A meta-analysis of the Masquelet technique and the Ilizarov bone transport method for the treatment of infected bone defects in the lower extremities

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Abstract

Purpose: To compare the clinical outcomes of the Masquelet technique and Ilizarov bone transport method for the treatment of patients with infected bone defects in the lower extremities. Methods: Eligible studies were searched from six databases until 12 April 2021. Data extraction was independently conducted by two investigators, which was followed by a quality assessment. Weighted mean difference (WMD) and 95% confidence interval (CI) were used to analyze continuous variables, while odds ratio (OR) and 95% CI were used to analyze categorical variables. All statistical analyses were conducted using RevMan 5.3 and Stata 12.0. Results: Thirteen articles were included in this meta-analysis. There was a significant difference observed in hospitalization costs (WMD [95% CI] = −1.75 [−2.50, −0.99] thousand US dollar, p < 0.00,001), final union time (WMD [95% CI] = −4.54 [−6.91, −2.17] months, p = 0.0002), time to full weight bearing (WMD [95% CI] = −1.73 [−3.36, −0.10] months, p = 0.04), quality of life (WMD [95% CI] = 7.70 [4.74, 10.67], p < 0.00,001), and the risk of complications (OR [95%CI] = 0.39 [0.19, 0.79], p = 0.009) between the Masquelet and Ilizarov groups. No significant differences in other outcomes were observed between the two groups. Conclusion: Masquelet technique exhibited the advantages in the lower hospitalization cost, shorter final union time, shorter time to full weight bearing, lower rate of complications, and better post-operative quality of life, compared with Ilizarov bone transport method. However, this finding should be confirmed in large-scale clinical samples.

Keywords

Infected bone defects in lower extremity, Masquelet technique, Ilizarov bone transport, Meta-analysis

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Highlights

1. Thirteen eligible studies (711 cases) were included in this meta-analysis.
2. In the Masquelet group, hospitalization costs, final union time, and time to full weight bearing were lower.
3. Post-operative quality of life in the Masquelet group was higher than that in the Ilizarov group.

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4. The Masquelet technique reduced the occurrence of complications in patients with infected bone defects in the lower limbs.

Introduction

The management of infected bone defects, mostly caused by high-energy trauma, \(^1\) is one of the most challenging problems in the field of orthopedics. \(^2\) Infection control and bone defect repair are important in the treatment process; improper therapy may cause ongoing infection at the fracture site, increase the risk of complications, and even result in amputation. \(^3\) Generally, the Masquelet technique \(^4\) and Ilizarov bone transport \(^5\) method are recognized as common treatment methods for the management of infected bone defects in the lower extremities. In brief, the Masquelet technique involves a two-stage process consisting of debridement and cement spacer insertion in the first stage and removal of the spacer and bone grafting in the second stage. \(^4,6\) The Ilizarov technique involves debridement and shortening of the affected bone before progressive lengthening over a frame. \(^5\)

In the past few years, a series of studies have been performed to compare the clinical outcomes between the Masquelet technique and Ilizarov bone transport. However, the results are inconsistent. For example, some studies have reported that bone defects patients treated with Ilizarov bone transport had a higher complication rates compared to those treated with Masquelet technique. \(^7,8\) However, Zhang et al. \(^9\) showed that the Ilizarov technique had lower complication rates and was superior to the Masquelet technique. In addition, some studies show that the therapeutic effects of the Masquelet technique are equivalent to those of the Ilizarov bone transport method. \(^10,11\) To summarize, it remains unclear which technique can achieve better clinical outcomes.

In the present study, we aimed to compare the clinical outcomes of the Masquelet technique and Ilizarov bone transport for the treatment of patients with infected bone defects in the lower extremities via a meta-analysis. This may provide comprehensive and objective suggestions for orthopedic surgeons when encountering such diseases.

Methods

Search strategy

This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA). The relevant studies were systematically searched from five databases, including PubMed, Embase, China National Knowledge Infrastructure, WAN FANG data, and the China Science and Technology Journal database, with the following keywords: “Masquelet,” “induced membrane,” “Ilizarov,” “bone transport,” and “bone defects.” The search string was adjusted according to the characteristics of the database, and the search steps and results of the PubMed database are listed in Supplementary Table 1. The search included data until 12 April 2021, without any language restrictions. Further, to obtain more eligible studies, manual searches on paper-based literature were conducted, and the relevant reviews as well as references of all included articles were also screened.

Study selection

The inclusion criteria were defined as follows: (1) only patients with infected bone defects in the lower extremities (fibula, femur, and tibia), (2) the Masquelet technique was performed in the intervention group, while the Ilizarov bone transport method was performed in the control group, (3) study types included randomized controlled trial (RCT), prospective clinical study, or retrospective clinical study (RCS), and (4) one or more of the outcomes specifically outlined were reported (hospital stay, hospitalization costs, final union time, time to full weight bearing, quality of life, Iowa score for the knee, Iowa score for the ankle, assessment of bone healing, functional assessment, and total complications).

The exclusion criteria were as follows: (1) summaries, conference abstracts, reviews, and other non-authoritative researches, (2) studies with incomplete data, and (3) repeated publications or studies that used the same data for multiple articles.

Data extraction and quality assessment

Literature screening was independently completed by two investigators. The following data from eligible studies were extracted: first author, publication year, study type, characteristics of the research participants (e.g. sample size, age, and gender), site and length of the bone defects, intervention, follow-up time, and outcome indicators. Disagreements were resolved by consensus.

Quality assessments for non-RCTs were conducted using Risk Of Bias In Non-randomized Studies of Interventions. \(^15\) While, quality assessments for RCTs were performed using Cochrane Collaboration’s tool for assessing risk. \(^13\)

Statistical analysis

All statistical analyses were conducted using the RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 software (Stata Corp, College Station, TX, USA). Weighted mean difference (WMD) and 95% confidence interval (CI) were used for continuous variables (hospital stay, hospitalization costs, final union
time, time to full weight bearing, quality of life, and Iowa scores), while odds ratio (OR) and 95% CI were applied for categorical variables (bone healing assessment, functional assessment, and total complications). A heterogeneity test was conducted using Cochran’s Q test and $I^2$ test. $p < 0.05$ and/or $I^2 > 50\%$ indicated significant heterogeneity, while $p \geq 0.05$ and $I^2 \leq 50\%$ implied no significant heterogeneity. Due to the methodological and clinical heterogeneity of the included studies, such as differences in study types, the random-effects model was applied to merge effects in this meta-analysis. Moreover, the funnel plot was employed to assess publication bias.

Results

Results of study selection

A flow chart of the study selection process is presented in Figure 1. Initially, 443 articles (PubMed: 54, Embase: 69, CNKI: 201, CQVIP: 16, and Wanfang: 103) were found. After elimination of duplicates, 352 studies remained. Among them, 331 articles were excluded after the screening of abstracts and titles. Eight studies were then excluded after reading the full texts. No eligible studies were found during the manual search. Finally, 13 articles were included in this meta-analysis.

Characteristics of the included study and quality assessment

Table 1 displays the characteristics of the 13 included studies (2 RCTs and 11 RCSs) in this meta-analysis. The publication years ranged between 2017 and 2020, and all of them were conducted in China. A total of 711 cases were collected, including 342 cases in the Masquelet group and 369 cases in the Ilizarov group. As for the information regarding bone defects, the study by Geng et al. did not report the site of the bone defects. Meanwhile, Huang et al. reported bone defects in the fibula, femur, and tibia. In addition, patients in five studies had bone defects in the femur or tibia, patients in another five articles only had bone defects in...
### Table 1. Characteristics of 13 included studies in this meta-analysis.

| Study          | Design of study | Site, fibula/Femur/Tibia | Follow-up, months | Intervention | n, M/f | Age, years | Length of bone defect, cm | Final union time, months |
|----------------|-----------------|--------------------------|------------------|-------------|-------|------------|--------------------------|------------------------|
| Geng, L 2019   | RCS             | NR                       | NR               | Masquelet   | 18, 12/6 | 42.8 ± 8.6 | 5.8 ± 2.1                | NR                     |
|                |                 |                          |                  | Iizarov     | 14, 10/4 | 39.4 ± 5.2 | 6.2 ± 2.4                | NR                     |
| Guo, JQ 2019   | RCS             | 0/11/19                  | 17.07 ± 2.69     | Masquelet   | 12, NR   | 32.6 ± 11.22 | 9.68 ± 2.95             | 60.0 ± 2.17            |
|                |                 |                          |                  | Iizarov     | 18, NR   | 19.22 ± 3.52 |                               |                        |
| Huang, CB 2019 | RCS             | 4/17/20                  | NR               | Masquelet   | 41, 27/14| 43.51 ± 5.98 | 4.98 ± 1.24             | NR                     |
|                |                 |                          |                  | Iizarov     | 40, 28/12| 42.12 ± 5.84 | 4.85 ± 1.13             | NR                     |
| Li, SY 2019    | RCS             | 0/0/15                   | 26 (15–41)       | Masquelet   | 15, 9/6  | 36.9 ± 5.2 | 9.5 ± 3.2 | 8.18 ± 2.95 | 17.34 ± 2.34 |
|                |                 |                          |                  | Iizarov     | 14, 8/6  | 38.9 ± 6.2 | 10.2 ± 5.0 | 10.48 ± 2.64 |
| Liu, L 2017    | RCS             | 0/0/14                   | 14 (9–18)        | Masquelet   | 9, 7/2   | 46.8 (28–60) | 11.4 (6–16) | 5.8 ± 1.67 |
|                |                 |                          |                  | Iizarov     | 37, 26/11| 44.9 (12–68) | 11.3 (7–15) | 6.5 ± 1.67 |
| Sun, ZB 2017   | RCS             | 0/0/27                   | 21.6 ± 6.5       | Masquelet   | 27, 20/7 | 36.2 ± 7.6 | 8.9 ± 2.2 | 5.21 ± 1.08 |
|                |                 |                          |                  | Iizarov     | 18, 12/6 | 34.5 ± 7.6 | 8.3 ± 2.1 | 7.22 ± 1.62 |
| Tong, K 2017   | RCS             | 0/0/13                   | 23.15 ± 9.49     | Masquelet   | 20, 15/5 | 39.85 ± 15.98 | 6.69 ± 3.74 | 10.15 ± 1.66 |
|                |                 |                          |                  | Iizarov     | 19, 15/4 | 38.47 ± 11.01 | 6.85 ± 3.44 | 17.21 ± 3.79 |
| Wei, GF 2017   | RCS             | 0/0/25                   | 6–24             | Masquelet   | 25, 14/11| 17–46       | 5–20        | 7.48 ± 1.53 |
|                |                 |                          |                  | Iizarov     | 21, 11/10| 22–61       | 5–20        | 9.1 ± 1.81 |
| Wu, JX 2019    | RCS             | 0/0/29                   | 12–18            | Masquelet   | 29, 20/9 | 35.49 ± 10.15 | 4.83 ± 1.73 | 7.22 ± 1.52 |
|                |                 |                          |                  | Iizarov     | 34, 21/13| 33.24 ± 9.66 | 9.13 ± 2.59 | 17.96 ± 5.49 |
| Yang, JW 2017  | RCS             | 0/0/14                   | 24.2 ± 4.7       | Masquelet   | 11, 9/2  | 35.31 ± 7.82 | 9.2 ± 1.8   | NR                     |
|                |                 |                          |                  | Iizarov     | 14, 11/3 | 37.84 ± 6.16 | 8.9 ± 2.1   | NR                     |
| Yang, LD 2018  | RCS             | 0/0/12                   | 14.5 (6–24)      | Masquelet   | 16, 12/4 | 39.50 ± 9.80 | 8.31 ± 2.77 | 7.13 ± 0.87 |
|                |                 |                          |                  | Iizarov     | 21, 15/6 | 36.24 ± 7.94 | 8.62 ± 2.52 | 7.57 ± 2.23 |
| Zhang, YX 2019 | RCT             | 0/0/41                   | NR               | Masquelet   | 86, 47/39| 41.88 ± 11.05 | NR         | NR                     |
|                |                 |                          |                  | Iizarov     | 86, 48/38| 40.61 ± 12.37 | NR         | NR                     |
| Zhou, WM 2020  | RCT             | 0/0/33                   | NR               | Masquelet   | 33, 18/15| 48.76 ± 5.28 | 11.13 ± 2.78 | NR                     |
|                |                 |                          |                  | Iizarov     | 33, 17/16| 48.35 ± 5.74 | 14.68 ± 5.35 | NR                     |

F, female; M, male; NR, not reported; RCS, retrospective clinical study; RCT, randomized controlled trial. ^p < 0.05.
the tibia, and patients in one article only had bone defects in the femur. The age of the patients ranged between 32.6 to 48.76 years old, and there was no significant difference in the male to female ratio between the two groups. Two RCTs did not report the length of the bone defects. Furthermore, except for the study by Wu et al., there were no significant differences observed in the length of bone defects between the two groups in the remaining studies.

The results of the quality assessment for RCSs and RCTs are presented in Supplementary Table 2 and Supplementary Table 3, respectively. The included studies exhibited moderate or uncertain risk of bias. Overall, the methodological quality of the included studies was moderate.

**Results of the meta-analysis**

**Days of hospital stay.** Three studies involving 278 patients (138 in the Masquelet group and 140 in the Ilizarov group) reported the hospital stay. Significant heterogeneity was detected ($I^2 = 84\%, p = 0.002$). The meta-analysis showed that the hospital stay in the Masquelet and Ilizarov groups was 26.43 days and 26.16 days, respectively (WMD [95% CI] = 0.67 [-1.59, 1.69] days, $p = 0.86$; Figure 2(A)), indicating that there were no statistical differences in days of hospital stay between the two groups.

**Hospitalization costs.** Three studies including 159 patients (74 in the Masquelet group and 85 in the Ilizarov group) reported the hospitalization costs. The pooled results indicated that the hospitalization costs in the Masquelet group (10.18 thousand US dollar) was significantly lower than that in the Ilizarov group (12.21 thousand US dollar) (WMD [95% CI] = -2.03 [-2.50, -1.56] thousand US dollar, $p < 0.00001$; Figure 2(B)), with no significant heterogeneity among all studies ($I^2 = 0\%, p = 0.74$).

**Final union time.** Nine studies including 401 patients (186 in the Masquelet group and 215 in the Ilizarov group) reported...
information regarding the final union time. The meta-analysis showed that the final union time in the Masquelet and Ilizarov groups was 7.59 months and 12.22 months, respectively (WMD [95% CI] = 4.54 [–6.91, 0.10] months, p = 0.0002; Figure 2(C)), suggesting that the final union time in the Masquelet group was significantly lower than that in the Ilizarov group. Meanwhile, significant heterogeneity was observed among the studies (I² = 96%, p < 0.00001).

**Time to full weight bearing.** Three studies involving 111 patients (58 in the Masquelet group and 53 in the Ilizarov group) reported the time to full weight bearing. The final meta-analysis suggested that the time to full weight bearing in the Masquelet group (7.67 months) was significantly lower than that in the Ilizarov group (9.45 months) (WMD [95% CI] = 1.73 [3.36, –0.10] months, p = 0.04; Figure 2(D)). Significant heterogeneity was observed among studies (I² = 81%, p = 0.005).

**Quality of life.** Three studies involving 145 patients (72 in the Masquelet group and 73 in the Ilizarov group) provided information about the quality of life that was assessed using the MOS 36-Item Short-Form Health Survey. Significant heterogeneity was observed among the studies (I² = 96%, p < 0.0001). The pooled results suggested that patients in the Masquelet group (92.38) had a significantly higher post-operative quality of life than those in the Ilizarov group (76.20) (WMD [95% CI] = 7.70 [4.74, 10.67], p < 0.00001; Figure 3(A)).

**Iowa score.** Information about the Iowa score of the knee was extracted from three studies (total 111 patients, 58 in the Masquelet group and 53 in the Ilizarov group). The pooled results showed that there was no significant difference in Iowa score of knee between the Masquelet (88.04) and Ilizarov groups (87.13) (WMD [95% CI] = 1.46 [-0.25, 3.17], p = 0.09; Figure 3(B)) with no significant heterogeneity (I² = 0%, p > 0.05). In addition, information on Iowa score of the ankle was recorded in three studies (58 in the Masquelet group and 53 in the Ilizarov group), and Iowa score of the ankle in the Masquelet and Ilizarov groups was 87.53 and 86.65, respectively. However, no significant differences in the Iowa score of the ankle were observed between the two groups (WMD [95% CI] = 0.38 [-1.27, 2.04], p = 0.65; Figure 3(C)). No significant heterogeneity was detected among the studies (I² = 0%, p > 0.05).

**Bone healing and functional assessment.** In this study, we used the bone healing assessment and functional assessment to reflect clinical outcomes. The excellent and good rate of bone healing and functional recovery was assessed by using different scales. In brief, the tool for Guo et al., Tong et al., and Wu et al. is Paley’s classification.

| Study or Subgroup | Masquelet | Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference [IV, Random, 95% CI] |
|-------------------|-----------|------|----|-------|------|----|-------|--------|----------------------------------|
| Sun, ZB 2017      | 77.5      | 10.6 | 27 | 76.9  | 11.3 | 18 | 14.6% | 0.60 [0.58, 0.71] |
| Wu, JX 2016       | 83.8      | 4.71 | 29 | 75.28 | 3.21 | 34 | 44.9% | 1.54 [1.29, 1.79] |
| Yang, LD 2018     | 95.8      | 3.19 | 16 | 76.43 | 4.21 | 21 | 40.3% | 9.38 [1.01, 17.76] |
| Total (95% CI)    | 72        |      | 73 | 100.0 |      |    |       | 7.70 [4.74, 10.67] |

*Heterogeneity: Tau² = 4.20; Chi² = 6.67, df = 2 (p = 0.05); I² = 67% Test for overall effect: Z = 5.09 (p < 0.00001)*

**Figure 3.** Comparison of life quality (A), Iowa score of the knee (B), and Iowa score of the ankle (C) between Masquelet and Ilizarov groups.
the assessment tool for Huang et al.\textsuperscript{15} and Liu et al.\textsuperscript{10} is Johner-Wruhs criteria\textsuperscript{24}; the tool used in Zhang et al.\textsuperscript{9} study is Chinese experts’ consensus on diagnosis and treatment of infection after internal fixation (2018 version).\textsuperscript{25} Both excellent and good were considered effective outcomes.

Five (573 patients involving 188 in the Masquelet group and 197 in the Ilizarov group) and four studies (196 patients involving 82 in the Masquelet group and 114 in the Ilizarov group) compared the bone healing and functional recovery between the two groups, respectively. The excellent and good rate of bone healing in the Masquelet group was 83.51% and that in the Ilizarov group was 88.32%. In addition, the excellent and good rate of functional recovery in the Masquelet and Ilizarov groups was 79.27% and 74.56%, respectively. However, there were no significant differences in this two factors between the Masquelet and Ilizarov groups (bone healing: OR [95% CI] = 0.68 [0.33, 1.40], \textit{p} = 0.29; Figure 4(A); functional recovery: OR [95% CI] = 1.60 [0.57, 4.50], \textit{p} = 0.37, Figure 4(B)). Meanwhile, the heterogeneity was not considered significant among these studies (\textit{I}^2 = 0\%, \textit{p} > 0.05).

### Total complications.

Eleven studies involving 619 patients (308 in the Masquelet group and 311 in the Ilizarov group) provided information regarding the total complications. Significant heterogeneity was found among the studies (\textit{I}^2 = 67\%, \textit{p} = 0.0008), and the result revealed that the rate of total complications in the Masquelet group (24.35\%) was significantly lower than that in the Ilizarov group (39.23\%) (OR [95% CI] = 0.39 [0.19, 0.79], \textit{p} = 0.009; Figure 4(C)).
Publication bias. Except for total complications, the number of eligible studies in the other outcome indicators was less than 10; hence, the test powers of the qualitative or quantitative test were relatively low. Therefore, this meta-analysis only conducted a publication bias test for the total complications. As shown in Figure 5, the funnel plot revealed that the distribution of scattered points was relatively symmetrical, suggesting that no significant publication bias was found between the studies for total complications.

Discussions

Evidence reveals that both Masquelet technique and Ilizarov bone transport method result in satisfactory bone and functional results in the treatment of infected bone defects in the lower extremities. In this study, we performed a meta-analysis to compare of efficacy and complications of these two techniques, including hospitalization costs, final union time, time to full weight bearing, excellent and good rate of bone healing as well as functional recovery, rate of total complications, and post-operative quality of life.

In terms of functional outcomes, our results indicated that patients in the Masquelet group had lower hospitalization costs, shorter final union time, shorter time to full weight bearing. The previous study generally agreed that the Masquelet technique is the induction of a pseudo-membrane by a physiological foreign body response surrounding a polymethyl methacrylate spacer, and then this spacer is replaced with a bone graft to stimulate bone union in the second stage.26 Meanwhile, membrane induced by Masquelet technique contains a variety of vascular growth factors, which can contribute to the proliferation and differentiation of osteoblasts, thereby accelerating the procession of bone mineral density and bone reconstruction.27 Therefore, compared to other techniques such as Ilizarov bone transport, the Masquelet technique preserves bone graft volume, reduces bone absorption, and prevents soft tissue growth, leading to shorter treatment times.26 These showed the advantages of Masquelet technique on the treatment of patients with infected bone defects, which could partly explain our findings.

Furthermore, a lower rate of total complications and better post-operative quality of life were found in the Masquelet group compared to Ilizarov group in this meta-analysis. Consistent with our findings, Wang et al.28 revealed that Masquelet technique could promote the union of bone fractures, facilitate the recovery of limb function, and reduce the occurrence of complications. Besides, several retrospective studies evaluated the efficacy of Masquelet technique for the treatment of patients with bone defects, and observed that patients had a good bone functional recovery without complications.29,30 Several studies have reported that more complications were observed in patients with bone defects treated by Ilizarov technique,31 which was also found in our meta-analysis. This may due to the fact that the external fixator needs to be fixed for a long time until the new bone is completely ossified, which involves many complications.32 Moreover, Ilizarov method may bring serious consequences to patients. For example, muscle impalement through transfixing wires may lead to loss of joint motion, needle-tract infection and pain, may cause discomfort and psychosocial problems of patients.33 Thus, these unavoidable difficulties and complications observed in the Ilizarov technique might affect clinical outcomes.34,35 Taken together, it is reasonable to presume that Masquelet technique had more advantages rather than Ilizarov bone transport used for patients with infected bone defects.
Our meta-analysis had several advantages. We searched multiple Chinese and English databases to ensure a comprehensive extraction of the eligible studies. The included outcome indicators were relatively complete. Furthermore, no significant publication bias was observed among the studies, indicating that the results were high reliability.

Limitation
Some limitations should be acknowledged in this meta-analysis. First, the type of research subjects varied greatly among the included studies, which might bring some clinical heterogeneity. Second, most outcome indicators were only recorded in a few studies, so a publication bias test was not performed. Third, all research participants are from China, so the extrapolation of the combined results is limited. Furthermore, there was limited number of randomized studies published; thus, we included retrospective studies to expand our sample size, which might influence the validity of the results to some extent. Due to the small number of included studies, it was impossible to conduct subgroup analysis to discover the source of the heterogeneity. Fourth, the excellent and good rate of bone healing as well as functional recovery was assessed by using different tools, which may affect our results. Finally, the methodological quality of the included studies was moderate, so the pooled results were insufficient to support the clinical priority of Masquelet technique. Therefore, more high-quality RCTs and an updated meta-analysis with a large sample size are required to verify the accuracy of these results.

Conclusions
In summary, the use of the Masquelet technique for treating patients with infected bone defects in the lower extremities offers some advantages compared with the ilizarov bone transport method. However, more RCTs with high-quality methods and data are needed to further test the present conclusion.

Authors’ contributions
Zhong Li, Kun Zhang carried out the conception and design of the research, Yao Lu, Qian Wang and Cheng Ren participated in the Acquisition of data. Teng Ma, Yibo Xu and Cheng Ren carried out the Analysis and interpretation of data. Ming Li, Cheng Ren and Liang Sun participated in the design of the study and performed the statistical analysis. Zhong Li participated in Obtaining funding. Cheng Ren, Ming Li, Teng Ma and Hanzhong Xue conceived of the study, and participated in its design and coordination and helped to draft the manuscript and revision of manuscript for important intellectual content. All authors read and approved the final manuscript.

Declaration of conflicting interests
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Ethics approval and consent to participate
This study was approved by Ethics Committee of Honghui Hospital, Xi’an Jiaotong University.

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Supplemental Material
Supplemental material for this article is available online.

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Appendix

List of abbreviations

WMD Weighted mean difference