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Healing of fracture nonunions treated with low-intensity pulsed ultrasound (LIPUS): A systematic review and meta-analysis

Ross Leighton[a], J. Tracy Watson[b], Peter Giannoudis[c,d], Costas Papakostidis[e], Andrew Harrison[f], R. Grant Steen[g,h,*]

[a] Division of Orthopaedic Surgery, Dalhousie University, Halifax, Nova Scotia, Canada
[b] Dept. of Orthopaedic Surgery, Saint Louis University School of Medicine, St. Louis, MO, USA
[c] Academic Dept of Trauma & Orthopaedics, School of Medicine, University of Leeds, UK
[d] NIHR Leeds Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK
[e] Hatzikostas General Hospital, Orthopaedic and Trauma Dept, Makriyianni Av, 45001, Ioannina, Greece
[f] Bioventus Cooperatief, Amsterdam, Netherlands
[g] Dept. of Orthopaedic Surgery, Louisiana State University Medical Center, New Orleans, LA, USA
[h] Bioventus LLC, 4721 Emperor Blvd, Suite 100, Durham, NC 27703, USA

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ABSTRACT

Introduction: Bone fractures fail to heal and form nonunions in roughly 5% of cases, with little expectation of spontaneous healing thereafter. We present a systematic review and meta-analysis of published papers that describe nonunions treated with low-intensity pulsed ultrasound (LIPUS).
Methods: Articles in PubMed, Ovid MEDLINE, CINAHL, AMED, EMBASE, Cochrane Library, and Scopus databases were searched, using an approach recommended by the Methodological Index for Non-Randomized Studies (MINORS), with a Level of Evidence rating by two reviewers independently. Studies are included here if they reported fractures older than 3 months, presented new data with a sample $N \geq 12$, and reported fracture outcome (Heal/Fail).
Results: Thirteen eligible papers reporting LIPUS treatment of 1441 nonunions were evaluated. The pooled estimate of effect size for heal rate was 82% (95% CI: 77–87%), for any anatomical site and fracture age of at least 3 months, with statistical heterogeneity detected across all primary studies ($Q = 41.2$ ($df = 12$), $p < 0.001$, $Tau^2 = 0.006$, $I^2 = 71$). With a stricter definition of nonunion as fracture age of at least 8 months duration, the pooled estimate of effect size was 84% (95% CI: 77%–91.6%; heterogeneity present: $Q = 21$ ($df = 8$), $p < 0.001$, $Tau^2 = 0.007$, $I^2 = 62$). Hypertrophic nonunions benefitted more than biologically inactive atrophic nonunions. An interval without surgery of <6 months prior to LIPUS was associated with a more favorable result. Stratification of nonunions by anatomical site revealed no statistically significant differences between upper and lower extremity long bone nonunions.
Conclusions: LIPUS treatment can be an alternative to surgery for established nonunions. Given that no spontaneous healing of established nonunions is expected, and that it is challenging to test the efficacy of LIPUS for nonunion by randomized clinical trial, findings are compelling. LIPUS may be most useful in patients for whom surgery is high risk, including elderly patients at risk of delirium, or patients with dementia, extreme hypertension, extensive soft-tissue trauma, mechanical ventilation, metabolic acidosis, multiple organ failure, or coma. With an overall average success rate for LIPUS >80% this is comparable to the success of surgical treatment of non-infected nonunions.

Abbreviations: LIPUS, low-intensity pulsed ultrasound; RCT, randomized clinical trial; MINORS, methodological index for non-randomized studies; PRISMA, preferred reporting items for systematic reviews and meta-analyses; CINAHL, cumulative index to nursing and allied health literature; AMED, allied and complementary medicine database; EMBASE, excerpta medica database; CI, confidence interval; PWSI, prior-without-surgery-interval; ICMJE, International committee of medical journal editors.

* Corresponding author at: Dept. of Orthopaedic Surgery, Louisiana State University Medical Center, New Orleans, LA, USA.
E-mail addresses: leightonr2@gmail.com (R. Leighton), watsonjt@slu.edu (J. T. Watson), pgiannoudi@aol.com (P. Giannoudis), costaspapakostidis@gmail.com (C. Papakostidis), Andrew.Harrison@bioventusglobal.com (A. Harrison), Grant.Steen@bioventusglobal.com (R. G. Steen).

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Introduction

Bone fractures fail to heal and become nonunion in roughly 5% of patients [1]. Nonunions have no expectation of spontaneous healing [2] and require intervention—surgical or otherwise—to revive the healing process. What remains contentious is the time point at which a non-healing fracture can be termed a nonunion. A survey of 335 practicing orthopedic surgeons [2] reported that surgeons define nonunion at a range of fracture ages, but there was a mode at 3 months and a second mode at 6 months.

A nonunion can unite when adequate stability is provided in an osteogenic environment. These conditions are generally achieved by operative means, including some form of bone fixation to provide adequate stability, decortication of bone ends, and application of bone graft material to enhance healing capacity [3]. Depending on nonunion location and the type of revision surgery, the success rate ranges from 68% to 96% [4]. However, revision surgery for established nonunions is technically difficult and carries risk of complications. Certain conditions at the nonunion site render operative intervention inevitable (*e.g.*, gross instability, malalignment, or limb-length discrepancy). When surgery is optional, more conservative modalities have been proposed to promote healing and avoid potential risks of revision surgery [5–8]. Among such options, low-intensity pulsed ultrasound (LIPUS) has been evaluated in clinical studies, and has demonstrated a positive effect on delayed unions and nonunions [6,9–18].

We undertook a systematic literature review and meta-analysis to obtain a summary estimate of effect size for the heal rate following LIPUS treatment of delayed unions and nonunions. We also sought to assess any factors that could affect the results of LIPUS treatment of delayed unions and nonunions.

Methods

This systematic review of the literature and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19,20].

Eligibility criteria and literature search

Eligibility criteria were defined before a comprehensive search of the relevant literature. Studies were considered eligible if they met the following inclusion criteria:

- LIPUS was used as an alternative to surgery for non-healing fractures.
- LIPUS treatment was applied at least 3 months after the last surgical procedure.
- At least one outcome of interest was provided (Heal/Fail).
- A clear definition of delayed union or nonunion was included.

The following exclusion criteria were used:

- Experimental and animal studies.
- Review papers, case reports, and letters to editors.
- Papers dealing with fresh fractures (less than 3 months old).
- Papers with fewer than 12 patients.

An electronic search of the MedLine database via the PubMed search machine was initially undertaken using the following search strategy: (((ultrasound[All Fields] AND bone[All Fields] AND stimulation[All Fields]) OR LIPUS[All Fields] OR PLIUS[All Fields] OR EXOGEN[All Fields] OR SAFHS[All Fields]) OR (Low[All Fields] AND Intensity[All Fields] AND pulsed[All Fields] AND ("ultrasonography"[Subheading] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasound"[All Fields] OR "ultrasonic"[MeSH Terms] OR "ultrasonics"[All Fields])))

The search was further extended to the Ovid MEDLINE, CINAHL, AMED, EMBASE, Cochrane Library, and Scopus databases. No language restrictions were imposed. Manual searches were done of the reference section of 10 recent LIPUS reviews [6,10–18], to yield articles that might have been missed, and co-authors contributed articles that might still have been missed. Reviewers independently assessed titles and abstracts of the retrieved articles. The full text was obtained for potentially eligible articles and evaluated against eligibility criteria. Disagreement between reviewers was resolved by discussion. Demographic and baseline characteristics and outcome data were extracted from eligible papers and tabulated in a predefined spreadsheet. Titles of journals, names of authors, and institutions were not masked to avoid duplication.

Quality assessment

The methodological quality of the primary studies was evaluated with the Methodological Index for Non-Randomized Studies (MINORS) [21]. This instrument consists of eight methodological items for non-randomized studies, each receiving a maximum of 2 points, so the ideal score is 16 for non-randomized studies. Each primary study was assigned a score independently by two reviewers [CP, PVG]. Studies were also evaluated by these assessors with a level of evidence rating [22]. Disagreements were resolved by consensus.

Statistics

The main outcome of interest (heal rate) was a proportion. Binary outcomes were expressed as odds ratios with 95% confidence intervals (CIs). Heterogeneity was assessed using Cochran χ^2 test and Higgin's I^2 statistic [23,24]. Heterogeneity was considered significant at $p < 0.1$, while an I^2 value greater than 50% was thought to represent significant heterogeneity. Pooling of proportions was done with OpenMeta[Analyst] software (accessed at www.cebm.brown.edu/openmeta) using the DerSimonian and Laird random effects model. For binary data (expressed as odds ratios) the Mantel-Haenszel statistical method was used with either fixed or random effects, depending on the degree of statistical heterogeneity present (when I^2 was above 50, a random effects model was used). RevMan (5.3) software (Review Manager, Nordic Cochrane Centre, Copenhagen, Denmark) was used to process binary data, produce pooled estimates of effect size, and test for presence of statistical heterogeneity. Comparison of heal rates between two groups was conducted with the Wilcoxon rank sum test.

Subgroup analysis

Subgroups were decided *a priori* based on anatomic location of the nonunion. Additional sub-groups were created based on factors that were thought to potentially impact treatment, including patient age, smoking status, fracture age, prior-without-surgery-interval (PWSI, defined as the time elapsed from the last surgical procedure until the commencement of LIPUS treatment), and number of prior surgeries.

Sensitivity analysis

We planned *a priori* to repeat our analysis after excluding studies of dubious eligibility, poor methodological quality, or outlying results. Confidence in the robustness of our findings would increase if this process did not produce materially different results compared with those of the original analysis.

Results

Search process

A total of 4611 references were evaluated (Fig. 1) to yield 10 eligible references on LIPUS treatment of human fracture nonunions [4,9,25–32]. Three references [33–35] were obtained outside the scope of the PubMed search, while 4608 references were found by PubMed. Two references that emerged in the PubMed search were excluded because they reported a registry [36,37]; both papers were superseded by a recent report about the same registry that included more patients and had fewer methodological flaws, but did not appear in the PubMed search [35]. Most references excluded from meta-analysis did not report on human bone fractures (Fig. 1). The treatment group of a randomized controlled trial (RCT) dealing with tibial delayed unions treated with either LIPUS or sham device [29] was used as a prospective cohort, and only data related to LIPUS were extracted for the pooled analysis.

A range of different definitions of fracture nonunion were used by authors of primary studies. All definitions were similar in that nonunion was defined as diagnosable at no less than 3 months post-fracture, and all definitions required radiological confirmation.

Tables 1–3 list basic demographic and baseline characteristics as well as follow-up details of component studies. All data reflect the potential presence of clinical diversity across included studies.

Publication bias

We did not set any language restriction during the search process. In addition, we evaluated publication bias by generating funnel plots for the outcomes of interest. The distributions of data points within the funnel plots were symmetrical, indicating that publication bias was unlikely (Fig. 2).

Quality assessment

MINORS scores ranged from 5 to 12 (mean: 8.7, median: 9) across primary studies (Table 3). The only RCT was rated as a prospective study, but only one arm of this study (treatment group) was used as a prospective cohort of cases [29]. More than half of the primary studies were Level II (Table 3).

Overall heal rate (all anatomical sites)

All 13 component studies (1441 nonunions) provided relevant data. The fracture age (time interval from fracture occurrence to commencement of LIPUS treatment) across all primary studies was at least 3 months. Three studies [26,34,35] included some patients who received an operative intervention within 3 months of commencement of LIPUS treatment, so the PWSI was <3 months. In order to avoid bias (contribution of the recent surgery to the final outcome) such cases were excluded from the pooled analyses. The pooled estimate of effect size for the heal rate, for any anatomical site of the nonunion and fracture age of at least 3 months was 82% (95% CI: 77–87%). Significant statistical heterogeneity was detected across primary studies ($Q = 41.2$ ($df = 12$), $p < 0.001$, $Tau^2 = 0.006$, $I^2 = 71$) (Fig. 3). Considering a stricter definition of nonunion as fracture age of ≥8 months, the calculated pooled estimate of effect size for the heal rate was 84% (95% CI: 77%–91.6%) and was derived from 9 studies (239 participants). Again, significant statistical heterogeneity was present: $Q = 21$ ($df = 8$), $p < 0.001$, $Tau^2 = 0.007$, $I^2 = 62$) (Fig. 4).

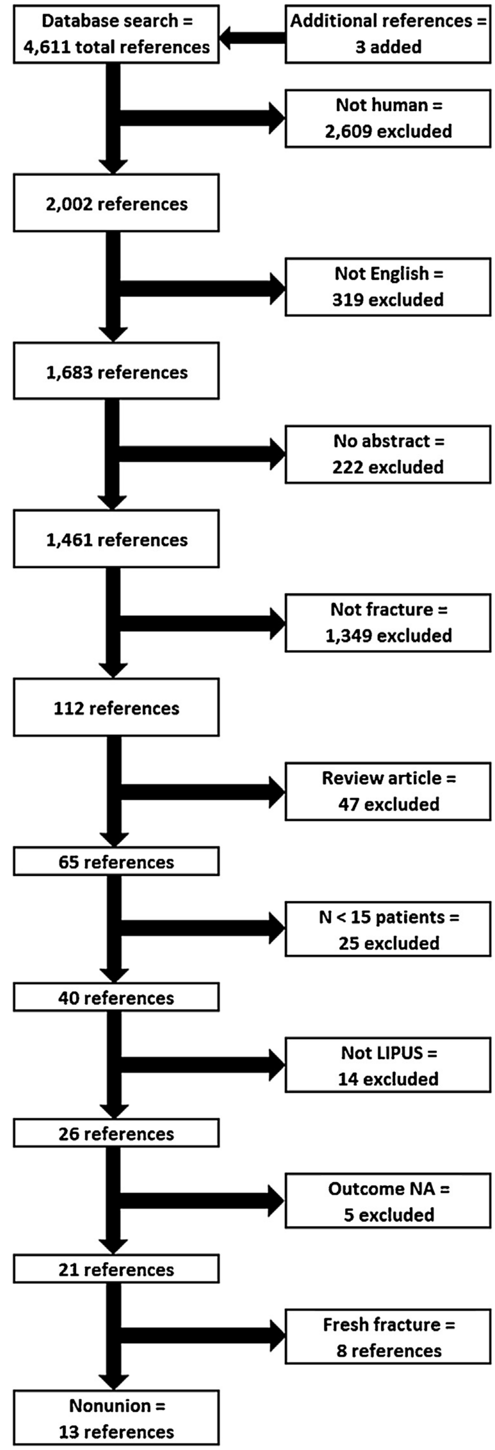

Fig. 1. Flowchart of the search process.

Subgroup analysis

We investigated the potential effect of patient age, fracture age, smoking habit, gender, type of nonunion, PWSI, and number of prior surgeries on outcome. Only type of nonunion and PWSI seemed to have an impact on final outcome. The odds of healing were twice as large in hypertrophic nonunions, compared to

Table 1
Demographic and baseline characteristics of included studies.

Study	Year	Study type	Period of study	Study N	Male: Female	Patient age yrs, mean (range)	Bone	Criterion for defining nonunion	Fracture ave. age, months (range)
Nolte et al.	2001	P, multi-center	1995–1997	28	16:12	47 (18–90)	Mix of bones	6 mo	14.2 (5.8–32)
Mayr et al.	2002	P	1995–1999	100	63:37	44 ± 2	Mix of bones	8 mo (nonunion), 4 mo (delayed)	11.6 ± 2.4
Lerner et al.	2004	R	1997–2001	17	14:3	32.7 (19–63)	Mix of long bones	6 mo?	11 (1–40)[a]
Pigozzi et al.	2004	P	2000–2002	15	12:3	35.5 ± 12.9 (18–60)	Mix of bones	9 mo	11 ± 2
Gebauer et al.	2005	P	1995–1997	66	40:26	46 ± 1.9 (14–86)	Mix of bones	8 mo	39 ± 6.2 (8–198)
Jingushi et al.	2007	P, multi-center	nr	72	52:20	40.4 (14–83)	Mix of long bones	3 mo	18.9 (3–159)
Rutten et al.	2007	P, multi-center	2000–2003	71	56:15	40 (17–89)	Tibia	6 mo	8.4 ± 0.48 (6–25.7)
Hemery et al.	2010	R	2006–2008	14	11:3	39 (16–62)	Tibia/Femur	6 mo	≥ 6
Schofer et al.	2010	RCT, multi-center	2002–2005	51	36:15	42.6 ± 14.6	Tibia	4 mo (del un)	14 (all >4 mo)
Roussignol et al.	2012	R	2004–2009	60	42:17	43 (17–85)	Mix of bones	6 mo	9 (5.4–45.8)
Watanabe et al	2013	R, cohort	1998–2007	151	110: 41	36.3 (16–82)	Mix of long bones	3mo (delayed) 6 mo (nonunion)	NR
Farkash et al	2015	R	2011–2013	29[b]	29:0	(18–34)	Scaphoid	3 mo	7 (3–12)
Zura et al.	2015	R, cohort	1994–1998	767[c]	408: 359	45.8 [SD,16.5]	Mix of bones	12mo	30 [SD:31.5]

Prospective, R: retrospective, RCT: randomized control trial, NR: not reported, M: male, F: female, frx age: fracture age (time interval from the occurrence of fracture till the start of LIPUS treatment), SD: standard deviation.
[a] Two cases were excluded from the pooled analysis, as respective fracture age was <3 months.
[b] A group of 13 cases was excluded from the final analysis as it represented in essence fresh scaphoid fractures diagnosed within 17 days from injury and treated conservatively for 3 months before commencing LIPUS treatment.
[c] A subgroup of 91 cases with PWSI $\geq$ 3 mo included in pooled analysis.

atrophic nonunions (Fig. 5). A PWSI <6 months was associated with a more favorable result (Fig. 6).

We further stratified nonunions by anatomical site and calculated heal rate (Table 4). No statistically significant difference was detected between upper and lower extremity long bone nonunions in heal rate (Table 5).

Sensitivity analysis

We repeated the pooled analysis after excluding studies that were regarded as weaker in methodological quality [26,30,34,35]. These studies had been assigned a score $\leq$6 in the MINORS scale. We also repeated the pooled analysis after excluding the study by Pigozzi [33], as it did not accurately report the PWSI. All above procedures did not substantially change results compared with the original procedure (Table 6).

Discussion

These findings indicate that LIPUS for nonunions can result in an increased heal rate, particularly when treatment was done within 3 to 6 months of the last revision surgery. Hypertrophic nonunions seemed to benefit more than biologically inactive atrophic nonunions. Almost one-third of the primary studies were assigned a low quality score, while the rating of the remainder was moderate in quality. The moderate rating was a result of retrospective study design, inadequate description of follow-up methodology, patient drop-outs and losses to follow-up, or lack of power analysis and sample size calculations in the primary studies.

Nevertheless, we believe our included studies constitute the best available material relevant to our review question.

Study limitations

Systematic reviews of the literature and meta-analyses provide the strongest scientific evidence when they pool data from high quality RCTs [38]. Unfortunately, this was not possible, so we had to rely on data extracted from observational studies.

There are several reasons that RCTs relevant to our research question are lacking. First, there is no sense that clinical equipoise exists in comparing surgery to other nonunion treatments; rather, it is assumed that surgery is required as first-line treatment [39]. Without perceived equipoise, surgeons are reluctant to undertake an RCT treating nonunion without surgery and Institutional Review Boards may be reluctant to approve such an RCT. Second, patient recruitment for an operative versus non-operative treatment protocol has been difficult in most countries, so it would take a long time to recruit enough patients to achieve reasonable statistical power. Third, there are standardized procedures for surgical debridement, but fixation, bone grafting, and post-operative patient management are surgeon and/or institution specific. This makes it hard to adequately control an RCT to evaluate LIPUS. Fourth, surgery is hard to blind [40,41], which makes it challenging to objectively assess outcomes. Fifth, once an intervention is recognized as useful, there may be little impetus to characterize exactly how useful it is [42]. Mayr proposed a prospective, placebo-controlled trial of LIPUS but his proposal was rejected; study authors were forced instead to do a prospective, consecutive-observation study [25]. It is our hope that this meta-

Table 2
Baseline characteristics of component studies and potential sources of clinical diversity.

Study	Prior without surgery interval (PWSI), mo	Initial treatment		Type of nonunion		Smoking habit		Prior surgeries, mean (range)	Previous history of infection
		Cons	Oper	Atrophic	Hypert	Active smokers	Non smokers		
Nolte et al.	12 (3.5–32)	8/29	21/29	17/29	12/29	11/29	18/29	1.52 (0−6)	2/29
Mayr et al.	≥3 mo	NR	NR	84/100	16/100	28/89	61/89	NR	0/100
Lerner et al.	11 (1–40)[a]	0/18	18/18	NR	NR	NR	NR	NR	NR
Pigozzi et al.	NR	7/15	8/15	NR	NR	NR	NR	0.6 (0–2)	NR
Gebauer et al.	24.2 ± 4.9 (4–197)	6/63	57/63	35/46	11/46	23/64	41/64	1.6 (0–7)	0/67
Jingushi et al.	11.5 (3–68)	0/72	72/72	32/72	40/72	NR	NR	1.7 (1–8)	10/72
Rutten et al.	6.4 (3–23.6)	18/72	53/71	54/71	17/71	24/55	31/55	1.2 (0–5)	3/71
Hemery et al.	12 (6–38)	0/14	14/14	3/14	11/14	NR	NR	1.7 (1–3)	6/14
Schofer et al.	≥4 mo	0/51	51/51	NR	NR	19/51	32/51	2	0/51
Roussignol et al.	> 6 mo	0/60	60/60	58/59	1/59	17/59	42/59	1.7 (1–4)	NR
Watanabe et al	Delayed 3.6 (3–6) Nonunion: 9.3 (6–32)	17/151	134/151	95/151	56/101	97/151	54/101	NR	NR
Farkash et al	≥3 mo[b]	29/29	0/29	NA	NA	NR	NR	0	0/16
Zura et al.	3 mo [c]	88/767	679/767	NR	NR	593/767	174/764	3.1 ± 2.3 (SD)	NR

Atr.: atrophic, Hypert: hypertrophic, NR: not reported, NA: not applicable (scaphoid).
[a] Cases with PWSI <3 months excluded from the pooled analysis.
[b] 13 cases excluded from the final analysis as they were fresh scaphoid fractures diagnosed within 17 days from injury and treated conservatively for 3 months before commencing LIPUS treatment.
[c] A subgroup of 91 cases with PWSI ≥3 mo included in pooled analysis.

Table 3
Treatment details, follow-up characteristics, and methodological quality of studies.

Study	Ultrasound device/Daily stimulation time	Duration of LIPUS treatment, mo mean (range)	Follow-up, mean (duration) mo	Drop out rate	MINORS rate	Level of evidence
Nolte et al.	Exogen 20 min	5 mo (1.7–13)	NR	29.2%	9	II
Mayr et al.	Exogen 20 min	5.1 mo	NR	17.3%	10	II
Lerner et al.	Exogen 20 min	6.6mo (3–12)	52 mo (15–72)	5.8%	6	IV
Pigozzi et al.	Exogen 20 min	3.1 mo (1.6–4.6)	(4.6–5.8) mo	0	10	II
Gebauer et al.	Exogen 20 min	4.7 ± 0.3mo	13.2 ± 0.68 mo	5.9%	12	II
Jingushi et al.	NR	7.9 mo (2–21)	NR	NR	8	II
Rutten et al.	Exogen 20 min	6.2 mo (1.7–24.3)	32.4 mo (13.2–55.2)	0	10	II
Hemery et al.	Exogen 20 min	≥3mo	NR	0	6	IV
Schofer et al.	Exogen 20 min	3.7 mo	4 mo	9.8%	11	II
Roussignol et al.	Exogen 20 min	5 mo (3–8)	6 mo	1.6%	9	III
Watanabe et al	Exogen 20 min	NR	12 mo	0	11	III
Farkash et al	Melmak 20 min	2.3mo (1–4)	NR	0	5	IV
Zura et al.	Exogen 20 min	5.9 mo [SD,4.2mo]	NR	40.3%	6	III

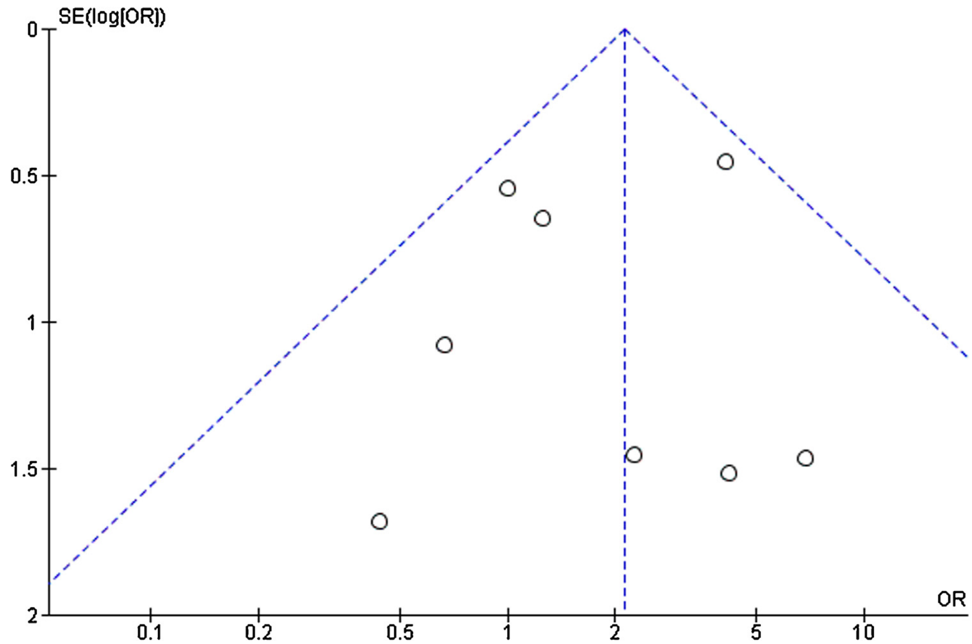

Fig. 2. Funnel plot of heal rate between hypertrophic and atrophic nonunions.

analysis will stimulate interest in an RCT to test the efficacy of LIPUS *versus* surgery.

Although we performed a comprehensive search of published literature without language restrictions, we acknowledge that possible errors in search strategy and failure to include unpublished reports could have resulted in missing data. However, we are confident we did not miss large reports that could have biased our estimate of effect size for several reasons. First, our results seem free of publication bias, as indicated by the relative symmetry of the respective funnel plot (Fig. 2). Second, other estimates based on binary data were also free of statistical heterogeneity. Finally, funnel plots of the intervention effect of binary outcomes against study size were uniformly symmetrical, suggesting it is unlikely we missed studies that would have had a statistically significant effect.

Results of analysis

Favorable results of LIPUS intervention were obtained when LIPUS was used as an alternative rather than an adjuvant to surgery. Our results suggest that nonunions that present within 3 to 6 months of fracture are candidates for LIPUS treatment.

Biologically active nonunions benefit more from application of LIPUS that do atrophic nonunions (Fig. 5). This is of interest because it is a common belief that the failure of hypertrophic nonunions to heal is due to mechanical instability [43]. A common surgical strategy to solve this problem is therefore revision of fixation without biological stimulation. Whether and how LIPUS promotes bone healing in a hypertrophic environment, without addressing mechanical instability, remains obscure. Of interest, patient age, patient gender, smoking habit, fracture age, and

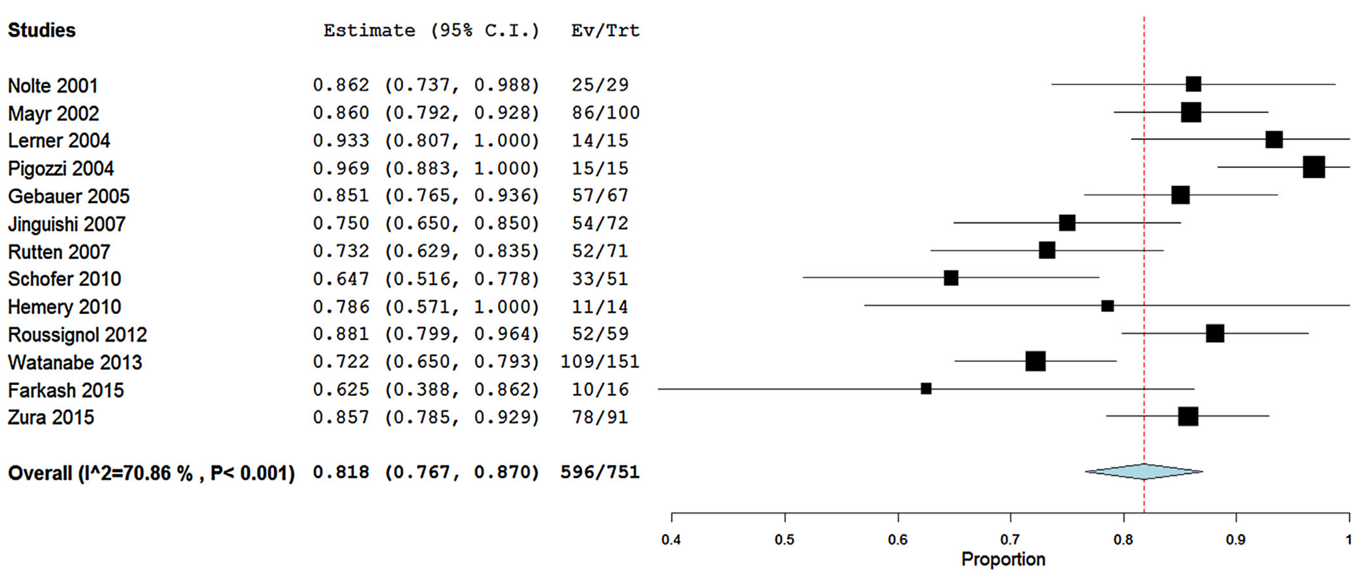

Fig. 3. Forest plot of heal rate across all primary studies.

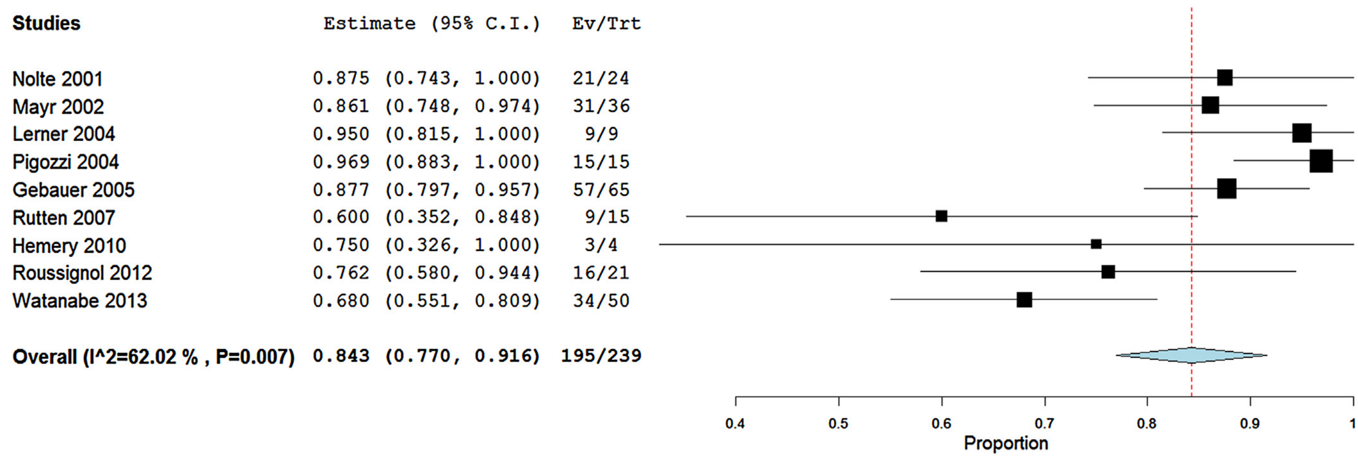

Fig. 4. Forest plot of heal rate across primary studies where nonunion was defined at 8 months.

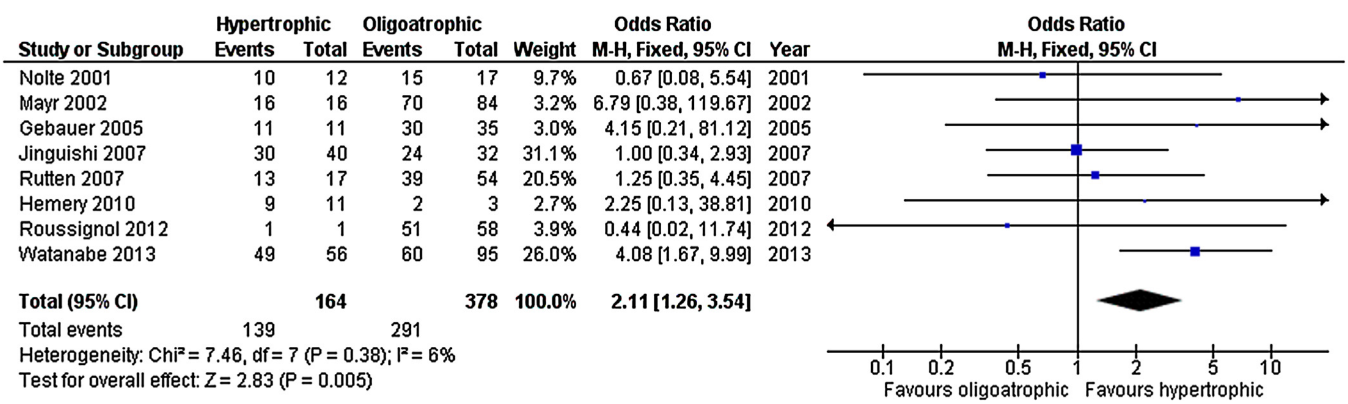

Fig. 5. Forest plot of comparison of hypertrophic vs atrophic nonunions in terms of heal rate.

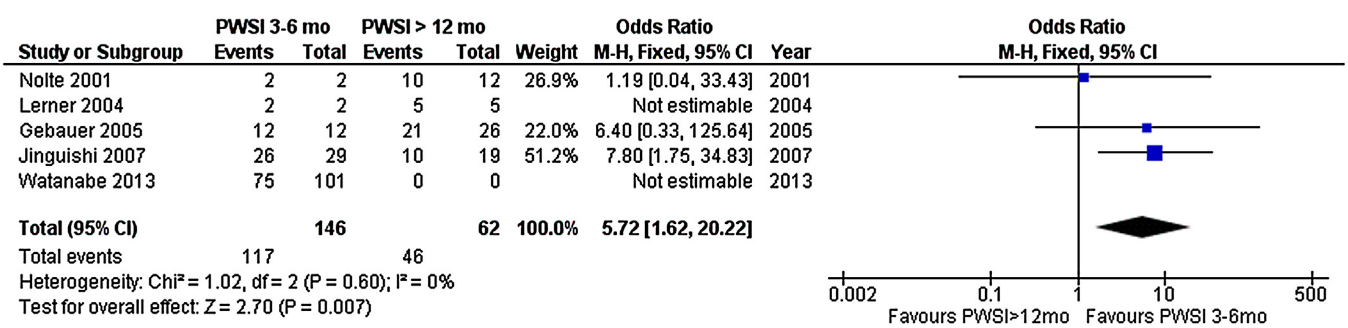

Fig. 6. Forest plot of heal rate according to prior without surgery interval (PWSI).

Table 4
Heal rates per anatomical site (subgroup analysis).

Fracture site	Number of references	Patient N	Heal Rate (Weighted mean)[a]	95% CI	Heterogeneity
Tibia	10	354	86%	79%–93%	Q = 47, df = 9, $p < 0.001$, $I^2 = 81$
Femur	9	110	80.4%	70.6%–90.3%	Q = 14, df = 8, p = 0.08, $I^2 = 42.6$
Scaphoid	6	61	78%	62.6%–93.5%	Q = 16, df = 5, p = 0.007, $I^2 = 68.5$
Humerus	6	44	74%	61.4%–86%	Q = 4, df = 5, p = 0.54, $I^2 = 0$
Radius + Ulna	5	18	77.5%	60%–95%	Q = 0.096, df = 4, p = 0.99, $I^2 = 0$

[a] DerSimonian and Laird, random effect model.

number of prior procedures had no impact on outcome. Moreover, it should be appreciated that PWSI ≥3 months was used as a prerequisite of eligibility, to avoid bias from concurrent use of surgery [4,25,27–29,31–34]. This provides evidence that LIPUS can

Table 5
Comparison of heal rates of long bones in upper and lower extremities (subgroup analysis).

Fracture site	N	HR (95% CI)	Median	p*
Tibia	354	86% (79%–93%)	87%	Tibia vs humerus: p = 0.3
Humerus	44	74% 61.4%–86%	75%	Humerus vs femur: p = 0.3
Radius + Ulna	18	77.5% 60%–95%	100%	Tibia vs radius + ulna: p = 0.09
Femur	110	80.4% 70.6%–90.3%	92%	Femur vs radius + ulna: p = 0.19

* Wilcoxon rank sum test.

heal nonunion fractures without concurrent surgery. Nevertheless, we cannot recommend LIPUS instead of surgery for all nonunions. Such a recommendation could only be made in the context of an RCT comparing LIPUS to surgery.

LIPUS was used as an adjunct to surgery in several studies reported here [9,26]. Initial treatment was conservative in 8 cases and operative in 21 cases, with additional treatments including bone grafting, reosteosynthesis, and other surgeries an average of 52 weeks prior to LIPUS [9]. While this study has the limitation that surgery could bias the results of LIPUS treatment, it supports the view that addition of LIPUS to surgical treatment can be helpful. Because data on LIPUS used as an adjunct to surgery is scarce, no strong recommendation can be made for adjunctive LUPUS [35].

Overall, LIPUS may be useful in patients for whom surgery is high risk. For example, surgery is not recommended for patients at risk of delirium due to old age, or patients with dementia, extreme hypertension, extensive soft-tissue trauma, mechanical ventilation, metabolic acidosis, multiple organ failure, or coma [44]. Avoidance of surgery in such patients may mean that non-surgical techniques such as LIPUS are especially valuable.

Conclusions

This systematic review and meta-analysis is supportive of the use of LIPUS in patients with a nonunion. Results are better in biologically active nonunions and when the modality is applied 3–6 months after the last revision surgery. Given an overall average success rate for LIPUS of better than 80% this rivals the success of surgical treatment of non-infected nonunions. An RCT of LIPUS *versus* surgery should be conducted so surgeons will be able to compare the success of surgical treatment with LIPUS treatment for nonunions.

Competing interests

All authors have completed the ICMJE uniform disclosure form. We declare that 4 authors had financial relationships with Bioventus LLC (summarized below) that could constitute a competing interest. However, neither Dr. Giannoudis nor Dr. Papakostidis had any relationships or activities with Bioventus that could have influenced the submitted work. None of the authors had non-financial competing interests. Conflicts of interest are summarized as follows:

Ethics approval and consent to participate

Not applicable; this is a literature review.

Consent for publication

Not applicable; this is a literature review.

Availability of data and material

All data generated or analyzed during this study are included in this published article and its Supplementary information files.

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All authors made substantive intellectual contributions to this study, according to the guidelines of the International Committee of Medical Journal Editors (ICMJE). No medical writers were involved in the completion of this manuscript. RL contributed to the study design, checked the citations, and drafted the manuscript; JTW checked the citations, and drafted the manuscript; PG checked the citations, graded the studies, performed the meta-analysis, and drafted the manuscript; CP checked the citations, graded the studies, performed the meta-analysis, and drafted the manuscript; AH contributed to the study design, screened the literature, and drafted the manuscript; RGS contributed to the

Table 6
Results of the sensitivity analysis.

Fracture site	N of studies	N of cases	HR (95% CI)	Median	P*
All studies	All 13	753	82% (77%–87%)	85%	
Exclusion of low quality studies	9 [a]	615	81.5% 75%–88%	85%	0.97
Additional exclusion of study with dubious eligibility	8 [b]	600	80% 74%–85.5%	80%	0.74

* Wilcoxon rank sum test.
a [9 studies include: Nolte, Mayr, Pigozzi, Gebauer, Jinguishi, Rutten, Schofer, Roussignol, Watanabe].
b [8 studies include: As above, excluding Pigozzi].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.injury.2017.05.016.

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