Systematic Review

# Effectiveness of Denervation Therapy on Pain and Joint Function for Patients with Refractory Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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**Background:** Recently, denervation therapy has been applied clinically for the treatment of intractable osteoarthritis (OA). This therapy provides an alternative for patients who are insensitive to conservative therapies or unwilling to receive surgery and general anesthesia. However, therapeutic effect of this method, especially the long-term efficacy, is still controversial.

**Objectives:** The aim of this systematic review was to examine the efficacy of denervation therapy for the treatment of OA, especially on pain alleviation and functional recovery in the short and long term.

**Study Design:** This systematic review and meta-analysis was designed to investigate whether denervation therapy is more useful than conservative methods for achieving clinical outcomes in patients with refractory OA.

**Methods:** A literature search was performed in MEDLINE, EMBASE, and the Cochrane library for studies published from inception to August 2018. From those found meeting the search criteria, manuscripts comparing the clinical efficacy of denervation therapy and control agents, such as conservative therapies or sham operation, were included in this study. After reviewing the titles, abstracts, and the full text, 6 studies were included in the quantitative synthesis. Data, including postoperative pain scores, rate of 50% pain relief, and joint functional scores were extracted and combined to obtain effect size and statistical significance.

**Results:** In terms of postoperative pain intensity, denervation therapy showed significantly better short-term (4, 12, and 24 weeks) pain relief. The rates of 50% pain relief at 12 and 24 weeks after operation were also higher compared with the control group. In terms of joint functional improvement, denervation therapy showed favorable outcomes at 4 and 12 weeks after treatment, but no significant difference was found at 24 weeks after procedure between the groups. Overall, better results were reported in denervation therapy with a relative high-grade of evidence.

**Limitation:** Analyses of long-term (one year and longer) effects could not be conducted owing to a lack of existing studies.

**Conclusions:** Denervation of the knee joint may become a promising therapy for patients with knee OA who are refractory to conservative treatment. This therapy can provide short-term therapeutic effect in pain alleviation for 6 months and joint function recovery for 3 months. The therapeutic effect in joint function may decrease 6 months after operation. The long-term efficacy in pain remission and function improvement is still elusive and controversial; therefore, further research with larger sample sizes are needed in the future.

**Key words:** Osteoarthritis, denervation therapy, radiofrequency, chronic pain, function, systematic review, meta-analysis

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Knee osteoarthritis (OA) is a worldwide health problem that usually affects patients over age 45 years and has a relatively high prevalence rate of 40% (1-3). Patients with knee OA are always offered conservative treatments, such as physical therapy, medication, and injection therapy (4,5). These therapies confer temporary benefits, but long-term or repeated application may have significant adverse effects, particularly in the elderly. Moreover, patients with moderate and severe symptoms rarely respond well to these treatments. For patients who are refractory to conservative therapies, surgical interventions such as arthroplasty and total knee replacement are valid and reliable options in alleviating pain and improving function (6). However, the operations are also associated with significant expense, morbidity, mortality, and persistent pain after surgery (7,8). Despite years of effort, the management of pain is still challenging. Recently, denervation therapy has been applied clinically for treatment of knee OA (9,10). This therapy provides an alternative for patients insensitive to conservative therapies or unwilling to receive surgery and general anesthesia. However, therapeutic effect of this method, especially the long-term efficacy, is still controversial.

Denervation treatments are traditionally used to alleviate pain arising from the spinal facet, sacroiliac joints, or neuropathic pain including trigeminal neuralgia (11,12). The basic premise lies in accurate placement of the electrode nearby the targeted nerves responsible for transmitting pain sensation. Then, therapeutic instruments work by disrupting the transmission of pain signals through thermal lesion or cryoneurolysis (13,14). Sensory innervation of the knee joint comes from the tibial nerve, common peroneal nerve, femoral nerve, and obturator nerve. As these nerves are mixed nerve fibers, setting them as lesion targets is impractical. When these nerves approach the knee joint, they give off periarticular or intraarticular branches that are pure sensory nerves (15,16). Under the guidance of ultrasound or fluoroscopy, the lesion of these nerves is feasible and may provide analgesic effect without affecting motor function.

Following the first report in 2011 (9), there have been multiple publications in the last few years that suggest a role for denervation therapy in providing short-term analgesic benefits for patients with intractable knee OA (10,17-20). As destruction of the nerves with these methods is always reversible, the knee pain may recur as time extends. To date, the therapeutic efficacy of this treatment, especially the long-term outcomes, are still controversial (9,17,19). Therefore, the aim of the systematic review was to examine the efficacy on pain alleviation and functional recovery in the short and long term after applying denervation therapy to the genicular nerves of patients with OA with chronic knee pain.

## Methods

The protocol for this systematic review and meta-analysis was registered at PROSPERO (registration number is CRD42018043489).

### Search Strategy

We searched 3 databases (PubMed, EMBASE, and the Cochrane library) from inception to August 2018. For PubMed and EMBASE, both controlled vocabulary terms (PubMed, MeSH, EMBASE, Emtree) and text word searching were conducted for each of the following search segments: "denervation," "radiofrequency," and "knee osteoarthritis." Every search was restricted to the English language. The reference list of included studies and relevant reviews were also manually searched for additional articles.

### Eligibility Criteria

We included randomized controlled trials (RCTs) and nonrandomized controlled trials (non-RCTs) that met the following inclusion criteria: 1) full text study, whether published or unpublished; 2) patients aged > 60 years; 3) previous conservative treatments > 3 months; 4) pain visual analog scale (VAS) > 30 mm in 100 mm or 3 cm in 10 cm; 5) radiologic OA grade > 2 according to the Kellgren-Lawrence (K-L) grading system (0 = none, 1 = doubtful, 2 = minimal, 3 = moderate, and 4 = severe); and 6) investigated and reported measures of pain intensity and joint function of denervation therapy versus control agents (conservative treatment including analgesic medication, intraarticular steroid or hyaluronic acids injection, sham operation). We allowed cointervention if they were offered equally to both arms of the trial. Studies were excluded if they met the following criteria: 1) they included patients with mental handicaps or psychiatric conditions precluding adequate communication; 2) there was presence of any contraindication for the invasive interventions, such as coagulation disorders, systemic or local infection, presence of connective tissue disease; 3) patients had intraarticular steroid or hyaluronic acids during the previous 3 months; and 4) patients had previous knee surgery.

### Study Selection

Two review authors (W.R. and M.C.) scrutinized all the titles and abstracts identified by the searches to determine which might fulfill the selection criteria. We obtained full reports of all the potentially eligible studies to determine if they met the inclusion criteria for the review. We included RCTs or non-RCTs reporting the therapeutic effects of denervation treatment for OA. Any uncertainty or disagreements were resolved through discussion.

### Data Collection and Analysis

Two review authors (W.R. and M.C.) independently extracted the following relevant data: study design, source of patients, sample size, inclusion and exclusion criteria, demographic characteristics (age range, gender, course of disease), radiologic OA grade (K-L grading system), type of denervation method, treatment used in the control group, analgesic outcome (postoperative pain scores, rate of 50% pain relief) and functional improvement (Western Ontario McMaster Universities OA index total score or WOMAC), and adverse effects duration of study follow-up. If data were missing, authors were contacted a maximum of 3 times, after which the data were considered irretrievable. The review authors resolved disagreements through discussion.

### Quality and Risk of Bias Assessment

Two authors (W.R. and M.C.) independently assessed the risk of bias. For RCTs, we determined the risk of bias using the Cochrane Collaboration tool. The risk of bias was used as input for the assessment of the quality of evidence for each outcome measure. Studies were considered with high risk of bias when 3 or more items were scored unclear or high, or when 2 items were scored high (21). We used the tool ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) to assess the quality and bias of non-RCTs (22).

### Assessment of Heterogeneity and Publication Bias

We performed formal statistical testing of heterogeneity between the trials using the Cochrane statistical software RevMan 5.3. (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark). The heterogeneity was assessed by using the Cochran chi-square-based Q statistic and $I^2$ test ($I^2$ = 0-25% represents no heterogeneity; $I^2$ = 25%-50% represents moderate heterogeneity; $I^2$ = 50%-75% represents large heterogeneity; $I^2$ = 75%-100% represents extreme heterogeneity). The value of $I^2 > 50\%$ would be considered substantial heterogeneity (23,24). Potential publication bias was assessed using funnel plot and Egger's regression test for all included studies and each subgroup analysis.

### Statistical Analysis

We conducted meta-analysis using software RevMan 5 (The Nordic Cochrane Centre for The Cochrane Collaboration) for all extracted data. When a significant Q test ($P < 0.10$) or $I^2 > 50\%$ indicated heterogeneity across studies, the random-effects model was used for meta-analysis, otherwise the fixed-effects model was used. Based on this, we calculated the pooled postoperative VAS score, WOMAC score, and rate of 50% pain relief at each follow-up point with its 95% CI. As the number for meta-analysis was limited, we did not conduct subgroup analysis. All statistical tests performed in this study were 2-tailed, and $P < 0.05$ was taken as being statistically significant.

## Results

### Study Selection

The flowchart of search results and study selection is reported in Fig. 1. The search yielded 213 hits of potentially eligible articles. Of the 213 articles, 45 were duplicates. A total of 159 articles were excluded after checking the titles and abstracts. Based on the eligibility criteria, another 3 of the 9 manuscripts were excluded after the full texts were reviewed. The exclusions left 6 studies (9,17-19,25,26) for the systematic review and meta-analysis. We collected the characteristics and details of the clinical outcomes of the 6 included articles.

### Study Characteristics

Among the 6 included studies, 5 were prospective RCTs, and the remainder was a prospective non-RCT. Although many tools can be used for nerve ablation, the method used in included studies was only radiofrequency ablation. The comparison set for denervation therapy includes sham operation, genicular nerve block, conventional analgesic therapy, and intraarticular knee injection. In the study of Shen et al (25), intraarticular knee injection of platelet-rich plasma and hyaluronate was received by all patients from both groups. The sample size of studies ranged from 35 to 151. The total study population consisted of 408 patients. Approximately 72% of the study population were women. Average pain duration characteristics were reported in

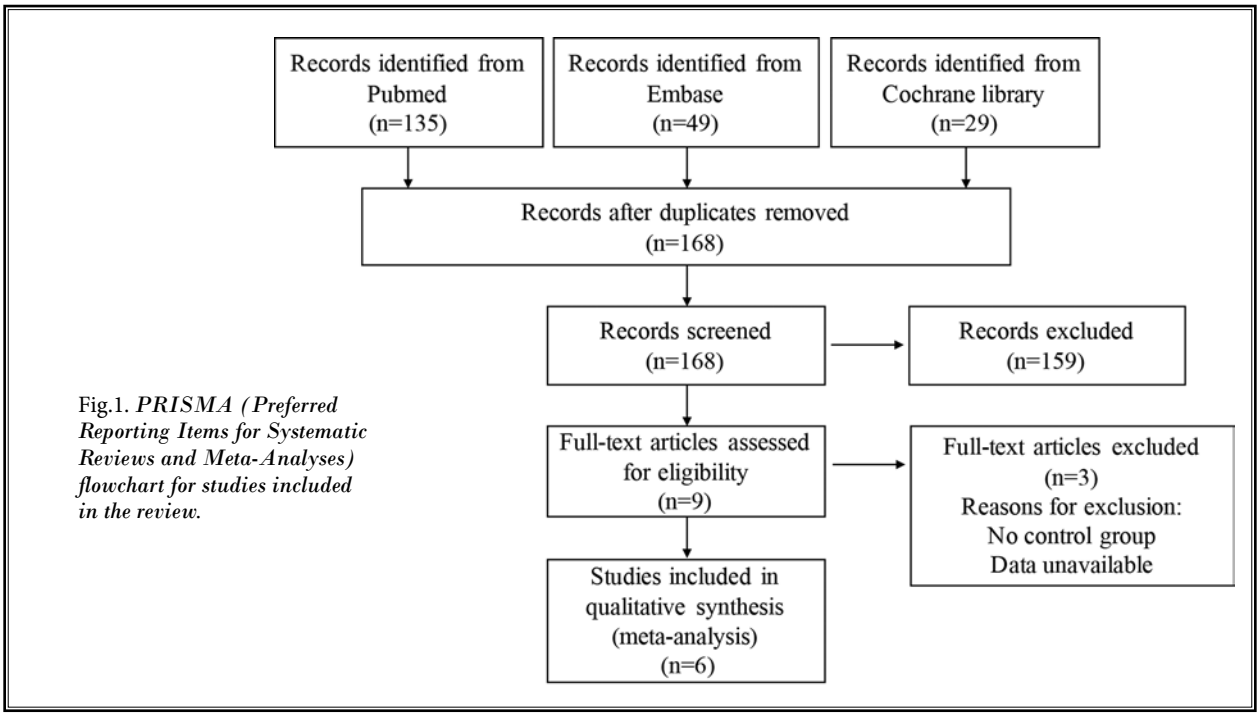


Fig.1. *PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for studies included in the review.*

Table 1. *Characteristics of patients within the included studies.*

| Study | Country | Sample Size (M/F) | Age, Years M (SD) | Course, Years M (SD) | Pain Intensity Before Treatment M (SD) | Follow-up Time Points (Weeks) |
|---|---|---|---|---|---|---|
| Ikeuchi et al (17) | Japan | 35 (4/31) | 77 (7.4) | 9.5 (6.6) | 57.5 (14.8)[a] | 4, 8, 12, 24 |
| Shen et al (25) | China | 54 (16/38) | 62.3 (9.9) | 5.0 (3.3) | 7.13 (1.04)[b] | 12 |
| El-Hakeim et al (19) | Egypt | 60 (21/39) | 59.4 (7.4) | 6.7 (4.3) | 7.0 (0.2)[b] | 2, 12, 24 |
| Choi et al (9) | Korea | 35 (5/30) | 67.2 (6.0) | 6.9 (3.9) | 77.7 (10.9)[a] | 1, 4, 12 |
| Sari et al (18) | Turkey | 73 (18/55) | 64 (9) | 5 (–) | – | 4, 12 |
| Davis et al (26) | USA | 151 (52/99) | 64.5 (12.6) | 10.0 (10.4) | 7.1 (1.3)[c] | 4, 12, 24 |

M/F, male/female; M (SD), mean (standard deviation).
[a]VAS from 0 to 100; [b]VAS from 0 to 10; [c]Numeric Rating Scale from 0 to 10.

studies and the means ranged from 5.0 to 10.0 years. The inclusion criteria for severity of knee OA differ. Two studies (17,19) included patients with knee OA with K-L grade 3-4 and 3 studies (9,18,26) recruited patients with K-L grade 2-4. Another one research did not describe the severity of knee OA. Table 1 and Table 2 provide the overview of participant characteristics and study characteristics.

## Methodological Quality and Risk of Bias

For 5 prospective randomized controlled studies, we used the Cochrane Collaboration tool to assess the methodological quality and risk of bias. Six domains of bias were evaluated, and the risk of bias summary is shown in Fig. 2. For the only one prospective non-randomized controlled study (17), we used ROBINS-I to assess the quality and bias. Because there was no blindness set to outcome assessor, the domain of "bias in measurement of outcome" was evaluated as moderate risk. The other 6 domains of bias were assessed as low risk. Integrating the results of all domains, the risk of bias in this nonrandomized controlled study is moderate.

## Assessment of Pain Alleviation after Denervation Therapy

No data concerning the long-term (one year and longer) pain relief effect of denervation treatment was

Table 2. *Characteristics of studies in the systematic review.*

| Study Details | Methods | Results | Conclusion |
|---|---|---|---|
| Ikeuchi et al (17)<br>Sample size = 35<br>Follow-up = 24 weeks<br>Prospective open-label controlled study<br>Knee OA, K-L grade 3-4 | Patients were assigned for genicular nerve RF treatment (RF group) and nerve block using local anesthesia (control group) according to the time they were referred to the hospital.<br>Outcomes were assessed with VAS, WOMAC scale, percentage of responder (≥50% decrease in pain intensity), and patient's global assessment. | RF group averaged significantly lower VAS scores than the control group for 12 weeks.<br>No significant difference between 2 groups on the WOMAC total score throughout the treatment cycle.<br>Percentage of responders was significantly higher in the RF group at 4, 8, and 12 weeks compared with the control group.<br>There was no significant difference in patient's global assessment between the RF and control groups at 24 weeks after treatment. | RF treatment for refractory anteromedial knee pain was effective for 2-3 months although all the patients were candidates for total knee arthroplasty. |
| Shen et al (25)<br>Sample size = 54<br>Follow-up = 12 weeks<br>Prospective RCT | Enrolled patients were randomly allocated into case group (genicular nerve RFTC plus injection of platelet-rich plasma and sodium hyaluronate) and control group (injection of platelet-rich plasma and hyaluronate).<br>Pain intensity, life quality, and knee function were assessed with VAS, SF-36 scale, and AKSS. | At 3-month follow-up, VAS scores of both groups apparently decreased compared with baseline. Case group scored much lower than control group.<br>At 3-month follow-up, case group scored significantly higher in physical functioning, bodily pain, general health perceptions, and vitality than controls, but not in physical role functioning, social role functioning, emotional role functioning, and mental health.<br>At 3-month follow-up, cases had significantly higher scores in pain, range of motion, stability, walking, and stair climbing than controls. | We strongly recommended the use of RFTC in the treatment of patients with knee OA for its beneficial role in relieving pain and improving the knee function and life quality. |
| El-Hakeim et al (19)<br>Sample size = 60<br>Follow-up = 24 weeks<br>Prospective single-blind RCT<br>Knee OA, K-L grade 3-4 | Patients were randomly allocated into one of 2 groups: Group A, RF ablation of genicular nerves; Group C, conventional analgesic therapy.<br>All patients were assessed by VAS for pain, WOMAC for disability (25), and Likert scale for patient satisfaction. | Follow-up VAS scales in both groups showed significant decreases when compared with basal value.<br>VAS values were significantly lower in Group A than Group C during the whole follow-up period.<br>The WOMAC index and its domains showed significant decreases compared with their basal value in each Group. The total WOMAC index showed significant differences by the sixth month only, with lower values in Group A.<br>WOMAC domains (pain and stiffness) showed significant differences in the third and sixth months, with lower values in Group A. WOMAC domain of difficulties was significantly lower in Group A in the sixth month.<br>Likert scale showed significantly higher values in Group A than Group C in the third and sixth months. | Radiofrequency is a safe and effective modality for pain alleviation. It can decrease joint stiffness and disabilities in patients suffering chronic knee OA. |
| Choi et al (9)<br>Sample size = 35<br>Follow-up = 12 weeks<br>Prospective double-blind RCT<br>Knee OA, K-L grade 2-4 | Patients were randomly assigned to receive percutaneous RF genicular neurotomy (RF group) or the same procedure without effective neurotomy (control group, sham operation)<br>Outcomes were assessed by VAS, the proportion of patients achieving at least 50% knee pain relief, OKS scale, and GPE. | Compared with baseline, VAS scores were lower at all postprocedure assessment points in the RF group, but only at one week in the control group. The RF group showed superior improvement compared with the control group at both 4 and 12 weeks. Many more patients in the RF group than the control group achieved at least 50% knee pain relief at 12 weeks.<br>The RF group OKS scales and patient satisfaction (GPE) were better than the control group at 4 and 12 weeks. | RF neurotomy of genicular nerves seems a safe, effective, and minimally invasive therapeutic procedure for patients with chronic knee OA with a positive response to diagnostic block. RF neurotomy can also be repeated if necessary. |
| Sari et al (18)<br>Sample size = 73<br>Follow-up = 12 weeks<br>Prospective RCT<br>Knee OA, K-L grade 2-4 | The patients were randomly assigned to undergo a genicular nerve RF neurotomy (Group RF) procedure and the intraarticular knee injection (Group IA).<br>Outcome was assessed with VAS and WOMAC. | At the first month and third month, scores of VAS, WOMAC total, and WOMAC subgroups in both groups were significantly lower than baseline.<br>Compared with Group IA, a significant reduction was observed in VAS and WOMAC total scores at the first month and VAS at the third month in the RF Group, as well as a significant healing in WOMAC stiffness scores at the third month and in physical function at the first month. | RF genicular neurotomy could be a safe and efficient treatment method that provides functional improvement and effective analgesia for elderly patients with OA. |

Table 2 (cont.). *Characteristics of studies in the systematic review.*

| Study Details | Methods | Results | Conclusion |
|---|---|---|---|
| Davis et al (26)<br>Sample size = 151<br>Follow-up = 24 weeks<br>Prospective RCT<br>Knee OA, K-L grade 2-4 | The patients were randomly assigned to undergo cooled radiofrequency ablation procedure (CRFA Group) and the intraarticular steroid injection (IAS Group).<br>Outcome was assessed with proportion of patients whose knee pain was reduced by 50% or greater, NRS, OKS, and GPE score. | Within both study groups at 1, 3, and 6 months, mean pain score was reduced compared with baseline.<br>At each follow-up interval, mean NRS was less in the CRFA Group than in the IAS Group, and mean reductions in the average NRS scores from baseline were greater in the CRFA Group. More patients of the CRFA Group reported ≥50% NRS reduction at 6 months.<br>Mean OKS improved at all endpoints within both study groups compared with baseline scores. The mean OKS were greater in the CRFA Group than in the IAS Group at 1, 3, and 6 months.<br>Compared with the IAS Group, a higher proportion of patients in the CRFA Group reported improved GPE at 3 and 6 months, but no difference at one month. | Cooled radiofrequency ablation is a safe and effective nonopioid option for managing pain and improving physical function and quality of life for patients with OA-related knee pain compared with IAS injection. |

AKSS, American Knee Society Score; GPE, Global Perceived Effect; NRS, Numeric Rating Scale; OKS, Oxford knee scores; RF, radiofrequency; RFTC, radiofrequency thermocoagulation; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.

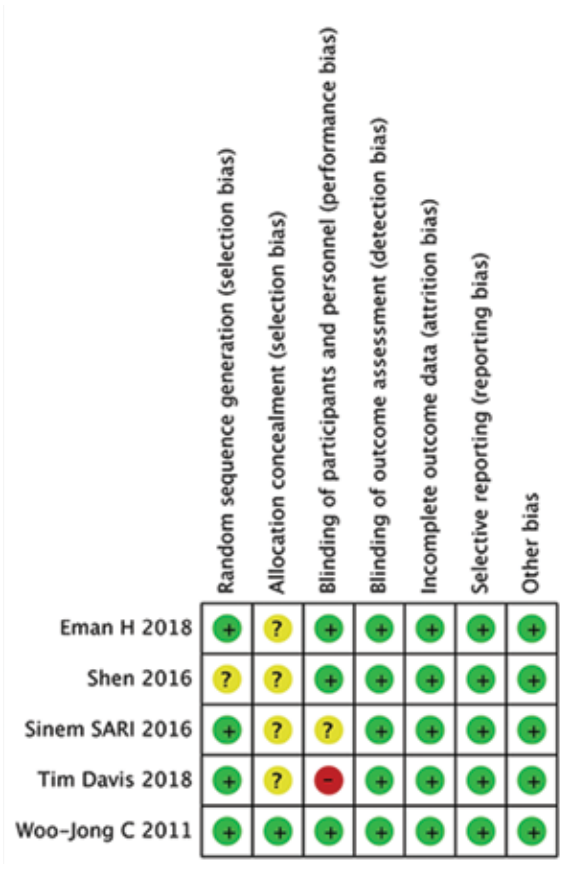


Fig. 2. *Risk of bias summary for randomized controlled studies.*

found in the included studies. Data of pain intensity 4, 12, and 24 weeks after operation was collected and reviewed. Three pain scores were used in the studies, including VAS (0-10), VAS (0-100), and Numeric Rating Scale (0-10).

Three studies provided the data regarding pain intensity 4 weeks after operation (9,17,26). Compared with baseline, postinterventional pain intensity significantly improved in the experimental group from 3 studies (9,17,26) and the control group (intraarticular steroid injection) from one study (26) (Table 2). We compared the postoperative pain intensity between the experimental and control group using a random-effects model, finding that patients in the experimental group who underwent denervation therapy averaged apparently lower pain scores than the control group (standardized mean difference [SMD]: –1.17; 95% confidence interval [CI]: [–2.26, –0.07]; $P = 0.04$; $I^2 = 89\%$; $P = 0.0001$) (Fig. 3).

A total of 5 studies (9,17,19,25,26) provided pain intensity scores 12 weeks after operation. Compared with baseline, patients in the experimental group from all studies experienced significant pain relief after intervention, whereas patients from only 3 control groups (19,25,26) received obvious pain alleviation. Data of postoperative pain intensity were pooled using a random-effects model and compared between the experimental and control group, finding that patients in the experimental group who received denervation therapy averaged significantly lower postinterventional pain scores (SMD: –1.24; 95% CI: [–1.90, –0.59]; $P < 0.00001$; $I^2 = 32\%$; $P = 0.21$) (Fig. 4).

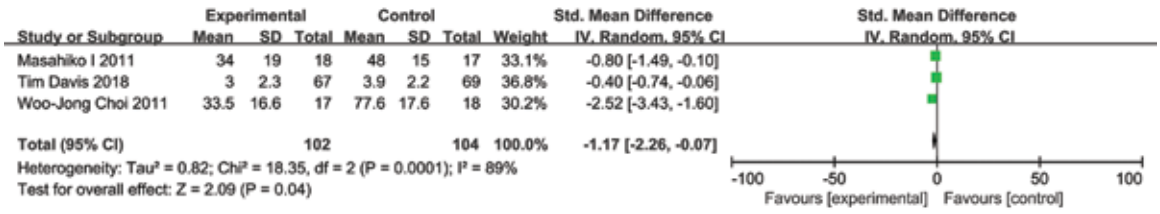


Fig. 3. *Pain intensity scores 4 weeks after intervention (VAS 0-100 was used in study Ikeuchi et al (17) and study Choi et al (9), Numeric Rating Scale 0-10 was used in study Davis et al (26)). Patients in the experimental group averaged significantly lower pain scores than the control group.*

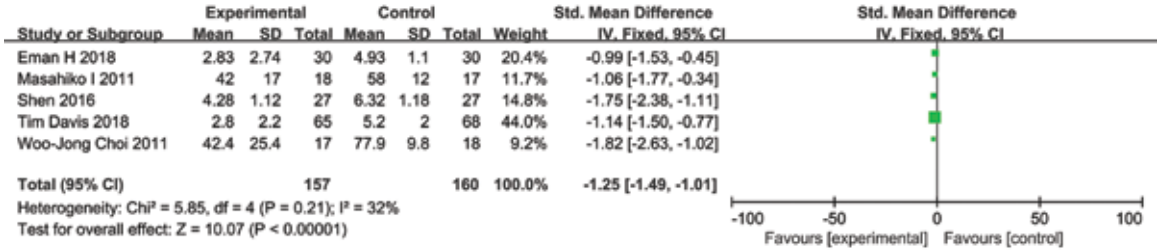


Fig. 4. *Pain intensity scores 12 weeks after intervention (VAS 0-100 was used in study Ikeuchi et al (17) and study Choi et al (9), VAS 0-10 was used in study El-Hakeim et al (19) and study Shen et al (25), Numeric Rating Scale 0-10 was used in study Davis et al (26)). Patients in the experimental group averaged significantly lower pain scores than the control group.*

A total of 3 studies provided the data regarding pain intensity 24 weeks after operation (17,19,26). Compared with basal value, pain intensity significantly improved after treatment in both the experimental group and the control group from 2 studies (19,26). We pooled postoperative pain scores using a random-effects model and compared the scores between the experimental and the control group, finding that patients in the experimental group who received denervation therapy scored significantly lower (SMD: –1.25; 95% CI: [–1.49, –1.01]; $P = 0.0002$; $I^2 = 76\%$; $P = 0.01$) (Fig. 5).

Fifty percent pain relief is another good index for assessing therapeutic effect after treatment. It was defined as a 50% or greater decrease in the pain score or the WOMAC pain subscale. Two studies (9,17) provided information about this index 12 weeks after treatment. Rates of 50% pain relief were 5.9% (1/17) and 0% (0/18) in the control groups, whereas the numbers were 33.3% (6/18) and 58.8% (10/17) in the experimental groups. Two studies (17,26) reported this rate 24 weeks after treatment. Rates of 50% pain relief were 0% (0/17) and 16.4% (11/67) in the control groups, whereas in the experimental groups the numbers were 5.5% (1/18) and 74.1% (43/58). We pooled the data using a random-effects model. The results indicated that the proportion of patients who had 50% pain relief was obviously higher in the experimental group than the control group at 2 follow-ups (12 weeks: [relative risk (RR): 10.96; 95% CI: (2.22, 54.21); $P = 0.003$; $I^2 = 0$; $P = 0.42$]; 24 weeks: [RR: 4.44; 95% CI: (2.55, 7.71); $P < 0.00001$; $I^2 = 0$; $P = 0.78$]) (Figs. 6 and 7).

## Assessment of Knee Functional Improvement after Denervation Therapy

We used the WOMAC total score to assess the functional improvement of the knee. Two studies (17,18) reported postinterventional WOMAC total score 4 weeks after treatment, but the results were different. The study of Sari et al (18) reported a significantly lower postinterventional WOMAC total score in the experimental group, but no obvious difference was found in the study of Ikeuchi et al (17). Using a random-effects model, the pooled data showed that postoperative WOMAC total score of patients in the experimental group who underwent denervation therapy was lower than the control group (SMD: –0.75; 95% CI: [–1.15, –0.36]; $P = 0.0002$; $I^2 = 0$; $P = 0.66$] (Fig. 8).

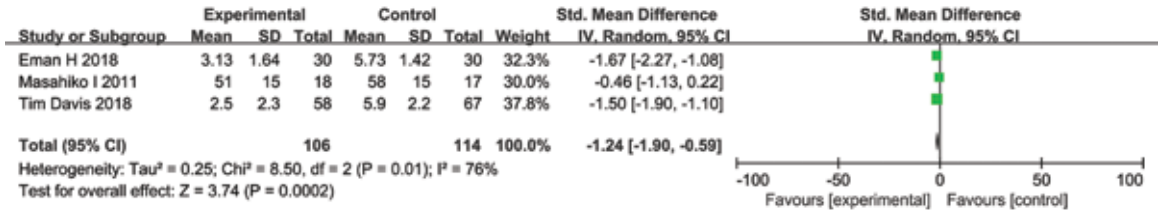


Fig. 5. *Pain intensity score 24 weeks after intervention (VAS 0-100 was used in study Ikeuchi et al (17), VAS 0-10 was used in study El-Hakeim et al (19), Numeric Rating Scale 0-10 was used in study Davis et al (26)). Patients in the experimental group averaged significantly lower pain scores than the control group.*

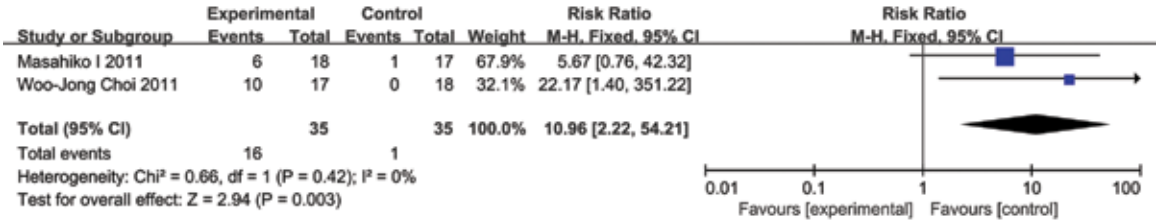


Fig. 6. *Proportion of patients who received 50% or greater pain relief compared with preintervention (12-week follow-up data). The proportion was significantly greater in the experimental group.*

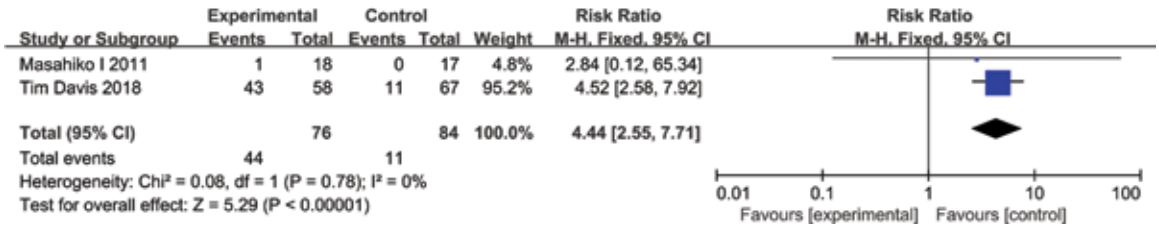


Fig. 7. *Proportion of patients who received 50% or greater pain relief compared with preintervention (24-week follow-up data). The proportion was significantly greater in the experimental group.*

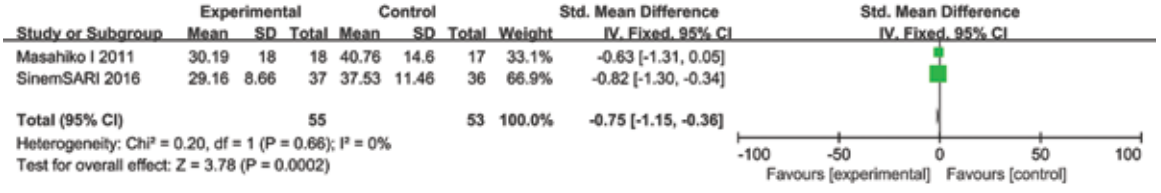


Fig. 8. *WOMAC score 4 weeks after intervention. Postinterventional WOMAC total score was significantly lower in the experimental group than the control group.*

Three studies (17-19) reported postinterventional WOMAC total score 12 weeks after treatment whose results differ from each other. Research of Ikeuchi et al (17) and Sari et al (18) found that there was no significant difference in postinterventional WOMAC total score between groups. However, El-Hakeim et al (19) reported obvious lower WOMAC total score after treatment in the experimental group. We pooled data using a random-effects model, finding that postoperative WOMAC total score in patients in the experimental group was lower than the control group (SMD: –0.42; 95% CI: [–0.73, –0.12]; $P = 0.007$; $I^2 = 0$; $P = 0.45$) (Fig. 9).

Two studies (17,19) reported postinterventional WOMAC total score 24 weeks after intervention. There was no significant difference between groups in the study of Ikeuchi et al (17). However, El-Hakeim et al (19) reported obvious lower postinterventional WOMAC total score in the experimental group. Data were pooled and compared between groups using a random-effects model, and there was no significant difference between groups (SMD: –0.39; 95% CI: [–0.80, 0.02]; $P = 0.06$; $I^2 = 26\%$; $P = 0.25$) (Fig. 10).

## Discussion

Health care for knee OA has mainly been provided via physiotherapy, medication, and intraarticular injection (27,28). Despite efforts to develop more rational therapeutic methods, platelet rich plasma (29) and stem cells (30) included, treatment for patients with moderate or severe knee OA has still been challenging. Denervation therapy has been applied clinically for treatment of knee OA since 2011 (9). This therapy provides clinicians an alternative for patients who are refractory to conservative treatment or unwilling to have surgery. Compared with knee replacement, denervation treatment is less traumatic and costs less. Additionally, the ultrasound-guided denervation treatment is nonradiative and as accurate-targeting as fluoroscopy (31-33). Several controlled studies have suggested the short-term efficacy of this treatment for alleviating pain. However, the therapeutic efficacy on pain intensity and joint function, especially the long-term effect, is still controversial. Therefore, the differing results urged us to conduct this systematic review and meta-analysis.

### Summary of Main Results

To the best of our knowledge, this meta-analysis is the most comprehensive and detailed study focused on the therapeutic effect of denervation treatment for refractory knee OA. Six prospective controlled studies were included in the review. Of these 6 studies, 5 were RCTs, and one was a non-RCT. In the search results, 2 methods

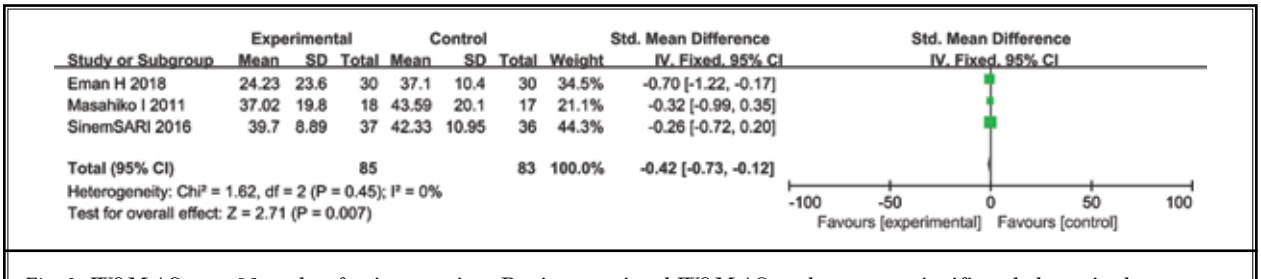


Fig. 9. *WOMAC score 12 weeks after intervention. Postinterventional WOMAC total score was significantly lower in the experimental group than the control group.*

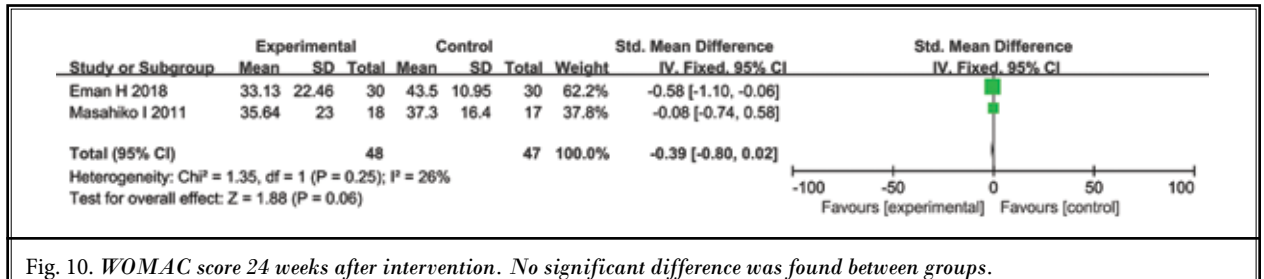


Fig. 10. *WOMAC score 24 weeks after intervention. No significant difference was found between groups.*

of denervation (thermal lesion and cryoneurolysis) were used (10,13,34). However, only radiofrequency thermocoagulation was applied in studies included in the final review. Compared with control groups (analgesic or intraarticular injection, sham operation), radiofrequency thermocoagulation of innervation of the knee joint can relieve chronic pain secondary to OA and improve function in a relatively short period.

### Pain Scores

The longest follow-up duration was 6 months. The outcome of pain relief at 4 weeks and 12 weeks in all included studies was consistent, but not at 24 weeks after operation. We combined postoperative pain scores at 4, 12, and 24 weeks after intervention from included studies. The forest plots for these 3 time points suggested that patients receiving denervation therapy had significantly better pain relief compared with the control groups. In the study of Ikeuchi et al (17), no significant difference was found in pain intensity at 24 weeks postoperation, leading to the controversy about the effect of denervation therapy. This outcome may also indicate a trend that the efficacy of pain alleviation may gradually recede as time extends.

A pain reduction of approximately 50% is commonly thought to be a good therapeutic outcome. It was obviously higher in the experimental group at 12 and 24 weeks after treatment. Because the rate was provided in only 2 studies, of which one weights too large (Figs. 6 and 7), there is a low level of confidence in the meta-analysis for rate of 50% pain relief. This low confidence level could increase the risk of random error, which may lead to a false conclusion.

### Joint Function

During the period of follow-up, the effect of denervation therapy in joint function improvement was not consistent among the included studies. At the time point of 4 weeks and 24 weeks, the results of 2 studies were combined. The WOMAC scale at 12 weeks after operation from 3 studies were pooled. The forest plots for these 3 time points suggested that denervation treatment significantly improved joint function at 4 weeks and 12 weeks, but not at 24 weeks. This result is not the same as previous studies, which showed positive outcomes in functional improvement at 24 weeks (13,35). As the sample number in our analysis is still small, there is a low level of confidence for this result.

### Limitations

There were some limitations to this systematic review. Two studies included patients with knee OA with K-L grade 3-4 and 3 studies recruited patients with K-L grade 2-4. Another one research did not describe the severity of knee OA. The severity of knee OA in patients included in different studies varies, which may be a confounding when conducting meta-analysis. Additionally, the comparisons in different researches vary, including sham operation, conventional analgesics, genicular block, and intraarticular injection therapy. The therapeutic effect of these treatments was different. It would be better if the comparisons were unified. As the included patients were those resistant to conservative therapy, assigning them to these treatments again in the study is still worth considering. Moreover, the statistic difference between pre- and postinterventional pain intensity is not equal to difference in clinical effect, whether pain improvement in pain intensity reached the minimally clinical important difference was not reported in studies.

Only 6 studies were finally included in the review, which was relatively small. We planned to observe the long-term effect of this therapy and whether it could postpone or avoid the reception of total knee arthroplasty. However, the duration of follow-up in all studies was relatively short. Several different scales for knee joint were used in the studies, making it impossible to combine all data. In addition, we should pay attention to the possibility that denervation may aggravate the degeneration of the knee. Therefore, to observe the clinical effect of knee joint pain in patients receiving the denervation, we still need longer observations and more homogeneous studies.

## Conclusions

Denervation of the knee joint may become a promising therapy for patients with knee OA who are refractory to conservative treatment. Based on results of meta-analysis, this therapy can provide short-term therapeutic effect in pain alleviation for 6 months and joint function recovery for 3 months. The therapeutic effect in joint function may decrease 6 months after operation. The long-term efficacy in pain remission and functional improvement is still elusive and controversial; therefore, further research with larger sample sizes are needed in the future.

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