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Systematic Review

The Analgesic Effectiveness of Genicular Nerve-targeted Cooled and Pulsed Radiofrequency Ablation for Osteoarthritis Knee Pain: A Systematic Review and Meta-analysis

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Background: Radiofrequency ablation (RFA) is a form of therapy for knee osteoarthritis (OA) pain that has become more popular in recent years. In addition to standard RF approaches, there are cooled and pulsed options. RFA could be used to treat the superolateral, superomedial, and inferomedial branches of the genicular nerves. Pulsed and cooled RF ablation on the genicular nerve to treat knee OA pain, however, has not yet been shown to be effective.

Objectives: We conducted a meta-analysis to assess nonconventional, pulsed or cooled, RFA on the genicular nerve to treat knee OA pain; intended our study to provide useful information in deciding whether to use nonconventional RFA because of its effectiveness.

Study Design: Meta-analysis study of nonconventional, pulsed or cooled, RFA on the genicular nerve to treat knee OA pain.

Methods: PubMed, Ovid MEDLINE, Scopus, and Cochrane Central were searched for eligible papers. In our literature review, procedures, posttreatment outcomes, follow-up data, and adverse events were compiled and analyzed from the selected studies. The National Heart, Lung, and Blood Institute Quality Assessment tool was used to assess therapeutic relevance and evidence strength. Our meta-analysis analyzed pre- and posttreatment pain and physical function scores. The primary outcome was pain measured with either the Visual Analog Scale or the Numeric Rating Scale. The secondary outcome was physical function measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.

Results: Our systematic review and meta-analysis includes 11 eligible publications (604 patients). Both cooled and pulsed RFA procedures targeting the genicular nerve resulted in considerable pain reduction at post one, 3, 6, and 12 months ($P < 0.005$). There was no significant improvement in physical function outcome for the cooled RFA technique in all follow-up visits. There was a significant improvement in physical function outcome for the pulsed RFA technique at the one-month and 3-month follow-up visits.

Limitations: Limitations include that there are a limited number of randomized controlled trials available, the methodology utilized for comparison is based on the change in outcome between baseline and follow-up visits. There are only a few papers that have reported physical function outcomes in complete WOMAC rating data.

Conclusion: At the 6-month follow-up, both cooled and pulsed RFA targeting the genicular nerve provided significant osteoarthritic pain alleviation. There is no different in pain relief between cooled and pulsed RFA targeting the genicular nerve for treating knee osteoarthritis. There was no significant functional improvement of cooled RFA in all follow-ups, but there was a significant functional improvement of pulsed RFA up to 3-month follow-up. According to our study, knee osteoarthritis pain can be efficiently treated with pulsed and cooled radiofrequency with few adverse effects.

Key words: Radiofrequency, pulsed radiofrequency ablation, cold radiofrequency ablation, pain intervention, osteoarthritis, genicular nerve

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Osteoarthritis (OA) is a degenerative joint disease that can lead to disability (1). Osteoarthritis is a chronic progressive degenerative disease whose etiology is unknown. Risk factors—including age, obesity, physical activity, and other genetic factors—influence this disease (1). Based on data from the World Health Organization, the global prevalence of OA is 9.6% in men and 18% in women older than 60 years. In Indonesia, the prevalence of OA reaches 15.5% (± 39 million) in men and 12.7% (± 32 million) in women from the total population of 255 million people (2,3). The high OA prevalence, plus the disease, can cause disability, limited activities of daily living, and limited joint motion due to pain;, these greatly influence society and the economy (2,4).

There is no agreed-upon therapy or procedure that can prevent the damage caused by OA. Current treatments such as physiotherapy, anti-inflammatory drugs, viscosity supplements, and interventional pain procedures using radiofrequency ablation (RFA) are symptomatic treatments aimed to relieve pain. Because the knee has such a complicated innervation, locating the exact nerve and relieving pain is challenging (5). Choi, et al (6) targeted 3 genicular nerve branches: the superolateral, superomedial, and inferomedial. They showed these branches to be a target for RFA (6). Fluoroscopy or ultrasound guidance was used to perform these procedures.

The conventional RFA method uses a low-risk, high-temperature probe to target specific sensory nerves that innervate the tissue. Choi, et al (6) were the first to introduce RF to treat knee OA, and it was further investigated in the following years. Besides the conventional technique, there are cooled and pulsed RF techniques which have also gained popularity. Cooled RFA is a unique method that employs conventional mechanisms to produce larger, local neuronal damage (7). Cooled RFA removes heat by pumping water inside the probe, lowering the tissue's thermal heat to around 60°C – 70°C. 'It is possible that the ability to target more neuronal tissue results in long-term pain remission and effectiveness (8). Pulsed RFA has been presented as an alternative to conventional RFA. In this technique, to prevent any unwanted complications and irreversible tissue damage, the tissue temperature reaches a maximum of 42°C (9,10). In pulsed RFA, the generator produces a pulse with 45 V amplitude for 20 milliseconds every 500 milliseconds. In a previous study, the pulsed RFA may have similar effects and the disruption is often reversible (11). So, the pulsed RFA may cause a recurrent pain effect or may develop deafferentation pain that is difficult to manage (12,13).

Our study aimed to examine the effectiveness of pulsed and cooled RF on targeted genicular nerve in patients with knee osteoarthritis. Our primary and secondary outcomes were pain and physical function effectiveness, respectively. A recent meta-analysis found that utilizing RFA to treat knee pain for 6 months reduced pain and improved joint function for 3 months (14).

In a prior meta-analysis (15), no differences were found among conventional, cooled, and pulsed RF for pain alleviation. Targeted nerve or location heterogeneity in this meta-analysis potentially resulted in inconsistencies in the effectiveness of the same RFA procedure across different studies, thus reducing its reliability (15). They also did not provide physical function as a secondary outcome (15).

We used meta-analysis to assess nonconventional, pulsed or cooled, RFA on the genicular nerve to treat knee OA pain. We intended this study to provide useful information for deciding whether to use nonconventional RFA because of its effectiveness.

Methods

Search Strategy

This study adhered to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We searched related articles from 4 electronic databases through January 10th, 2022. The databases were PubMed, the Cochrane Library, Scopus, and Ovid MEDLINE. The search query utilized included the keywords "genicular nerve radiofrequency" and "knee osteoarthritis" or "OA knee" to retrieve relevant articles. Key word combinations were utilized to identify relevant articles from the 4 databases. We removed duplicate articles and screened eligibility indicators. In order to conduct a screening analysis, the pertinent references from the included studies were manually searched to address our specific issue.

Eligibility Criteria

The articles were deemed eligible based on the following criteria: (a) the effectiveness of pulsed or cooled RFA was assessed; (b) studies that were conducted to investigate the use of RFA in targeting the genicular nerve; (c) patients with knee OA were included in the study; (d) pain levels were assessed using either the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS-11); (e) a physical function outcome score was utilized to evaluate the physical function level of the patients. In addition, articles must be written in English.

Articles were excluded based on the following criteria: (a) traditional RFA investigations; (b) studies conducted on animals or cadavers; (c) articles written by editors; (d) correspondences addressed to the editor; (e) evaluations of existing literature; (f) summaries of presentations given at conferences; (g) no outcomes were observed with regards to VAS or NRS-11 scores.

Types of Outcomes

The primary outcome: our study evaluates the effectiveness of genicular nerve RFA in alleviating knee pain associated with OA. We employed 2 different pain rating scales, namely the VAS and the NRS-11, to measure the analgesic effectiveness of the treatment. The VAS and NRS-11 are commonly employed for evaluating pain intensity. In the context of our meta-analysis, it is possible to utilize these 2 scales interchangeably.

Secondary outcome: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used in our study to analyze the physical function outcomes after genicular nerve RFA to treat knee OA pain.

Data Extraction

The articles included in our study were analyzed for various data such as the name of the first author, publication year, sample size, mean age, type of RFA procedures, measurements of outcomes, follow-up periods, and reported adverse events. In cases where the mean and SD could not be extracted from the papers listed, efforts were made to establish communication with the corresponding authors via email.

Quality Assessment

The methodological quality of each article was evaluated utilizing the clinical relevance scale of the National Heart, Lung, and Blood Institute (NHLBI), as well as the methodology for quality assessment of controlled intervention studies and quality assessment for pre-post studies without a control group, for case report and case series studies.

Statistical Analysis

We conducted 2 analyses: one for pain outcome and one for physical function outcome. The aforementioned data were divided into distinct subcategories, based on the duration of the follow-up period, in order to facilitate subgroup analysis. The study's follow-up periods were categorized into 4 distinct intervals: one month (equivalent to 3 - 4 weeks), 3 months, 6 months, and 12 months.

We utilized standardized mean difference (SMD) and 95% CI in order to evaluate the effectiveness of treatment for decreasing pain levels pre- and posttreatment. We used mean difference (MD) and 95% CI to evaluate the outcome. The I^2 statistic and χ^2 test were applied to determine article heterogeneity. The heterogeneity among included papers was evaluated with the I^2 score and χ^2 score. If heterogeneity is existed (I^2 score > 50% or a *P* value of the χ^2 test < 0.05) , then a random-effects model was utilized to calculate the effect size. Otherwise, a fixed-effect model was adopted. We used RevMan 5.1 (The Nordic Cochrane Centre for The Cochrane Collaboration) to conduct the statistical analyses.

Ethical Approval

Our study did not raise any issues regarding the privacy or safety of the patients. Thus, human or animal ethical approval was not required.

Results

Literature Review

After implementing an automated procedure to eliminate ineligible records, a total of 177 records were retrieved from 4 databases: consist of 102 from PubMed, 40 from Ovid MEDLINE, 28 from Scopus, and 7 from the Cochrane Library (Fig. 1). Forty-five duplicates were identified and subsequently excluded, while 69 records were manually labelled as ineligible. Title and abstract analyses were used for screening the remaining 63 articles. A total of 19 reports were retrieved and screened by full-text analysis resulting in 5 records being excluded. Three articles did not provide specific outcomes and the others were not original research. Finally, our systematic review identified 14 eligible publications, but three studies did not provide comprehensive data, so we included the remaining 11 studies in our meta-analysis.

Main Characteristics

From 2015 through 2021, 14 qualitative reviews and 11 quantitative synthesis publications (with 604 patients) were published (Table 1). They were all published in English. This study involved the treatment of a total of 14 patients, with 8 patients receiving cooled RFA and 6 patients receiving pulsed RFA. The RFA procedure involved targeting genicular nerves in all of the approaches utilized. Each study utilized 9 fluoroscopy and 5 ultrasound imaging methods. All patients presented symptoms of pain related to OA in the knee joint. The study population exhibited an age range of 47.78 to 75.3 years old. Eight studies used the VAS while 6 used the NRS-11 to evaluate pain levels. The follow-up period varied from one week to 12 months. While 3 studies reported adverse events, there were 9 studies that reported no adverse events. In those 3 studies, 31 patients had minor adverse events such as pain, numbness, stiffness, and postprocedure edema.

Quality Assessment

Each study's quality was evaluated using the NHLBI for clinical relevance scale (Table 2), quality assessment of controlled intervention studies (Table 3), and quality assessment for before-after (pre-post) studies with no control group studies (Table 4). In our meta-analysis, however, we did not include a control group. All studies described their patients in detail to permit comparison of interventional pain practices.

For all studies, patients with knee OA were diagnosed based on radiographic evaluation. All articles described the intervention and treatment setting with clarity. All of the studies measured and reported clinically relevant outcomes; none of them reported any conflicts of interest. To assess the outcome, all studies relied on self-reported data. Moreover, they all reported that the benefit of the intervention and treatment outweighed the potential and reported harms. All of the studies were conducted over more than one week of follow-up periods. the comparability was not assessed however, we still assessed controlled and noncontrolled intervention studies for qualitative synthesis.

For the methodological quality assessment of the controlled interventional studies, there were 9 studies described as a randomized trial; all of them had adequate randomization with the treatment groups blinded to participants and providers (Table 3). All of the groups were equal in important

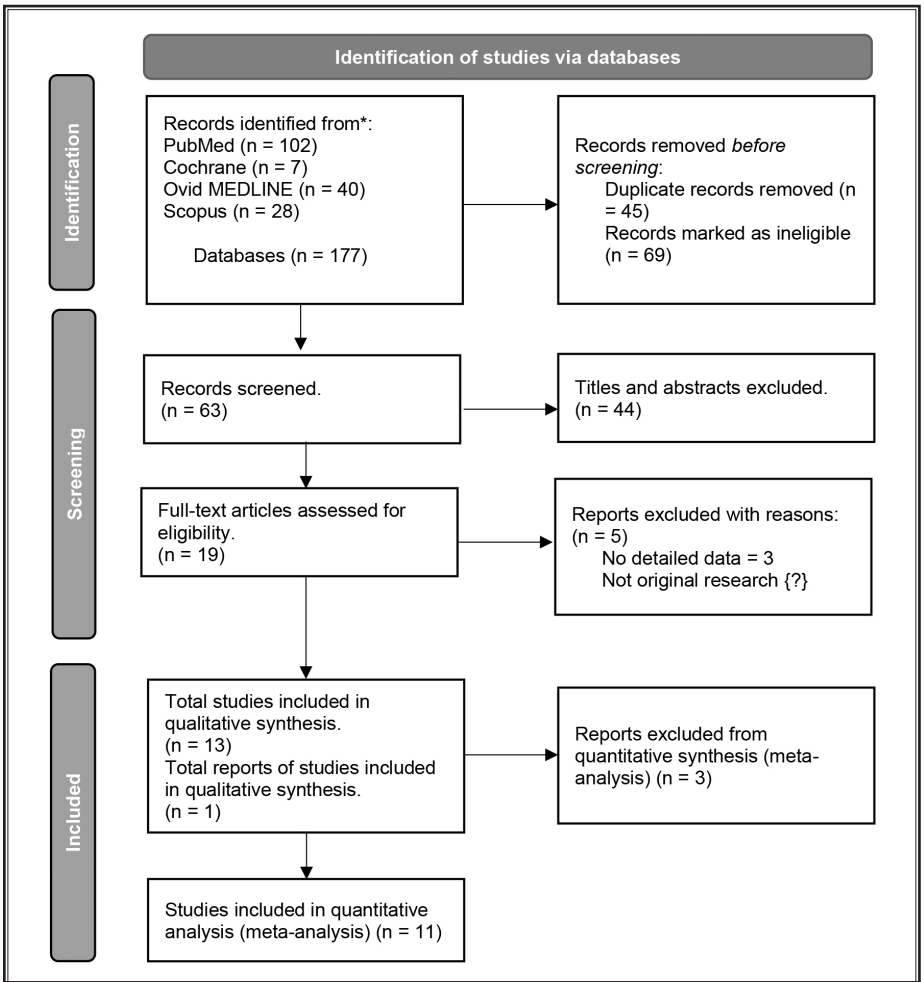


Fig. 1. *PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened and the full texts retrieved*

Table 1. *Main characteristics of the articles included in this study.*

No	Author	Year	Study Design	Size (N)	Mean Age	RFA Method	Imaging Modality	Nerve Target	Follow-up	Scoring Method	Results	Adverse events
1	Bellini and Barberi (25)	2015	retrospective case series	9	72 (46-91)	cooled RFA	fluoroscopy	genicular	1, 3, 6, 12 mos	VAS, WOMAC	Treatment significantly improved knee pain and QOL at all follow-ups	none reported
2	McCormick et al (28)	2017	cross-sectional survey and retrospective chart review	33	66 (62-77)	cooled RFA	fluoroscopy	genicular	8 (6-10) mos	NRS, PGIC, MQS III,	19% resulted in complete pain relief,	none reported
3	Reddy et al (29)	2016	prospective case series	4	64.5 (63-66)	cooled RFA	fluoroscopy	genicular	6, 12 mos	NRS, MQS III	80%-100% improvement in knee pain, improved daily function including walking and climbing stairs, improved MSQ III scores	none reported
4	Davis et al (24)	2018	randomized controlled trial	76	63 (SD=12)	cooled RFA	fluoroscopy	genicular	1, 3, 6 mos	NRS, OKS, GPE	CRFA group had more favorable outcomes in NRS, OKS, pain reduction, and GPE	none reported
5	Chen et al (16)	2020	randomized controlled trial	89	63.3 (SD=10.7)	cooled RFA	fluoroscopy	genicular	1, 3, 6, 12 mos	NRS, WOMAC, GPE	significantly reduced pain, significantly better improvement WOMAC score at 6 months follow up, significantly better general health	18 minor adverse events (numbness, stiffness, swelling, post procedure pain)
6	Rayamajhi et al (30)	2021	cross sectional study and retrospective chart review	30	68.10 (SD=11.17)	cooled RFA	ultrasound	genicular	1, 6 mos	NRS	significantly reduced pain in all follow-ups	N/A
7	Kocayigit and Beyaz (31)	2021	retrospective study	29	65.72 (SD=10.84)	cooled RFA	fluoroscopy	genicular	2, 6, 12 wks	VAS, WOMAC	treatment resulted in significantly improved knee pain and QOL at all follow-ups	none reported
8	Wong et al (32)	2020	retrospective study	50	67.3 (SD=14.4)	cooled RFA	fluoroscopy	genicular	2 wks, 1, 3, 6 mos	VAS, KOOS, WOMAC	KOOS, WOMAC significantly improved, significantly reduced pain at 6 months follow up	none reported
9	Han et al (26)	2020	randomized controlled trial	31	53.6 (SD=19.1)	pulsed	ultrasound	genicular	1, 3, 6 mos	VAS, WOMAC	significantly reduced pain and improved WOMAC score in all follow-ups	N/A
10	Erdem and Sir (33)	2019	retrospective study	17	69 (52-97)	pulsed	ultrasound	genicular	3 wks, 3 mos	VAS, WOMAC	significantly reduced perceived pain and disability	none reported
11	Arican et al (34)	2020	prospective study	20	55.2 (SD=3.24)	pulsed	fluoroscopy	genicular	1, 4, 12 wks	VAS, WOMAC, PGIC	50% reduced pain and improved functional status score in 4th and 12th weeks	none reported
12	Leoni et al (35)	2020	retrospective study	78	75.3 (SD=7.9)	pulsed	fluoroscopy	genicular	3, 6 mos	NRS, WOMAC, PGIC	significant reduction of pain and QOL at all follow ups	none reported

Table 1 continued. *Main characteristics of the articles included in this study.*

No	Author	Year	Study Design	Size (N)	Mean Age	RFA Method	Imaging Modality	Nerve Target	Follow-up	Scoring Method	Results	Adverse events
13	Elawamy et al (17)	2021	randomized controlled trial	100	47.78 (SD=6.9)	pulsed	ultrasound	genicular	3, 6, 12 mos	VAS, ISK	significantly reduced pain, significantly lower ISK over the whole follow-ups	2 patients had pain at site of injection and resolution in 1 week
14	Santana-Pineda et al (18)	2020	randomized controlled trial	95	74.1 (72.2-76.0)	pulsed	ultrasound	genicular	1,6,12 mos	VAS, WOMAC, SF-12, MQS III	significantly reduced pain and improved WOMAC score in all follow-ups	8 patients had pain and 3 patients had fall

VAS, visual analog score; NRS, numeric rating scale; WOMAC, the Western Ontario and Mc Master Universities Osteoarthritis Index; PGIC, Patient Global Impression of Change; MQS III, Medication Quantification Scale III; OKS, Oxford Knee Score; GPE, Global Perceived Effect; KOOS, Knee Injury and Osteoarthritis Outcome Score; ISK, Index of Severity for Knee disease; SF-12, short form survey-12.

variables that could influence outcomes. Overall the drop-out rate of all studies was low (< 20%) and the differential drop-out rate was low (< 15%). All outcomes were evaluated using valid and reliable measures that were applied consistently across all study patients.

There were 5 studies with no control group for methodological quality assessment of before-and-after (pre-post) investigations (Table 4). All studies described eligibility criteria. They were measured with valid, reliable, and consistent scoring methods. Following baseline, all studies had a low loss to follow-up (< 20%); those who were lost to follow-up were included in our analysis.

Meta-analysis

a. Primary outcome: Pain scores (VAS and NRS-11)

iv. Pain scores at one-month posttreatment

A total of 8 studies, regardless of the type of nonconventional RFA technique used, measured the one-month follow-up pain score using either VAS or NRS-11. These findings revealed heterogeneity (I^2 = 90%), so we adopted a random-effects model. At one-month posttreatment, the improvement was significant for reducing pain (random-effects model: 8 records, SMD = 3.42; 95% CI, 2.69 – 4.16; P < 0.00001 for one month vs baseline) (Fig. 2A).

A total of 5 studies evaluated cooled RFA. They measured the one-month follow-up pain score using either the VAS or NRS-11. Our analysis showed evidence of heterogeneity (I^2 = 80%), so the studies were analyzed with a random-effects model. Posttreatment, patients had significant pain reduction (random-effects model: 5 records, SMD = 2.92; 95% CI = 2.29 – 3.54; P < 0.00001 for one month vs baseline) (Fig. 2B).

A total of 3 studies evaluated pulsed RFA. They measured the one-month follow-up pain score using either the VAS or NRS-11. We found evidence of heterogeneity (I^2 = 91%) and used a random-effects model for calculating the data. Patient's pain improved significantly at one-month posttreatment (random-effects model: 3 records, SMD = 4.67; 95% CI = 3.76 – 5.58; P < 0.00001 for one month vs baseline) (Fig. 2C).

Pain Scores at 3-months Posttreatment

A total of 9 studies, regardless of the type of nonconventional RFA technique used, measured the 3-month follow-up pain score using either VAS or NRS-11. These findings revealed heterogeneity (I^2 = 87%), so we adopted a random-effects model. At 3-months posttreatment, the improvement was significant for reducing pain (random-effects model: 9 records, SMD = 3.00; 95% CI, 2.69 – 4.16; P < 0.00001 for 3 months vs baseline) (Fig. 3A).

A total of 5 studies evaluated cooled RFA. They measured the 3-month follow-up pain score using either the VAS or NRS-11. Our analysis showed evidence of heterogeneity (I^2 = 31%), so the studies were analyzed with a fixed-effects model. Posttreatment, patients had significant pain reduction (random-effects model: 5 records, SMD = 2.85; 95% CI, 2.59 – 3.10; P < 0.00001 for 3 months vs baseline) (Fig. 3B).

A total of 4 studies evaluated pulsed RFA. They measured the

3-month follow-up pain score using either the VAS or NRS-11. We found evidence of heterogeneity (I^2 = 93%) and used a random-effects model for calculating the data. Patient's pain improved significantly at 3-months posttreatment (random-effects model: 4 records, SMD = 3.28; 95% CI, 1.97 – 4.59; P < 0.00001 for 3 months vs baseline) (Fig. 3C).

Pain scores at 6-months Posttreatment

A total of 9 studies, regardless of the type of nonconventional RFA technique used, measured the 6-month follow-up pain score using either VAS or NRS-11. These findings revealed heterogeneity (I^2 = 87%), so we adopted a random-effects model. At 6-months posttreatment, the improvement was significant for reducing pain (random-effects model: 9 records, SMD = 2.39; 95% CI, 1.92 – 2.87; P < 0.00001 for 3 months vs baseline) (Fig. 4A).

A total of 5 studies evaluated cooled RFA. They measured the 6-month follow-up pain score using either the VAS or NRS-11. Our analysis showed evidence of heterogeneity (I^2 = 50%), so the studies were analyzed with a fixed-effects model. Posttreatment, patients had significant pain reduction (random-effects model: 5 records, SMD = 2.78; 95% CI, 2.52 – 3.03; P < 0.00001 for 6 months vs baseline) (Fig. 4B).

A total of 4 studies evaluated pulsed RFA. They measured the 6-month follow-up pain score using either the VAS or NRS-11. We found evidence of heterogeneity (I^2 = 81%) and used a random-effects model

Table 2. *The clinical relevance grade of the included studies.*

Manuscript	A) Patient	B) Interventions	C) Outcomes	D) Effect size	E) Benefit vs harm	Grade
Arican et al (34)	+	+	+	U	+	4/5
Bellini et al (25)	+	+	+	-	+	4/5
Chen et al (16)	+	+	+	+	+	5/5
Davis et al (24)	+	+	+	-	+	4/5
Elawamy et al (17)	+	+	+	+	+	5/5
Erdem and Sir (33)	+	+	+	+	+	5/5
Han et al (26)	+	+	+	+	+	5/5
Mccormick et al (28)	+	+	+	+	+	5/5
Rayamajhi et al (30)	+	+	+	-	+	3/5
Reddy et al (29)	+	+	+	U	+	4/5
Kocayigit and Bezas (31)	+	+	+	+	+	5/5
Leoni et al (35)	+	+	+	+	+	5/5
Wong et al (32)	+	+	+	+	+	5/5
Santana-Pineda et al (18)	+	+	+	+	+	5/5

Table 3. *Methodological quality assessment of controlled intervention studies.*

Manuscript	1	2	3	4	5	6	7	8		9	10	11	12	13	14	Grade
Chen et al (16)	+	+	+	+	+	+	+	+		+	+	+	+	+	+	14/14
Davis et al (24)	+	+	+	+	+	+	+	+		+	+	+	+	+	+	14/14
Elawamy et al (17)	+	+	+	+	+	+	+	+		+	+	+	+	+	+	14/14
Erdem and Sir (33)	-	NA	+	-	-	+	+	+		+	+	+	-	+	+	9/14
Han et al (26)	+	+	+	+	+	+	+	+		+	+	+	CD	+	+	13/14
Kocayigit and Bezas (31)	-	-	+	NA	NA	+	+	+		+	+	+	NR	+	CD	8/14
Leoni et al (35)	-	-	+	NA	NA	+	+	+		+	+	+	NR	+	+	9/14
Wong et al (32)	+	+	+	+	-	+	+	+		+	+	+	NR	+	+	12/14
Santana-Pineda et al (18)	+	+	+	+	+	+	+	+		+	+	+	+	+	+	14/14

CD, cannot determine; NA, not applicable; NR, not reported

Table 4. *Methodological quality assessment for before-after (pre-post) studies with no control group*

Manuscript	1	2	3	4	5	6	7	8	9	10	11	12	Grade
Arican et al (34)	+	+	+	+	+	+	+	CD	+	+	-	NR	9/12
Bellini et al (25)	+	+	+	-	-	+	+	+	+	+	+	-	9/12
Mccormick et al (28)	+	+	+	+	+	+	+	-	+	+	+	+	11/12
Rayamajhi et al (30)	+	+	CD	+	-	+	+	-	+	+	+	+	9/12
Reddy et al (29)	+	+	+	+	CD	+	+	-	+	+	+	+	10/12

CD, cannot determine; NA, not applicable; NR, not reported

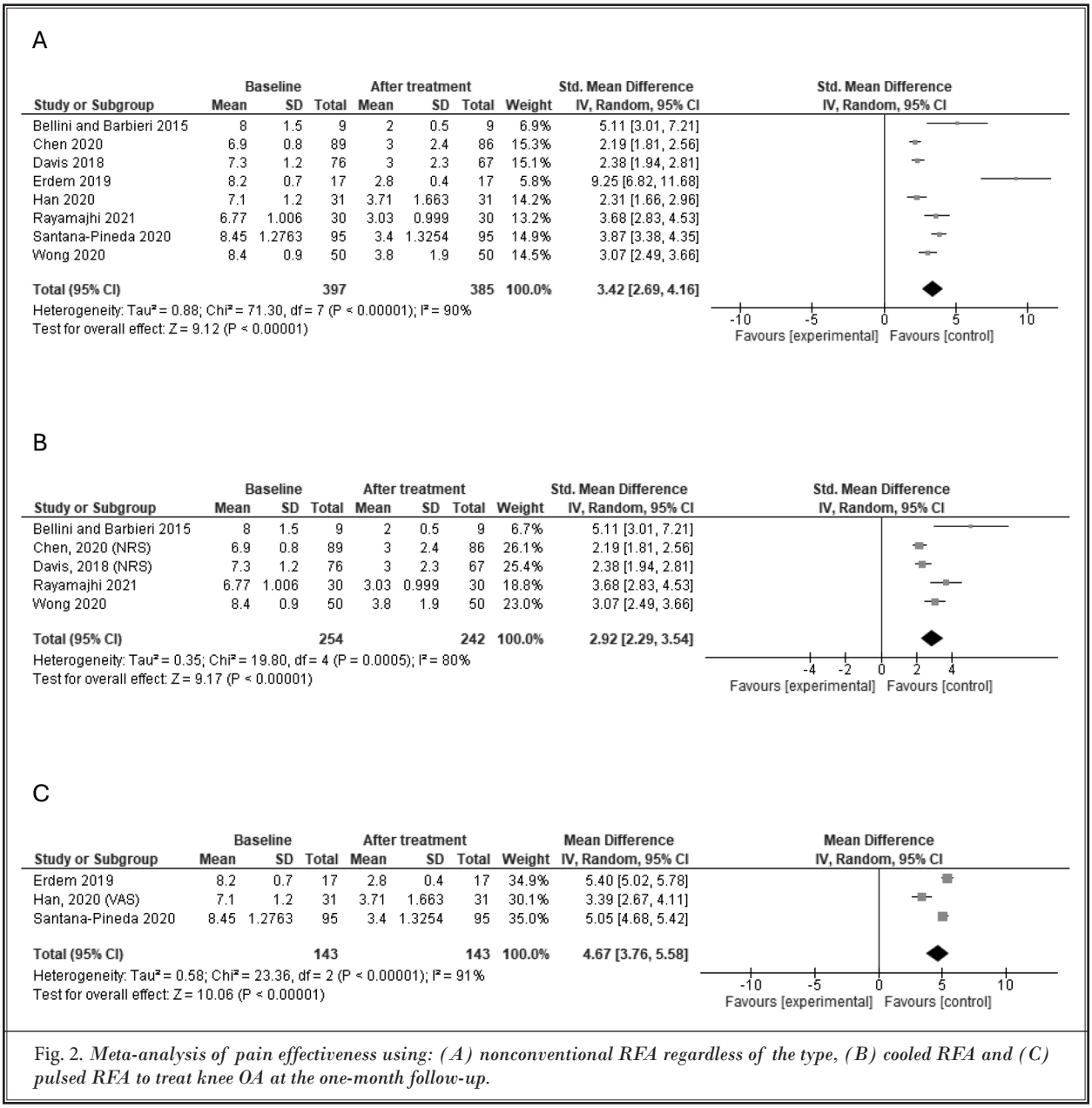


Fig. 2. *Meta-analysis of pain effectiveness using: (A) nonconventional RFA regardless of the type, (B) cooled RFA and (C) pulsed RFA to treat knee OA at the one-month follow-up.*

for calculating the data. Patient's pain improved significantly at 6-months posttreatment (random-effects model: 4 records, SMD = 1.76; 95% CI, 1.25 – 2.28; $P < 0.00001$ for 6 months vs baseline) (Fig. 4C).

Pain Scores at 12-months Posttreatment

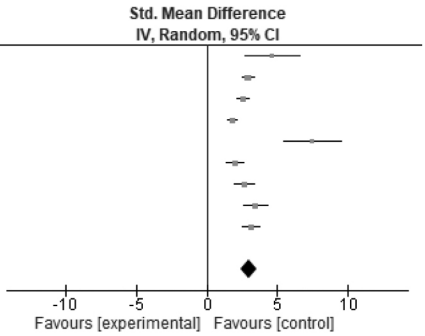
Only 4 studies, regardless of the type of nonconventional RFA technique used, measured the 12-month follow-up pain score using either VAS or NRS-11. These findings revealed heterogeneity ($I^2 = 96\%$), so we adopted a random-effects model. At 12-months posttreatment, the improvement was significant for reducing pain (random-effects model: 4 records, SMD = 1.96; 95% CI, 0.90 – 3.02; $P < 0.0003$ for 12 months vs baseline) (Fig. 5A).

Two studies evaluated cooled RFA. Our analysis showed evidence of heterogeneity ($I^2 = 84\%$), so the studies were analyzed with a random-effects model.

A

Study or Subgroup	Baseline Mean	SD	Total	After treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellini and Barbieri 2015	8	1.5	9	2.3	0.7	9	5.5%	4.64 [2.69, 6.59]
Chen, 2020 (NRS)	6.9	0.8	89	2.3	2.1	84	13.5%	2.91 [2.48, 3.34]
Davis, 2018 (NRS)	7.3	1.2	76	2.8	2.2	65	13.4%	2.58 [2.13, 3.03]
Elawamy, 2021 (VAS)	5.85	1.226	100	3.52	1.359	100	14.0%	1.79 [1.46, 2.12]
Erdem 2019	8.2	0.7	17	3.2	0.6	17	5.3%	7.49 [5.48, 9.50]
Han, 2020 (VAS)	7.1	1.2	31	4.13	1.663	31	12.5%	2.02 [1.40, 2.64]
Kocayigit and Beyaz 2021	8.97	1.05	29	4.79	1.91	29	11.9%	2.68 [1.96, 3.40]
Leoni 2020	9.2	0.97	27	4.5	1.63	27	11.1%	3.45 [2.59, 4.31]
Wong 2020	8.4	0.9	50	3.5	2	50	12.7%	3.14 [2.54, 3.73]
Total (95% CI)			**428**			**412**	**100.0%**	**3.00 [2.42, 3.58]**

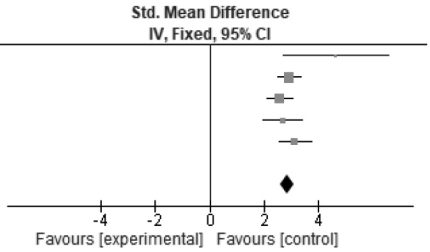
Heterogeneity: $Tau^2 = 0.60$; $Chi^2 = 61.35$, df = 8 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: $Z = 10.14$ ($P < 0.00001$)



B

Study or Subgroup	Baseline Mean	SD	Total	After treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bellini and Barbieri 2015	8	1.5	9	2.3	0.7	9	1.7%	4.64 [2.69, 6.59]
Chen, 2020 (NRS)	6.9	0.8	89	2.3	2.1	84	35.1%	2.91 [2.48, 3.34]
Davis, 2018 (NRS)	7.3	1.2	76	2.8	2.2	65	32.1%	2.58 [2.13, 3.03]
Kocayigit and Beyaz 2021	8.97	1.05	29	4.79	1.91	29	12.5%	2.68 [1.96, 3.40]
Wong 2020	8.4	0.9	50	3.5	2	50	18.6%	3.14 [2.54, 3.73]
Total (95% CI)			**253**			**237**	**100.0%**	**2.85 [2.59, 3.10]**

Heterogeneity: $Chi^2 = 5.80$, df = 4 ($P = 0.21$); $I^2 = 31\%$
Test for overall effect: $Z = 21.88$ ($P < 0.00001$)



C

Study or Subgroup	Baseline Mean	SD	Total	After treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Elawamy 2021	5.85	1.226	100	3.52	1.359	100	28.9%	1.79 [1.46, 2.12]
Erdem 2019	8.2	0.7	17	3.2	0.6	17	17.4%	7.49 [5.48, 9.50]
Han 2020	7.1	1.2	31	4.13	1.663	31	27.6%	2.02 [1.40, 2.64]
Leoni 2020	9.2	0.97	27	4.5	1.63	27	26.1%	3.45 [2.59, 4.31]
Total (95% CI)			**175**			**175**	**100.0%**	**3.28 [1.97, 4.59]**

Heterogeneity: $Tau^2 = 1.51$; $Chi^2 = 40.51$, df = 3 ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: $Z = 4.91$ ($P < 0.00001$)

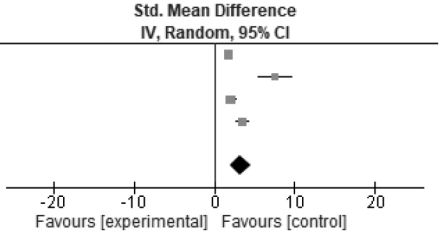


Fig. 3. *Meta-analysis of pain effectiveness using: (A) nonconventional RFA regardless of the type, (B) cooled RFA and (C) pulsed RFA to treat knee OA at the 3-month follow-up.*

Posttreatment, patients had no significant pain reduction (random-effects model: 2 records, SMD = 3.59; 95% CI, 0.95 – 6.24; $P < 0.008$ for 12 months vs baseline) (Fig. 5B).

Two studies evaluated pulsed RFA. We found evidence of heterogeneity ($I^2 = 90\%$) and used a random-effects model for calculating the data. Patient's pain did not improve significantly at 12-months posttreatment (random-effects model: 2 records, SMD = 1.39; 95% CI, 0.44 – 2.34; $P < 0.004$ for 12 months vs baseline) (Fig. 5C).

b. Secondary outcome: Physical function outcome (WOMAC)

i. Physical function outcome at one-month posttreatment

A total of 5 studies, regardless of the type of nonconventional RFA technique used, measured the one-month follow-up physical function score using the

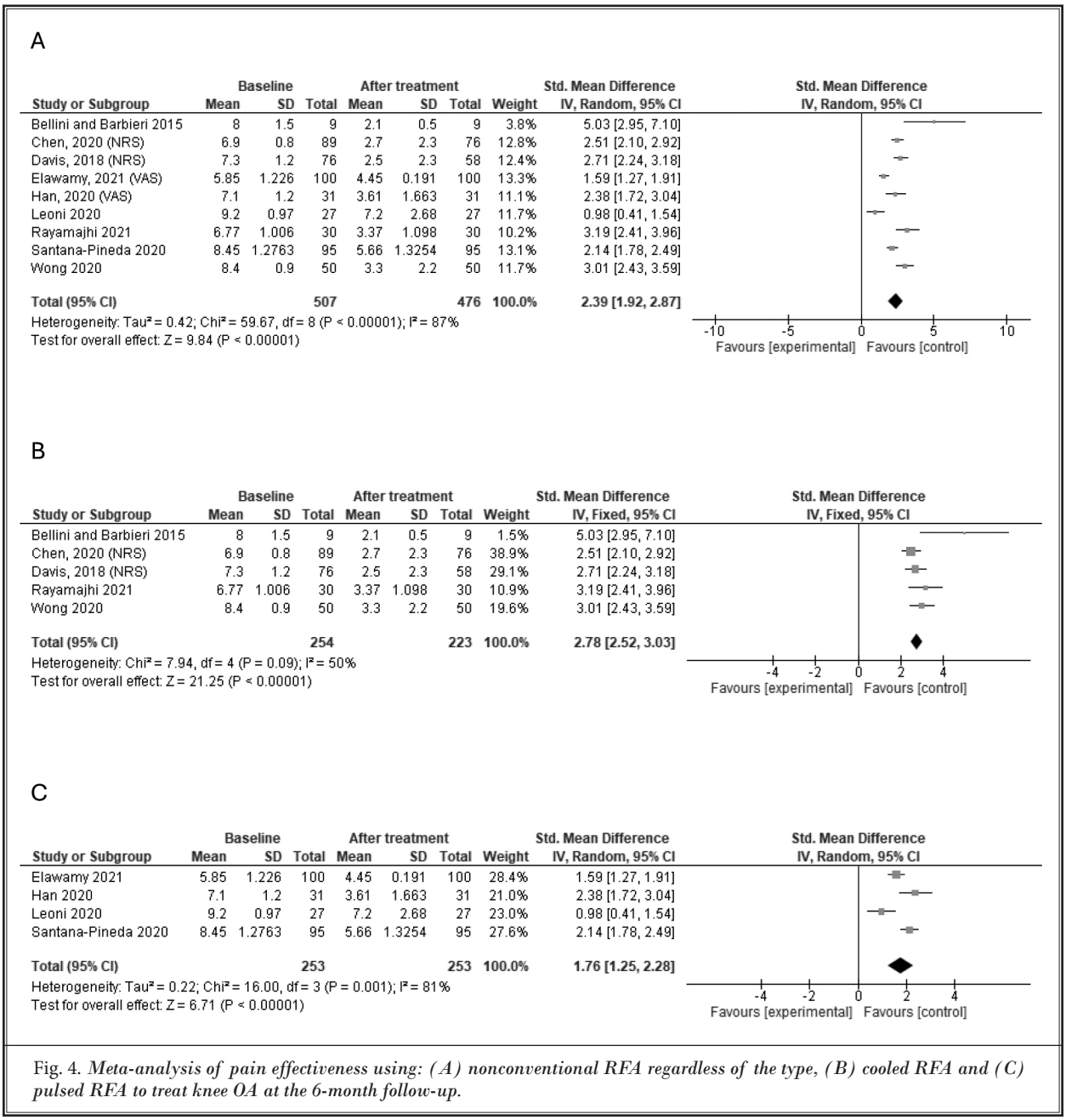


Fig. 4. *Meta-analysis of pain effectiveness using: (A) nonconventional RFA regardless of the type, (B) cooled RFA and (C) pulsed RFA to treat knee OA at the 6-month follow-up.*

WOMAC. These findings revealed heterogeneity (I^2 = 36%), so we adopted a fixed-effects model. At one-months posttreatment, the physical function improvement was significant (fixed-effects model: 5 records, MD = 28.25; 95% CI, 1.92 – 26.45; $P < 0.00001$ for one month vs baseline) (Fig. 6A).

Two studies evaluated cooled RFA and measured the one-month follow-up physical function score using the WOMAC. Our analysis showed evidence of heterogeneity (I^2 = 99%), so the studies were analyzed with a random-effects model. Posttreatment, patients had no significant physical function improvement (random-effects model: 2 records, MD = 48.84; 95% CI, 11.12 – 86.57; $P < 0.01$ for one month vs baseline) (Fig. 6B).

Three studies evaluated pulsed RFA and measured the one-month follow-up physical function score using the WOMAC. Our analysis showed evidence of heterogeneity (I^2 = 55%), so the studies were analyzed with a random-effects model. Posttreatment, patients had significant physical function improvement (random-effects model: 3 records, MD = 28.05; 95% CI, 24.71 – 31.39; $P < 0.00001$ for one month vs baseline) (Fig. 6C).

ii. Physical function outcome at 3 months posttreatment

A total of 5 studies, regardless of the type of nonconventional RFA technique used, measured the 3-month follow-up physical function score using the WOMAC. These findings revealed heterogeneity (I^2

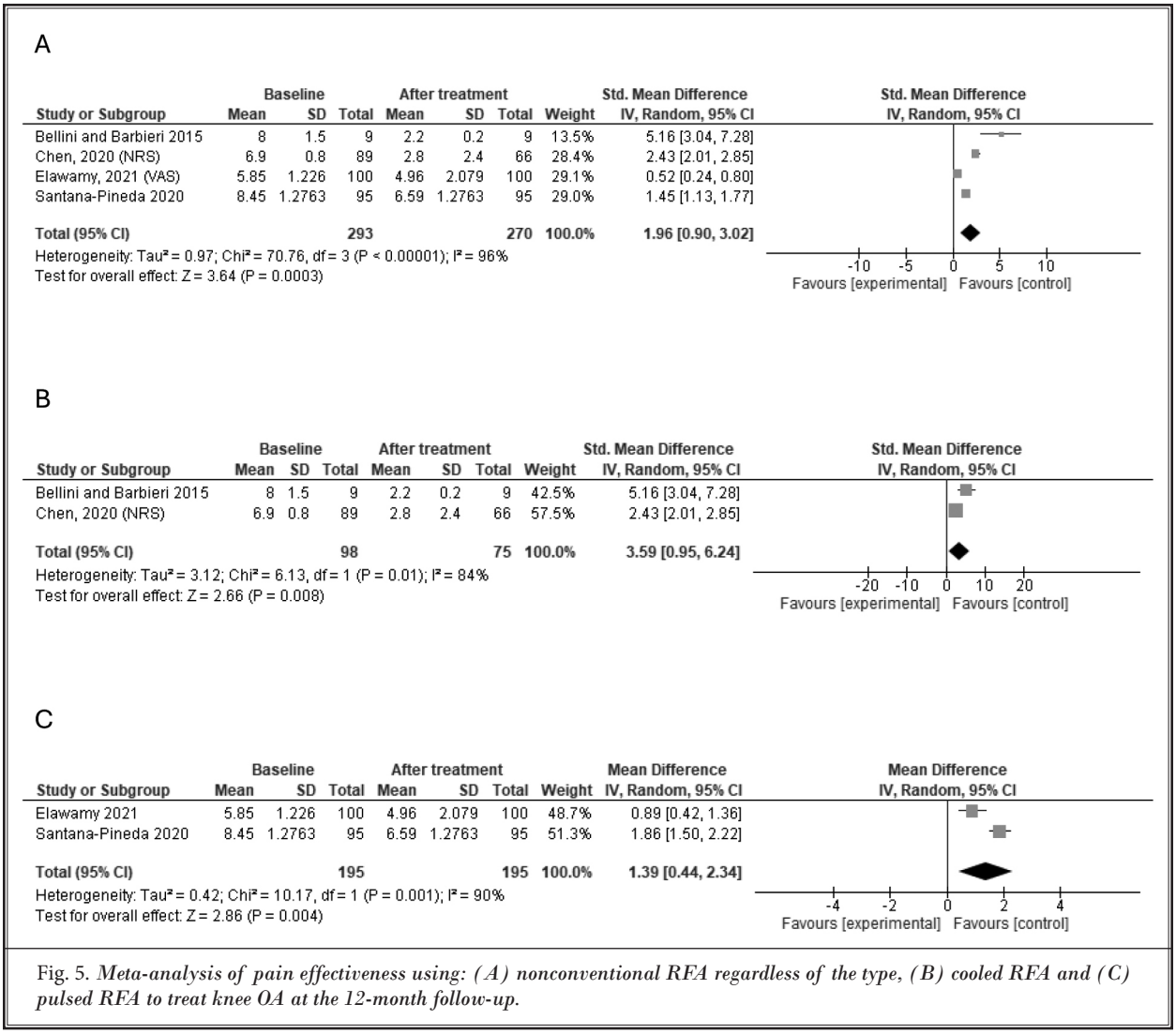


Fig. 5. *Meta-analysis of pain effectiveness using: (A) nonconventional RFA regardless of the type, (B) cooled RFA and (C) pulsed RFA to treat knee OA at the 12-month follow-up.*

= 65%), so we adopted a random-effects model. At 3-months posttreatment, the physical function improvement was significant (random-effects model: 5 records, MD = 26.93; 95% CI, 22.41 – 31.46; $P < 0.00001$ for 3 months vs baseline) (Fig. 7A).

Three studies evaluated cooled RFA and measured the 3-month follow-up physical function score using the WOMAC. Our analysis showed evidence of heterogeneity ($I^2 = 99\%$), so the studies were analyzed with a random-effects model. Posttreatment, patients had no significant physical function improvement (random-effects model: 3 records, MD = 40.81; 95% CI, 11.68 – 69.93; $P < 0.006$ for 3 months vs baseline) (Fig. 7B).

Two studies evaluated pulsed RFA and measured the 3-month follow-up physical function score using the WOMAC. Our analysis showed no evidence of heterogeneity ($I^2 = 0\%$), so the studies were analyzed with a fixed-effects model. Posttreatment, patients had significant physical function improvement (fixed-effects model: 2 records, MD = 25.43; 95% CI, 23.09 – 27.77; $P < 0.00001$ for 3 months vs baseline) (Fig. 7C).

Physical Function Outcome at 6 Months Posttreatment

A total of 3 studies, regardless of the type of nonconventional RFA technique used, measured the 6-month follow-up physical function score using the WOMAC. These findings revealed heterogeneity (I^2

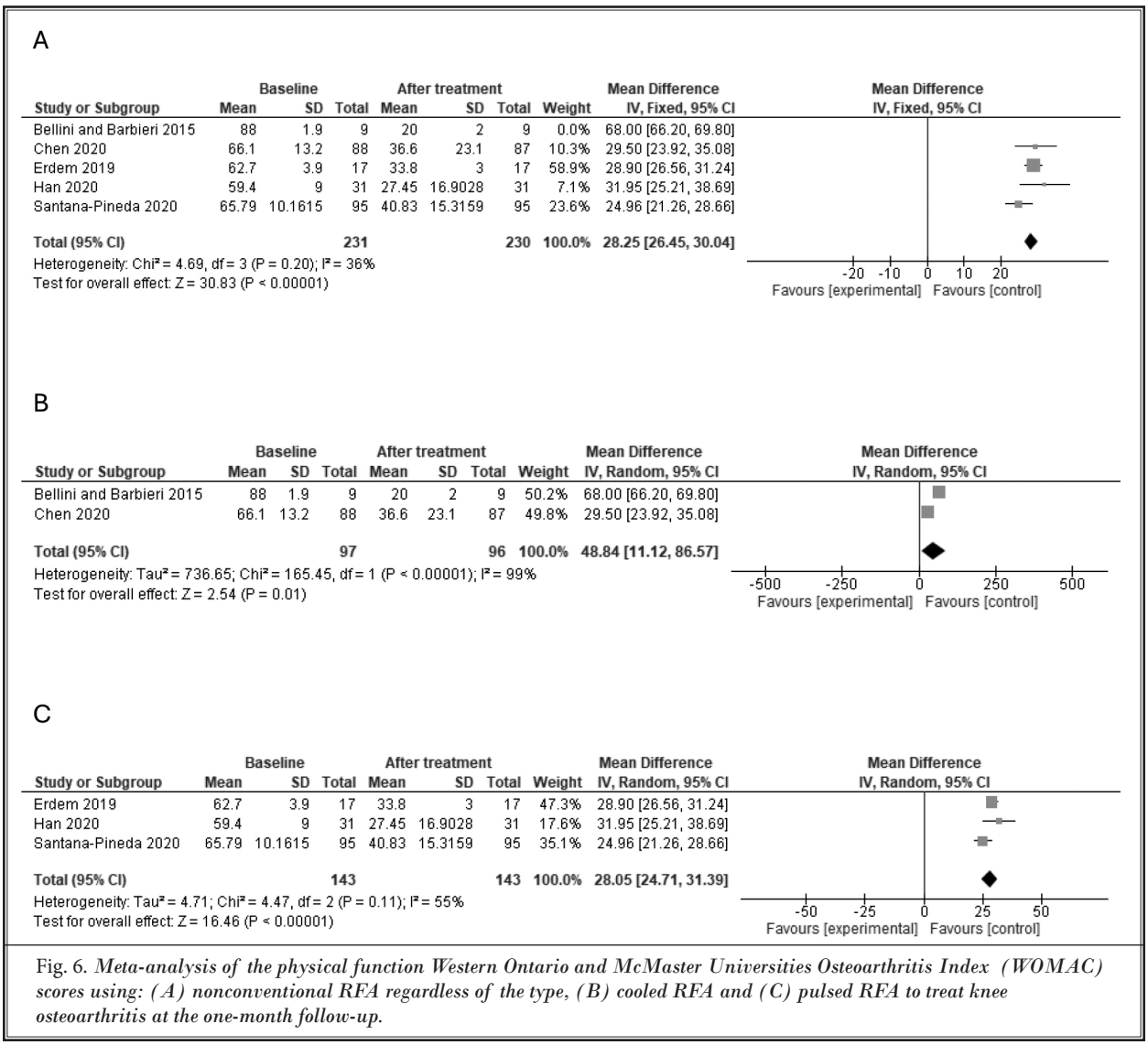


Fig. 6. *Meta-analysis of the physical function Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores using: (A) nonconventional RFA regardless of the type, (B) cooled RFA and (C) pulsed RFA to treat knee osteoarthritis at the one-month follow-up.*

= 99%), so we adopted a random-effects model. At 6-months posttreatment, the physical function improvement was significant (random-effects model: 4 records, MD = 27.53; 95% CI, 16.17 – 38.89; $P < 0.00001$ for 6 months vs baseline) (Fig. 8A).

Two studies evaluated cooled RFA and measured the 6-month follow-up physical function score using the WOMAC. Our analysis showed evidence of heterogeneity ($I^2 = 99\%$), so the studies were analyzed with a random-effects model. Posttreatment, patients had no significant physical function improvement (random-effects model: 2 records, MD = 49.87; 95% CI, 16.06 – 83.68; $P < 0.004$ for 6 months vs baseline) (Fig. 8B).

Two studies evaluated pulsed RFA and measured the 6-month follow-up physical function score using the WOMAC. Our analysis showed evidence of heterogeneity ($I^2 = 94\%$), so the studies were analyzed with a random-effects model. Posttreatment, patients had no significant physical function improvement (fixed-effects model: 2 records, MD = 25.14; 95% CI, 10.30 – 39.98; $P < 0.0009$ for 6 months vs baseline) (Fig. 8C).

Physical Function Outcome at 12 Months Posttreatment

A total of 3 studies, regardless of the type of nonconventional RFA technique used, measured the 12-month

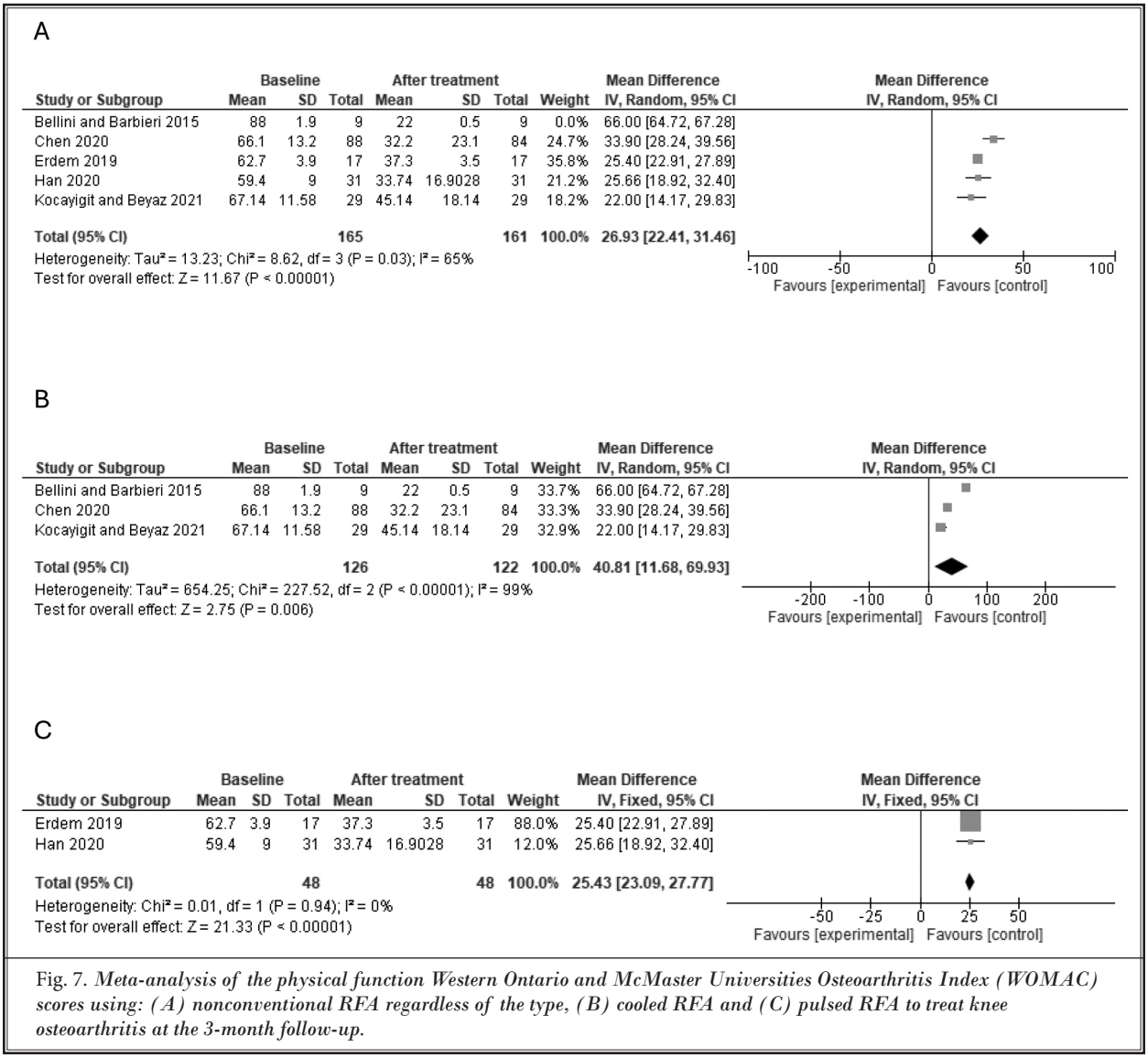


Fig. 7. *Meta-analysis of the physical function Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores using: (A) nonconventional RFA regardless of the type, (B) cooled RFA and (C) pulsed RFA to treat knee osteoarthritis at the 3-month follow-up.*

follow-up physical function score using the WOMAC. These findings revealed heterogeneity (I^2 = 100%), so we adopted a random-effects model. At 12-months posttreatment, the physical function improvement was not significant (random-effects model: 3 records, MD = 37.77; 95% CI, -2.56 to 78.11; $P < 0.07$ for 12 months vs baseline) (Fig. 9A).

Two studies evaluated cooled RFA and measured the 12-month follow-up physical function score using the WOMAC. Our analysis showed evidence of heterogeneity (I^2 = 99%), so the studies were analyzed with a random-effects model. Posttreatment, patients had no significant physical function improvement (random-effects model: 2 records, MD = 50.29; 95% CI, 16.19 – 84.98; $P < 0.004$ for 12 months vs baseline) (Fig. 9B).

Only one study evaluated pulsed RFA and measured 12-month follow-up for functional physical function score using the WOMAC. Therefore, a meta-analysis could not be conducted..

2. Adverse events

Out of the 14 articles that employed nonconventional RFA, only 3 documented any posttreatment adverse events (16-18). Two articles (17,18) reported that the adverse events were not serious.

One article reporting on cooled RFA (16) reported posttreatment adverse events such as swelling, stiffness, and.

One article (17) reporting on pulsed RFA reported posttreatment pain that resolved within one week.

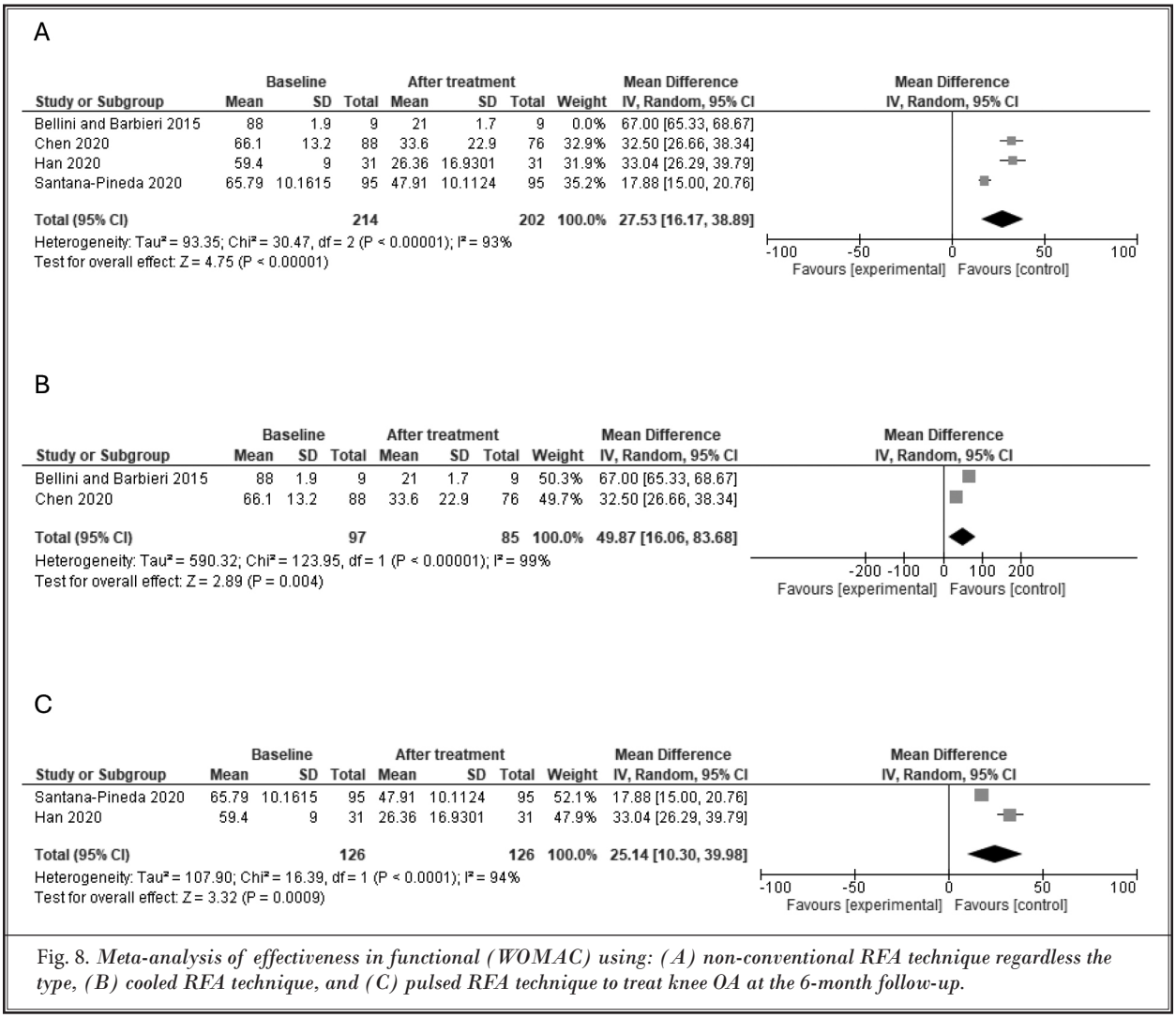


Fig. 8. *Meta-analysis of effectiveness in functional (WOMAC) using: (A) non-conventional RFA technique regardless the type, (B) cooled RFA technique, and (C) pulsed RFA technique to treat knee OA at the 6-month follow-up.*

3. Risk of bias evaluation

Publication bias was evaluated using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Observational studies carry a significant risk of bias arising from the randomization method. From the selection bias analysis, there were 3 studies (16-18) at high risk because they did not report the random sequence generation and allocation concealment clearly. Although one study (24) concerns in some categories, there were 4 studies (25,26,28,29) that reported the generation and concealment of the random allocation sequence clearly.

We judge the detection bias as high risk because there were only 3 studies (17,24,25) using a blind outcome assessment. Our attrition bias analysis was low risk because there were 7 studies (16-18,24-26,29) with low-risk bias and there was only one study (28) with high risk bias due to missing outcome data. We determined that the reporting bias posed a low risk. We concluded that there were 3 studies (16,26,28 with a high risk of bias, 3 with some bias concerns (17,24,29), and 2 with a low risk of bias (18,25).

Discussion

For almost 10 years, traditional RF has been utilized to treat arthritic knee pain. The targeted nerve also varies to treat knee pain, such as the femoral sensory branch, common peroneal, saphenous, tibial, and obturator nerves. These particular branches are referred to as the genicular nerves (19). The genicular nerves have been identified as a reliable target for ablation therapy and have been reported to effectively alleviate pain associated with knee osteoarthritis (20). So, to standardize the treatment procedure, we used the genicular nerves as the therapy target.

There are publications that measure the effectiveness of conventional RF but there are limited publications that measure the effectiveness of nonconventional RF. Pulsed and cooled RFA are the 2 forms of nonconventional RF that have been most widely published. Traditional RFA works by ablating the nerve with high heat and energy. Pulsed RFA was developed to avoid damaging neural tissue by using a lower temperature and energy. By using internally cooled RF probes, cooled RFA was designed to increase lesion size.

In our review, we used a meta-analysis for evaluating the analgesic potency of distinct treatments by comparing baseline to follow-up visits. This meta-analysis technique was utilized in previous meta-analyses (15,21). To evaluate the effectiveness of different forms of RFA, eligible studies such as randomized controlled trials were included; the findings of a previous meta-

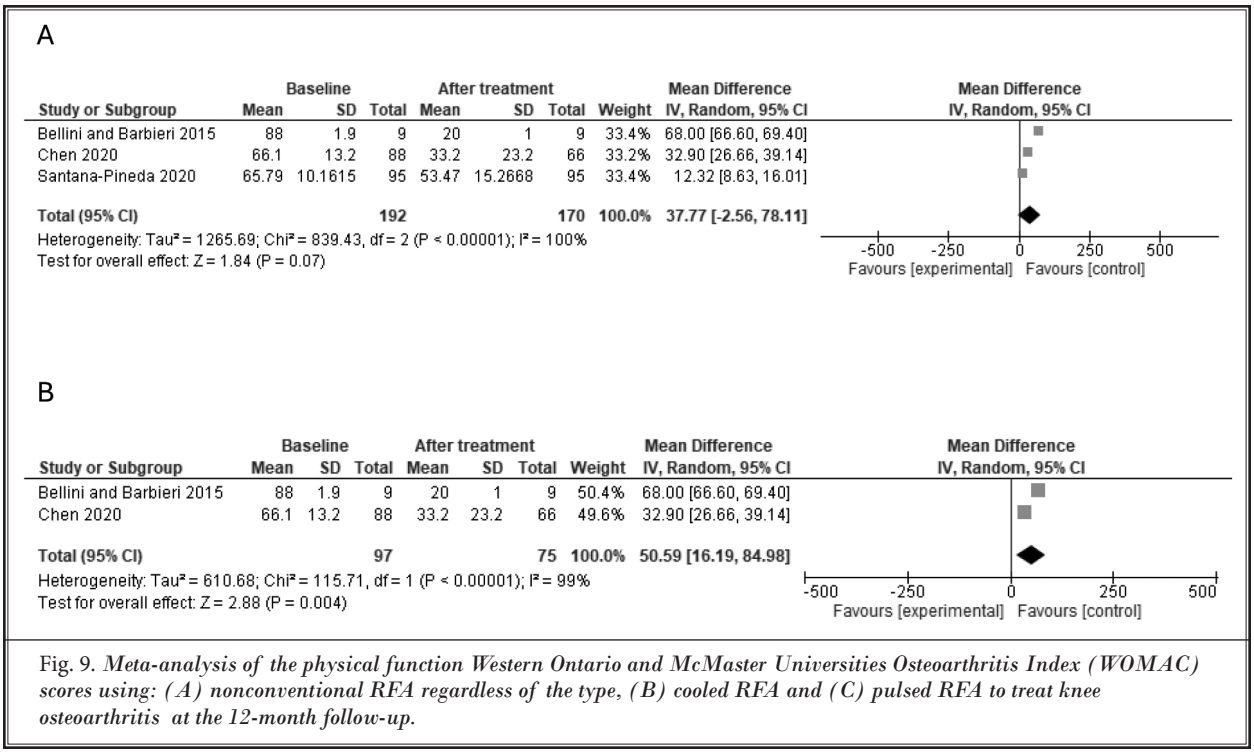


Fig. 9. *Meta-analysis of the physical function Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores using: (A) nonconventional RFA regardless of the type, (B) cooled RFA and (C) pulsed RFA to treat knee osteoarthritis at the 12-month follow-up.*

analysis had a high degree of evidence (22). However, few randomized controlled trials evaluating different types of RFA procedures in the treatment of knee osteoarthritis pain have been conducted. Consequently, the utilization of meta-analysis presented challenges in assessing the correlation between the RFA technique and the management of knee osteoarthritis. Subsequently, the present study assessed the alteration in pain and physical function outcomes during follow-up appointments, relative to the baseline, and the findings were deemed reliable (15).

The aim of our meta-analysis was to compare the outcome of cooled and pulsed RFA for reducing pain in knee osteoarthritis. Our findings indicate that all forms of nonconventional RFA demonstrated significant pain reduction during follow-up visits at one, 3, and 6 month intervals, regardless of the specific type of nonconventional RFA utilized, when compared to baseline levels.

At one- and 3-month follow-up visits, both cooled and pulsed RFA showed significant improvement in knee osteoarthritis pain reduction compared to baseline levels. At 12-month follow-up, both cooled and pulsed RFA were measured in our meta-analysis; the result was no significant improvement. The pain reported in our meta-analysis may occur due to post-treatment neuron regeneration; it would decrease the effectiveness in pain relief by the time (9). Moreover, the long-term outcome, which is more than a 12-month follow-up, of nonconventional RFA is still debatable (23-25). Our findings indicate that neuron regeneration frequently occurs after 12 months.

We used the WOMAC score in our investigation to determine the physical function outcome of all nonconventional RFAs, independent of kind. The results show that all nonconventional RFA, regardless of the type, produced significant improvement in physical function as measured by the WOMAC score at one-, 3-, and 6-month follow-up visits compared with baseline level. This result is the same as a previous study that reported that pain relief contributes to physical function recovery (26). However, the long-term physical function improvement (at 12-months) is not significant.

This is not contradicting because most patients in pain may not be using their joints during daily activities and may lead to muscle wasting and weakness (27). Cooled RFA and pulsed RFA had no significant improvement in functional outcome using WOMAC scores in all follow-ups. This finding could be because there are only a few articles that give comprehensive functional results using the WOMAC score, and we are unable to compare functional outcomes using other scoring methodologies. However, the pulsed RFA technique had significant improvement in functional outcomes using WOMAC scores only at the one and 3-month follow-up visit and as in the previous study, the long-term functional improvement may be comprehendible with the pain outcome (27,28).

Limitations

The limitations of this meta-analysis study could have an impact on our conclusions. First, because there are a limited number of randomized controlled trials available, the methodology utilized for comparison is based on the change in outcome between baseline and follow-up visits. Second, there are only a few papers that report functional outcomes in complete WOMAC rating data. Because we had a similar number of articles on cooled and pulsed RFA for knee osteoarthritis pain in our meta-analysis, we believe our conclusion is valid.

Conclusions

The primary outcome of both cooled and pulsed RFA targeted genicular nerve for treating knee OA pain was considerable pain reduction at 6-month follow-up. There is no different in pain relief between cooled and pulsed RFA targeted genicular nerve for treating knee osteoarthritis. In the secondary outcome, there was no significant functional improvement of cooled RFA in all follow-up, but there was a significant functional improvement of pulsed RFA up to 3-month follow-up. However, the studies showed promising results for the treatment of knee osteoarthritis pain by pulsed and cooled radiofrequency and offer substantial benefit with minimal adverse events.

Author Contributions

B.S, A.N.R, H.H, S.D, contributed to the conception of the work. B.S, D.A, A.N.R, H.H, S.D, contributed to the design of the work. B.S, D.A, M.B.Y, conducted the literature search. B.S, D.A, M.B.Y, conducted selection, data extraction, the assessment of study quality, and analysis. B.S, D.A, wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

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