Efficacy of Adjuvant Treatment for Fracture Nonunion/Delayed Union: A Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background

Fracture nonunion/delayed union seriously affects physical and mental health and quality of life. The aim of this study was to evaluate the relative efficacy of different adjuvant treatments for nonunion/delayed union by network meta-analysis.

Methods

A comprehensive search was performed to identify randomized controlled trials (RCTs) evaluating adjuvant treatment in the management of nonunion/delayed union. A network meta-analysis reporting on healing rate, healing time, and adverse effect (AE) outcomes was conducted to assess and compare different interventions.

Results

Thirty studies were included in analysis. For healing rate outcome, bone marrow aspirate (BMA) + autologous cancellous bone (ACB) was found to be significantly better than ACB alone (Odds ratio: 0.12; 95% confidence interval: 0.03, 0.59). In the ranking results, BMA+ platelet-rich plasma (PRP) (96%), BMA+ACB (90%), and BMA alone (82%) showed relative advantages in healing rate. Low-intensity pulsed ultrasonography (LIUS) intervention significantly shortened the healing time compared with ACB (Standardized mean difference: -8.93; 95% confidence interval: -14.37, -3.48). LIUS (99%), BMA+PRP (74%), and bone morphogenetic proteins (BMPs) (69%) have relative advantages.

Conclusions

Among the current intervention strategies, BMA and combination with PRP and ACB can improve the healing rate of nonunion/delayed union. LIUS can significantly shorten the healing time. However, large-scale, well-designed studies are still needed to confirm the results.

Trial registration: retrospectively registered

Introduction

Fracture nonunion is defined as a fracture that cannot heal in the expected time without further intervention [1]. Delayed union of fractures can be considered a sign of nonunion [2]. The clinical manifestations included persistent pain, instability of fracture fragments, and disability. As health care resources, the risk of nonunion/delayed union varies worldwide and is reported to be between 1.9% and 4.9% [3]. Either biological or mechanical factors can contribute to the occurrence of nonunion, which seriously affects physical and mental health and quality of life and increases health care costs and financial burdens to societies.

There is a lack of clinical and radiographic consensus on the standardized definition of nonunion [4, 5]. The US Food and Drug Administration defines nonunion as a fracture that has failed to heal for at least 9 months and has shown no signs of healing for 3 consecutive months [6]. For clinicians, a simplified definition refers to a fracture that cannot be healed without further intervention [7]. The basic principle of treatment is to provide mechanical and biological support for bone nonunion. Fracture stabilization and immobilization are the primary conditions for treatment [8].

Autologous cancellous bone (ACB) grafts are considered the "gold standard" treatment; however, they are limited by pain at the donor site and potential damage to the arteries, nerves and tissues around the donor bone [9]. For nonunion, in addition to surgery and ACB transplantation, adjuvant therapy is also a method to improve the healing rate, including physiotherapy, bioactive substance treatment, and oral drugs [10].

In recent meta-analyses, various adjuvant strategies for nonunion were analyzed, in which the application of bone morphogenetic proteins (BMPs) can significantly shorten the healing time, but there are complications of heterotopic ossification [11, 12]. Platelet-rich plasma (PRP) also accelerated nonunion healing, but bisphosphonate had no significant effect [6, 13]. In a network meta-analysis study, it was considered that low-intensity pulsed ultrasonography (LIUS) has more advantages than electrical

stimulation in the healing effect of fresh fractures [14]. The aim of this study was to evaluate the relative efficacy of different adjuvant treatments for nonunion/delayed union by network meta-analysis.

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two authors separately conducted literature retrieval, study eligibility, data extraction, and quality assessment with inconsistency solved by discussion and decided by the corresponding author.

Literature search

A literature search of PubMed, EmBase, Cochrane, Ebscohost, and Scopus was performed from databases incipient to November 2021 for randomized controlled trials (RCTs) evaluating adjuvant treatment in the management of nonunion/delayed union. The brief retrieval formula was “(fracture) AND random* AND (((Non-Union) OR (Delayed Union)) OR (Mal-Union)) OR (nonunion)) OR (nonunions))”. The references of related reviews were also screened to prevent omissions.

Inclusion and exclusion criteria

Briefly, we included RCTs evaluating adjuvant therapy for patients with nonunion or delayed union. The inclusion criteria were as follows: 1, the study was RCT design; 2, nonunion/delayed union patients were analyzed; 3, the intervention was adjuvant therapy; 4, the control was another adjuvant therapy or blank control which was different from the intervention; 5, The outcome reported fracture healing rate and/or fracture healing time. The exclusion criteria were as follows: 1, intervention studies on fresh fractures; 2, animal and experimental studies; and 3, studies that did not report the predetermined outcomes. Furthermore, reviews, case reports, conference abstracts, editorials, and comments were also excluded.

Data extraction and quality assessment

The contents were extracted by two authors, and disagreements were resolved by consensus. The following data were extracted: the first author's name, publication year, study location, sample size, patients' average age, fracture site, clinical diagnosis, intervention, control and follow-up. The outcomes were radiographic/clinical healing rate, healing time, and adverse effect (AE). The methodological quality of the eligible studies was evaluated with the Cochrane risk of bias tool.

Statistical analysis

Discontinuous variables were pooled using odds ratios (ORs) with 95% confidence intervals (CIs), and continuous variables were pooled using standard mean differences (SMDs) with 95% CIs. A random-effects network meta-analysis with a frequentist framework was adopted. Network plots were generated for each outcome, with nodes representing the type of therapeutic strategy, lines between nodes representing direct comparison, and edges of lines representing the precision of comparison. Inconsistency was locally assessed by calculating the difference between direct and indirect estimates in network analysis. For each outcome, we estimated the ranking probability of the therapeutic strategy being at each possible rank for each therapeutic strategy using a surface under the cumulative ranking curve (SUCRA). Comparison-adjusted funnel plots were used to determine the possible publication bias. $p < 0.05$ was considered a significant difference, and data were analyzed by R language (version 4.0.3) with the “netmeta” package (version 1.5-0).

Results

Literature search

In this study, 2035 articles were identified after duplications were removed. After screening the titles and abstracts, 1907 articles were excluded. The full texts of the remaining 128 articles were assessed. The following articles were excluded due to: reviews (55); study about nonadjuvant therapy (18); study on fresh fracture (10); conference abstract (6); duplicate publication (2); study about same therapeutic strategies (2); no predetermined outcomes reported (2); comments (2); study on children congenital anomaly (1). Finally, thirty studies were included in the analysis [15–44] (Figure 1).

The inclusion study was published from 1984 to 2020. The research is mainly located in Asia, North America, and Europe. The sample size from each study was relatively small, with a maximum of 140 patients. One study included adolescent patients [17]; however, we do not think it will impact the overall results. The interventions analyzed included physiotherapy (LIPU, extracorporeal shock wave (ESWT), electromagnetic field (EMF) therapy), and bioactive substance treatment (PRP, BMP, bone marrow aspirate (BMA, including mesenchymal stem cells)). and oral drugs (strontium ranelate (Protelos), Chinese traditional medicine (CTM)). The average follow-up period ranged from 3 months to 7.6 years (Table 1). After comprehensive consideration of the risk of bias, although all studies were RCT designs, the major factor affecting the quality was the lack of blindness of patients and intervention personnel, as well as the blindness of the outcome assessor. This may lead to a subjective influence on the healing judgment, which makes the results tend to be positive (Figure 2).

Table 1
Characteristics of the included studies.

Study	Location	Sample size	Average age	Fracture site	Interventions	Control	Follow-up
Tang YF 2020[15]	China	66	20-56	Tibia	PRP+BMA	BMA	16-36 Month
Marion Mühldorfer-Fodor 2020[16]	Germany	68	29(16-60)	Scaphoid	EWST+ACB	ACB	24 Weeks
Ahmad I 2020[17]	Pakistan	101	31.46±13.9	Tibia (major)	PROTELOS	CONTROL	3 Months
Samuel G 2018[18]	Indian	40	34.3±9.49;39.35±10..39	Tibia (major)	PRP	CONTROL	36 Weeks
Carlos AO 2017[19]	Germany	16	37.14±10.22;38.88±15.36	Humerus	PRP+ACB	ACB	36 Weeks
Hernigou P 2017[20]	France	80	41.2±18.2	Tibia	BMA+ACB	ACB	7.6 (5-10) Years
Zhang S 2017[21]	China	47	38.29±7.49;36.57±8.31	Tibia (major)	PRP+BMA	BMA	9-15 Months
Zhao ZC 2017[22]	China	92	18-70	Femur	PRP	CONTROL	12 Months
Ghaffarpasand F 2016[23]	Iran	75	26.5±5.8;26.3±6.2	Femur, Tibia	PRP	CONTROL	12 Months
Zhang H 2016[24]	China	24	33.45;32.69	Tibia	BMA	CONTROL	12-34 Months
Streit A 2016[25]	usa	8	47(24-63)	Fifth metatarsal	EMF	CONTROL	24 Weeks
Christian von Ruden 2016[26]	Germany	49	44(19-77)	Ulnar, Radial	BMP+ACB	ACB	6 Months
Zhai L 2016[27]	China	63	39.6(23-50);38.1(20-49)	Femur, Tibia	BMA+ESWT	ESWT	12 Months
Shi HF 2013[28]	China	58	41.1±14.5;38.4±11.6	Femur, Tibia	EMF	CONTROL	3 Months
Huang ZJ 2011[29]	China	64	47.3±22.2	Ulna or radius (major)	CTM	CONTROL	3 Months
Schofer MD 2010[30]	USA	101	42.6±14.6;45.1±11.9	Tibia	LIUS	CONTROL	16 Weeks

Abbreviations: ACB: autologous cancellous bone; BMA: bone marrow aspirate; BMP: bone morphogenetic proteins; CTM: Chinese traditional medicine; EMF: electromagnetic fields; ESWT: extracorporeal shock wave; LIUS: Low-intensity pulsed ultrasonography; PROTELOS = Strontium ranelate; PRP: Platelet-Rich Plasma.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Study	Location	Sample size	Average age	Fracture site	Interventions	Control	Follow-up
Yuan JG 2010[31]	China	140	34±2	Humerus, Tibia	BMA	ACB	3 Months
Sun YP 2009[32]	China	40	43±6	Tibia (major)	BMP+ACB	ACB	11-20 Months
Angelo Cacchio 2009[33]	Italy	126	42.7±5.9	Tibia Femur	ESWT	CONTROL	24 Months
Rutten S 2008[34]	Netherlands	13	42-63	Fibula	LIUS	CONTROL	3 Months
G.M Calori 2008[35]	Italy	120	43(19-65)	Humerus, Tibia (major)	BMP	PRP	9 Months
Bilic R 2006[36]	Croatia	18	23±5;22±5;19±4	Scaphoid	BMP+ACB	ACB	24 Months
Ricardo M 2006[37]	France	21	26.7(17-42)	Scaphoid	LIUS	CONTROL	1-4 Years
Calori GM 2006[38]	Italy	29	47±2.56;35.3±1.76	Femur, Tibia	BMP	PRP	9 Months
Simonis RB 2002[39]	UK	34	32(16-61)	Tibia	EMF	CONTROL	6 Months
Friedlaender GE 2001[40]	USA	122	38±16;34±11	Tibia	BMP+ACB	ACB	24 Months
Cook SD 1999[41]	USA	30	na	Tibia	BMP	ACB	9 Months
Scott G 1994[42]	UK	23	43(23-87)	Femur, Tibia	EMF	CONTROL	6 Months
Sharrard WJW 1990[43]	UK	51	34.7(18-84);45.4(18-76)	Tibia	EMF	CONTROL	12 Weeks
Barker AT 1984[44]	UK	17	34(19-72)	Tibia	EMF	CONTROL	48 Weeks
Abbreviations: ACB: autologous cancellous bone; BMA: bone marrow aspirate; BMP: bone morphogenetic proteins; CTM: Chinese traditional medicine; EMF: electromagnetic fields; ESWT: extracorporeal shock wave; LIUS: Low-intensity pulsed ultrasonography; PROTELOS = Strontium ranelate; PRP: Platelet-Rich Plasma.							
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).							
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For more information, visit: http://www.prisma-statement.org/							

In the classification of adjuvant therapeutic strategies, for long bone nonunion treatment, surgical stabilization was necessary, but for short bones, it was not. Therefore, surgical fixation was adopted according to actual needs and not considered in strategies. However, ACB, as the gold standard treatment, might affect adjuvant therapy and is considered a strategy. In addition, it should be noted that in the healing rate outcome, both intervention groups might achieve fracture healing during the follow-up period. In this case, the healing time is an important supplement to assess adjuvant therapy effects.

For healing rate outcome, 15 intervention strategies were analyzed, including ACB, BMA, BMP, CTM, EMF, ESWT, LIUS, PROTELOS, PRP, their combinations, and blank control (Figure 3, A). In pairwise comparisons, except ESWT (OR: 1.76; 95% CI: 0.24, 13.00) and BMA+ESWT (OR: 0.79; 95% CI: 0.15, 4.27), which were not significantly different from the blank control, the other strategies were significantly better than the control. Compared to ACB, only BMA+ACB was found to be significantly better (OR: 0.12; 95% CI: 0.03, 0.59). In the SUCRA ranking results, BMA+PRP (96%), BMA+ACB (90%), and BMA alone (82%) showed relative advantages in healing rate (Figure 4, A). A comparison-adjusted funnel plot did not show potential publication bias (Figure 5, A).

For the healing time, a total of 13 intervention strategies were analyzed, including ACB, BMA, BMP, CTM, EMF, ESWT, LIUS, PRP, their combination, and blank control (Figure 3, B). In the pairwise comparison, BMP (SMD: -2.61; 95% CI: -5.01, 0.22) and LIUS (SMD: -8.85; 95% CI: -12.85, -4.86) interventions had significantly shorter healing times than the blank control. Compared with ACB, only LIUS intervention significantly shortened the healing time (SMD: -8.93; 95% CI: -14.37, -3.48). In the SUCRA ranking results, LIUS (99%), PRP+BMA (74%), and BMP (69%) had relative advantages (Figure 4, B). No publication bias was detected according to the funnel plot (Figure 5, B).

For AE outcome, a total of 7 intervention strategies were analyzed, including ACB, BMA, BMA+ACB, BMP, EMF, ESWT, PRP, and control (Figure 3, C). Compared with the control, EMF (OR: 13.21; 95% CI: 1.58, 110.40) and ESWT (OR: 4.90; 95% CI: 1.38, 17.43) had higher AE risk. In the SUCRA ranking results, BMA+ACB (95%) had relatively few side effects (Figure 4, C). Although no publication bias was detected (Figure 5, C), the AE results included malunion, infection, reoperation, and adverse drug reaction with high heterogeneity.

Discussion

In this study, adjuvant treatments for fracture nonunion/delayed union were comprehensively analyzed by network meta-analysis. Adjuvant therapeutic strategies include ACB, BMA, BMP, CTM, EMF, ESWT, LIUS, PROTELOS, PRP, and their combinations. In the healing rate results, BMA+PRP, BMA+ACB, and BMA have relative advantages that support BMA application in nonunion/delayed union treatment. The healing time results showed that LIUS and BMP, especially LIUS, could significantly shorten the healing time. In the AE results, it was considered that EMF and ESWT interventions may bring a high risk of AE.

BMA harvested from bone marrow includes multiple types of progenitor cells and is injected into the fracture site, which is considered a useful treatment for bone regeneration. Centrifugal concentration is beneficial to improve the effect [45]. Especially for atrophic nonunion, the proliferation and osteogenic differentiation ability of mesenchymal stem cells were inhibited, and BMA was beneficial to supplement more active mesenchymal stem cells [46]. Generally, long bone nonunion and delayed union treatment require surgical intervention, BMA is easier to obtain and local application. Therefore, compared to other cell therapy-related diseases, it has the advantage of convenience. BMA mainly has three application strategies, including intraoperative injection, transplantation after in vitro expansion, and soaked ACB or other bone graft materials [47, 48]. However, after expansion, multiple injections to the fracture site are needed, and osteofascial compartment syndrome should be specially considered. In addition to BMA and BMA+ACB, BMA+PRP also achieved ideal effects. PRP contains active cytokine components, such as platelet derived growth factor and vascular endothelial growth factor, which can further promote osteogenic-angiogenic coupling in bone formation with BMA [49].

LIUS is a physical intervention approved by the FDA for nonunion treatment [50 11216689]. As extracorporeal equipment, pressure waves could be delivered transcutaneously to the fracture site with slight heat. Its mechanism may vary, including the promotion of bone regeneration, angiogenesis, and nerve regeneration [51, 52]. The results of this study also suggested that it may be the only intervention to shorten the healing time of nonunion/delayed union compared with ACB.

BMPs are the most widely used growth factors in bone nonunion, especially BMP2. It has been confirmed to be successful in new bone formation, but heterotopic ossification is also a major problem in clinical application. In this study, BMPs significantly shortened the healing time without increasing the AE risk or even tended to reduce the occurrence. However, supraphysiological dose application and the lack of a controlled delivery system lead to heterotopic ossification that needs well-planned surgical excision [53–55]. This serious AE still raises concern in the clinical application of BMP.

Limitations

The presented study has several limitations. First, this study was performed at the study level, instead of at the individual level, and hypertrophic nonunion and atrophic nonunion patients could not be analyzed in subgroups. Second, there was no limited place at the time of study publication, but a long-time span (nearly 40 years) may bring about great changes in medical conditions. Third, the study included different types of nonunion/delayed union, including long and short bone fractures, so there was heterogeneity among the studies. Fourth, radiographic healing was adopted as a priority, and clinical healing was also adopted if radiographic healing was not reported. Fifth, the impact of drug dosage or electromagnetic intensity on fracture healing was not assessed due to the small number of eligible studies.

Conclusions

In summary, this study showed that among the current intervention strategies, BMA and combination with PRP and ACB can improve the healing rate of nonunion/delayed union. LIUS can significantly shorten the healing time. However, large-scale, well-designed studies are still needed to confirm the results.

Abbreviations

ACB
autologous cancellous bone
AE
adverse effect
BMA
bone marrow aspirate
BMPs
bone morphogenetic proteins
CTM
Chinese traditional medicine
EMF
electromagnetic field
ESWT
extracorporeal shock wave
LIUS
low-intensity pulsed ultrasonography
OR
Odds ratio
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP
platelet-rich plasma
RCTs
randomized controlled trials
SMD
standardized Mean difference
SUCRA
surface under the cumulative ranking curve

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are presented in this published article and its additional information files. Meta-analysis data can be requested from corresponding author.

Competing interests

The authors declare that they have no competing interests.

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None

Authors' contributions

WL and GC were responsible for the conception and design, data synthesis and analysis, interpretation of data and drafting the manuscript. XZ and YM screened the literature and assessed risk of bias independently. JY, YZ, RF, and KJ contributed to conception and design, supervised the project, validated the data, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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None

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Figures

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Figure 1

Flowchart illustrating the literature search and the selection of included studies

Figure 2

Risk of bias graph for each included study

Figure 3

Network plots of the outcomes of therapeutic strategies on nonunion/delayed union in the network meta-analysis. A: healing rate; B: healing time; C: adverse effect. ACB: autologous cancellous bone; BMA: bone marrow aspirate; BMP: bone morphogenetic proteins; CTM: Chinese traditional medicine; EMF: electromagnetic fields; ESWT: extracorporeal shock wave; LIUS: low-intensity pulsed ultrasonography; PROTELOS = strontium ranelate; PRP: platelet-rich plasma.

Figure 4

Forest plot of network meta-analysis comparisons between therapeutic strategies and blank control. A: healing rate; B: healing time; C: adverse effect. ACB: autologous cancellous bone; BMA: bone marrow aspirate; BMP: bone morphogenetic proteins; CI: confidence interval; CTM: Chinese traditional medicine; EMF: electromagnetic fields; ESWT: extracorporeal shock wave; LIUS: low-intensity pulsed ultrasonography; OR: odds ratio; PROTELOS = strontium ranelate; PRP: platelet-rich plasma; SUCRA: surface under the cumulative ranking curve.

Figure 5

Comparison-adjusted funnel plots of each outcome in the network meta-analysis. A: healing rate; B: healing time.