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ARTICLE

The use of low-intensity pulsed ultrasound in hand and wrist nonunions

Michael H. Elvey[a], Robert Miller[b], Keng Suan Khor[a], Evangelia Protopapa[c], Maxim D. Horwitz[b] and Alistair R. Hunter[a]

[a]University College London Hospitals, London, UK; [b]Department of Plastic Surgery and Hand Surgery, Chelsea and Westminster Hospital, London, UK; [c]Department of Tissue and Energy, UCL Division of Surgery and Interventional Sciences, London, UK

ABSTRACT
The management of hand and wrist nonunions is challenging and alternatives or adjuncts to surgery to promote healing are an attractive prospect. Low-intensity pulsed ultrasound (LIPUS) is reported to improve bone healing and is supported for use in nonunions. However, evidence supporting its use for established nonunions is based largely on long bones, with little evidence guiding use in the hand and wrist. The objective of this study is to present our experience using LIPUS in established nonunions of the hand and wrist. This is a retrospective cohort study of hand and wrist nonunions managed with LIPUS in two UK tertiary referral centers. Nonunion was defined as the failure of fracture healing at a minimum of 9 months post injury. Demographic and clinical data including nonunion site, union rates, surgery and time from surgery to LIPUS application were obtained from electronic patient and LIPUS device records. Patients were subcategorized into early or delayed LIPUS applications groups. Twenty-six hand and wrist nonunions were treated with LIPUS alone or as a surgical adjunct. The overall union rate was 62%. Age, sex, fracture characteristics and previous treatment had no significant effect on union rates. There was no association between LIPUS timing and union following adjustment for co-variates. Our findings suggest previously quoted union rates using LIPUS for lower limb nonunions may not be achievable in the hand and wrist. However, LIPUS offers a safe adjunct to surgery and may offer a potential alternative when surgery is not feasible. Further prospective comparative studies are required before the efficacy of LIPUS for hand and wrist nonunions is proven.

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Introduction

The management of hand and wrist nonunions present unique challenges. These include the technical difficulty of (re)operating on small bones of questionable structural quality and the tendency for the small joints to stiffen resulting in unacceptable loss of function. A cost-effective nonsurgical alternative has an obvious attraction, as does any technology that might augment union rates in small bones with tenuous blood supply.

The use of ultrasound waves to stimulate bone formation was first reported in 1950 [1]; however, it was not until the 1980's that the technology was successfully applied to the treatment of human fractures [2]. Over the next two decades a growing evidence base resulted in the US Food and Drug Administration (FDA) and the UK National Institute for Health and Care Excellence (NICE) approving Low-Intensity Pulsed Ultrasound (LIPUS) as a primary and adjuvant treatment for managing acute fractures [3]. However, despite a growing body of evidence, questions remain over its benefits. A recent meta-analysis in the British Medical Journal concluded that LIPUS did not improve outcomes important to patients and probably had no effect on radiographic bone healing in acute fractures but was unable to provide conclusions on the efficacy in nonunions [4]. In 2013, NICE issued guidelines supporting the use of LIPUS for established nonunions [3]. This guidance was based largely on evidence evaluating long bone nonunions and consequently there is little evidence to guide the use of LIPUS in the hand and wrist [3]. Despite this LIPUS continues to be used for these challenging nonunion cases.

The aim of this paper is to present our experience of using LIPUS to treat established nonunions of the hand and wrist and to compare our findings with the existing literature through a systematic literature review.

Materials and methods

We performed a retrospective cohort study of nonunions managed with LIPUS in two UK tertiary referral hand and wrist units between February 2015 and January 2017. Nonunion was defined as the failure of an acute fracture to heal at a minimum of 9 months post injury with no evidence of radiological healing within the last 3 months. Inclusion criteria consisted of an established nonunion of the distal upper-limb (distal radius/ulnar, carpus, metacarpals and phalanges) treated with LIPUS alone, or in conjunction with surgery, with a minimum of 12 months follow up following commencement of LIPUS. All patients were prescribed a low-intensity (30 mW/cm^2) pulsed ultrasound device (EXOGEN, Bioventus, LLC, Durham, NC) daily for 20 min over the fracture site for a minimum of 3 months. There were no age restrictions or other exclusion criteria.

Two senior authors reviewed the clinical notes and imaging to confirm the study criteria were met. Two separate investigators (R. M. and S. K.) collected demographic and clinical data from electronic patient records and Exogen therapy devices. Union was

CONTACT Robert Miller robmiller90@gmail.com Department of Plastic Surgery and Hand Surgery, Chelsea and Westminster Hospital, 369 Fulham Road, Chelsea, London SW10 9NH, UK

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confirmed by CT where possible and X-ray (XR) in the remainder of cases. Union was defined as a continuous trabecular pattern over more than 50% of the cross section of the nonunion site on the CT or cortical continuity in three of four cortices on two orthogonal radiographs [5,6]. Fractures were described as displaced if there was any displacement seen on imaging. Union rates at 12 months following commencement of LIPUS and at final clinical follow up were recorded.

We subcategorized patients who had undergone nonunion surgery prior to commencing LIPUS into an early LIPUS group (<3 months) and a delayed LIPUS group (>3 months). This reflected real-life practice in our units where patients tended to be commenced on LIPUS immediately postoperatively when there was a concern about the ability to heal, or at a later stage beyond 3 months when there was a concern about the rate of healing.

Statistical analysis

Normal distribution of data was assessed by the Shapiro–Wilk test and visual inspection of the histograms. Descriptive statistics are reported as means with standard deviation (SD) and range for normally distributed data, and medians with interquartile ranges (IQR) for non-normally distributed data. Hypotheses were tested with two-sided tests. The association between union and the timing of the application of LIPUS and co-variates of interest were assessed using Chi-squared tests, or Fisher's exact tests when any cells had an expected cell count of less than 5, and a Bonferroni post-hoc correction. The co-variates of interest included age, sex, smoking status, fracture characteristics and previous surgical treatment. Scaphoid fractures were also analysed as a sub-group. We used a Mantel–Haenszel test to test the association between the timing of the application of LIPUS and union at 12 months and final clinical follow up, by adjusting for co-variates. A p-value of $<.05$ was considered to be significant.

Results

Patient demographics, fracture characteristics, treatment and union rates are shown in Table 1. Further stratification and statistical analysis of co-variates is shown in Tables 2 and 3.

Twenty-seven nonunions were treated over the study period. One patient was excluded due to insufficient data, leaving 26 cases (20 males, six females) for analysis. This consisted of 19 scaphoids (8 proximal pole and 11 waist), 5 forearm (2 ulnar and 3 radius) and two hand (1 phalangeal and 1 metacarpal) fractures (Table 1). The mean age was 28 years (SD 9.8, range 8–51). Thirty-six percent (5/14) of patients with a documented smoking status (14/26) were smokers. Median time from fracture to LIPUS treatment was 553 days (IQR 495). Twenty-five (96%) patients had surgery prior to starting LIPUS with a median of 1 operation prior to initiation of LIPUS (range: 0–3). The only patient not operated on prior to LIPUS was a scaphoid waist fracture. Five patients were managed operatively at the time of the acute fracture, which subsequently went on to a nonunion. Twenty patients had delayed surgery for an established nonunion. Seven patients underwent one or more revision surgeries, of these four were scaphoids. All operated cases were managed with internal fixation, apart from two cases using Kirschner wire fixation, one of which united (Table 1). Of the scaphoid cases, 17 were treated with internal Acutrak screw (Acumed®, Hillsbro, OR) fixation, of which 15 had bone grafts (most commonly from the distal radius). Of these, two had vascularized bone grafts, of which neither united at 12 months. One had no operative intervention, two were treated with internal Acutrak screw (Acumed®, Hillsbro, OR) fixation alone without bone grafting (1 united) and one case was treated with K-wire and bone grafting, which failed to unite. Of the non-scaphoid group 5/7 were treated with bone graft, of which 2 united at 12 months with one progressing to union later. None were vascularized bone grafts.

Fourteen patients started LIPUS within 12 weeks of surgery (early LIPUS group) with 11 patients starting after three months (delayed LIPUS group). Of this, 13 scaphoids were in the early group versus 5 in the delayed group. The median duration of LIPUS treatment was 14 weeks (IQR 27). The union rate at 12 months was 54% (14/26) overall and 58% within the scaphoid subgroup (11/19), determined on CT scan in 65% of cases. Two patients who had not healed at 12 months progressed to union after 12 months of LIPUS (one scaphoid and one ulnar) without further operative intervention resulting in a final union rate of 62% overall and 63% for scaphoids alone. Four nonunion cases underwent revision surgery after a minimum of 12 months of LIPUS with two achieving a subsequent union.

There was no significant difference in union rates between the early and delayed LIPUS groups ($p = 1$) for pooled analysis or subgroups (Table 2). Of the scaphoid nonunions, 50% (4/8) of proximal and 36% (4/11) of waist fractures failed to unite. There was no difference between union rates within scaphoid fracture type sub-groups when divided into early and late treatment groups (Table 3). Patient age, sex, fracture characteristics, and previous treatment had no significant effect on union rates in either the overall study population or the two subgroups after application of a Bonferroni correction. There was no association between the timing of the application of LIPUS and union following adjustment for co-variates (Table 3). Within Table 3, p-values represent comparison between union rates and specific co-variants within early and late subgroups. Mantel–Haenszel p-values represent comparison between union rates and specific co-variants between early and late subgroups.

Discussion

In 2013, NICE issued guidelines supporting the use of LIPUS for established nonunions, defining nonunion as failure of fracture healing after 9 months [3]. However, this guidance was largely based on evidence evaluating long-bone nonunions. The use of LIPUS in fracture nonunions was first reported in 1996 where an 85% union rate was reported in 385 cases [7]. Subsequently, there have been numerous independent case series but in the majority these studies have involved long bones and the lower limb [5,8–10]. There is little evidence to guide the use of LIPUS in the hand and wrist in the treatment for fractures, prevention of nonunions or the treatment of nonunions.

Studies investigating LIPUS in hand a wrist nonunion can be broadly divided into studies involving patients as part of a larger heterogeneous study or specific series of scaphoid nonunions. Overall, studies investigating the application of LIPUS in scaphoid nonunions have heterogeneous study samples, unclear inclusion criteria regarding nonunion definition and the presence or absence of previous surgery, and the variability in the results between studies may reflect these mixed cohorts of patients [11–17] (Table 4).

Scaphoid nonunions within these studies numbered between five [12] and 118 [11]. One study randomized patient to sham or ultrasound devices (11 out of 21) following the operative treatment of scaphoid nonunions by vascularised graft [14]. All cases united and the authors found that scaphoid healing was

Table 1. Summary table of cases.

Patient Age (yrs)	Sex	Bone	Location	Displaced	Smoker	No. of operations pre LIPUS	Last operation pre LIPUS[b]	Last surgery to LIPUS (days)	Fracture Age at beginning of LIPUS (days)	Fracture age at last surgery (days)	Union within 12 months of LIPUS	Imaging modality
25	M	Sc	Proximal	Y	N	1	ORIF & bone graft	7	3427	3420	Yes	CT
31	M	Sc	Proximal	N	N	1	ORIF & bone graft	10	551	541	Yes	X-ray
20	F	Sc	Waist	Y	U.K	1	ORIF & bone graft	10	474	464	Yes	X-ray
29	M	Sc	Waist	N	Y	1	ORIF, vascularised bone graft, radial styloidectomy & denervation	12	554	542	No	CT
28	M	Sc	Waist	N	U.K	1	ORIF & bone graft	15	355	340	Yes	CT
32	M	Sc	Proximal	N	N	1	ORIF & bone graft	17	617	600	Yes	CT
25	M	Sc	Waist	N	N	1	ORIF & bone graft	20	800	780	Yes	CT
27	M	Sc	Waist	N	Y	1	ORIF & bone graft	23	493	470	Yes	X-ray
25	M	Sc	Proximal	N	N	2	K-wire & bone graft	31	838	807	No	CT
16	M	Sc	Proximal	N	N	1	ORIF & vascularised bone graft	39	381	342	No	CT
43	M	Sc	Waist	N	Y	2	Screw exchange & bone graft	40	1907	1867	No	CT
26	M	Sc	Proximal	N	N	1	ORIF, bone graft & radial styloidectomy	50	2976	2926	No	CT
8	M	Sc	Waist	Y	U.K	1	ORIF & bone graft	70	3931	3861	Yes	X-ray
19	M	Sc	Proximal	Y	Y	1	ORIF & bone graft	121	522	401	No	X-ray
17	F	Sc	Waist	Y	U.K	2	ORIF & bone graft	128	979	851	No[a]	CT
27	M	Sc	Proximal	Y	U.K	1	ORIF & bone graft	248	255	7	Yes	X-ray
45	F	Sc	Waist	Y	U.K	3	ORIF & K-wire[b]	276	283	7	Yes	CT
19	F	Sc	Waist	Y	U.K	1	ORIF	441	456	15	No	CT
33	M	Sc	Waist	N	U.K	0	N/A	N/A	241	N/A	Yes	CT
16	M	Radius	Distal	N	N	1	Osteotomy & bone graft	76	2092	2016	No	CT
51	M	Radius	Metaphyseal	Y	U.K	3	External fixation & bone graft	126	633	507	Yes	CT
31	F	Radius	Distal Radius	O.M	U.K	1	Corrective Osteotomy	351	351	0	Yes	X-ray
34	M	Ulna	Shaft	Y	U.K	1	ORIF & bone graft	283	284	1	No[a]	CT
40	M	Ulna	Distal	Y	U.K	1	ORIF & bone graft	380	384	4	No	CT
31	F	Phalanx	Proximal Phalanx Shaft	O.M	Y	3	Open reduction & K-wires	437	742	305	No	X-ray
23	M	MC	Shaft	Y	N	3	ORIF & bone graft	210	890	680	Yes	X-ray

[a]Progressed to union after 12 months.
[b]Trans-scaphoid peri-lunate fracture K-wired.
Sc: scaphoid; OM: osteotomy for malunion; UK: unknown.

accelerated by 40% by LIPUS and overall achieved 100% union rate. A key confounder to result interpretation across studies preventing comparison is the variability in surgery timing, type and reporting prior to LIPUS application.

Recently, there have been a number of meta-analyses relating to LIPUS. Leighton defined nonunion as a fracture age of a minimum eight months and reported a union rate of 84% across body sites (95% confidence interval [CI]: 77%–91.6%) in nine studies (239 participants) [18]. Significant statistical heterogeneity was present and it was not possible to ascertain how many of these nonunions involved the hand and wrist, furthermore the authors declared a significant conflict of interest. Seger reported outcomes specifically of LIPUS for undisplaced scaphoid nonunions [19], reporting a similar mean union rate of 78.6% (95% confidence interval [CI] of 62.8–90.9%) and an average healing time of 4.2 months. However, results should be treated with caution as several cases included started LIPUS within 3 months of their acute fracture and therefore at most represent a delayed union.

Schandelmaier et al. recently published a systematic review to assess whether LIPUS improved radiographic healing and patient reported outcomes in acute fractures, nonunions or osteotomies at any location [4]. Based on moderate quality evidence, they found that LIPUS had no effect on time to return to work or the number of subsequent operations and only trials with high risk of bias showed benefit. Based on randomized controlled trials at low risk of bias, they found that LIPUS had no effect on pain reduction, days to full weight bearing, or days to radiographic healing. Importantly in the context of this study, these conclusions related specifically to fresh fractures as they were unable to identify any good quality direct evidence for the role of LIPUS in nonunions.

Our overall union rate was 62% at 12 months and 63% for scaphoids alone. A further two patients united after further revision surgery raising the overall union rate to 69% at the time of publication. This is lower than union rates reported in the literature with exception to the small independent series [9,15]. It is also lower than the 80% union rates quoted in recent systematic reviews of outcome following nonunion surgery for scaphoids [20,21]. Our lower union rates could be attributable to reporting bias, differing inclusion criteria for nonunion, the inclusion of hand and wrist nonunion sites other than scaphoids, although this appears to make little overall difference on results, or

Table 2. Comparative table of early versus late application of LIPUS post-surgery.

LIPUS timing	Healed	Failed	Healed (%)	*p* Value
Early				
Scaphoid only	8	5	62%	1.0
All 'early' cases	8	6	57%	1.0
Late				
Scaphoid only	3	2	60%	1.0
All 'late' cases	7	4	64%	1.0

Table 3. Early vs. late LIPUS application and union at 12 months with stratification by co-variates.

	Early LIPUS (<3 months)					Late LIPUS (>3 months)					
	Healed	Failed	Healed (%)	*p* Value[a]		Healed	Failed	Healed (%)	*p* Value[a]	Prevalence difference (%)	Mantel–Haenszel test (*p*-value)[b]
Patient age (year)				.3	Patient age (year)				.7		.8
0–19	1	2	33		0–19	1	2	33		33	
20–39	7	3	70		20–39	4	1	80		−10	
40–59	0	1	0		40–59	2	1	67		−67	
Sex				1	Sex				1		.8
Male	7	6	54		Male	4	2	67		−13	
Female	1	0	100		Female	3	2	60		40	
Smoker				1	Smoker				.3		.5
Yes	1	2	33		Yes	0	2	0		33	
No	4	4	50		No	1	0	100		−50	
Fracture age (months)				1	Fracture age (months)				.02[c]		.6
8–12	1	0	100		8–12	4	0	100		25	
13 –18	3	2	60		13–18	0	3	0		60	
19–24	1	0	100		19–24	1	1	50		50	
25–36	1	1	50		25–36	2	0	100		−50	
>36	2	3	40		> 36	0	0	N/A		N/A	
Bone				.4	Bone				.9	0	1.0
Scaphoid Proximal	3	3	50		Scaphoid Proximal	1	1	50		0	
Scaphoid Waist	5	2	71		Scaphoid Waist	2	1	67		5	
Radius	0	1	0		Radius	2	0	100		−100	
Ulna	0	0	N/A		Ulna	1	1	50		N/A	
Metacarpal	0	0	N/A		Metacarpal	1	0	100		N/A	
Phalanx	0	0	N/A		Phalanx	0	1	N/A		N/A	
Fracture displacement				.2	Fracture displacement				N/A		.7
Displaced	3	0	100		Displaced	6	3	67		33	
Undisplaced	5	5	50		Undisplaced	0	0	N/A		N/A	
No. of operations pre lipus				.2	No. of operations pre lipus				.7		.7
0	0	0	N/A		0	0	0	N/A		N/A	
1	8	4	67		1	3	3	50		17	
2	0	2	0		2	1	0	100		−100	
3	0	0	N/A		3	3	1	75		N/A	

[a]*p* Values represent comparison between union rates and specific co-variants within early and late subgroups.
[b]Mantel–Haenszel *p* values represent comparison between union rates and specific co-variants between early and late subgroups.
[c]Not significant after Bonferroni correction.
N/A: not applicable.

Table 4. Literature review summary.

Study	Year	Methodology (level of evidence)	Study period	Nonunion criteria (months)	Mean age (range)	Total number nonunions	Hand and wrist nonunions	Nonunion site	Mean age of fracture, week (range)	Heal rate	Mean heal time, week (range)	Determined
Rubin et al. [10]	2001	Retrospective cohort - exogen registry (III)	Exogen registry up to 2000	7.5	NR	1546	118	Scaphoid (118)	87.6 (NR)	101/118 (86%)	19.9 (NR)	NR
Nolte et al. [11]	2001	Prospective case series (II)	1995–1997	6	47 (18 – 90)	29	5	Scaphoid (5)	65.8 (24.4 – 90)	4/5 (80%)	20.3 (13 – 30.3)	Clin + XR
Pigozzi et al. [12]	2004	Prospective case series (III)	2000 – 2002	9	35.5 (18 – 60)	15	9	Distal Radius (1) Scaphoid (8)	48.1 (+/−8.6)	9/9 (100%)	9.2 wk (8 – 20)	Clin + XR
Gebauer et al. [8]	2005	Prospective case series (III)	Undefined	8	46 (14 – 86)	67	6	scaphoid (6)	156 (+/−24.8)	2/6 (33%)	24.1 (22.4 – 25.7)	Clin + XR
Ricardo et al. [13]	2006	Double blinded randomised control (II)	1999 – 2004	3	26.7 (17 – 42)	21	21	Scaphoid (9 waiste, 12 proximal pole)	152 (12 – 520)	21/21 (100%)	10.7 (+/−4.8)	Clin + XR
Farkash et al. [14]	2015	Prospective case series (III)	2011 – 2013	3	(18 – 34)	16	16	Scaphoid (16)	28 (12 – 48)	10/16 (63%)	8.8 range (7 – 28)	Clin, XR, CT
Zura et al. [16]	2015	Retrospective cohort - exogen registry (III)	1994 – 1998	12	45.8 (SD 16.5)	767	55	Scaphoid (55)	30 m (SD 13.5)	48/55 (87.2)	24.0 (+/−16.2)	Clin, XR

SD: standard deviation; Clin: clinical; XR: X-ray; CT: computed tomography; NR: not reported.

different criteria for determining union. The strengths of our study include a clear and accepted definition of nonunion, a 65% rate of CT confirmation of union/nonunion, and our study size. As the largest independent series to date our study population comprises 42% of the total independently reported cases in the literature and support the next largest independent series [15] which reported a 63% union rate in 16 prospectively followed scaphoid nonunions (which is identical to our 63% scaphoid union rate at 12 months). We believe this more accurately represents the true rate of union post LIPUS application; however, the influence of LIPUS on healing rates remains unclear.

We subcategorized our patients into early and late LIPUS groups as this most accurately represented the practice of surgeons in our units. Our review of the clinical notes suggested that decision making fell into a pattern of two scenarios. We did not investigate the rationale for individuals' choices for LIPUS timing on a case by case basis. In scenario one, a preoperative decision was made to begin LIPUS once the surgical wound had fully healed due to concerns with healing potential. In scenario two, a postoperative decision was made based on a lack of radiological healing progression. The timing of LIPUS did not have any significant effect on the chance of progression to union, in contrast to Leightons meta-analysis which reported improved results when used 3–6 months after unsuccessful revision surgery. This may reflect a unique characteristic of hand and wrist nonunions. Conversely, in accordance with Leightons meta-analysis, we found that in our series neither patient or fracture characteristics or previous treatment had any effect on the chance of progressing to union [18]. This was the same for the scaphoid subgroup and combined results. From our results, there appears to be no difference in union outcome with surgical technique used (both in the scaphoid subgroup and overall cohort). As the majority of patients had open reduction internal fixation with non-vascularised bone graft, statistical analysis comparing to other techniques is not appropriate.

This study is limited by the retrospective design and it is underpowered to provide definitive conclusions. Our literature review highlights that there is a clear requirement for prospective data. The barriers to randomized controlled studies comparing LIPUS to the gold standard of nonunion surgery have been consistently documented in previous publications [18]. However, larger prospective sham study investigating the role of LIPUS as a standalone or adjuvant treatment for hand and wrist nonunions is achievable. Although this may influence results, our cohort consists of contrasting and complex cases and so no routine surgical protocol is appropriate. Indeed, this reflects a realistic challenge when faced with these nonunions. All cases were managed hand and wrist specialists in tertiary centres. Furthermore, we acknowledge that healing is only one measure of outcome in nonunion surgery and we support that any future prospective work should include patient-related outcome measures and functional scores. Lastly, to future studies should include an interrogation of LIPUS delivering devices to record the percentage of patient compliance with treatment. Unfortunately, this was not possible in our study.

Based on our results and current experience, we believe that the benefit of LIPUS remains unproven, both for scaphoid and distal upper limb nonunions, but will play an on-going role in nonunion management in conjunction with surgery until further evidence is available. However, in cases where surgery is contraindicated or patients decline operative management, or where the risks of surgery are sufficiently great as to concern the surgeon that reconstruction is unlikely to be successful, LIPUS may offer a safe alternative.

Disclosure statement

The authors declare that they have no conflict of interest.

ORCID

Robert Miller http://orcid.org/0000-0001-7090-2710

References

[1] Maintz G. Animal experiments in the study of the effect of ultrasonic waves on bone regeneration. Strahlentherapie. 1950;82(4):631–638.

[2] Xavier CM, Duarte LR. Estimulaca ultra-sonica de calo osseo: Applicaca clinica. Rev Bras Ortop. 1983;18:73–80.

[3] Higgins A, Glover M, Yang Y, et al. Exogen ultrasound bone healing system for long bone fractures with non-union or delayed healing: a nice medical technology guidance. Appl Health Econ Health Policy. 2014;12(5):477–484.

[4] Schandelmaier S, Kaushal A, Lytvyn L, et al. Low intensity pulsed ultrasound for bone healing: systematic review of randomized controlled trials. BMJ. 2017;356:j656.

[5] Rutten S, van den Bekerom MP, Sierevelt IN, et al. Enhancement of bone-healing by low-intensity pulsed ultrasound: a systematic review. JBJS Rev. 2016;3:4.

[6] Hackney LA, Dodds SD. Assessment of scaphoid fracture healing. Curr Rev Musculoskelet Med. 2011;4(1):16–22.

[7] Duarte LX, Choffie M, McCabe JM. Review of nonunions treated by pulsed low-intensity ultrasound. Proceedings of the 1996 Meeting of the Société Internationale de Chirurgie Orthopaedique et de Traumatologie (SICOT). Amsterdam; 1996. p. 110.

[8] Schofer MD, Block JE, Aigner J, et al. Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: Results of a randomized sham-controlled trial. BMC Musculoskelet Disord. 2010;11(1):229.

[9] Gebauer D, Mayr E, Orthner E, et al. Low-intensity pulsed ultrasound: effects on nonunions. Ultrasound Med Biol. 2005;31(10):1391–1402.

[10] Jingushi S, Mizuno K, Matsushita T, et al. Low-intensity pulsed ultrasound treatment for postoperative delayed union or nonunion of long bone fractures. J Orthop Sci. 2007;12(1):35–41.

[11] Rubin C, Bolander M, Ryaby JP, et al. The use of low-intensity ultrasound to accelerate the healing of fractures. J Bone Joint Surg Am. 2001;83-A:259–270.

[12] Nolte PA, van der Krans A, Patka P, et al. Low-intensity pulsed ultrasound in the treatment of nonunions. J Trauma. 2001;51(4):693–702.

[13] Pigozzi F, Moneta MR, Giombini A, et al. Low-intensity pulsed ultrasound in the conservative treatment of pseudoarthrosis. J Sports Med Phys Fitness. 2004;44:173–178.

[14] Ricardo M. The effect of ultrasound on the healing of muscle-pediculated bone graft in scaphoid non-union. Int Orthopaed (SICO). 2006;30(2):123–127.

[15] Farkash U, Bain O, Gam A, et al. Low-intensity pulsed ultrasound for treating delayed union scaphoid fractures: case series. J Orthop Surg Res. 2015;10(1):72.

[16] Carlson EJ, Save AV, Slade JF, et al. Low-intensity pulsed ultrasound treatment for scaphoid fracture nonunions in adolescents. J Wrist Surg. 2015;04(02):115–120.

[17] Zura R, Della Rocca GJ, Mehta S, et al. Treatment of chronic (>1 year) fracture nonunion: heal rate in a cohort of 767 patients treated with low-intensity pulsed ultrasound (lipus). Injury. 2015;46(10):2036–2041.

[18] Leighton R, Watson JT, Giannoudis P, et al. Healing of fracture nonunions treated with low-intensity pulsed ultrasound (lipus): a systematic review and meta-analysis. Injury. 2017;48(7):1339–1347.

[19] Seger EW, Jauregui JJ, Horton SA, et al. Low-intensity pulsed ultrasound for nonoperative treatment of scaphoid nonunions: a meta-analysis. Hand. 2018;13(3):275–280.

[20] Ferguson DO, Shanbhag V, Hedley H, et al. Scaphoid fracture non-union: a systematic review of surgical treatment using bone graft. J Hand Surg Eur Vol. 2016;41(5):492–500.

[21] Pinder RM, Brkljac M, Rix L, et al. Treatment of scaphoid nonunion: a systematic review of the existing evidence. J Hand Surg Am. 2015;40(9):1797–1805.e3.