Low-Intensity Pulsed Ultrasound for Nonoperative Treatment of Scaphoid Nonunions: A Meta-Analysis

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Abstract

Background: Scaphoid fractures progress to nonunion rates of up to 15% when non-displaced, and are even more frequent when the fracture is displaced. Standard treatment in these cases is surgery; however, individuals unable to undergo this operation, or for those who wish to try more conservative measures, there may be benefit from nonoperative options. Of these, low-intensity pulsed ultrasound (LIPUS) has been shown to improve fracture nonunion healing. The purpose of this study was to perform a comprehensive meta-analysis of relevant literature to determine success of the use of LIPUS for treatment of scaphoid nonunion. **Methods:** Utilizing PubMed, Embase, and Ovid databases, we performed a literature search using key terms for scaphoid nonunions. A total of 686 studies met initial search criteria. Studies reporting fewer than 5 cases, those not published in English, those not related to LIPUS nonoperative scaphoid nonunion treatment, and those without sufficient data were excluded. Five studies met these criteria, and statistical analysis was performed to determine overall union rates. **Results:** The use of LIPUS on 166 nonunions reported a mean healing index of 78.6%. The average time to union following LIPUS treatment was 4.2 months. **Conclusions:** While surgical intervention is still the standard, our results show that LIPUS may serve as a nonoperative alternative to scaphoid nonunion in certain cases. The results are encouraging in which these challenging fracture a nonunions can heal without further surgical intervention in the majority of patients.

Keywords: scaphoid, nonunion, nonoperative, hand, LIPUS

Introduction

Scaphoid fractures account for approximately two-thirds of carpal bone fractures.²⁰ These fractures have high nonunion rates, which can be from 5% to 10% in nondisplaced fractures and up to 45% in displaced fractures.² It has been suggested that these high nonunion rates are due to the attenuated/precarious blood supply to the proximal pole of the scaphoid bone, resulting in subsequent nonunion and avascular necrosis rates of up to 55%.^{23,40} In addition, other authors attribute this high nonunion rate to the fact that up to 80% of this bone is covered in cartilage, which impedes callus formation.³¹

Multiple options exist to treat scaphoid nonunions; however, the most common treatment is operative with multiple bone grafting and internal fixation options. Surgical choices are driven by factors including fracture location (proximal, middle, and distal), level of displacement, and the presence of avascular necrosis. Other surgical options include 4-corner fusion with scaphoid excision and proximal row carpectomy in cases where nonunion has progressed to scaphoid nonunion advanced collapse (SNAC).^{7,14} In cases where

surgery is contraindicated or when there have been multiple failed operative attempts, alternative nonoperative treatments have been investigated. Low-intensity pulsed ultrasound (LIPUS) is a noninvasive treatment using a pulsed 30 mW/cm² ultrasound signal for 20-minute intervals per day over a period of several weeks, with the exact time frame varying based on severity of nonunion and fracture response to the treatment.¹³ LIPUS treatment has been shown to elicit bone remodeling activity in rodents,⁴⁶ as well as accelerate the healing of both long bones and carpal bones in humans.^{11,18,43}

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As scaphoid fractures have the potential to result in nonunion at relatively high rates, and not all patients are optimal surgical candidates or amenable to surgical intervention, a comprehensive review of current literature is needed to assess these nonoperative methods of healing. Therefore, we systematically reviewed all studies evaluating LIPUS nonoperative treatment of scaphoid nonunion fractures. The purpose of this study was to: (1) comprehensively review LIPUS use in the treatment of scaphoid nonunions, and (2) evaluate the overall success of LIPUS treatment in healing scaphoid nonunion fractures.

Materials and Methods

We conducted a systematic literature search of clinical studies using MEDLINE (PubMed), Ovid, and Embase to identify nonoperative modalities utilized for the management of scaphoid nonunions using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁸ This was performed by 2 of the authors (J.J., E.S.), who evaluated all studies published from January 1966 to June 2015 using a combination search terms including “Scaphoid,” “Ultrasound,” “LIPUS,” “Low-intensity ultrasound,” “Pseudoarthritis,” “non-union,” “nonunion,” “alternative,” “non-operative,” and “non-surgical.” A total of 686 studies were identified following this comprehensive search.

The authors read all abstracts to assess the articles for eligibility using the following inclusion criteria: (1) full-text reports, (2) randomized controlled trials (RCTs), cohort studies, and randomized crossover studies, (3) studies involving patients with scaphoid fractures, (4) studies containing LIPUS as a nonoperative treatment for scaphoid nonunion fractures, and (5) studies that reported union rates as an outcome measure. Studies published in languages other than English and whose outcome measures did not specifically differentiate scaphoid statistics from other fractures were excluded. The definition of the term “nonunion” in comparison to “delayed union” in the literature varies from 3 to 12 months without healing after the last treatment.⁴⁵ To standardize our search, we set the inclusion criteria as a nonunion scaphoid fracture persisting 3 months after the most recent treatment attempt. In addition, scaphoid nonunions with associated advanced carpal collapse were excluded from this analysis.

Upon reading these abstracts, total of 38 potential studies were identified. These were then cross-referenced to identify an additional 27 potential studies. We then carefully evaluated these 65 studies, and 5 studies ultimately met the inclusion criteria and were included in the final analysis. Of those studies excluded, 52 were unrelated to our eligibility criteria, and the other 8 were excluded for the following reasons: 2 studies only evaluated acute fractures (less than 3 months old),^{15,16,26,48} 2 studies assessed the use of LIPUS immediately following surgery,^{4,37} and 4 studies used the same U.S.

Food and Drug Administration (FDA) data registry for data analysis (hence, only the most comprehensive studies were included).^{9,25,39,47}

A summary of the search methodology is included in Figure 1. The 5 studies that met our inclusion criteria are detailed in Table 1. The data for the studies were compiled into an electronic spreadsheet (Microsoft Excel, Microsoft Office, Redmond, Washington, USA). Statistical analysis was performed using statistical software (MedCalc, MedCalc Software bvba, Ostend, Belgium). We performed Forest plots of the total success of LIPUS treatment. Success was defined as definitive healing confirmed by imaging (radiograph, computed tomography). Within all cohorts, healing rate was defined as the percentage of cases that achieved bony union following each specific intervention.

Results

We reviewed a total of 5 studies reporting on 166 cases of scaphoid nonunion. Of these cases, the average reported patient age was 31 years (range, 18–49 years) with an average fracture age of 20.1 months. LIPUS-treated scaphoid nonunions reported a mean healing rate of 78.6% (95% confidence interval [CI] of 62.8% to 90.9%) and an average time to confirmed healing of 4.2 months (Figure 2). Nonunion fractures were clinically determined to be nondisplaced, and no cases of avascular necrosis were included in final analysis. Confirmation of union was made using radiograph in all cases, with Farkash et al⁸ using computed tomography in addition to radiography in some cases.

Of the 4 studies that reported fracture location, 23/29 cases achieved union following LIPUS treatment when the nonunion was at the waist of the scaphoid, as compared with 11/15 at the proximal pole and 1/2 at the distal pole.^{8,10,30,33} In addition, Pigozzi et al³³ reported 2 comminuted nonunion fractures, which both went on to union following an average of 2 months of LIPUS treatment. Four studies reported a total of 43 cases that were initially treated conservatively using casting, reporting a union rate of 77% following LIPUS, as compared with a union rate of 83% (5/6) when LIPUS was administered following unsuccessful surgical correction.^{8,10,30,33}

Discussion

Current treatment of scaphoid nonunion is predominately surgical; however, nonoperative treatments may provide an additional alternative to operative modalities when surgery is contraindicated or not desired by the patient. Through our comprehensive literature search, we identified 5 studies utilizing ultrasound (LIPUS) treatment that showed a combined healing percentage of 78.6%. High success rates were seen with multiple fracture types, as well as in cases where LIPUS was attempted following different failed treatments.

Figure 1. Search methodology flowchart.

There were several limitations to this study. Although our study is a comprehensive review of the available literature, we were limited by the lack of studies utilizing prospective data, as such future research is needed in the nonoperative treatment of scaphoid nonunions. As noted earlier, the definition of a nonunion is not universally established. As the fracture age in our cohort on average was significantly higher than our 3-month cutoff, we feel confident that these fractures as a whole represent true nonunion cases. Finally, studies where the manuscript was in a language other than English were excluded from this analysis; however, as the majority of the research in this field has been published in English, we feel this review and analysis is an accurate representation on the topic.

There is a significant amount of supporting research for the use of LIPUS for fracture healing in both animal^{34,41} and human models.^{18,22,24,38} Specifically studying fresh scaphoid fractures, a RCT of 60 patients by Mayr et al²⁵ reported a 30% reduction in time to healing when using LIPUS as a supplement to operative treatment. In the study, fractures

treated with casting and LIPUS healed on average in 43 days compared with 62 days in the control group which received standard casting. In addition, when LIPUS was used immediately following operative treatment in 10 patients, healing was accelerated by 40% compared with control patients who received a nonfunctional sham ultrasound device (56 days with treatment vs 94 days without treatment).³⁷ These studies supplement our results for the efficacy of LIPUS for treating scaphoid fractures both acutely, following surgery, and at the stage of nonunion. The economic appeal of LIPUS treatment was not directly measured in these studies; however, research by Mehta et al²⁷ showed a reduction in cost of over \$6,000 when comparing operative with LIPUS treatment of fracture nonunions. Clinical efficacy and economic advantage thus contribute toward making LIPUS a viable treatment option for the orthopedic surgeon who is faced with a scaphoid nonunion in the face of a suboptimal or reluctant surgical candidate.

The mechanism of LIPUS action appears to be related to enhanced endochondral ossification of the cartilaginous

Table 1. Low-Intensity Pulsed Ultrasound Use for Scaphoid Nonunion.

Study	LOE	Ultrasound treatment	Treatment frequency	% Males	Age in years (range)	Average fracture age in months (range)	Fracture heal rate	Treatment months to union (range)
Farkash et al ⁸	III	20-min dose, 30 mW/cm ² , 1.5 mHz frequency	Daily home treatment	100	NR (18-34)	5.2 ± NR (3-12)	22/29	2.3 ± NR (1-4)
Gebauer et al ¹⁰	III	20-min dose, 30 mW/cm ² , 1.5 mHz frequency	Daily home treatment	100	33.5 (24-49)	104.5 ± 79.6 (4.4-169.8)	2/6	5.6 ± 16.3 (5.2-6.0)
Pigozzi et al ³³	III	20-min dose, 30 mW/cm ² , 1.5m Hz frequency	Daily home treatment	100	27.9 (18-44)	11.2 ± 2.0 ^a	8/8	3.0 ± 1.5 (1.6-4.7)
Nolte et al ³⁰	II	20-min dose, 30 mW/cm ² , 1.5 mHz frequency	Daily home treatment	80	31.4 (18-46)	12.0 ± 6.9 (6.1-22.5)	4/5	4.75 ± 2.1 (3.0-7.1)
Rubin et al ³⁹	III	20-min dose, 30 mW/cm ² , 1.5 mHz frequency	Daily home treatment	NR	NR (>18) ^b	20.4 ± NR	101/118	4.6 ± NR

Note. LOE = level of evidence; NR = not reported; FDA = U.S. Food and Drug Administration.

^aOverall statistic, not specific to included scaphoid fractures.

^bAge or subjects not indicated; however, FDA Registry contains participants aged 18 and older.

Figure 2. Forest-plot demonstrating union rates utilizing low-intensity pulsed ultrasound.

bone at the fracture site. In vitro reports show increased osteogenic differentiation and expression following LIPUS treatment.^{3,17} In addition, increased vascularity at the fracture site modulated in part by vascular endothelial growth factor production has been reported in rodent studies.⁶ The believed mechanism when utilizing LIPUS is mechanical motion which is induced by the ultrasonic wave, with this micro-displacement of bone there is a resulting increased signaling to integrin associated pathways.⁴² Cyclooxygenase-2 (COX2) is a key mediator in this pathway, as it is the rate-limiting enzyme for prostaglandin E2 expression, which is

implicated in the osteogenic cascade.³⁶ The importance of this mediator was elucidated using COX2 knockout mice, which showed no significant improvement in fracture healing when compared with the non-LIPUS-treated controls.²⁹ Furthermore, COX2 inhibiting nonsteroidal antiinflammatory drugs have been shown to reduce fracture healing; however, the impact on their use with LIPUS treatment has yet to be established.¹²

In cases of nonunion with a displaced fracture, as well as when avascular necrosis exists, there is very limited research on LIPUS treatment, and it's important to note that surgical correction remains the standard of care. In these instances, screw fixation as well as bone grafting procedures have been utilized.^{21,32,35} More recently, vascularized bone grafting has been utilized as a means of reintroducing blood supply to the scaphoid when it has been compromised by injury.^{5,19}

Separate from LIPUS treatment, additional nonoperative treatments have been considered as potential options for nonunion scaphoid fractures. Extracorporeal shock wave therapy uses focused electrical shock waves delivered to the site of the nonunion in an operating room setting over the course of 1 to 5 sessions.^{31,44} By comparison, pulsed electromagnetic field therapy utilizes a traditional cast that is worn with an embedded electromagnetic device over the nonunion that is activated throughout the duration of the casting.¹ The relative paucity of research limits comprehensive analysis of these modalities at this time; however, these new options present potential alternatives for the practicing clinician in the future.

In summary, scaphoid nonunions are not uncommon, and may be costly, painful, and require one or more interventions

to treat. In cases where surgery is contraindicated or the patient does not wish to have a surgical procedure, LIPUS may provide a viable treatment alternative. Although operative treatment remains the more widely used treatment option, the success of the studies we analyzed is encouraging for the future use in properly select cases.

Ethical Approval

The data evaluated in this study is publicly available, no institutional review board approval was required.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Informed consent was obtained when necessary

Declaration of Conflicting Interests

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