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REVIEW

Effect of Genicular Nerve Block (GNB) on Pain in Lesions of the Knee Joint: A Meta-Analysis of Randomized Controlled Trials

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Abstract: To explore the effect of genicular nerve block (GNB) on pain in lesions of the knee joint. Computerized searches of randomized controlled trials were conducted in PubMed, EMbase, Cochrane Library, and Web of Science, with a search time frame until January 2024. Methodological and experimental quality was assessed using the risk of bias assessment tool recommended by the Cochrane Handbook. A meta-analysis was conducted of the pain score (as the primary outcome measure) using Review Manager 5.4 and Stata 17. Thirteen studies involving a total of 731 patients were ultimately included. In the comparison of GNB and non-GNB, the analysis results of analgesic effects at all visits showed [SMD=−0.51, 95% CI (−0.89, −0.14)]. Analysis of analgesic effects at a visit at 1 month showed [SMD=−0.79, 95% CI (−1.55, −0.02)]. Subgroup analysis for the control group showed [SMD=−4.07,9 5% CI (−4.10, −1.84)]. Currently, available evidence suggests that GNB may be an effective analgesic therapy and superior to other regimens in the treatment of lesions of the knee joint.

Keywords: knee joint, pain, genicular nerve block, meta-analysis

Introduction

With the increase in the number of aging countries around the world, joint lesions and the sites involved by them have gradually aroused medical attention. The incidence of osteoarthritis, a disease that is most likely to occur in middle-aged and older people, is also increasing year by year. Juvenile idiopathic arthritis (JIA) is one of the most common chronic forms of arthritis in adolescents. It has a prevalence of 1/1000 people, and the knee joint is the most common site affected by JIA (40–60% of cases).[1] Lesions of the knee joint affect the ability to move and quality of life (QoL) in patients.[2] Usually, due to decreased movements, there are decreases in muscle strength and bone mass as well as an increased risk for fractures in patients. In addition, the experience of pain in osteoarthritis of the knee usually changes from intermittent weight-bearing pain to more persistent chronic pain, and then, patients had strong expectations for analgesic treatment.[3] This will undoubtedly bring great psychological pressure to patients. Patients with lesions of the knee joint, whether treated surgically or conservatively, often suffer from prolonged pain, which poses a great challenge for physicians to improve the QoL in patients and to minimize their mobility limitations and psychological distress.

As a new approach to regional analgesia at an independent site, genicular nerve block (GNB) has begun to arouse attention from pain physicians in recent years. According to Tran's cadaveric study, the knee joint is innervated by sensory branches of the tibial, common peroneal, femoral, and obturator nerves. The sensory branches around the knee joint are called genicular nerves. A medication for GNB can sufficiently spread to the above branches to block their impulse conduction so as to relieve pain around the joint.[4] In addition, according to a previous report by Radwan et al,

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GNB was effective in reducing opioid use during treatment.[5–7] Overuse of opioids often causes adverse reactions such as nausea, vomiting, generalized pruritus, risk of addiction, and respiratory depression in patients.

Current analgesic treatments for the peripheral sensory branch of the knee nerve alone mainly encompassed high-dose peripheral tissue infiltration, steroid injection, physiotherapy, electrical stimulation therapy, or radiofrequency ablation for patients, but there is controversy about the GNB and its analgesic effects. Qudsi-Sinclair, Tabur, and Elashmawy et al all reported different findings,[6] This meta-analysis was therefore aimed at statistically investigating the currently published reports on GNB to further clarify the effects of GNB on pain in lesions of the knee joint and explore feasible regimens.

Materials and Methods

Literature Search

Using subject headings + free-text terms, two authors (W.M.L, F.L.X) systematically searched PubMed, EMbase, Cochrane Library, and Web of Science databases, with a search time frame until January 2024. Chinese and English keywords contained the knee joint, pain, nerve block, and chemical denervation. A complete search strategy is shown in Supplementary Material S1.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) randomized controlled trials; (2) patients with lesions of the knee as study subjects; (3) only GNB considered; (4) NRS or VAS pain score contained in the Results section; (5) studies published in English. Exclusion criteria: (1) duplicate studies; (2) meeting minutes; (3) systematic reviews; (4) no GNB as a research topic; (5) no NRS or VAS score outcomes; (6) no data extractable from a study. The authors W.M.L and F.L.X screened studies independently and selected a study only when both of them agreed that the study met the inclusion criteria. The two authors resolved discrepancies between them through discussion. Only when they failed to reach an agreement after discussion, a third author (F.C) would be consulted. The process of literature selection is shown in Figure 1.

Data Extraction

The following information about the included studies was collected: the author's name, country/region, year of publication of a study, number of patients, diagnosis, type of a control group, study drug, time of a visit, type of pain scale, and pain score. The two authors (W.M.L and F.L.X) extracted the information from studies independently. The pain score at a visit was used as the primary outcome measure, and subgroup analysis was conducted based on the type of interventions in the control group and the experimental drugs.

Quality Assessment

The risk of bias was assessed independently by three authors (W.M.L, F.L.X and C.L) using the Cochrane Handbook. The risk of bias in each study was assessed as low, unclear or high. Assessment involved the aspects: random sequence generation, allocation concealment, blinding of investigators and participants, blinding of outcome assessors, observer bias, completeness of outcome data, selective reporting of study results, and other sources of bias. When a screened study was assessed as conforming in all the aspects above, it would be considered to be at "low risk" of bias, indicating that the study was of high quality. When a screened study was assessed as conforming in some of the aspects above, it would be considered to be at "intermediate risk" of bias, indicating that the study was of unclear quality. When a screened study was assessing as non-conforming in all the aspects above, it would be considered to be at "probable risk" of bias, indicating that the study was of low quality. Any discrepancies among the three authors were resolved through discussion with a study supervisor (X.H.B).

Statistical Analysis

Collected data were analyzed using Stata 17.0. Continuous variables were presented using the mean difference (MD) and 95% confidence interval (CI) as effect sizes. Heterogeneity among the included studies was assessed using I2 or Q statistics. $I2 \geq 50\%$ indicated high heterogeneity among the included studies, and meta-analysis was conducted using a random-effects model. Potential sources of heterogeneity would be identified by sensitivity analysis, and subgroup analysis. $I2 < 50\%$ indicated low

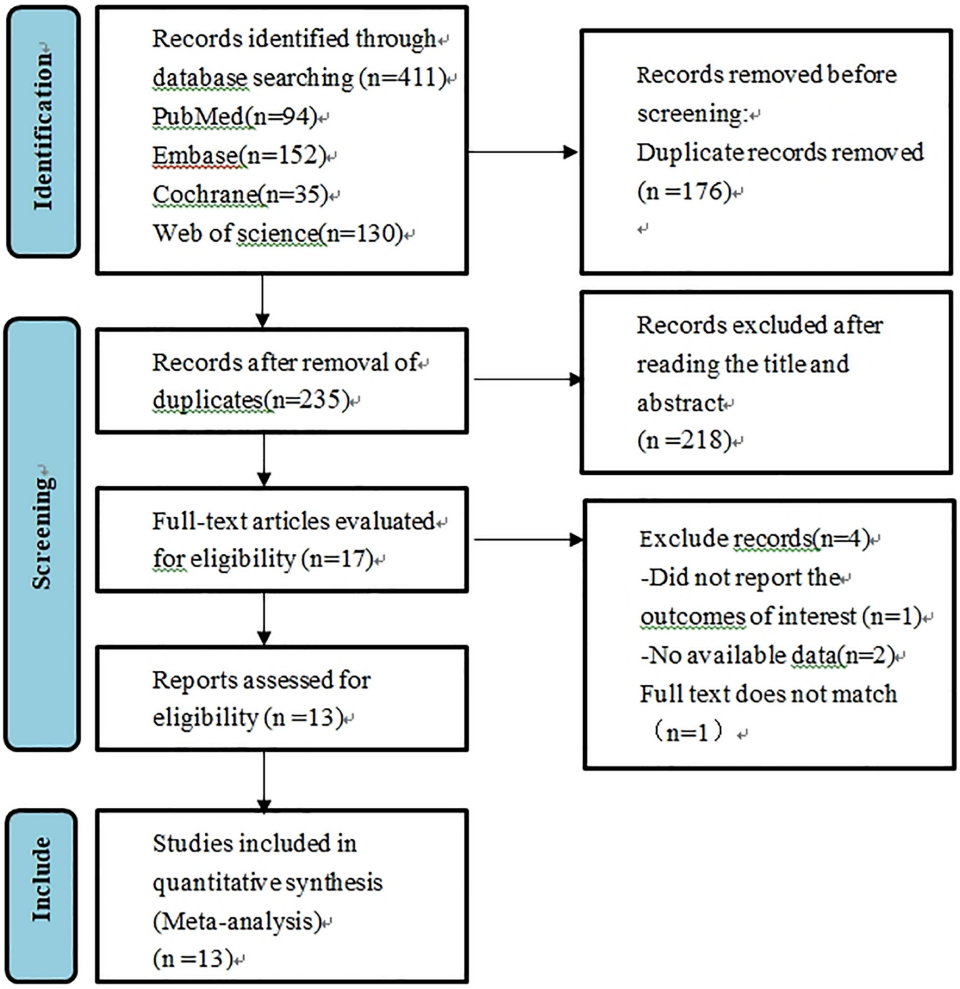

Figure 1 PRISMA flow diagram of the study process. PRISMA, Preferred Reporting Items for Systematic review and Meta-analysis.

heterogeneity among the included studies, and a fixed-effects model was used for analysis. Besides, the presence or absence of publication bias across the included studies was determined using the Egger's test. If $P < 0.05$, it indicated no significant publication bias across various studies.

Results

Process and Results of Literature Search

A total of 411 studies were initially retrieved from the databases. Of them, 176 duplicates were removed, 218 were excluded after their titles and abstracts were read, and four were excluded after their full texts were read. In the end, a total of thirteen randomized controlled trials[6–18] with 731 patients were included in this meta-analysis. The process of study selection is shown Figure 1.

General Characteristics of the Included Studies

The patient characteristics, intervention, and primary outcome measures in the included studies were summarized. Pain score was used as one of primary outcome measures in all the included studies. Their general characteristics are shown in Supplementary Material S2.

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Risk-of-Bias Assessment Figure

The included thirteen studies[6–18] were subjected to risk of bias assessment by the three authors (W.M.L, F.L.X, and C.L) using the Cochrane Handbook. The results showed that the studies were at low or unclear risk of bias in various aspects, as shown in Figures 2 and 3.

Result of Meta-Analysis

Efficacy Rate of GNB

Effects of GNB at All Visits

From the thirteen studies,[6–18] the data on pain scores at all visits after GNB in a total of 731 patients were extracted. The data at a single visit time point were analyzed. There was high heterogeneity among various studies (I^2 = 92.0%, P < 0.001). A meta-analysis based on the random effects model showed that at all visits, GNB was able to effectively reduce pain scores in patients [SMD = −0.51; 95% CI (−0.89, −0.14)], as shown in Figure 4.

In a total of five studies[9,10,12,14,15] (204 patients), pain scores were determined at a visit at 1 month after GNB. The data on pain scores at 1 month were meta-analyzed. The results showed [SMD=−0.79; 95% CI (−1.55, −0.02)], as shown in Figure 5

Pain Scores at 6 hours

In a total of four studies[7,11,13,17](233 patients), pain scores were determined at a visit at 6 hours after GNB. The data on pain scores at 6 hours were meta-analyzed. The results showed no significant difference [SMD = 0.32; 95% CI (−0.51, 1.15)], as shown in Supplementary Material S2.

Pain Scores at 12 hours

In a total of three studies[11,16,17](145 patients), pain scores were determined during a visit at 12 hours after GNB. The data on pain scores at 12 hours were meta-analyzed. The results showed no significant difference [SMD=−2.5; 95% CI (−5.04, 0.03)], as shown in Supplementary Material S2.

Pain Scores at 24 hours

In a total of six studies[7,9,11,13,16,17](301 patients), pain scores were determined at a visit at 24 hours after GNB. The data on pain scores at 24 hours were meta-analyzed. The results indicated no significant difference [SMD=−0.78; 95% CI (−1.69, 0.12)], as shown in Supplementary Material S2.

Pain Scores at 2 weeks

In a total of four studies[6,8,10,18](145 patients), pain scores were determined at a visit at 2 weeks after GNB. The data at

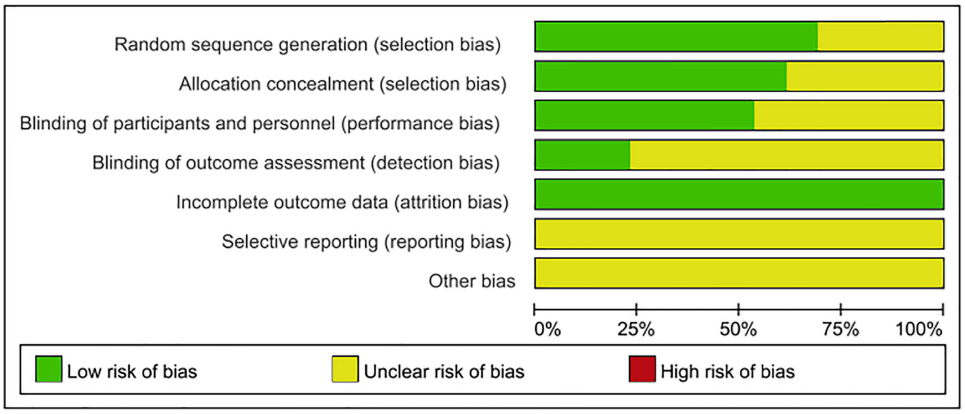

Figure 2 Risk of bias summary.

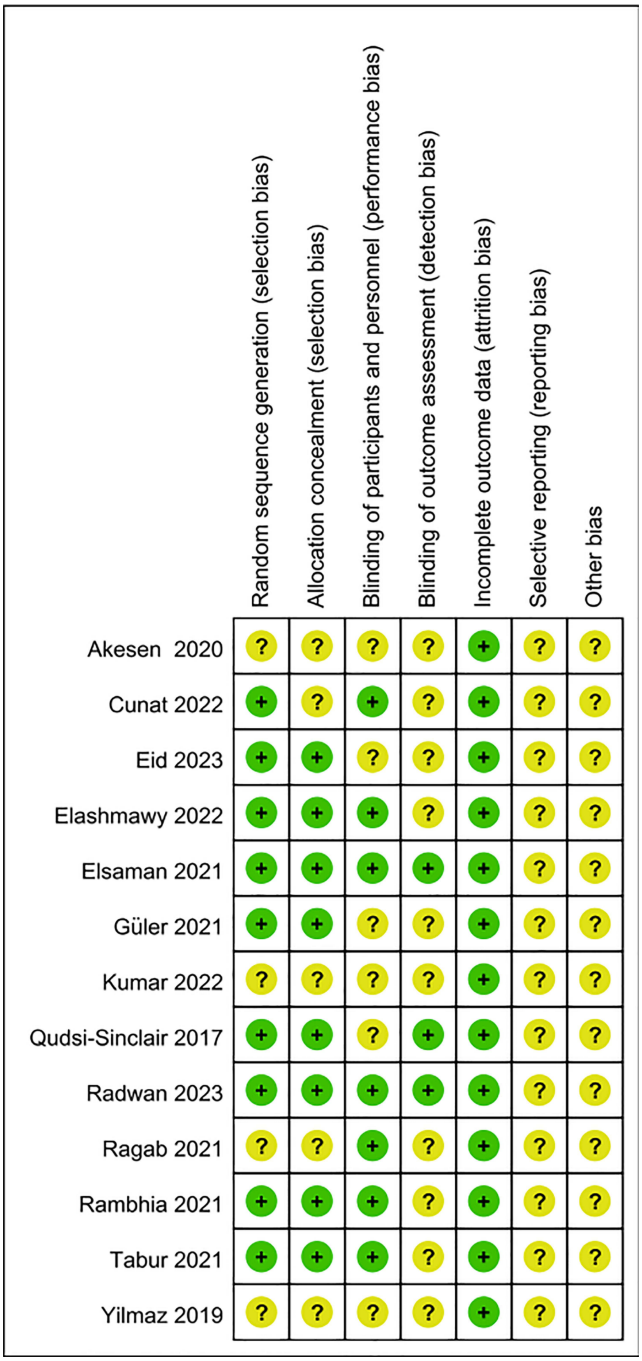

Figure 3 Cochrane Risk of Bias 2.0 Tool included randomized controlled trials. The green circle indicates low risk of bias, and the yellow circle indicates unclear risk of bias.

the visit were subjected to meta-analysis. The results suggested no significant difference [SMD=−0.67; 95% CI (−1.5, 0.16)], as shown in Supplementary Material S2.

Pain Scores at 3 Months

In a total of six studies[6,8,9,12,15,18](145 patients), pain scores were determined at a visit at 3 months after GNB. The data at the visit were subjected to meta-analysis. The results indicated no significant difference [SMD=−0.70; 95% CI (−1.45, 0.04)], as shown in Supplementary Material S2.

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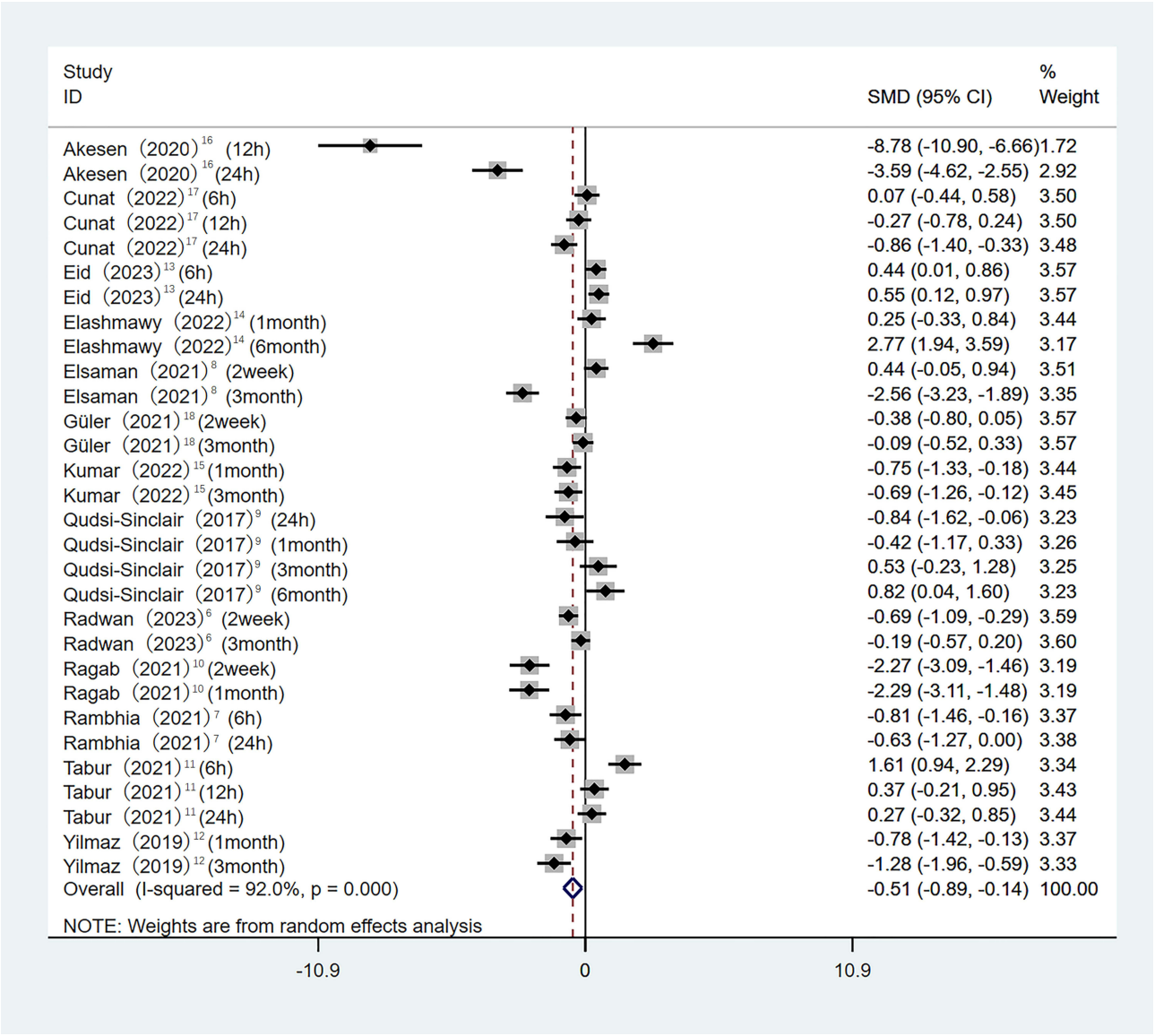

Figure 4 Analysis of pain scores at all visits in the studies based on the random effects model Pain scores at 1 month.

Western Ontario and McMaster Universities Arthritis Index (WOMAC) Score

The WOMAC is an important standard for functional assessment of osteoarthritis. Six studies[8,12,15–18] used the WOMAC. The WOMAC score results were statistically meta-analyzed. The statistical results are shown in Supplementary Material S2. The statistical results showed no significant differences [SMD=−0.37; 95% CI (−1.09, 0.35)].

Subgroup Analysis of the Effects of GNB

Subgroup Analysis by Control Group

Subgroup analysis by control group was conducted of the data at all visit time points in the studies. The results showed [SMD=−0.21, 95% CI (−0.54, 0.13)] (no statistically significant difference) in the active placebo group, and [SMD= −4.07, 95% CI (−4.10, −1.84)] in the non-active placebo group, as shown in Figure 6.

The results of subgroup analysis by control group showed [SMD = 0.67, 95% CI (−0.11, 1.46)] (no statistically significant difference) at 6 hours, [SMD = 0.03, 95% CI (−0.6, 0.66)] (no statistically significant difference), and [SMD = 0.2, 95% CI (−0.95, 0.56)] (no statistically significant difference) at 24 hours in the active placebo group, as well as

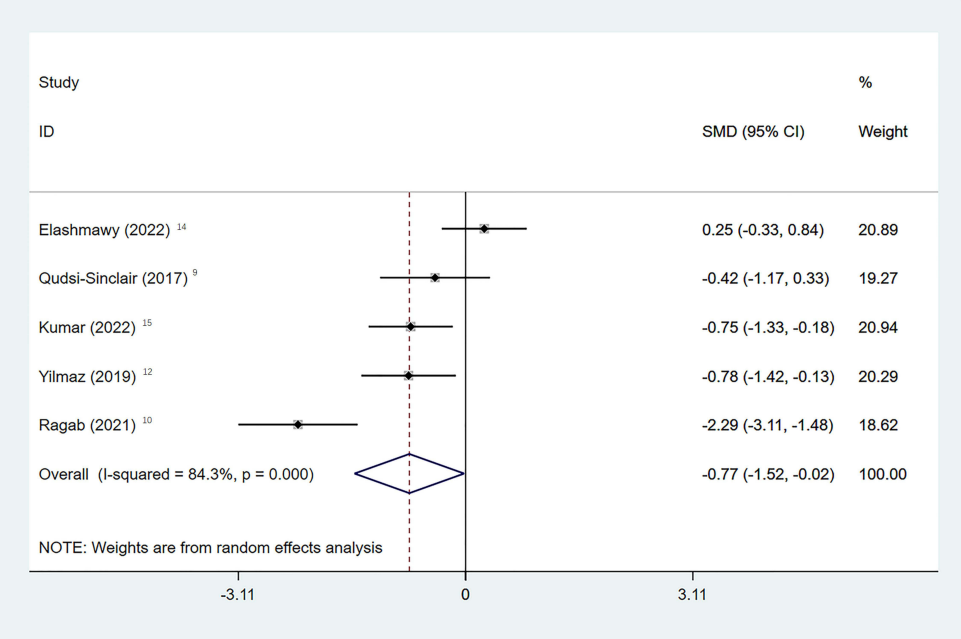

Figure 5 Analysis of pain scores at 1 month.

[SMD=−0.78, 95% CI (−4.97, 0.81)] (no statistically significant difference) in the non-active placebo group, as shown in Supplementary Material S3.

Subgroup Analysis by Diagnosis

Subgroup analysis by diagnosis was conducted for all the patients included in the studies. Analysis of the data on pain scores at 2 weeks in patients with knee arthritis showed no statistically significant difference [SMD = −1.29, 95% CI (−3.15, 0.57)]. For patients with chronic knee osteoarthritis, the results showed no statistically significant differences at 1 month [SMD = −0.86, 95% CI (−1.79, 0.07)] and 3 months [SMD = −0.65, 95% CI (−1.32, 0.03)], as shown in Supplementary Material S3.

Subgroup Analysis by Medications

Subgroup analysis by medication used in all the studies was conducted. No statistically significant differences were observed at 6 hours in the group treated with bupivacaine + a steroid [SMD = 0.40, 95% CI (−1.98, 2.77)] at 24 hours in the group treated with bupivacaine [SMD=−1.49, 95% CI (−5.54, 2.56)] and the group treated with bupivacaine + a steroid [SMD = −0.17, 95% CI (−1.06, 0.71)], at 2 weeks in the group treated with bupivacaine + a steroid [SMD = −1.29, 95% CI (−3.15, 0.57)], at 1 month in the group treated with lidocaine + a steroid [SMD = −1.51, 95% CI (−3.00, −0.03)], and at 3 months in the group treated with lidocaine [SMD = −0.09, 95% CI (−0.59, 0.78)] and the group treated with lidocaine + a steroid [SMD = −0.65, 95% CI (−1.81, 0.50)], as shown in Supplementary Material S3.

Subgroup Analysis by Scoring Scales

Subgroup analysis by scoring scales used in all the studies was conducted. When NRS was used to assess pain score, the subgroup analysis results showed no statistically significant differences in pain score at 6 hours [SMD = −0.06, 95% CI (−0.74, 0.61)] and 24 hours [SMD = −0.42, 95% CI (−1.20, 0.36)]. For studies that used VAS, no statistically significant differences were found in pain score at 12 hours [SMD = −4.15, 95% CI (−13.12, 4.82)], 24 hours [SMD = −1.64,95% CI (−5.41, 2.14)], 1 month [SMD=−0.86, 95% CI (−1.79, 0.07)], and 3 months [SMD=−0.93, 95% CI (−1.73, −0.13)], as shown in Supplementary Material S3.

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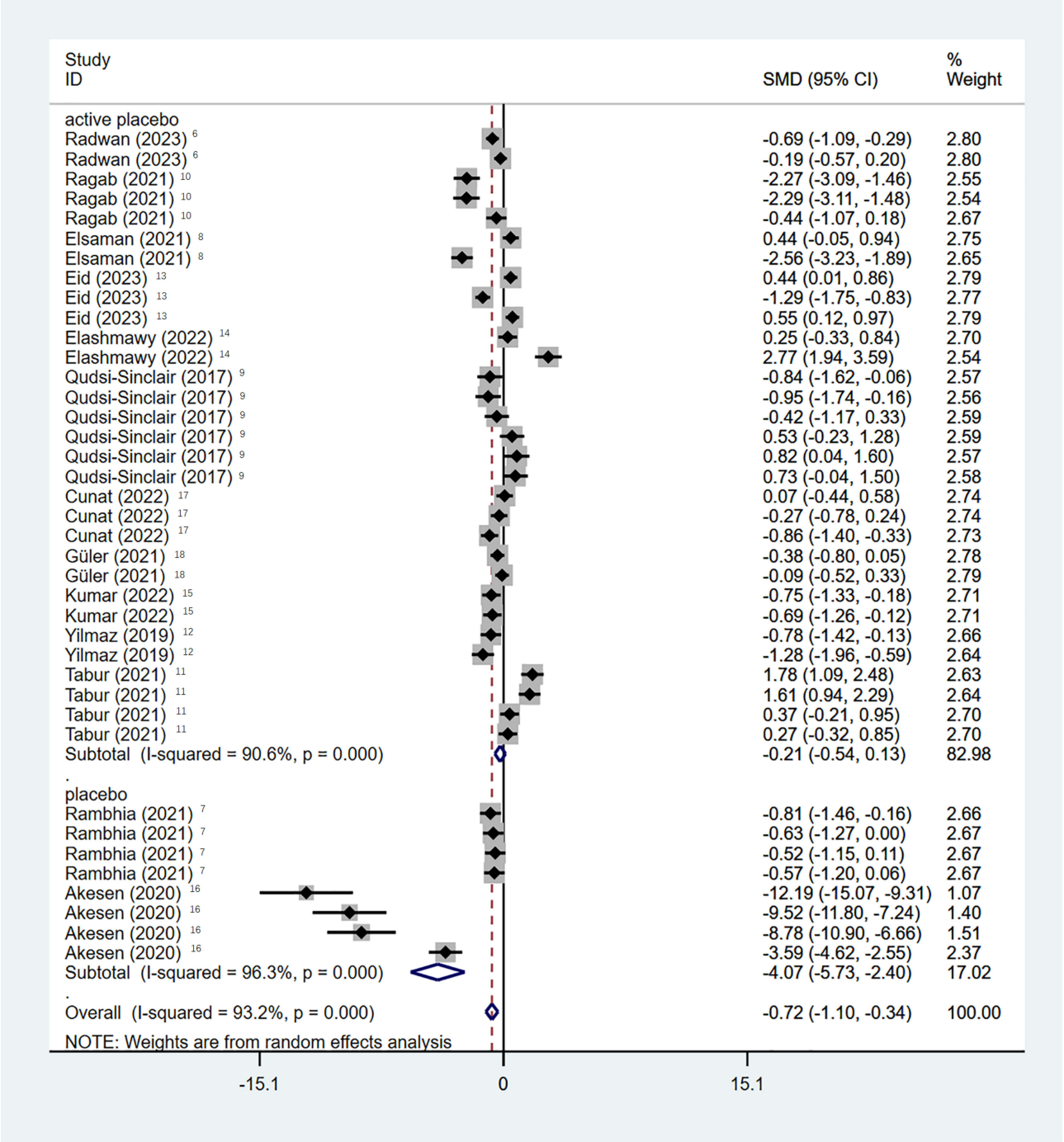

Figure 6 Subgroup analysis by control group regarding the data at all visit time points.

Sensitivity Analysis

Sensitivity analysis of the data at each visit was conducted by exclusion of the studies one by one. The results showed no significant change, ie, the data were stable, as shown in Figure 7. Sensitivity analysis of the data at a visit at 1 month is shown in Figure 8.

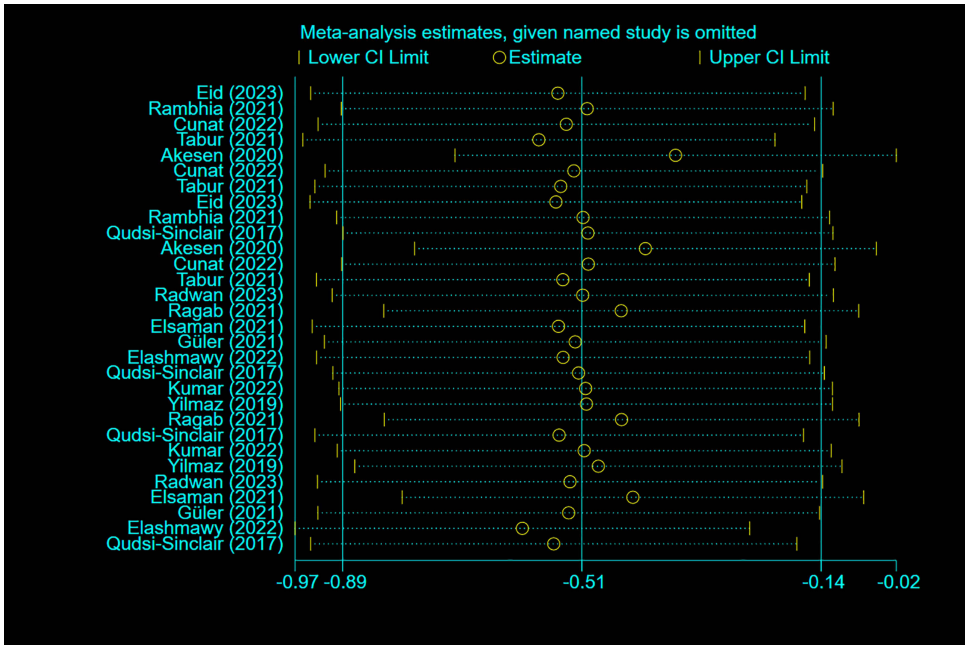

Figure 7 Sensitivity analysis of the data at all visit time points.

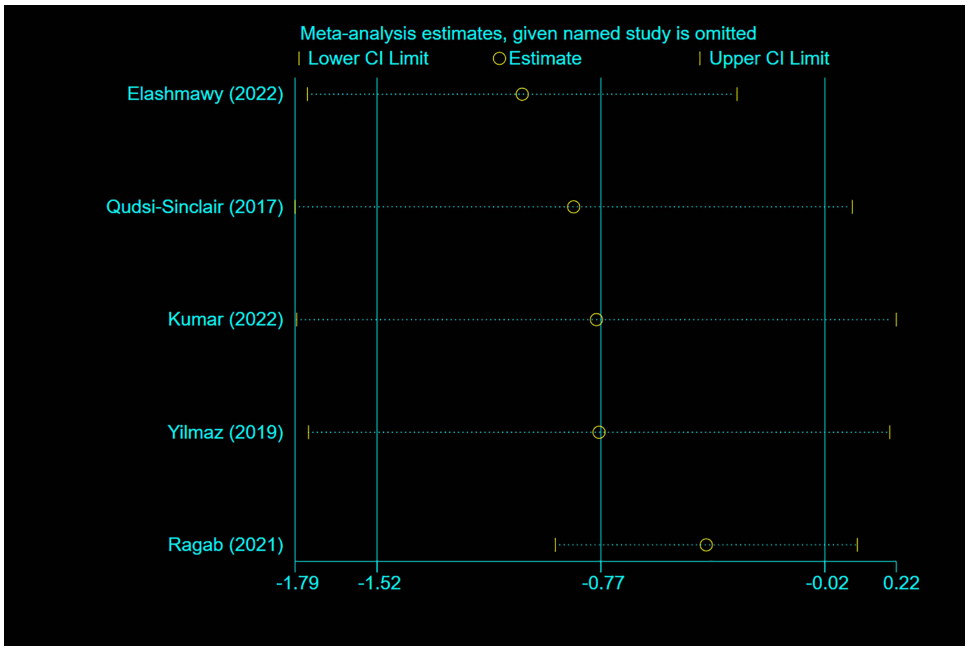

Figure 8 Sensitivity analysis of pain scores at 1 month.

Egger's Test Results

The Egger's test was performed for meta-analysis of the data on pain scores at all visits and the data on pain scores at 1 month. The results showed a significant change in pain scores at all visits (P = 0. 25), as shown in Figure 9. In contrast, there was almost no publication bias for the data on pain scores at 1 month (P = 0.204), as shown in Figure 10.

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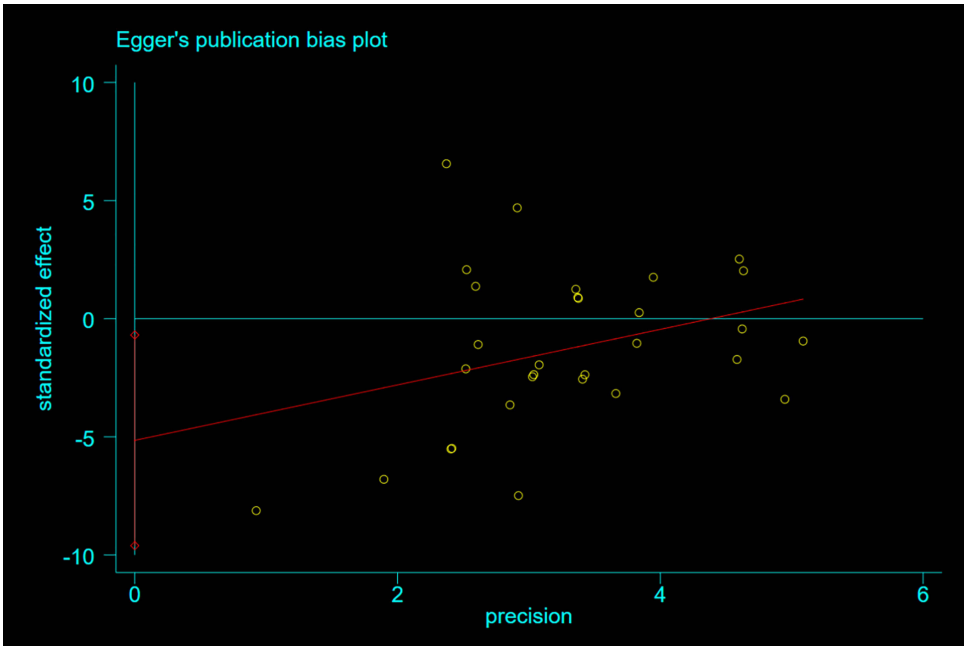

Figure 9 Egger's test for analysis of the data at all visits.

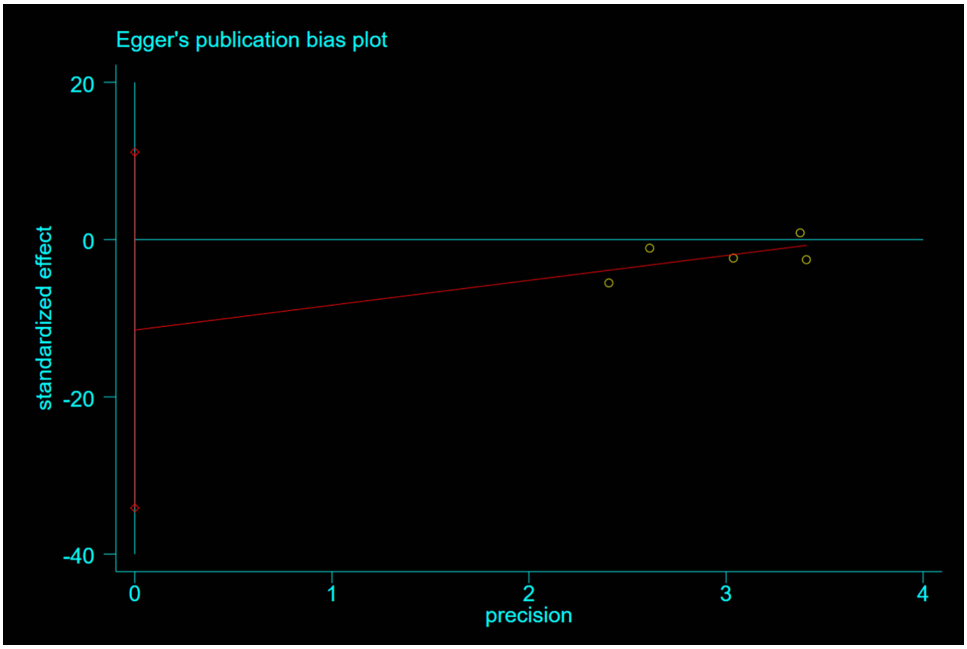

Figure 10 Egger's test for analysis of pain scores at 1 month.

Discussion

This meta-analysis compared the analgesic effects of GNB and other analgesic regimens in various lesions of the knee joint. This meta-analysis included 13 randomized controlled trials with 731 patients. Currently available data showed that GNB was superior to other analgesic regimens.

Pain scores at each visit in each study included were summarized and subjected to meta-analysis. Several studies confirmed that GNB had significant advantages over other analgesic regimens such as electrical stimulation therapy, physiotherapy, and steroid injection.[6,10,12,15,16,18] In addition, GNB was more effective than placebo.[7,16] However, a study by Eid and a study by Cunat found that peripheral tissue infiltration for analgesia might be superior to GNB in short-term efficacy.[13,17] This meta-

analysis showed no statistically significant differences. Given high heterogeneity among the data, sensitivity analysis was performed and showed no significant change. Considering that peripheral infiltration block is characterized by extensive non-selectivity, injection is performed recklessly by physicians. Therefore, a large volume of a medication is needed to help spread it to nerve endings in the knee. This may be related to the difference in medication volume between the two regimens as well as the manipulation. However, GNB is able to more accurately identify a target through the ultrasound equipment.[4]

Three of the thirteen studies drew different conclusions.[9,11,14] Of them, Tabur concluded that the femoral + anterior sciatic (FAS) nerve block appeared to have better analgesic effects. However, their visit time after FAS nerve block was only 24 hours, and patients reported a sense of increased foot weight and slowing down of foot movement. In contrast, no motor block occurred after GNB.[11] It was also reported by Hakkalamani.[18] However, it was also reported that patients undergoing total knee arthroplasty (TKA) had a 0.3%-10% chance of developing common peroneal nerve injury after neuroplasty with or without postoperative nerve block, and they possibly presented with falls.[19] In addition, Qudsi-Sinclair et al and Elashmawy et al chose to compare GNB with nerve root radiofrequency ablation and nerve root neurolysis. Qudsi-Sinclair et al compared GNB with nerve root radio-frequency ablation. Their report confirmed the results of our subgroup analysis of pain scores at 1 month, but they concluded that nerve root radiofrequency ablation was more effective at visits at more than 1 month to 6 months, and GNB might be more advantageous for cost.[9] In contrast, Elashmawy et al performed a comparative study only at 1 month and 6 months, and their results were closer to the later study results of Qudsi-Sinclair et al. However, both of their experiments caused permanent damage to the nerves involved.

For more detailed corroboration, subgroup analysis was conducted of the thirteen studies based on active placebo and ineffective placebo. The results showed that GNB was more advantageous than ineffective placebo.

This meta-analysis did not include literature reports on GNB compared with therapeutic approaches including cryoablation and oxygen-ozone therapy. Panagopoulos,[20] Noori-Zadeh[21] and Sconza[22] assessed the analgesic effects of cryoablation and oxygen-ozone therapy in lesions of the knee joint. Their results showed that oxygen-ozone therapy and cryoablation were effective for the treatment of pain in lesions of the knee joint. However, there are still some uncontrollable factors. For example, oxygen-ozone therapy requires multiple treatments, and there are problems such as difficulty controlling the concentration for treatment and no uniform standard concentration. The International Scientific Committee for Ozone Therapy (ISCO3) recommends avoiding large-volume oxygen-ozone therapy in a guideline. In the treatment of demyelination, cryoablation causes minor but still irreversible nerve injuries and possibly inevitable functional injuries.

This meta-analysis still has certain limitations. Firstly, pain rating scales are somewhat subjective and limited by patients' ability to understand them. Secondly, the included randomized controlled trials were highly heterogeneous, and there were certain differences in blinding method development among several studies. The above reasons may have led to the occurrence of bias. Finally, because of the lack of data at 6 months and more than 6 months, long-term analysis of data at longer time points was infeasible.

Conclusions

In summary, this meta-analysis showed that GNB had advantages over ineffective placebo, steroid injection alone, local infiltration block, physiotherapy, and transcutaneous electrical nerve stimulation. If analgesia is required for patients after arthropathy to minimize its impact on mobility, the choice of GNB may avoid such situation. Moreover, if GNB is popularized in economically underdeveloped and regionally unstable regions, it may provide an excellent therapeutic regimen for many people to improve their quality of life, reduce mobility limitations in patients, and resolve psychological distress. However, it should be noted that during the use of GNB for analgesic treatment, it is required to conduct follow-up visits with patients at 3–6 months after treatment and determine whether pain gets worse, and if necessary, block should be repeated.

Abbreviations

GNB, Genicular nerve block; TKA, Total Knee Arthroplasty; FAS, femoral + anterior sciatic nerve block.

Disclosure

Weiming Li and Fenglian Xu are co-first authors for this study. The authors report no conflicts of interest in this work.

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