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When Is a Fracture Not "Fresh"? Aligning Reimbursement With Patient Outcome After Treatment With Low-Intensity Pulsed Ultrasound

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Objective: The clinical value of low-intensity pulsed ultrasound (LIPUS) for fresh fracture is known. Yet, in the absence of a definition of what "fresh" is, payers have adopted study inclusion criteria drawn from randomized clinical trials as de facto definitions of which patients should be treated, with "fresh" defined as <1 week old. Patients with fracture may thus be ineligible for LIPUS treatment after week 1, which potentially denies access to patients who could benefit from LIPUS. We seek to characterize the inflection point at which heal rate declines.

Design: Prospective cohort.

Setting: Food and Drug Administration–mandated nationwide postmarketing surveillance registry.

Patients: Observational cohort of 5983 registry enrollees.

Intervention: LIPUS, 20 min/d.

Main Outcome Measure: Fracture heal rate. Logistic regression was used to model the odds ratio of nonunion from week 1 to week 12. Covariates in the model included age, gender, body mass index, open fracture, and smoking.

Results: We estimated the time point at which a fracture responds to LIPUS as well as during the first week after fracture. There was significant bone-to-bone variation; metatarsal was "fresh" until week 7, ankle until week 9, humerus until week 10, and femur and radius until week 12. Healing was significantly impacted by patient age, body mass index, and open fracture (all, $P \leq 0.02$).

Conclusions: Our results suggest that fractures of the metatarsal, femur, humerus, ankle, and radius respond to LIPUS treatment, as if they were still fresh at least 6 weeks longer than the eligibility allowed under current coverage policies.

Key Words: nonunion, low-intensity pulsed ultrasound

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

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INTRODUCTION

Robust literature demonstrates the clinical value of low-intensity pulsed ultrasound (LIPUS) in the treatment of fresh bone fractures.[1] However, most published studies used an arbitrary time after fracture to define a "fresh fracture" for study inclusion. In the absence of an accepted clinical definition of fresh fracture, many third-party payers have adopted these study inclusion criteria as de facto definitions of what constitutes a fresh fracture. For example, 3 major payers all use the definition of a fresh fracture as a fracture less than 7 days old, whereas a delayed union or nonunion is defined as a fracture older than 12 weeks.[2–4] Therefore, between week 1 and week 12, patients with bone fracture are ineligible for reimbursement for LIPUS therapy. Exclusion of fractures that are 2–12 weeks old could potentially deny access to patients who might benefit from LIPUS.

We use data from a LIPUS Registry[5,6] to determine whether there is statistical evidence of a time-related decrement in heal rate (HR) of bones treated with LIPUS, which may indicate when a fracture can no longer be considered "fresh." We hypothesize that there is an inflection point in the plot of HR versus time, such that at some time point (X) between week 2 and week 12, the HR possible with LIPUS declines.

METHODS

This study was formally exempted from ethical approval by the Institutional Review Board of Duke University[5,6] because data were drawn from a postmarket registry required by the Food and Drug Administration. HR in this registry has been previously reported,[5–7] and we use similar methods here.

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This is a single-arm, retrospective, observational cohort study of a convenience sample of consecutive consenting patients who enrolled prospectively in a registry for the EXOGEN device (Bioventus LLC, Durham, NC). Inclusion criteria were that patients be males or nonpregnant females, 18 years of age or older at enrollment. Patients signed informed consent at enrollment, and they were instructed to use the device for 20 continuous minutes each day until healed.

Registry data for a 4-year period were validated by a registered nurse who manually compared every patient's paper record with the digital record.[5] To be analyzed, each patient was required to have 4 data points[5]:

1. Date of fracture: calendar date when the fracture occurred
2. Date LIPUS treatment started: calendar date when LIPUS treatment began
3. Date LIPUS treatment ended: calendar date when LIPUS treatment ended
4. Outcome: a dichotomous variable of healed/failed at treatment end, as determined by the prescribing physician. For a fracture to be healed, the fracture had to meet clinical and radiological criteria:
   (a) Absence of pain with use and on manual stress
   (b) At least 3 of 4 cortices bridged with callus on x-ray views

These data were used to calculate a derived variable of interest:

1. Weeks to treatment (WTT): time from fracture to LIPUS treatment in weeks.

Analysis focused on the HR for all bones pooled and for any bone separately for which there were more than 250 patients.[7] Week X is the inflection point in the plot of HR with WTT (from week 1 to week 12). The inflection point occurs at week X, when both of the following conditions are met:

1. There is no significant difference in odds of union versus nonunion from week 1 to week X
2. The odds of union versus nonunion are significantly different from week X until week 12.

Covariates adjusted in the logistic regression model include gender, age, body mass index (BMI), fracture severity (open/closed), and tobacco smoking. Missing values were imputed using the most frequent value for categorical covariates; for instance, 5 missing gender values were assigned to the most common gender of male. For continuous covariates (eg, BMI), a monotonic propensity score-based imputation for missing values used an approximate Bayesian bootstrap imputation[8] applied to each group,[9] using PROC MI in SAS software 9.4 (SAS Institute, Cary, NC).

Logistic regression was used to model the log odds of union versus nonunion. The logistic regression model included weeks to LIPUS treatment, week X indicator, week-by-indicator interaction, and covariates. To identify an inflection point at week X, we fitted a logistic regression equation for each of the 12 weeks, and then we selected a final model based on the minimum Akaike Information Criterion or AIC.[10] If the final model satisfied 2 criteria, we defined week X as the inflection point:

1. There is no significant change in slope from week 1 to week X
2. There is a significant change in either intercept or slope after week X.

If the model failed to converge, we dropped problematic variables from the model and concluded that week X is the inflection point. Finally, we exponentiated from the log odds to obtain the odds ratio, which we report.

RESULTS

Demographic variables for all 5983 patients in this analysis are summarized in Table 1. The median patient was 45 years old, male, overweight by BMI, had closed fracture, and never smoked. However, there were more open fractures in this sample than in a random sample of patients with fracture,[11] which may mean that these patients were prescribed LIPUS because they were perceived to be in a high-risk group. Similarly, the rate of smoking (current/past/missing) was somewhat higher than expected in a random sample of patients with fracture.[11] Eight bones had sufficient patient data (>250 patients) to be analyzed separately for an inflection point. This approach can potentially determine when a fracture is no longer able to heal and when it was "fresh".

Parameter estimates of the regression model for all bones (N = 5983) are shown in Table 2. The AIC was used to determine that the minimum value was at week 10 (data not shown), suggesting that there is an inflection point at week 10

TABLE 1. Demographic Description of Patients in the Study

Variable	Before Imputation	After Imputation
Weeks to LIPUS	12 [5, 25]	12 [5, 25]
Age, y	45 [34, 57]	45 [34, 57]
Gender		
Male	3349 (55.98)	3354 (56.06)
Female	2629 (43.94)	2629 (43.94)
Missing	5 (0.08)	0
BMI, kg/m^2	25.6 [22.7, 29.0]	25.5 [22.7, 28.9]
Fracture severity		
Open	1150 (19.22)	1150 (19.22)
Closed	4833 (80.78)	4833 (80.78)
Smoking status		
Current smoker	1131 (18.90)	1131 (18.90)
Past smoker	1040 (17.38)	1040 (17.38)
Never smoked	3047 (50.93)	3047 (50.93)
Missing	765 (12.79)	765 (12.79)
Fractured bone		
Tibia	1708 (28.55)	1708 (28.55)
Tibia/fibula	1161 (19.40)	1161 (19.40)
Femur	854 (14.27)	854 (14.27)
Metatarsal	655 (10.95)	655 (10.95)
Radius	460 (7.69)	460 (7.69)
Humerus	459 (7.67)	459 (7.67)
Scaphoid	399 (6.67)	399 (6.67)
Ankle	287 (4.80)	287 (4.80)

Categorical variables are reported as frequency (%), whereas continuous variables are reported as median [q1, q3]. There were 5 missing gender variables which were assigned as the more frequent value of male. There were 1240 (20.7%) missing values for BMI, which were imputed. There were 765 (12.8%) missing values for smoking status, which were treated as a separate category.

TABLE 2. Summary of Parameter Estimates in the Final Model for All Bone Fractures

Source	Odds Ratio (95% Confidence Interval)	Wald Statistic	P
Intercept (β0)	129.7 (60.45–278.3)	156.0	<0.0001
Week (β1)	0.981 (0.905–1.062)	0.23	0.6307
Intercept marginal reduction to heal at week 10 (β2)	0.364 (0.225–0.588)	17.08	<0.0001
Slope marginal reduction to heal at week 10 (β3)	1.017 (0.939–1.102)	0.17	0.6813
Age	0.984 (0.977–0.991)	22.26	<0.0001
Gender (male)	1.159 (0.929–1.446)	1.72	0.1896
BMI	0.979 (0.962, 0.996)	5.96	0.0146
Fracture (open)	0.732 (0.565–0.947)	5.62	0.0178
Current smoker	0.778 (0.591–1.025)	3.19	0.0742
Past smoker	0.839 (0.635–1.107)	1.54	0.2143
Missing smoking status	1.478 (0.995–2.196)	3.74	0.0530

Global Ho: all β = 0: Wald χ^2 = 148.11, df = 10, P = <0.0001.
Area under the receiver operating characteristic curve = 0.687.
Hosmer–Lemeshow goodness-of-fit test: P = 0.6527.
The final model for 8 bone fractures pooled together (N = 5983), adjusting for covariates including age, gender, BMI, fracture severity, and smoking status as appropriate. Confidence intervals, test statistics, and P values for each individual coefficient (β) are based on the Wald test, whereas the test statistic and P value for the joint effect of β2 and β3 are based on the likelihood ratio test. The Hosmer–Lemeshow goodness-of-fit test results suggest that the model fits the data.

in the HR for all bones (Fig. 1). The regression suggests that there is no significant decrement in the rate of healing before week 10 (week X). In addition, there is a significant difference in the rate of healing for all bones ($P < 0.0001$), when comparing the time period before and after week 10. The logistic model was significantly impacted by patient age, patient BMI, open fracture, and an interaction term (Table 2). The Hosmer–Lemeshow test of goodness of fit was nonsignificant (Table 2). For this test, the null hypothesis was that the model fits the data; so, failing to reject the null suggests that the model does fit the data. The area under the receiver operating characteristic curve was 0.687, suggesting that the model adequately predicts the inflection point (Table 2). Overall, we conclude that the logistic regression model identified an inflection point at week 10, suggesting that the HR of patients with fracture at any point within the first 10 weeks is the same, whereas the HR for fractures older than 10 weeks is somewhat less (Fig. 1).

Parameter estimates for 8 bones separately are also shown in Table 3. For all bones pooled and for 5 bones separately, there is an inflection point, with the earliest inflection point at week 7 in the metatarsal. The ankle has an inflection point at week 9, the humerus has an inflection point at week 10, and the femur and radius have an inflection point at week 12. This indicates that all of these fractures may be considered "fresh" long after 1 week has passed. For 3 other bones, an inflection point could not be identified; this was usually the result of nonconvergence of the model. For 2 bones (ankle, scaphoid), model convergence was hindered by fracture severity (open/closed), but the model converged for the ankle when fracture severity was dropped from the model. For radius, model convergence was hindered by smoking status, but the model converged when smoking status was dropped from the model.

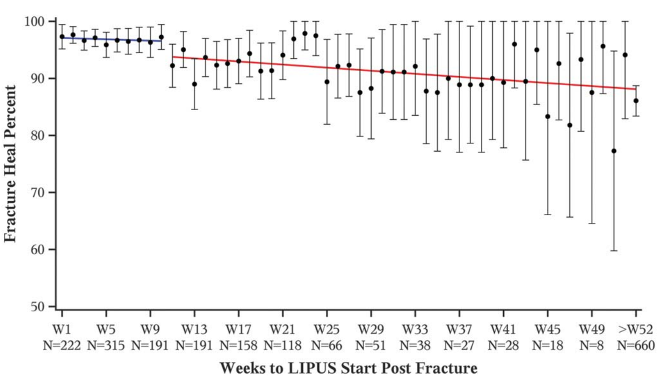

FIGURE 1. Fracture HR for the 8 most common fractures pooled together (N = 5983). This plot shows a change in slope and intercept at week 10, such that the logistic regression fit at week 1 to week 10 is significantly different from the regression fit thereafter.

DISCUSSION

We present a logistic regression approach to estimate when a fracture treated with LIPUS no longer responds as if it were a fresh fracture (defined as 1 week by most payers). For all bones pooled (N = 5983), there is an inflection point at week 10, consistent with the hypothesis that fractures less than 10 weeks old heal as well as a 1-week-old fracture when treated with LIPUS (Table 2). When HR as a function of WTT is plotted, there is a clear visual signal consistent with a change in HR at about week 10 (Fig. 1). When the same model is applied to other bone fractures, results suggest that fractures of the femur, humerus, ankle, metatarsal, and radius treated with LIPUS respond to treatment as if they were fresh fractures for at least 7 weeks (Table 3), not the 1 week allowed under current coverage policies. It is worth noting that,

TABLE 3. Inflection Point for Each Bone Evaluated, as Determined by the Logistic Regression Model

Bone Fractured	Nonunions/ Unions	Week X in the Final Model	Inflection Point
All bones pooled	379/5604	Week 10	Yes
Tibia	92/1616		No
Femur	77/777	Week 12	Yes
Tibia/fibula	65/1096		No
Humerus	58/401	Week 10	Yes
Ankle	28/259	Week 9	Yes*#
Metatarsal	23/632	Week 7	Yes
Scaphoid	19/380		No#
Radius	17/443	Week 12	Yes$

Nonconvergence of the model is denoted (*). In the case of nonconvergence, the cause could be assigned by dropping covariates to allow model convergence. Nonconvergence due to fracture severity (#) is distinct from nonconvergence due to smoking status ($).

although there is a decrement in healing after week 10 (Fig. 1), the HR at week 20 is still approximately 94%.

Patients who could benefit from LIPUS may routinely be denied coverage. Definitions of fresh fracture used by some payers were simply imported into payment plans from clinical trials, with little consideration as to when a fracture will not respond to LIPUS as well as a fresh fracture responds. As we have shown here, there is likely to be a benefit conferred to patients from LIPUS long after patients cannot routinely obtain reimbursement from payers. Current payer recommendations which deny the benefit of this modality can have an adverse impact on a patient's course of fracture healing.

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Invited Commentary

Fracture healing is a biological process that occurs at various rates over time depending on several factors including, among others, the bone involved, the location within the bone, the patient's age, and the patient's medical condition. The orthopaedic community has had a great deal of difficulty and frustration in defining when a fracture is healed, and indeed this determination often remains a clinical one with only supportive objective evidence.

In an attempt to enhance the natural fracture repair process, in the 1980s, we studied the effects of low-intensity ultrasound on the healing of tibial shaft fractures treated in a cast.[1] We conducted the first randomized clinical trial of this modality, and it demonstrated a modestly positive effect. In designing the study, 2 features were essential: (1) controlling for as many variables as possible and (2) distinguishing this noninvasive method from electrostimulation which had been popularized earlier in that decade for the treatment of fracture nonunions (fractures which certainly were not "fresh" and had no potential to heal without further intervention).

To meet the first criterion of controlling variables, it was necessary to select patients who had sustained their tibial fracture within a very narrow window of time (7 days) so that the relatively small study groups would be comparable. Thus, all these study patients had fresh fractures, but that inclusion criterion was never intended to mean that someone with a fracture which is more than seven days old does not also have a fresh fracture. This current elegant study clearly reinforces that point as fractures that were 7 weeks or more along still responded well to the ultrasound therapy.

To meet the second criterion of distinguishing ultrasound from electrostimulation, we selected the term fresh to contrast the fractures we treated from established nonunions. We never defined fresh in the published article, using it only in a very generic sense, and we never intended more for this term than for it to provide a soft distinction from an ununited fracture.

To use the term "fresh fracture" as only descriptive of a fracture that is less than 8 days old is incorrect, inappropriate, and unnecessarily restrictive. Most importantly, such an interpretation should never be used to restrict patient care. The authors should be congratulated on bringing this important distinction to our attention.

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