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REVIEW ARTICLE

A Network Meta-Analysis Evaluating Different Bone Stimulation Technologies on Fracture Healing Outcomes

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ABSTRACT

Background: Low Intensity Pulsed Ultrasonography (LIPUS) and Electrical Stimulation (ESTIM) are two commonly prescribed non-invasive techniques for the treatment of fresh fractures and fracture non unions. To date, no Randomized Controlled Trials (RCTs) have directly compared the efficacy of LIPUS versus ESTIM on fracture healing.

Methods: We conducted a network meta-analysis that indirectly compared LIPUS with ESTIM for fracture healing (union). Relevant data were extracted and trials were assessed for study quality and risk of bias. We used both standard and network meta-analytic techniques to synthesize the data.

Results: Our literature search identified 27 eligible trials. In patients with a delayed/nonunion fracture, ESTIM treatment suggested a significant benefit compared to placebo (risk ratio [RR] 1.95, 95% Confidence Interval [CI] 1.17–3.25; P=0.01). There was no significant benefit in patients with fresh fractures treated with ESTIM (RR=1.02, 0.95 to 1.11 95% CI; P=0.55). LIPUS had no significant effects in patients with a fresh fracture compared to placebo (RR=1.02, 0.98 to 1.05 95% CI; P=0.41), and there was not enough data on healing of delayed/nonunion with LIPUS treatment. The network meta-analysis indirectly comparing LIPUS to ESTIM found a stronger treatment effect using ESTIM vs placebo (OR=2.42, 95% CI 1.50-4.08) compared to LIPUS vs placebo (OR=1.61, 95% CI 1.00-3.05).

Conclusion: The results of this network meta-analysis suggest ESTIM may improve fracture healing rates more than LIPUS. Direct comparative trials with safeguards against bias are needed to confirm or refute the indirect analysis conducted in this network meta-analysis.

Introduction

Fractures are associated with significant socioeconomic burden [1]. Approximately 7.9 million fractures occur annually in the United States and up to ten percent of fractures experience prolonged healing. Delayed unions and non unions often require secondary surgical procedures, resulting in profound personal and societal economic costs due to decreased patient function,

health-related quality of life, and ability to return to activity [2]. While orthopedic surgeons continue to seek advances in surgical technique, it is becoming more apparent that a new surgical procedure or implant is unlikely to solve the more complex and challenging clinical problems. As a result, adjunct therapies, including bone growth stimulators, are being used to augment fracture care [3]. Indeed, a survey of 450 orthopedic surgeons found that 45% of surgeons were using bone growth stimulators as an integral part of their fracture management strategy with increases of bone growth stimulator sales over the past 10-15 years reflecting this [3,4].

While a number of bone growth stimulators are now available on the market, the technology is primarily based on either Low-Intensity Pulsed Ultrasonography (LIPUS) or Electrical Stimulation (ESTIM). Both are mainly non invasive modalities with extensive basic science research in potential mechanisms of action such as the creation of micromechanical stress, stimulation of growth factor and cytokine pathways as well as stimulation of collagen synthesis [2,5].Despite these potential mechanisms of action, clinical research and previous systematic reviews of this research LIPUS and ESTIM in both fresh fractures and delayed/nonunion have demonstrated inconsistent results [6-9].

Currently, there are no randomized controlled trials that have directly compared LIPUS versus ESTIM in fracture patients; however, a network meta-analysis was conducted in 2014 comparing these two modalities [9]. This network meta-analysis focused on the outcome of fracture healing and found that neither LIPUS nor ESTIM (compared with standard care) was effective in improving union rates at 3, 6 or 12 months in fresh fractures. However, they did suggest a potential but non-significant benefit of LIPUS at 6 months. In patients with a delayed union or nonunion, ESTIM showed a borderline significant effect in improving union rates (compared with standard care) at 3 months, but not at 6 or 12 months. Data were not available to compare LIPUS with standard care in nonunion populations.

Given these inclusive findings and the publication of several additional RCTs since 2013, we have conducted a systematic review and updated network analysis comparing LIPUS and ESTIM on healing outcomes in fracture patients.

Methods

1. Eligibility criteria

We included published RCTs that evaluated the efficacy of LIPUS and/or ESTIM in patients with fractures. The inclusion criteria were studies that: 1) evaluated LIPUS and/or ESTIM (including: electrical stimulation, capacitive coupling, electromagnetic field, pulsed electromagnetic field, or combined magnetic field), 2) included patients with fresh fractures, delayed fracture union, and/or fracture non-unions, 3) RCT study design with a placebo comparator, and 4) reported fracture healing outcomes. We included meeting abstracts if sufficient data was provided, and excluded studies not published in English.

2. Identification of studies

We conducted systematic literature searches of the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases (Appendix A).We also conducted a manual review of reference lists of recent systematic reviews and meta-analyses as well as a search of related articles in Pub Med.

3. Screening and assessment of eligibility

One reviewer with methodological expertise and content expertise independently reviewed the titles and abstracts of articles identified in the literature searches in order to determine if the articles should be considered for inclusion. The reviewer erred on the side of inclusivity and any disagreements resulted in the article proceeding to full-text review. Following the screening of the titles and abstracts, two reviewers independently reviewed the full-text articles that were identified in the title and abstract screening for eligibility. Any conflicts were discussed in order to achieve consensus. Articles that met the inclusion criteria were selected for data extraction.

4. Assessment of methodological quality

Two reviewers independently graded the methodological quality of each included study using the Cochrane Collaboration's Risk of Bias tool [10]. The Cochrane Risk of Bias tool separates judgments about

risk of bias from inadequate reporting of methodology. If agreement could not be reached, a third reviewer was consulted.

5. Data extraction

One reviewer extracted data from eligible studies using a pre-designed and piloted case report form and a second reviewer independently verified the data extracted. We extracted data pertaining to the study design, participant demographics, fracture characteristics and management, LIPUS and ESTIM treatment details, and fracture healing outcomes.

6. Data analysis

Our analyses were based on the methodology used in the 2013 network meta-analysis [9]. To compare and pool data across trials for outcomes that measured fracture healing, we calculated Risk Ratios (RRs) and the associated 95% confidence intervals (CIs).

We completed standard meta-analyses to compare LIPUS and ESTIM with the respective control arms. For the purposes of our analyses of dichotomous outcomes, we merged possible union and nonunion into 1 category (delayed/nonunion) in order to be conservative with respect to our treatment effect estimates.

We used a random-effects approach for our meta-analyses. We examined heterogeneity using χ2test and I2 and Tau2statistics.We interpreted heterogeneity using the guidelines proposed by the Cochrane Handbook [11].We generated the following a priori hypothesis to explain variability between studies: studies with greater risk of bias will have larger effects than studies with lower risk of bias. We performed all standard meta-analyses using Cochrane Review Manager 5.3 software [12].

For our network meta-analysis, we used a Bayesian hierarchical random effects models for mixed multiple treatment comparisons, which fully preserves randomized treatment comparisons within trials [13]. A network meta-analysis was performed only if two conditions were satisfied:

1) The common comparator (control arm) in both trials evaluating LIPUS and trials evaluating ESTIM were considered similar to conduct an indirect comparison of the two bone stimulation therapies, and

2) The standard meta-analysis of each bone stimulation therapy versus standard care showed either significant benefit, or the point estimates of the bone stimulation therapies were in opposite directions (e.g., one suggesting potential benefit and the other suggesting potential harm).

We calculated Odds Ratios (OR) with 95% confidence intervals. Studies with 100% events observed in both the treatment group and placebo group were excluded from analysis, as they do not contribute information. A healed fracture as defined by the study was considered an event.

We used a freely available Microsoft-Excel-based tool titled NetMetaXL [13] and WinBUGS [14,15] to conduct the network meta-analysis. WinBUGS coding support was provided by the National Institute for Health and Care Excellence (NICE) Decision Support Unit Evidence Synthesis TSD Series [16].

Results

1. Literature search results

Our electronic database search identified 1,879articles that were potentially relevant to our systematic review and meta-analysis. After reviewing the titles and abstracts of these studies, 1,804 were excluded. We reviewed the full-text of the remaining 50articles and excluded an additional 25 studies. Therefore, we identified 25initialarticles that met our eligibility criteria. Our manual review of reference lists of key articles identified an additional two articles. Therefore, 27 studies are included in our review [17-43] (Figure 1).

2. Study characteristics

The majority of studies were published from 2000-2009, and were most commonly conducted in Europe (44.4%), followed by North America (22.2%) and Asia (14.8%) (Table 1). There were 16 single center studies (59.3%) and 11 multi-center studies (40.7%).

3. Patient demographics and fracture characteristics

A total of 1927 fractures (ESTIM=414, LIPUS=543, Placebo=970) were included in all studies, with a mean age of 40.11 and an average of 62.8% males included

(Table 2). The most common fracture location was the tibia followed by the femur and scaphoid. Initial management of a fracture was frequently managed using external material (cast, brace, etc.) or treated with nail or plate fixation.

4. Treatment frequencies and durations

Bone stimulation treatment frequencies and durations (Table 3) were quite similar between studies. Average treatment duration for each treatment was 11.08 weeks for ESTIM, 12.52 weeks for LIPUS and 10.23 weeks for placebo.

Table 1: Study Characteristics.

Characteristic	Total (%) (N=27)
Year of Publication	
1990-1999	7 (25.9)
2000-2009	11 (40.7)
2010-2016	9 (33.3)
Study Location	
North America	6 (22.2)
South America	2 (7.4)
Europe	12 (44.4)
Asia	4 (14.8)
Africa	1 (3.7)
Australia	2 (7.4)
Study Setting	
Single Centre	16 (59.3)
Multi Centre	11 (40.7)
Mean Sample (SD)	75.48 (97.70)

Table 4: Network Characteristics.

Characteristic	Number
Number of Interventions	3
Number of Studies	16
Total Number of Patients in Network	1,267
Total Number of Events in Network	1,004
Total Possible Pairwise Comparisons	3
Total Number Pairwise Comparisons With Direct Data	2
Number of Two-arm Studies	16
Number of Multi-Arms Studies	0
Number of Studies With No Zero Events	15
Number of Studies With At Least One Zero Event	1
Number of Studies with All Zero Events	0

Table 2: Patient Demographics.

Demographics	ESTIM	LIPUS	Placebo
Mean Age (SD)	38.69 (10.68)	41.64 (13.47)	40.01 (12.24)
% Male	69.2 (23.19)	55.2 (30.49)	64.1 (24.15)
Mean Treatment Duration (SD)	11.07 (7.48)	12.51 (14.60)	10.23 (6.59)
Total Fractures Analyzed	414	543	970
Fracture Type			
Fresh Fracture	335	533	879
Delayed/Non-Union	79	10	91
Fracture Location			
Tibia	237	351	594
Scaphoid	75	25	106
Malleolus	0	34	34
Femur	96	0	101
Radius	2	71	73
Clavicle	0	52	49
Humerus	3	0	2
Metatarsal	0	10	10
Ulna	1	0	1
Initial management of fracture			
Surgery (Osteotomy)	18	0	16
External (Cast, brace)	131	96	226
Nail	139	294	461
Plate	42	0	31
Screw and K wires	30	11	46
External fixation (n.s.)	30	10	42
Closed fixation (n.s.)	14	0	8
Other	10	118	128
Not reported	0	14	12

Table 3: Treatment Details.

Treatment Details	ESTIM	LIPUS	Placebo
Average treatment duration (weeks)	11.08 (±7.88)	12.52 (±15.48)	10.23 (±4.51)
Average weighted timing for proportion healed (months)	7.42	9.73	4.65
Treatment frequency (MHz)	0.023 (±0.026)	1.5 (±0)	N/A
Type of device	OrthoPak Bone Growth Stimulator Systems Ossatec- Uden Ossatron - High Medical Technology Orthopulse II - Ossatec IFC with suction cups Ossatec- Uden EBI Bone Healing System - Biomet	Exogen - Smith and Nephew SAFHS – Exogen SAFHS 2A- Exogen Theramed 101B	N/A

Table 5: Network Intervention Characteristics.

Treatment	# Studies	# Events	# Patients
Placebo	16	479	639
LIPUS	6	308	353
ESTIM	10	217	275

5. Risk of bias summary

Risk of bias assessment is provided in (Figure 2). Risk of bias assessment did not change from the review conducted by Ibrahim et al. [9] for the same included studies. Overall studies demonstrated minimal bias with respect to categories of selection bias, detection bias, performance bias, and blinding of healthcare providers, yet many studies were at a high risk of bias due to incomplete outcome reporting and poor compliance. Although poor compliance is an issue in many studies, one could argue that this is a pragmatic reflection of clinical practice.

6. Clinical outcomes

6.1. Effect of ESTIM on rate of fracture union: Average weighted timing for proportion healed was 7.42 months for ESTIM, 9.73 months for LIPUS and 4.65 months for placebo. The pooled effect size of ESTIM yielded a non-significant risk ratio (RR) of 1.15 (0.98 to 1.35, 95% CI; P=0.09) when compared to placebo (Figure 3). We found moderate heterogeneity between the pooled studies (Tau2=0.04, I2=70%).

7. ESTIM on fresh fractures

In patients with fresh fractures (n=335), ESTIM, had no significant effects on improving union rates (RR=1.02, 0.95 to 1.11 95% CI; P=0.55) compared to placebo (Figure 3). Little heterogeneity was observed within the fresh fracture studies (Tau2=0.00, I2=12%).

8. ESTIM on delayed unions/nonunion

A significant improvement was observed in delayed/non-union fractures (n=79) when using ESTIM compared to placebo (RR=1.95, 1.17 to 3.25 95% CI; P=0.01) (Figure 3). Moderate heterogeneity was observed in delayed/non-union fracture studies (Tau2=0.09, I2=37%).

9. Effect of LIPUS on rate of fracture union

There was a non-significant pooled treatment effect observed in comparing LIPUS vs placebo (RR=1.02, 0.99 to 1.05, 95% CI; P=0.31) (Figure 4).

10. LIPUS on fresh fractures

In patients with a fresh fracture (n=553), LIPUS had no significant effects on improving union rates (RR=1.02, 0.98 to 1.05 95% CI; P=0.41) compared to placebo

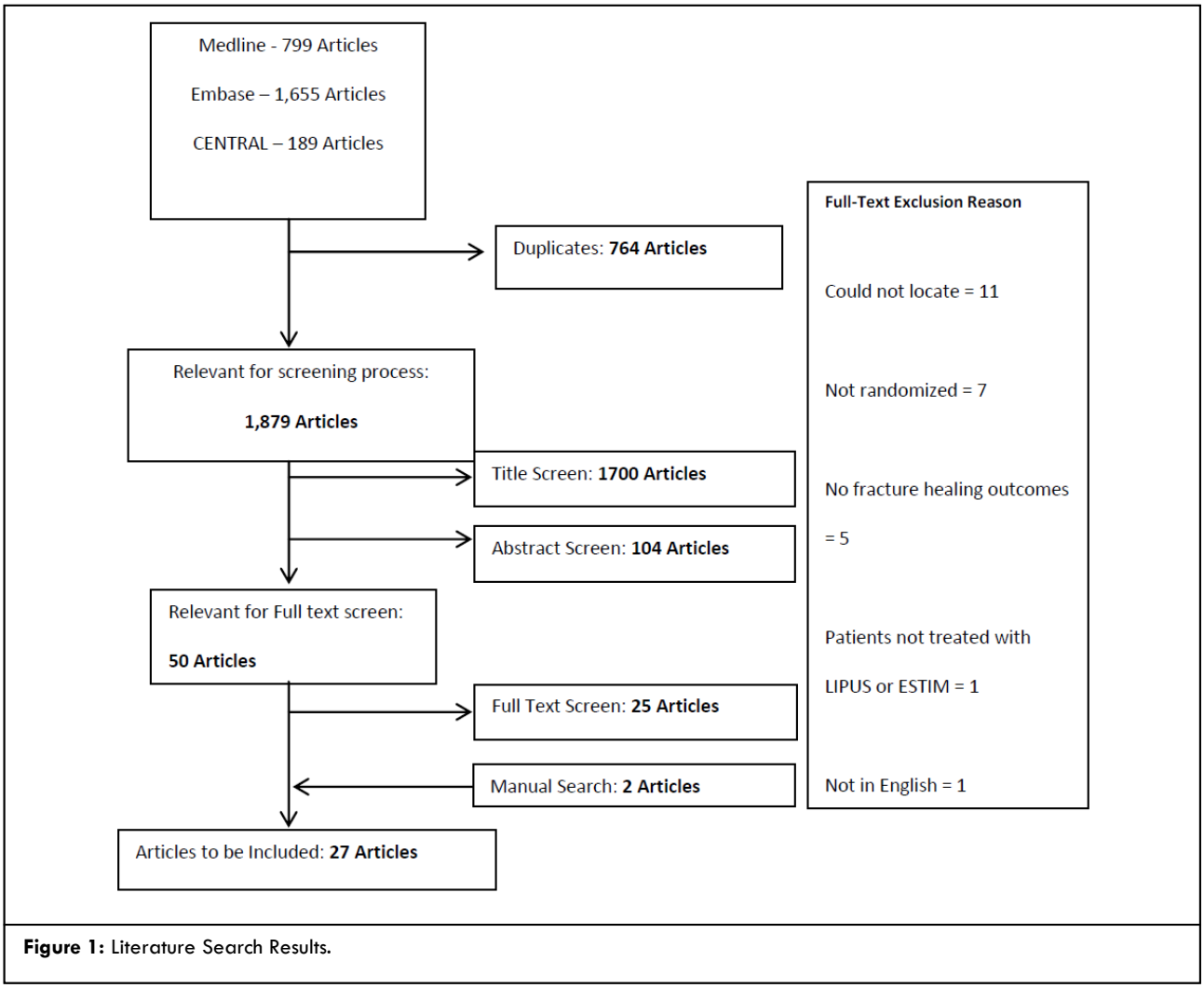

Figure 1: Literature Search Results.

(Figure 4). There existed little to no heterogeneity observed within the fresh fracture studies (Tau2=0.00, I2=4%). Six out of 12 fresh fracture studies comparing LIPUS vs placebo were conducted prior to 2005. Four of these six studies observed 100% fracture healing (union) event rate between treatment groups.

11. LIPUS on delayed unions/nonunion

Only one study was included in the delayed/nonunion fractures analysis (n=10), thus a total treatment effect could not be calculated (Figure 5).

12. Network meta-analysis of ESTIM and LIPUS on fracture union rates

The network meta-analysis included 16 out of 23 studies, with 1267 total patients and 1004 events of fracture union rates (Tables 4 and 5). Seven studies [31,32,34-36,41,42] were removed from analysis, as both treatment arms had the same number of events equal to the number of participants. All seven studies that were removed compared LIPUS vs placebo. Therefore, 16 studies were included in the analysis. The network meta-analysis found a non-significant indirect head-to-head comparison effect favoring ESTIM over placebo (OR=1.47, 0.69 to 3.24 95% CI) (Figure V). ESTIM showed a stronger treatment effect vs placebo (OR=2.42, 1.50 to 4.08 95% CI) compared to LIPUS vs placebo (OR=1.61, 1.00 to 3.05 95% CI).

Discussion

1. Fresh fractures

Our systematic review found that there was no difference between LIPUS and placebo on fracture healing rates (complete union). An indirect comparison between ESTIM and LIPUS suggests that ESTIM may be a more effective treatment. Our findings were consistent with the network meta-analysis conducted in 2014 [9], as neither LIPUS nor ESTIM (compared with placebo) were effective in improving union rates in fresh fracture

populations. Many studies had shown positive effects of shockwaves (ESTIM) in promoting bone healing in both acute fracture and nonunion models in animal experiments [44-48]. Wang et al. observed that the rate of nonunion was much higher in femur fractures compared to tibial fractures, which may have been attributed to higher energy impact in fractures of the femur than the tibia [22]. Other studies that observed significant efficacy of ESTIM include other fracture locations such femoral neck fractures [23]. ESTIM has been shown to treat chronic non-union of high energy long bone fractures, therefore studies using ESTIM therapy on small bone fractures (ie. acute scaphoid fractures) may not establish a large clinically significant effect compared to other fracture locations [21,27].

Six out of 12 fresh fracture studies comparing LIPUS *vs* placebo were conducted prior to 2005; four of these six studies observed 100% fracture healing (union) event rate between treatment groups. Conversely, studies conducted within the last decade observed larger treatment effects, suggesting that the study methodology and/or LIPUS technology have improved substantially. Little heterogeneity was observed between studies, suggesting that studies are comparable.

There is some clinical literature that suggests LIPUS has the greatest benefit in at-risk patient populations where fracture healing is impaired due to either the type of fracture or by patient life-style [37,49-51]. Despite this, a recently published meta-analysis has shown that LIPUS may reduce the time to fracture healing, but may not directly provide benefit with respect to functional recovery or delayed/non-union rates [52]. Additionally, the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) was recently conducted to evaluate the use of LIPUS in accelerating functional recovery and radiographic healing among patients with operatively managed tibial fractures [29]. Investigators found no difference in radiographic healing between LIPUS and a sham devicor in health-related quality of life outcome measurements. More evidence is required to better understand the clinical application of LIPUS vs placebo in fracture healing.

2. Delayed and nonunion

The author of the 2013 review found that ESTIM showed a borderline significant effect at 3 months, but not at six or 12 months in patients with a delayed union or nonunion; however, our meta-analysis comparing ESTIM *vs* placebo observed a significant benefit using ESTIM over an average weighted proportion healing time of 7.42 months. These discrepancies are due to the outcome splitting in the review conducted by Ibrahim et al [9] at different time intervals rather than an overall fracture-healing rate. A recently published meta-analysis by Aleem and colleagues found similar results, where ESTIM was favored over placebo for radiographic nonunion at last reported follow-up to 12 months [53]. Our meta-analysis further elucidated these findings, suggesting a significant benefit in ESTIM compared to placebo in the management of delayed unions/nonunion.

3. Network meta-analysis

The lack of trials directly comparing LIPUS *vs* ESTIM necessitated the use of network meta-analysis methodology. Seven studies comparing LIPUS *vs* placebo were removed from the network meta-analysis since they would not contribute any information to the magnitude of the treatment effect. This methodology follows other published network meta-analyses that have also removed studies with a zero event rate difference between treatment groups, as they cause convergence issues that preclude the ability to perform the analysis [54-56].This is an inherent limitation in a Bayesian network meta-analyses [57]. Appropriate correction methods need to be determined to keep studies with zero event differences within the analysis. Thus, the lack of efficacy of LIPUS compared to placebo is evident; many studies did not observe a difference in fracture healing rates between treatment arms.

ESTIM may prove to be a better device compared to LIPUS based on the mechanism of action of the two devices. ESTIM works via direct electrical current, capacitive coupling, and inductive coupling to create an electrical field that may stimulate proliferation and differentiation of osteogenic cells and enhance fracture healing [58]. ESTIM may also assist in increasing DNA synthesis by chondroblasts, increasing collagen synthesis and mineralization and angiogenesis, and increasing

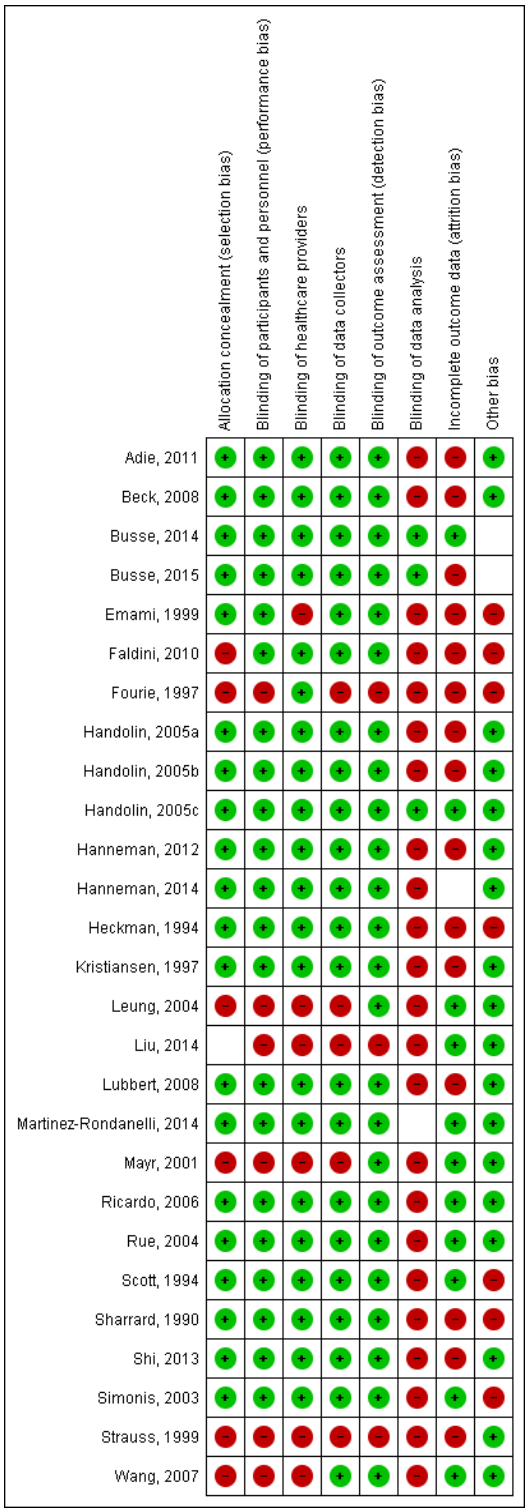

Figure 2: Risk of Bias Summary.

rate of amino acid transportation [58]. Although the exact mechanism of action for LIPUS on fracture healing is not completely understood, it is possible that LIPUS might work by reproducing the effect of functional loading by inducing low level mechanical forces at the fracture site [59]. These differences at a cellular level may be the reason for dissimilarities in treatment efficacy. Further insight into the mechanism of action of these devices, as well as higher quality head-to-head clinical trials will provide empirical evidence to better distinguish LIPUS and ESTIM bone stimulators.

4. Strength and limitations

The strengths of our systematic review include a comprehensive search, duplicate assessment of eligibility, data abstraction and risk of bias, and use of the GRADE approach to summarize the quality of evidence. Detailed analyses of the data were also conducted. Confidence in our treatment effect estimates was low due to a relatively high risk of bias in the included studies; therefore, we rated down risk of bias in our assessment as per the GRADE system for rating quality of evidence per outcome. This low rating is due to several studies (55%) with incomplete outcome data reported. This is a result of poor patient compliance amongst these studies. Approximately 73% of patients complied to≥50% of all recommended treatments. Although this may reflect patient utilization in real clinical settings, this moderate adherence to treatment compliance may lead to biased conclusions. Smaller studies were also exposed to similar issues in incomplete outcome data due to compliance issues, which largely reduced our confidence in the estimated treatment effect. Furthermore, an insufficient number of studies reported mean and SD time to fracture healing to allow for pooled comparisons between treatments.

There were limitations within the four separate meta-analyses comparing fracture healing rates of ESTIM *vs* LIPUS *vs* placebo. Only one study was included in the delayed union/non-union subgroup for LIPUS *vs* placebo, thus a treatment effect could not be achieved. Fracture union rates may fail to take into account faster healing if the difference in fracture healing appears between reported time points. We had limited data to pool estimates of time to fracture healing in our meta-analyses and network meta-analysis.

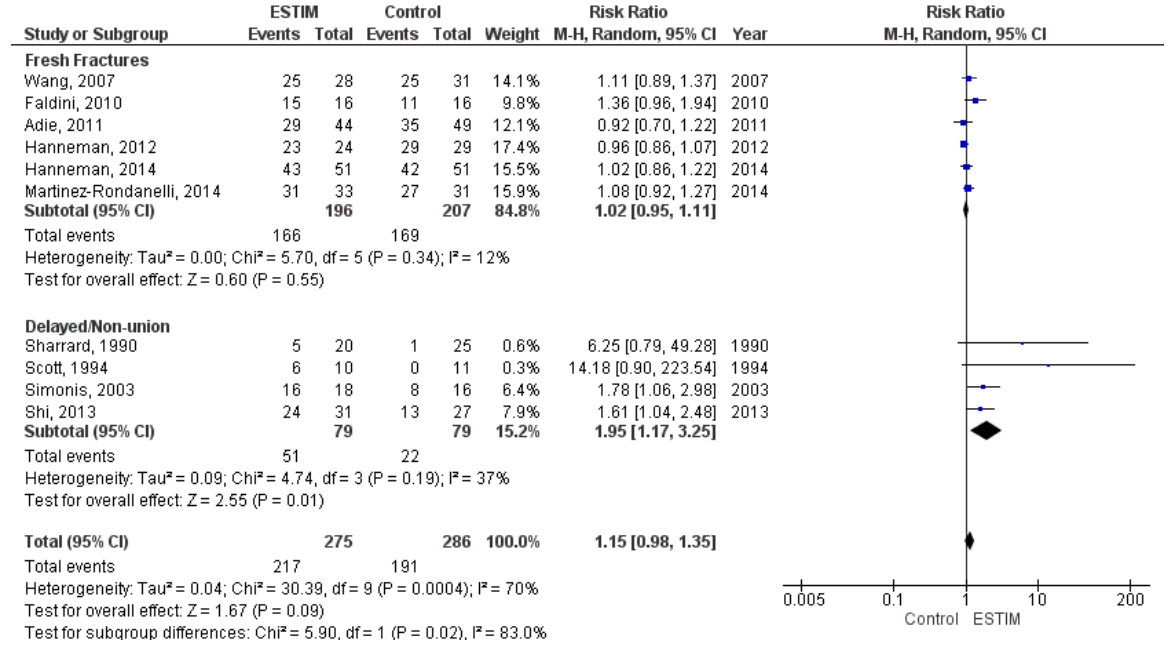

Figure 3: Forest Plot of Fracture Healing ESTIM vs Control.

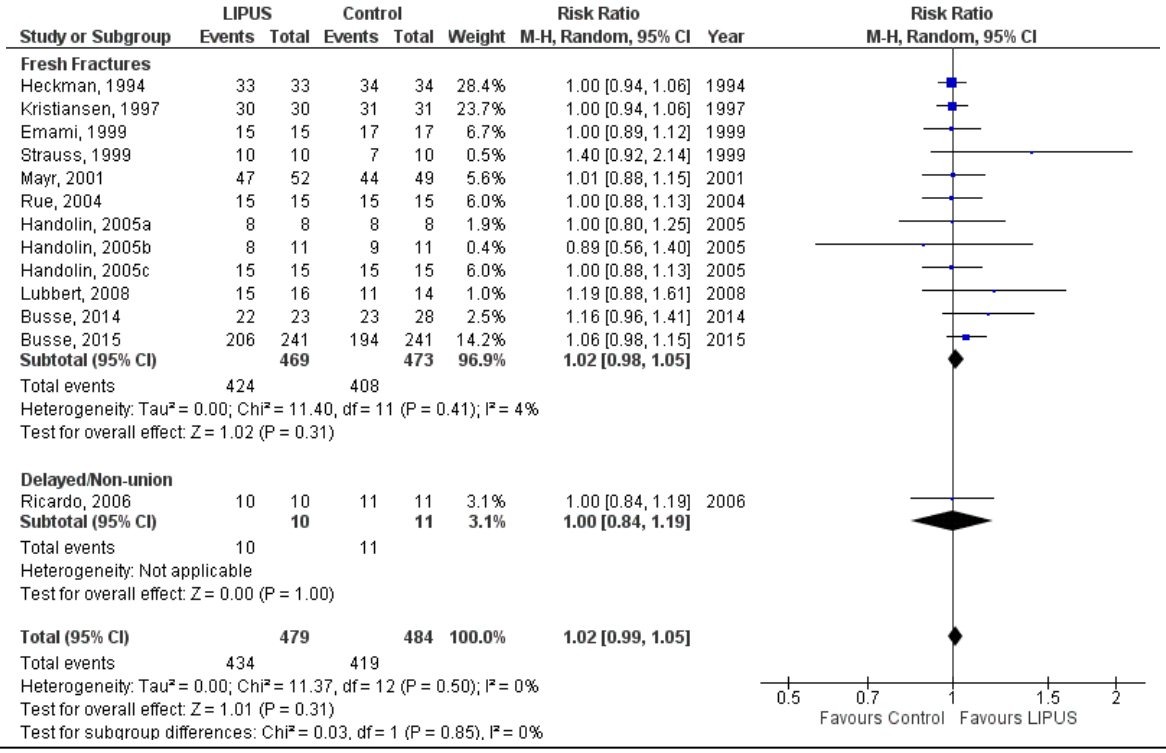

Figure 4: Forest Plot of Fracture Healing LIPUS vs Control

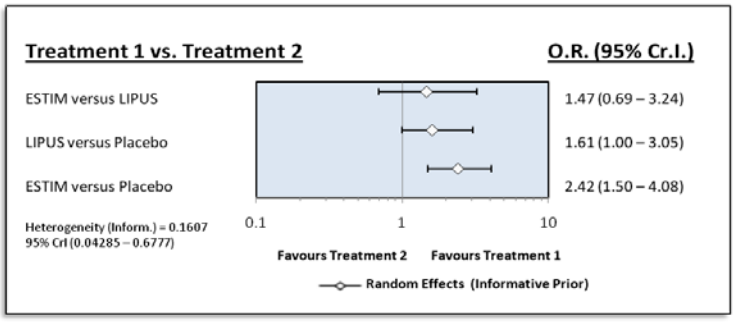

Figure 5: Network Meta-analysis Forest Plot of Total Fracture Healing ESTIM vs LIPUS vs Placebo.

Conclusion

This updated systematic review and network meta-analysis suggests that when compared to placebo, ESTIM demonstrated significant fracture healing improvements in patients with delayed/nonunion. Furthermore, both ESTIM and LIPUS did not demonstrate a significant benefit in fracture healing rates in patients with fresh fractures. Our results also suggest that ESTIM had preferable fracture healing rates when compared to LIPUS. Head-to-head comparisons of ESTIM *vs* LIPUS *vs* placebo in a randomized controlled trial that also included both fracture healing and functional outcomes would provide a direct comparison and help establish the role of bone stimulation devices in the care of the patients with a fracture.

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