness and gross motion, and we used the standard visual analog scale (VAS) to determine baseline and follow-up pain levels for each patient.

We evaluated all patients with plain radiographs of the affected extremity and classified the nonunion according to the system of Weber and Cech as described by Brinker.14 Ninety patients (67%) were classified as atrophic and 44 (33%) were classified as hypertrophic. We obtained computed tomography (CT) scans to confirm the nonunion in 47 patients (35%) when the diagnosis was not clear from plain radiographs and clinical examination. In addition, one patient presented with MRI scans confirming nonunion. We evaluated all 105 patients (78%) with a history of previous surgery using baseline laboratory values that included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and leukocyte count. In 10 patients in whom infection was suspected preoperatively, owing to elevated serologies, a labeled nuclear study was obtained.15 In all cases of revision surgery (105 nonunions), we obtained intraoperative cultures. We treated positive cultures with organism-specific antibiotics and obtained an infectious disease consultation.

All patients in this report were treated surgically for their fracture nonunion. The method of treatment was left to the discretion of the treating surgeon. The following general principles were followed: patients were treated with internal fixation (no previous surgery), revision internal fixation (previous fixation) (Fig. 1), external fixation (limb deformity or preoperative suspicion of infected nonunion), and a graft procedure, whether autogenous iliac crest or iliac crest aspirate with adjunct bone morphogenic protein (BMP) and an appropriate carrier.16-21 Although the definition of major deformity was somewhat subjective and depended on the anatomic site, we defined it as limb deformity that was grossly visible (Fig. 2). In the cohort of patients who did not have prior surgery, 58% had gross deformity, 58% had some motion at the nonunion site, and 81% had tenderness to palpation or motion at the nonunion site. In the cohort of patients who had previous surgery, 32% had gross deformity, 33% had some motion at the nonunion site, and 83% had tenderness to palpation or motion at the nonunion site. Two patients received an implantable bone stimulator as part of their surgery. Forty-three other patients were prescribed an external electrical bone stimulator as an adjunct for use after surgery. Compliance using this device was measured by verbal confirmation only.

Postoperatively, all patients with positive intraoperative cultures were treated with 6 weeks of organism-specific antibiotics under the care of an infectious disease specialist. Patients were followed with infection-specific laboratory tests, including ESR and CRP, until normalized as a measure of response to antibiotic treatment.

Patients were followed at routine postoperative intervals. Postoperative complications were recorded. We considered any postoperative infection or need for revision ORIF to be a major complication.

Determination of clinical healing was made by the treating surgeon based on clinical parameters, such as absence of pain on weightbearing at a lower extremity nonunion site, and radiographic criteria, defined as bridging of three of four cortices on orthogonal radiographic views at a particular follow-up. For upper extremity sites, the same radiographic criteria held with the absence of pain at the site with use of the extremity. In cases in which radiographic and clinical union were equivocal, we obtained a CT scan to confirm healing at the site. Twenty-two of the 134 patients (16%) had postoperative CT scans to confirm union or nonunion; 11 confirmed union whereas 11 confirmed persistent nonunion. For purposes of this study, healing was also supported by documentation from an attending radiologist’s report in addition to the treating physician’s determination. In order to confirm concordance of the diagnosis of radiographic union, all radiographs immediately postoperative through the latest follow-up were reviewed in a blinded fashion. Three attending orthopaedic surgeons (two involved in this study [KAE, RID] and one who was not [NCT]), and one musculoskeletal radiologist [LR] also an investigator on this paper reviewed all radiographs. Radiographic healing was reported as occurring by 3, 6, 12, 18, or 24 months, or not healed. We used kappa statistics to assess the inter-rater agreement in the radiographic determination of healing. The kappa statistic for fractures that ultimately healed was 0.43. For fractures considered healed in less than 3 months, the kappa was 0.41; for those considered healed between 3 and 6 months, the kappa was 0.53; for those healed between 6 and 12 months, the kappa was 0.44; and for those with longer healing times (12 to 24 months), the kappa was 0.27.

Specific factors examined for correlation with healing included: demographics, such as age, gender, and BMI; injury factors, such as mechanism of initial injury, length of nonunion, history of infection, and history of neurovascular injury; social factors, such as tobacco use and level of education; and surgical factors, such as surgeon experience,
type of graft used, and use of bone morphogenic proteins at surgery.

**Statistical Analysis**

We used linear regression to compare demographic, surgical, and postoperative factors between patients who achieved healing and those who did not at each follow-up. Logistic regression analysis was performed to assess the correlation between specific baseline and surgical characteristics and healing. The regression coefficients for each covariate are presented along with their associated p-values. Stata® 10 statistical software (StataCorp LP, College Station, TX) was used for all analyses.

**Result**

One hundred and one patients (76%) with a mean age of 50 years healed their nonunions by a mean of 6 months (range, 3 to 16) following one surgery. Twenty-two patients (16%) with a mean age of 47 years required more than one intervention and healed their nonunions by a mean 11 months (range, 4 to 23). Eleven patients (8%) with a mean age of 50 years failed to heal at an average of 12 months follow-up. Of these 11 patients, 9 (81%) had persistence of their nonunion despite undergoing multiple nonunion surgeries. Table 1 reports the odds ratios and confidence intervals for the various factors and their associations with the healing of a long bone nonunion. Higher surgeon volume (minimum of 15 nonunion surgeries per year) was associated with a greater success in achieving ultimate healing. The development of a complication was associated with need for more than one surgical intervention. The complications encountered in our three cohorts included: infected nonunion sites, wound dehiscence, pin tract infections, postoperative hematoma, hardware failure, amputation, and development.
of a Charcot ankle. In the group of patients who healed after one surgery, 11 complications occurred in 11 patients for a complication rate of 11%. Fifteen complications were documented in 15 patients for a complication rate of 68% in patients who required more than one surgery and eventually healed. Lastly, 16 complications were seen in the 11 patients who never healed. The complication rate for this cohort was 100% and four of these patients (36%) suffered more than one complication (Table 2). The development of a postoperative complication was associated with failure to achieve successful union following surgical intervention for a fracture nonunion (Table 2).

Overall, 19 patients (15%) who healed their nonunions had an infected nonunion compared to 5 patients (46%) who never healed their nonunions. For the purposes of this analysis, we considered any patient with a positive culture as having an “infected nonunion.” These patients were treated with culture directed antibiotics for a minimum of 6 weeks or until healing was demonstrated. In the subgroup of patients who healed after one surgery, there were eight patients (8%) with infected nonunions. In the subgroup of patients who healed after multiple surgeries, 11 patients (50%) had an infected nonunion (Table 2).

We looked at the choice of bone grafts utilized in the various operations. Options included: autogenous iliac crest bone graft, autogenous iliac crest aspirate alone, autogenous iliac crest aspirate with a commercially available bone morphogenic protein (BMP), BMP alone, or BMP and allograft cancellous chips. Individually, none of these strategies appeared to be advantageous; however, when we divided the options into those that utilized an autogenous source versus those that did not, we found use of an autogenous graft source plus BMP was significantly associated with healing (p = 0.04).

We found no associations between tobacco use, patient age, body mass index, history of a previously open fracture, use of a bone stimulator, limb deformity, and nonunion classification with successful nonunion healing. Nineteen of the 123 patients (15%) who did achieve union at the latest follow-up had a history of infection at some point during their treatment. In addition, this group had a mean 3.4 previous procedures (range, 0 to 10 procedures).

**Discussion**

Overall, 92% of patients with established long bone nonunions achieved healing following operative intervention

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**Table 1** Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Nonunion (NU) for Each of the Following Patient Characteristics

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR</th>
<th>95% CI</th>
<th>Interpretation of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>High volume Surgeon (vs low)</td>
<td>0.15</td>
<td>0.05 – 0.47</td>
<td>NU 85% less likely</td>
</tr>
<tr>
<td>Complication (vs none)</td>
<td>9.0</td>
<td>2.6 – 31.7</td>
<td>NU 9 times more likely</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.0</td>
<td>0.94 – 1.05</td>
<td>No increase in NU per increase in year of age</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.97</td>
<td>0.85 – 1.10</td>
<td>No increase in NU per increase in BMI</td>
</tr>
<tr>
<td>Women (%)</td>
<td>0.41</td>
<td>0.07 – 2.3</td>
<td>Women 59% less likely - NS</td>
</tr>
<tr>
<td>High velocity (vs low)</td>
<td>0.37</td>
<td>0.06 – 2.3</td>
<td>NU 63% less likely – NS</td>
</tr>
<tr>
<td>Cigarette use (vs none)</td>
<td>1.3</td>
<td>0.27 – 6.4</td>
<td>NU 30% more likely – NS</td>
</tr>
<tr>
<td>Nerve injury (vs none)</td>
<td>1.59</td>
<td>0.11 – 22.7</td>
<td>NU 59% more likely – NS</td>
</tr>
<tr>
<td>Arterial injury (vs none)</td>
<td>6.3</td>
<td>0.06 – 681.7</td>
<td>NU &gt; 6x more likely – NS</td>
</tr>
</tbody>
</table>

Non-significant = NS

**Table 2** Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healed after one surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected Nonunion Site</td>
<td>8</td>
<td>8.0</td>
</tr>
<tr>
<td>Pin Tract Infection</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Wound Dehiscence</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Healed after multiple surgeries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardware Failure</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Infected Nonunion Site</td>
<td>11</td>
<td>50.0</td>
</tr>
<tr>
<td>Pin Tract Infection</td>
<td>2</td>
<td>9.0</td>
</tr>
<tr>
<td>Postoperative Hematoma Requiring I&amp;D</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Never healed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardware Failure</td>
<td>5</td>
<td>45.5</td>
</tr>
<tr>
<td>Amputation</td>
<td>3</td>
<td>27.0</td>
</tr>
<tr>
<td>Infected Nonunion Site</td>
<td>5</td>
<td>45.5</td>
</tr>
<tr>
<td>Wound Dehiscence</td>
<td>2</td>
<td>18.0</td>
</tr>
<tr>
<td>Charcot Ankle</td>
<td>1</td>
<td>9.0</td>
</tr>
</tbody>
</table>
be handled on a case-by-case basis, and the patient should 

In this series, we found that successful nonunion repair was 85% more likely to occur with a surgeon volume of greater than 15 cases per year. The association between higher volume and improved outcomes has been previously demonstrated in the orthopaedic as well non-orthopaedic literature.27-29 A systematic review of the literature by Halm and associates noted that 69% of the surgeon based studies investigating the relationship between volume and outcomes showed a clear relationship of better outcomes with increased volume.23 Our findings here corroborate the conclusions of these studies.

The development of postoperative complications in this study was associated with a 9 times greater likelihood of failure to achieve union. The complications encountered were infected nonunion sites, wound dehiscence, pin tract infections, postoperative hematoma, hardware failure, amputation, and development of a Charcot ankle. In our series, we found that 60% of the nonunions that required at least two procedures to heal and 64% of the nonunions that failed to heal were associated with a postoperative complication. This stands in contradistinction to nonunion that healed after only one procedure where a complication rate of only 8% was noted. We, therefore, consider the development of a postoperative complication to be a reliable prognostic indicator for outcome. A number of recent nonunion studies in long bones have noted the association between postoperative complications, most commonly infections, and failure to achieve union.24,25

Overall we noted that infected nonunions were among the most difficult to treat often requiring multiple procedures to achieve union and most prone to failure of treatment. Out of a total of 24 infected nonunions, 5 never healed, and 11% required more than one surgical procedure. A recent article by Prasarn and colleagues26 reviewed a series of 11 distal femoral infected nonunions. All fractures achieved eventual union, but a total of 14 procedures were performed on these 11 patients. Within the abundant literature on infected long bone nonunions, many investigators report multiple procedures being necessary for resolution of the nonunions in the setting of a previous or current infection. No definitive recommendations have been written regarding the treatment of these difficult nonunions secondary to a predominance of heterogeneous level IV research data.27 As such, each of these cases is to be handled on a case-by-case basis, and the patient should be counseled about the likelihood of multiple surgical procedures to achieve union as well as the possibility of failure to unite.

We also compared the types of bone graft utilized in the procedures, and although all grafts contained an osteoinductive substance, the grafts incorporating some type of autogenous graft yielded significantly better healing results. The choice of graft in this study was left up to the discretion of the surgeon and included iliac crest alone, iliac crest aspirate, BMP alone, BMP and aspirate as well as BP and cancellous chips. Evidence exists that BMP-7 is as efficacious as autograft bone at achieving union in long bone fracture nonunions. Friedlander and coworkers22 has shown in a prospectively randomized study of tibial nonunions that BMP-7 is as effective as autologous bone graft alone at achieving union without the donor site morbidity that is associated with iliac crest autograft.

Bong and associates24 have shown that BMP-7 acting as an adjuvant to autologous graft is an effective bone grafting strategy in humeral nonunions. A number of studies from the spine literature have shown that spinal fusion can be achieved using either BMP-7 alone or in combination with an autograft.27,29,30 Our observation that healing was seen more frequently when autograft was utilized as opposed to when osteoinductive allograft was used alone contradicts some of these studies; however, a dedicated study protocol would be required to prove this.

Interestingly, our review found no relationship between tobacco use, patient age, body mass index, history of a previously open fracture, or the use of a bone stimulator with the ability to achieve union. Although these patient-related factors are widely considered to be patient variables that may affect outcomes, the numbers in this study were likely not sufficient to demonstrate an impact. Further enrollment and follow-up of patients into our nonunion database may help discern a relationship between the above factors and outcomes.

Limitations of this study include failure to evaluate patients in subgroups by bony segments as this may have further implications for outcomes related to the specific injury or anatomic sites. Additionally, this analysis was performed with a suboptimal number of patients; therefore, we chose to analyze these patients as a single cohort who all presented at the same time in their disease state (a symptomatic unhealed fracture). In addition, a standardized treatment protocol did not exist, as each surgeon treated the patients as per their preference. Another important limitation of any nonunion study is the ability to confidently assess the presence of union as studies have shown this assessment lacks consensus.32,33 Our observers only showed moderate agreement when it came to assessing radiographic healing.

In conclusion, our data is similar to other studies assessing outcomes following other complex reconstructive procedures. It appears that more experienced (higher
volume) reconstructive surgeons and the development of fewer postoperative complications is associated with greater success following repair of a long bone nonunion. In addition, the presence of infection during treatment is also associated with failure to achieve successful union in these cases. In this series, higher union rates were demonstrated when an autogenous graft was utilized in conjunction with an osteoinductive allograft. These findings should be considered by treating surgeons who attempt to manage these difficult injuries.

Conflict of Interest Statement

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent or licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

References

