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Treatment of chronic (>1 year) fracture nonunion: Heal rate in a cohort of 767 patients treated with low-intensity pulsed ultrasound (LIPUS)

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ABSTRACT

Background: Established fracture nonunions rarely heal without secondary intervention. Revision surgery is the most common intervention, though non-surgical options for nonunion would be useful if they could overcome nonunion risk factors. Our hypothesis is that low-intensity pulsed ultrasound (LIPUS) can enhance heal rate (HR) in fractures that remain nonunion after one year, relative to the expected HR in the absence of treatment, which is expected to be negligible.

Methods: We collated outcomes from a prospective patient registry required by the U.S. Food & Drug Administration. Patient data were collected over a 4-year period beginning in 1994 and were individually reviewed and validated by a registered nurse. Patients were only included if they had four data points available: date when fracture occurred; date when LIPUS treatment began; date when LIPUS treatment ended; and a dichotomous outcome of healed vs. failed, assessed by clinical and radiological criteria. Data were used to calculate two derived variables: days to treatment (DTT) with LIPUS, and days on treatment (DOT) with LIPUS. Every validated chronic nonunion patient (DTT > 365 days) with complete data is reported.

Results: Heal rate for chronic nonunion patients ($N = 767$) treated with LIPUS was 86.2%. Heal rate was 82.7% among 98 patients with chronic nonunion ≥5 years duration, and 12 patients healed after chronic nonunion >10 years (HR = 63.2%). There was more patient loss to follow-up, non-compliance, and withdrawal, comparing chronic nonunion patients to all other patients ($p < 0.0001$). Patient age was the only factor associated with failure to heal among chronic nonunions ($p < 0.004$). Chronic nonunion patients averaged 3.1 surgical procedures prior to LIPUS, but some LIPUS-treated patients were able to heal without revision surgery. Among 91 patients who received LIPUS ≥90 days after their last surgery, HR averaged 85.7%, and the time from last surgery to index use of LIPUS averaged 449.6 days.

Conclusions: Low-intensity pulsed ultrasound enhanced HR among fractures that had been nonunion for at least 1 year, and even healed fractures that had been nonunion >10 years. LIPUS resulted in successful healing in the majority of nonunions without further surgical intervention.

Introduction

Approximately 93% of patients heal successfully after fracture [1–4]. However, certain fracture types and certain patient characteristics make a fracture more prone to nonunion; for example, one report concluded that 16% of patients with open fracture develop delayed union or nonunion [5]. Though definitions vary, nonunion is broadly accepted as diagnosable 26–30 weeks

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after fracture [6]. Patients diagnosed with nonunion are thought to have a very low probability of healing without intervention, and this value approaches zero for chronic nonunions [7].

Revision surgery is the most common intervention for nonunion and it is usually successful [8]. In cases of gross bone instability, broken hardware, or malalignment, there is no acceptable alternative to surgery. However, revision procedures can fail for many reasons [9], including advanced patient age [10], comorbid conditions such as diabetes [11] or habitual use of tobacco [12,13], frequent use of non-steroidal anti-inflammatory (NSAID) medications [13], and perhaps even genetic predisposition [14]. In short, patients may fail revision surgery for the same reasons that they failed initial surgery. Surgical revision is also technically difficult [15] and carries risks inherent to any surgery. Therefore, a non-surgical option for treating fracture nonunion could be useful, especially if it was effective in the presence of risk factors for surgical failure. Low-intensity pulsed ultrasound (LIPUS) may be one such option [7,16].

We evaluated a large cohort of chronic nonunion patients treated with LIPUS. The LIPUS system used (EXOGEN®, Bioventus, LLC, Durham, N.C.) is a Class III non-invasive device approved by the U.S. Food & Drug Administration (FDA) on the basis of prospective clinical trials in healing of nonunions [7,16] and fresh fractures [17,19]; subsequent trials also demonstrated clinical efficacy in delayed union [18].

A chronic nonunion is here defined as a fracture that has failed to heal for more than 12 months, using clinical and radiographic criteria, at which time the nonunion diagnosis is not in doubt [6]. The study population was drawn from a validated, FDA-required post-market registry of consecutive patients who used the Exogen device, with data published in part previously [19–21]. Our hypothesis is that low-intensity pulsed ultrasound (LIPUS) can induce healing in chronic nonunion fractures.

Patients and methods

The present study was designed as a single arm, retrospective, observational cohort study of a convenience sample of consecutive consenting patients who had enrolled prospectively in a registry for the Exogen device. Inclusion criteria were that patients be males or non-pregnant females 18 years of age or older at enrollment. Patients signed an informed consent at enrollment, and were instructed to use the device for 20 continuous minutes every day until healed.

This study was formally exempted from ethical approval by the Institutional Review Board of the lead author's institution [21] because data were drawn from a post-market registry meant to satisfy FDA reporting requirements. Heal rate (HR) in an acute-fracture cohort of patients treated with LIPUS has been reported [21], and we use similar methods here.

Registry data for the period from 14 Oct 1994 until 15 Oct 1998 were validated by a registered nurse who manually compared every patient's paper record to the digital record [21]. To be analyzed, each patient was required to have four data points [21]:

- **Date of fracture**: Calendar date when the fracture occurred
- **Date LIPUS treatment started**: Calendar date when LIPUS treatment began
- **Date LIPUS treatment ended**: Calendar date when LIPUS treatment ended
- **Outcome**: A dichotomous variable of healed/failed at treatment end, as determined by the prescribing physician. For a fracture to be healed, the registry protocol specified that a fracture had to meet both clinical and radiological criteria:
  - Clinically solid and free of pain on manual stress
  - At least three of four cortices bridged on X-ray views

These data were used to calculate 2 derived variables of interest [21]:

- **Days-to-treatment (DTT)**: Time from fracture to LIPUS treatment
- **Days-on-treatment (DOT)**: Time from LIPUS treatment until treatment end

All patients with DTT, DOT, and outcome were analyzed if they had chronic nonunion, defined as DTT > 365 days. Patients with DTT, DOT, and outcome have been reported for a cohort of 4190 patients with DTT < 90 days [21]. Some chronic nonunion data are presented in comparison with cohorts having shorter DTT periods. Patients who healed with LIPUS are also contrasted with patients who did not heal.

The *t*-statistic (Satterthwaite method for unequal variances) was used to compare means and the Fisher's exact test and χ^2 test were used to test for trend across fracture cohorts [21]. Conservatively, only *p*-values <0.01 were reported, since a large sample size is prone to yield statistical significance in the absence of clinical significance; using a smaller *p*-value threshold reduces this risk. Ninety-five percent confidence intervals (CIs) were calculated for percent-healed point estimates. All data were analyzed using SAS software, v9.3 (Cary, NC).

Results

A total of 7884 fractures in the registry had the 4 required data elements [21]. These included 4190 acute fractures (≤90 days old at the start of treatment), 2927 fractures characterized as delayed union/nonunion (91–365 days old at the start of treatment), and 767 fractures that were chronic nonunions (DTT > 365 days old at the start of treatment). The HR for all registry fractures (*N* = 7884) was 93.9%, while the HR for chronic nonunion fractures (*N* = 767) was 86.2%.

The average age for patients with a chronic nonunion was 45.8 years (Table 1). Neither height nor weight was outside the range of normal, although body-mass index (BMI) suggests that these patients were overweight.

Heal rate could not be calculated for chronic nonunion patients whose records lacked outcome data, and these patients were not included in the cohort of 767 chronic nonunion fractures. We evaluated the excluded population to determine why the outcome was missing and whether the missing data could potentially distort the HR results. The number of chronic patients for whom there was any record in the registry was *N* = 1286. The most cited explanation for missing data was loss to follow-up (*N* = 207), with fewer patients designated as non-compliant (*N* = 113), withdrawn (*N* = 101), missing outcome (*N* = 85), deceased (*N* = 3) or other (*N* = 10) (Fig. 1). Loss to follow-up, when contrasted with a

Table 1
Summary of demographic data for 401 men (52.3% of the sample) and 348 women (45.4% of the sample) in the cohort of patients with chronic nonunion; 18 patients were of unknown gender. Mean "Smoking years" includes 296 patients (50%) who never smoked.

Variable	N=	Mean	SD
Age (years)	764	45.8	16.5
Days to treatment (DTT)	767	912.5	959.8
Days on treatment (DOT)	767	179.5	127.9
Weight (pounds)	619	174.4	44.7
Height (inches)	625	67.5	4.6
Body-mass index	616	26.7	5.6
Smoking years (mean)	593	7.0	11.9

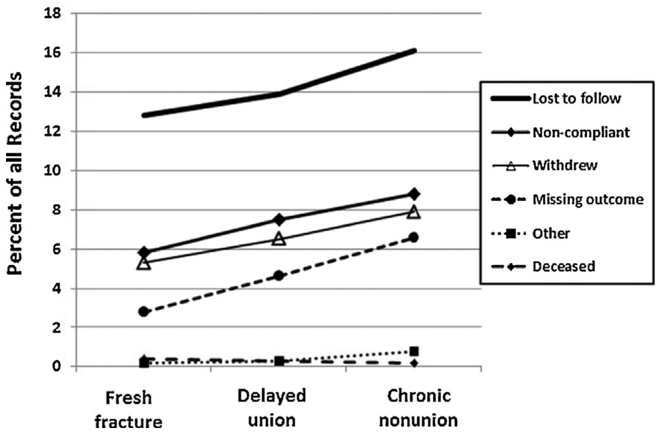

Fig. 1. Summary of the disposition of fractures in the Exogen registry database expressed as a percentage of any record in the registry, for each cohort of patients. Patients in the "Chronic nonunion" cohort ($N = 1286$, including all patients not assessed as to outcome) are compared to patients in the "Fresh fracture" ($N = 5765$) and the "Delayed union" ($N = 4382$) cohorts. This presentation shows that patients in the chronic cohort of patients were substantially more likely to be non-compliant or lost to follow-up, less likely to be retained in the registry, and more likely to fail in response to treatment.

combination of the other dispositions, was significantly and substantially different in the chronic cohort ($p = 0.0008$). Conversely, the proportion of patients who died or were otherwise unaccounted for was comparable across all cohorts (Fig. 1).

We tested whether patients were systematically lost to follow-up, potentially distorting results, by examining demographics of the patients lacking outcome information (Table 2). Patients lacking an outcome were on average 3.7 years younger ($p < 0.0001$), male ($p < 0.01$), and stopped using LIPUS 39 days sooner ($p < 0.0001$). Because these differences are not linked to worse outcomes, it suggests that the heal rate data were not biased in favour of healing by exclusion of patients with missing outcomes.

There were no significant predictors of failure to heal in the chronic cohort except age (Table 3). Mean body-mass index, percent open fracture, number of comorbidities (*e.g.*, cardiovascular disease, hypertension, vascular insufficiency, renal disease, diabetes, alcoholism, arthritis, osteoporosis, and cancer), number of medications, and number of smoking years – none of these factors differed significantly between healed and failed patients in the chronic cohort. Even multiple prior surgical procedures did not predispose a patient to fail LIPUS treatment; chronic nonunion patients who healed averaged 3.1 surgical procedures prior to healing. Patient age was significant ($p < 0.004$), as was DOT ($p < 0.0001$), presumably as a result of the failure to heal. Chronic nonunions that healed did so in an average of 5.6 months, after remaining unhealed for an average of 28.7 months prior to LIPUS (Table 3).

For chronic nonunions treated with LIPUS, HR decreased with increasing patient age (Fig. 2). However, the magnitude of this decrease was modest. Compared with the overall HR of 86.2%, the observed HR for patients aged 70–79 was 83.3% (40 of 48 fractures healed). For patients 80 years or older, the observed HR was 77.8% (14 of 18 fractures healed). A regression equation fitted to these data (HR = 96.2% − (0.2%*number of years)) can be used to predict HR for patients of any age. According to this model, HR was only 12% lower for patients treated with LIPUS at age 80 (calculated

Table 2
Comparison of chronic nonunion patients whose records include a healing outcome to the records of chronic patients that lacked a healing outcome. This approach was used in the tables that follow, to identify risk factors associated with failure to heal, so here we test whether these risk factors are associated with lack of an outcome. Mean "Smoking years" includes 296 patients (50%) who never smoked.

Entire registry sample	Outcome (±SD)	*N* or %	No outcome (±SD)	*N* or %	Significance
Patient age (years)	45.8 (±16.5)	764	42.1 (±16.0)	518	<0.0001
Weight (lb)	174.4 (±44.7)	619	179.5 (±46.2)	370	NS
Height (in)	67.5 (±4.6)	625	68.1 (±6.2)	375	NS
Body-mass index	26.7 (±5.6)	616	27.3 (±6.6)	368	NS
Days-to-treatment (mean)	912.5 (±959.8)	767	946.9 (±1008.0)	519	NS
Days-on-treatment (mean)	179.5 (±127.9)	767	140.7 (±115.6)	517	<0.0001
Female (vs. male) (%)**	359 (vs. 408)	46.8%	204 (vs. 314)	39.4%	0.01
Open (vs. closed fracture) (%)**	111 (vs. 588)	15.9%	86 (vs. 382)	18.4%	NS
Surgical procedures (mean)	3.1 (±2.3)	388	3.1 (±2.5)	239	NS
Comorbidities (mean)	1.4 (±0.8)	165	1.4 (±0.7)	99	NS
Medications (mean)	0.5 (±0.7)	474	0.6 (±0.8)	227	NS
Smoking years (mean)	7.0 (±11.9)	593	8.8 (±12.2)	355	NS

** *p* values are from *t*-tests, except comparisons with an asterisk, which were tested using Fischer's exact test because they are dichotomous variables.

Table 3
Comparison of chronic nonunion patients who healed with LIPUS to LIPUS-treated chronic patients who failed to heal. This approach should be very sensitive to risk factors that increase the risk of treatment failure, so we accept $p < 0.01$ as a minimum level of significance. Reported means for "Surgical procedures", "Comorbidities", "Medications", and "Smoking years" all include patients who reported zero values (e.g., no surgical procedures).

Chronic nonunion cohort	Healed	*N* or %	Failed	*N* or %	Significance
Patient age (years)	45.1 (±16.5)	658	50.0 (±16.2)	106	0.004
Weight (lb)	173.6 (±42.8)	534	179.8 (±55.3)	85	NS
Height (in)	67.5 (±4.7)	540	67.2 (±4.0)	85	NS
Body-mass index	26.6 (±5.3)	531	27.6 (±6.7)	85	NS
Days-to-treatment (mean)	872.5 (±866.9)	661	1161.1 (±1387.0)	106	NS
Days-on-treatment (mean)	168.2 (±113.6)	661	250.1 (±179.7)	106	<0.0001
Female (vs. male) (%)**	307 (vs. 354)	46.4%	52 (vs. 54)	49.1%	NS
Open (vs. closed fracture) (%)**	100 (vs. 503)	16.6%	11 (vs. 85)	11.5%	NS
Surgical procedures (mean)	3.1 (±2.1)	331	3.2 (±3.1)	57	NS
Comorbidities (mean)	1.4 (±0.8)	143	1.3 (±0.6)	22	NS
Medications (mean)	0.5 (±0.8)	420	0.6 (±0.6)	54	NS
Smoking years (mean)	6.8 (±11.5)	510	8.6 (±14.1)	83	NS

** *p* values shown are from *t*-tests, except comparisons with an asterisk, which were tested using Fischer's exact test because they are dichotomous variables.

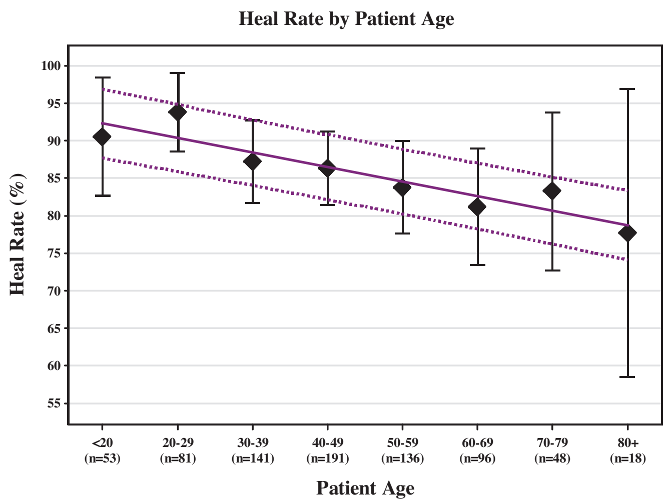

Fig. 2. Summary of the effect of patient age on heal rate in the chronic cohort of patients. Shown is the heal rate for each age category, with upper and lower 95% confidence intervals. A simple linear regression is also shown, with the 95% confidence interval for patient predicted values. The regression equation is: HR = 96.2% − (0.2%*Year).

Table 4
Impact of bone fractured on heal rate (HR) in the chronic cohort. Every bone represented in the database by more than 20 fractures is tabulated.

Bone	Healed	Failed	HR (%)	Lower CI (%)	Upper CI (%)
All fractures	661	106	86.2	83.7	88.6
All closed fractures	503	85	85.5	82.7	88.4
All open fractures	100	11	90.1	84.5	95.6
Tibia	168	21	88.9	84.4	93.4
Femur	129	24	84.3	78.6	90.1
Radius/Ulna	60	10	85.7	77.5	93.9
Humerus	52	13	80.0	70.3	89.7
Tibia/Fibula	50	6	89.3	81.2	97.4
Scaphoid	48	7	87.3	78.5	96.1
Ankle	35	6	85.4	74.5	96.2
Metatarsal	31	5	86.1	74.8	97.4
Foot	20	3	87.0	73.2	100.0

HR = 80.2%) than for patients treated at age 20 (calculated HR = 92.2%).

Fracture HR was not significantly impacted by how quickly treatment started; we did not identify a point beyond which LIPUS was ineffective (Fig. 3). The HR was 82.7% among 98 patients who started LIPUS at least 5 years after fracture, and 12 of these patients healed after chronic nonunion >10 years duration (HR = 63.2%). Although the HR for patients with >10 year nonunions was lower (as expected for such extreme cases), the overall difference in HR was not significant between fractures 1–2 years old (87.9%) and fractures >3 years old (82.9%).

Different fractured bones had different HRs in the chronic cohort (Table 4). Open fractures had a higher HR than closed fractures, but this difference was not statistically significant. Type of surgical procedure performed prior to LIPUS had no significant impact on HR among chronic nonunion patients (Fig. 4). Use of intermedullary nails did not result in significantly decreased HR relative to other forms of internal or external fixation or to conservative treatment.

Some chronic nonunions treated with LIPUS were able to heal without revision surgery (Table 5). We characterized HR in chronic nonunion patients for whom LIPUS treatment was given ≥90 days after the last revision surgery, and for whom there was no subsequent record of revision surgery after LIPUS treatment began. Individual bones are reported if there were ≥10 patients in the category. Remaining bones were pooled into an "All other bones" category. Among 767 patients with chronic fracture, patients were excluded because: there was an exclusionary surgical procedure (*e.g.*, pathological fracture) or a procedure lacked a treatment date (*N* = 209); there was no record of surgery, but we were unable to confirm that surgery did not happen (*N* = 400); surgery was done <90 days prior to LIPUS (*N* = 58); or there were apparent errors in the database (*N* = 9). The nonunion HR from LIPUS in the absence of surgery averaged 84.3% across the 4 bones reported, and 85.7% across all 91 LIPUS-treated chronic fractures (Table 5). The time interval between last revision surgery and index use of LIPUS averaged 449.6 days among the 91 LIPUS-treated bones.

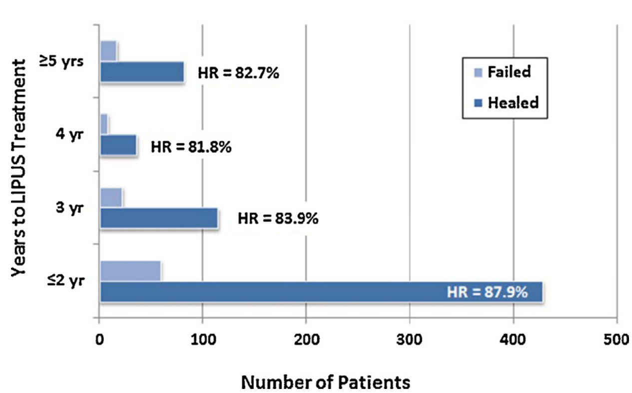

Fig. 3. Heal rate (HR) as a function of years to LIPUS treatment. There are no significant differences in HR as a function of years to treatment.

Discussion

The current cohort of 767 chronic nonunion patients treated with LIPUS represents the largest chronic cohort reported to date. In fractures that had not healed for at least one year, 86.2% of

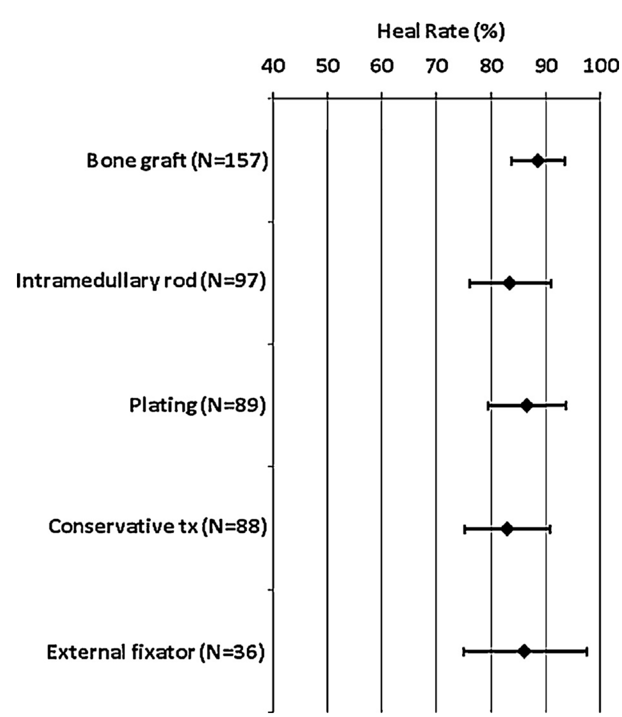

Fig. 4. Overall heal rate (HR) in the chronic cohort of patients was 86.2% (95% confidence interval: 83.7–88.6%). Procedures which were represented more than 20 times in the dataset are shown. Although "Bone graft" offers the highest overall HR, most procedures offer comparable HR, among patients treated with LIPUS.

Table 5
Fracture heal rate (HR) among chronic nonunion patients with LIPUS treatment ≥90 days after the last revision surgery. This characterizes HR when chronic nonunion patients are treated with LIPUS alone. "Days to LIPUS" is the average number of days from the last surgical treatment to the time when LIPUS treatment began.

Bone	# Prior surgeries	Healed	Failed	HR (%)	Days to LIPUS (average)
Tibia	1	7	0	100.0	–
	2	4	3	57.1	–
	≥3	9	2	81.8	–
	Average	20	5	80.0	443.4
Tibia + Fibula	1	3	1	75.0	–
	2	3	0	100.0	–
	≥3	3	0	100.0	–
	Average	9	1	90.0	464.8
Femur	1	5	3	62.5	–
	2	1	0	100.0	–
	≥3	11	0	100.0	–
	Average	17	3	85.0	347.2
Humerus	1	4	0	100.0	–
	2	5	0	100.0	–
	≥3	4	2	66.7	–
	Average	13	2	86.7	523.5
All other bones	1	12	2	85.7	–
	2	2	0	100.0	–
	≥3	5	0	100.0	–
	Average	19	2	90.5	509.8
	Overall average	78	13	85.7	449.6

patients healed with LIPUS. The average fracture age was 28.7 months at the start of LIPUS treatment, and patients had an average of 3.1 prior attempts at surgical repair, yet the average time to heal was 5.6 months with LIPUS (Table 3). Patient age in the chronic cohort was correlated with HR; nevertheless, patients aged 70–79 and 80+ had an observed HR of 83.3% and 77.8%, respectively. A linear regression of these data shows that the heal rate for an 80-year-old was only 12% less than the HR for a 20-year-old (Fig. 2). Type of surgical treatment received prior to LIPUS did not significantly impact HR (Fig. 4), and some LIPUS-treated patients were able to heal chronic nonunions without revision surgery (Table 5).

Compared with patients who received LIPUS for fresh fractures, chronic nonunion patients were less likely to be compliant and less likely to complete treatment (Fig. 1). The reasons for this are unclear. However, patients lost to follow-up were younger and more likely to be male (Table 2), and such factors have been associated with lack of compliance in RCTs. Since neither age nor gender was associated with lower HR, we do not believe that the reported HR was biased by patients lost to follow-up.

Few risk factors emerged as correlates of treatment failure in the chronic cohort (Table 3). Open fracture, BMI, number of prior surgeries, and number of comorbidities did not differ significantly between healed and failed. One interpretation is that these risk factors are not predictive of treatment-refractory nonunion. An alternative explanation is that LIPUS treatment mitigated these risk factors and lessened their role in nonunion pathology. We cannot exclude either of these explanations with the current data.

The HR of 86.2% we report is consistent with other reports of LIPUS treatment for nonunion [7,16,22–27]. Nine previous studies of LIPUS for nonunion have reported HRs ranging from 73% to 100% [7,16,19,22–27], with a median HR of 86%. Our results are also consistent with a systematic review of LIPUS for nonunions, which reported an HR of 87% in 594 nonunions from 8 studies, with a mean fracture age of 22.2 months and mean heal time of 4.8 months [28].

The HR we observed in the current cohort is also within the range of reported HRs for nonunion revision surgery. A review of 23 papers on surgical revision reported HRs between 68% and 96%, with a mean of 86% [16]. Another group reviewed the literature on exchange nailing for diaphyseal femur or tibia nonunions and found HRs from 72% to 100% [29]. The same procedure in infected nonunions and segmental bone defects yielded a HR of 85% [30]. Most recently, a single-centre prospective registry of 272 surgically revised nonunions reported a HR of 75% after the first surgery and 95% after two or more revision attempts [31].

Nonunion surgery can be associated with clinically significant morbidities. Iliac crest bone graft (ICBG) is considered by many to be the gold standard for nonunion treatment, and a review on the subject cited HRs as high as 87–100% [32]. However, ICBG is associated with a high rate of donor site morbidity; among 170 patients, 24% reported harvest site numbness 3.5 years after surgery, and 19% reported that harvest site pain resulted in difficulty with routine chores [33]. Even without ICBG, surgery introduces greater risk than LIPUS treatment, especially in vulnerable patients [25]. In a recent study of 134 surgically revised long-bone nonunions, complication rates from surgery were reported to be 11% in patients who healed after one nonunion procedure, 68% in patients who healed after multiple revisions, and 100% in patients who failed to heal [34].

If LIPUS offers a HR comparable to surgery, with fewer associated morbidities, why is LIPUS not considered the gold standard for treatment of chronic nonunion? This is a complex question, but the simplest answer is that there are no RCTs that directly compare LIPUS to modern surgical techniques for nonunion [35]. In the absence of such trials, clinicians should be reluctant to recommend LIPUS over the proven benefits of nonunion surgery. However, the National Institute for Health and Care Excellence (NICE) in the United Kingdom evaluated the evidence supporting LIPUS to promote healing of fracture nonunion [35]. NICE concluded that "clinical evidence supports the use of [LIPUS] in non-union long bone fractures... which have not healed after 9 months." LIPUS use in such cases was calculated to result in a cost savings of $1726 per patient, due to avoidance of surgery [35]. A more recent study concluded that patients who received nonunion surgery had total medical costs that averaged $6289 higher than patients who received LIPUS only [36]. LIPUS-only treatment of nonunion was projected to result in a cost savings of $4 billion annually in the United States [36]. NICE concluded that "successful use of [LIPUS] may eliminate the need for surgery and its associated complications" [35]. This suggests an urgent need for a direct comparison of LIPUS to surgery for fracture nonunion.

An inherent limitation of registry studies is the lack of untreated controls and the absence of blinding; both patients and physicians are aware of the type of treatment. Nevertheless, the absence of controls in the current study must be placed in context: surgery had already been attempted an average of 3.1 times prior to the start of LIPUS treatment and patients probably did not anticipate success with LIPUS (Table 3). We also note that RCTs are problematic in the study of established nonunion because the use of an untreated or placebo control group is considered unethical for fractures that will not heal without intervention [7,16].

Registries do have certain advantages, most notably in cohort size. This cohort is perhaps the largest group of consistently defined chronic nonunion fractures in the literature. By contrast, most case series are small, reporting a few dozen patients. In addition, bias can be significant in case series because they are often written when a clinician notices something out of the ordinary: a rare fracture; an unexpectedly high (or low) heal rate; or an unanticipated side effect. Thus, case series are unusual by nature. Retrospective analyses also tend to be smaller and prone to bias (positive or negative), as most are based on records from a single centre. Here we report a large sample from a 4-year period in which a consecutive series of patients from multiple centres were prescribed LIPUS to treat chronic nonunion. In addition, the registry reports real-world outcomes on many different fractures treated by many different physicians. Its results are applicable to a range of fracture locations, patient populations, and clinical settings.

The pathophysiology of failed fracture healing remains incompletely understood, and the current data offer few clues for predicting treatment failures with LIPUS. The 13.8% of chronic nonunion patients who did not heal with LIPUS differed in no obvious way from patients who did heal (Table 3). One exception was patient age, which showed a small but significant correlation with lower HR. However, given the 80% heal rate in 80-year-old patients, the clinical significance of this observation seems low. Factors often linked to poor healing, such as medical comorbidities, smoking, prior surgeries, and fracture age, did not predict treatment failure here. Other studies on refractory nonunions have noted that such patients often have undiagnosed endocrine or metabolic disorders [37] and may have uncharacterized genotypic risk factors [38]. It is possible that a large multivariate analysis of patient risk factors might reveal why some patients are prone to nonunion, and this work is currently underway.

Conclusions

LIPUS treatment was associated with a high rate of healing (86.2%) in a registry cohort of 767 nonunion fractures that had failed to heal for at least one year prior to treatment. The LIPUS heal rate is comfortably within the range of heal rates reported after surgical revision, suggesting that LIPUS treatment may provide comparable benefit to surgery. If outcomes are equivalent, safety issues would favour LIPUS, which is non-invasive and has no known contraindications. Thus, LIPUS therapy may represent an effective, low-risk alternative to surgical revision in the setting of impaired fracture healing.

Conflict of interest

All authors of this manuscript have potential financial competing interests. R. Zura, G.J. Della Rocca, and S. Mehta are consultants for Bioventus, which makes a LIPUS device, and all have received speaker fees and travel reimbursement. A. Harrison, C. Brodie, J. Jones, and R.G. Steen are employees of Bioventus. None of the authors has any non-financial competing interests.

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