Pain Research and Management

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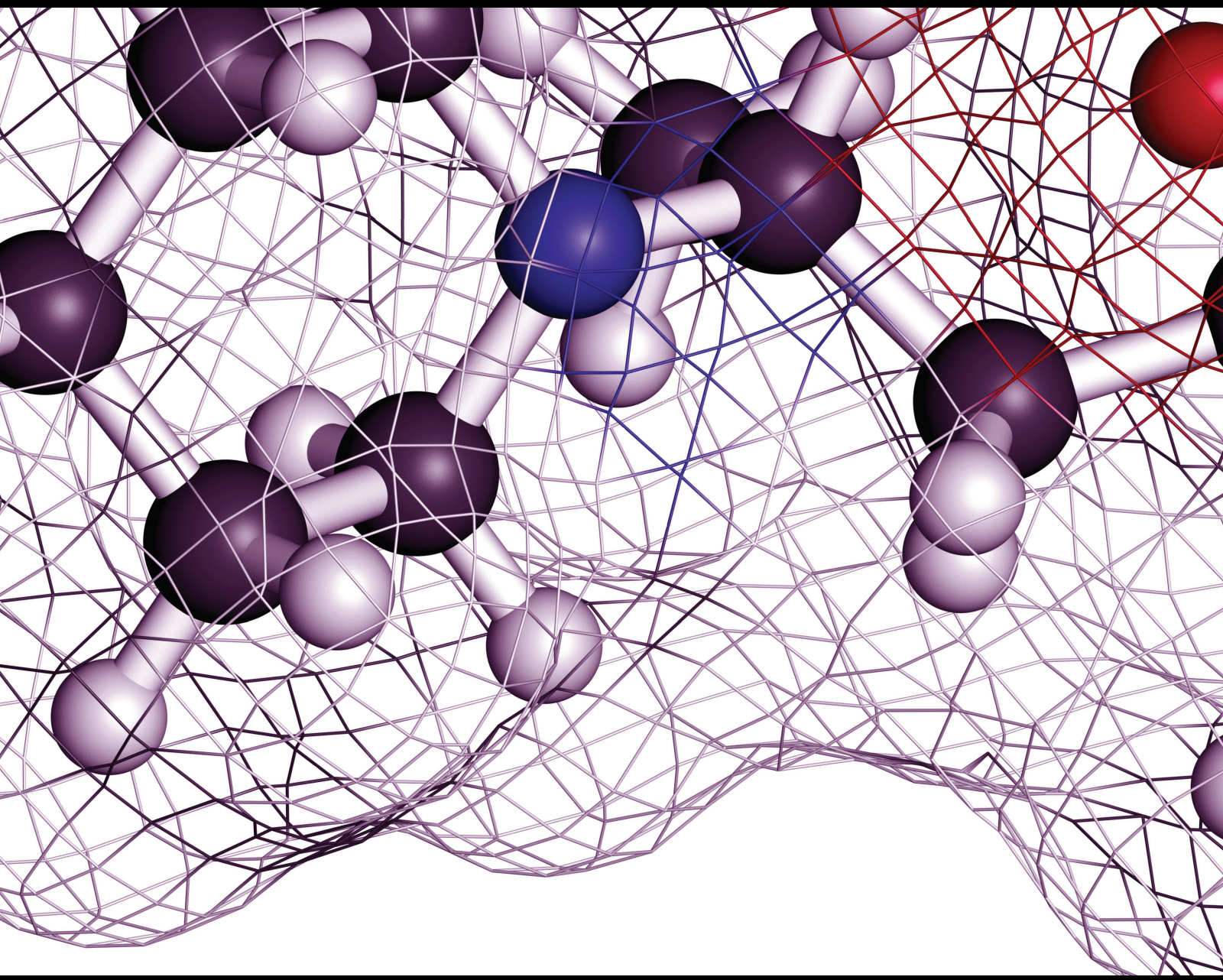

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Contents

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Research Article

Comparison of Effectiveness and Safety between Intraoperative 3D-CT-Guided and C-Arm-Guided Percutaneous Balloon Compression for Idiopathic Trigeminal Neuralgia: A Multi-Center Retrospective Study

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Objectives. To compare 3D-CT-guided and C-arm-guided percutaneous balloon compression (PBC) in terms of effectiveness and safety. *Methods*. The medical records and follow-up data of patients with idiopathic trigeminal neuralgia who underwent 3D-CT-guided or C-arm-guided PBCs in Beijing Tiantan Hospital and the Characteristic Medical Center of the Chinese People's Armed Police Force between February 2018 and March 2020 were retrospectively reviewed and analysed. *Results*. A total of 291 patients were included. Among them, 212 patients underwent PBC treatment with 3D-CT and others with C-arm. One (0.5%) patient in 3D-CT group and 4 (5.1%) patients in C-arm group failed to receive PBC treatment because of failure of foramen ovale (FO) puncture ($P = 0.020$). Among patients with successful attempts, 5 (2.4%) patients in the 3D-CT group and 11 (14.7%) patients in the C-arm group received more than one needle pass during the procedure ($P < 0.001$). The 3D-CT group required less time than the C-arm group for puncture ($P < 0.001$) and for the whole operation ($P < 0.001$). The groups shared similar initial relief rates ($P = 0.749$) and similar recurrence-free survival during follow-ups for a median of 22 months ($P = 0.839$). No puncture-related complications occurred in either group and the two groups had similar incidences of compression-related complications. *Conclusion*. 3D-CT facilitated FO puncture and improved success rate of PBC. The overall time efficiency of PBC was also increased with 3D-CT. Thus, 3D-CT is a potentially useful image guidance technology for treating idiopathic trigeminal neuralgia by PBC.

1. Introduction

Trigeminal neuralgia (TN), with an annual incidence of 4.3–27/100,000, is one of the most common craniofacial pain syndromes [1–3]. Manifesting as paroxysmal attacks of pain that feel like electric shocks in one or more trigeminal nerve branches, TN imposes a significant burden on patients' quality of life [3]. Pharmacological interventions do not reliably bring long-lasting pain relief, and drug treatments produce severe side effects in half of all cases, leaving patients in need of surgery as an alternative [1, 4]. According to the International Classification of Headache Disorders 3rd edition (ICHD-3), TN can be classified into three subgroups: classic TN, secondary TN, and idiopathic TN (ITN) [5]. Different from other subgroups where neurovascular compression or underlying diseases can easily be identified, ITN does not show significant abnormalities in electrophysiological tests or MRI scans, which makes etiological

targeted surgeries impossible [5]. Other surgeries, such as percutaneous balloon compression (PBC), gamma knife radiotherapy, glycerol rhizotomy, and radiofrequency thermocoagulation, have repeatedly been reported to be useful for pain control in TN for which pharmacological treatments have failed [1, 6–9].

Among these surgical options, PBC is a commonly used microinvasive technique and shows potential in the control of TN [6, 9, 10]. However, PBC involves the cannulation of foramen ovale (FO) which requires clinicians to overcome a challenging learning curve and is a very important procedural component [11–14]. Incorrect cannulation can hinder the success of PBC, and repeated attempts to achieve correct needle placement may cause severe complications [15]. In addition, 2–4% of patients reportedly have significant anatomic variations in the FO, making PBC an especially difficult procedure in these patients [13, 16, 17]. Clinicians are continuously searching for visual methods to help identify the puncture route and validate the positions of both the FO and the balloon to obtain more reliable puncture results and better PBC results [12, 14–16, 18]. Monoplanar and biplanar x-ray fluoroscopy was the first introduced [12, 19, 20]. In recent years, C-arm imaging has become a common assistive tool for this procedure. More advanced methods such as Dyna-CT and neuronavigation have also been reported to be helpful [11–14]. Recently, Mendes et al. reported that intraoperative CT guidance was useful in the puncture of narrow or difficult-to-access FO [17, 21]. Previous studies also reported intraoperative CT scan to be a convenient tool with advantages in operations involving FO puncture for the treatment of TN [18, 22].

However, comparison between different image-guided approaches has rarely been reported, and the application value of intraoperative CT guidance in PBC for TN has been inadequately reported. Hence, we performed this retrospective multi-centric study to compare the effectiveness and safety of intraoperative CT-guided PBC treatment and the common C-arm-guided PBC treatment in patients with ITN.

2. Materials and Methods

2.1. Study Design and Patient Population. After obtaining approvals from the Institutional Review Boards (IRBs) of Beijing Tiantan Hospital, Capital Medical University (BTH-CMU), and Characteristic Medical Center of the Chinese People's Armed Police Force (CMC-CAPF), the medical records and follow-up data of all patients who underwent PBC for ITN in the Department of Pain Management at BTH-CMU and the Institute of Neurotrauma Repair at CMC-CAPF between February 2018 and March 2020 were retrospectively collected and reviewed for analyses. The requirement for informed consent was waived by both IRBs because of the retrospective nature of this study and de-identification was performed during data collection. This study was reported in accordance of STROBE guideline.

The inclusion criteria were as follows: (1) patients older than 18 years old; (2) patients who suffered from craniofacial pain fulfilling the characteristics of ITN as defined by ICHD-3 and who had preoperatively received a clinical diagnosis of ITN; and (3) patients who underwent intraoperative 3D-CT-guided or C-arm-guided PBC of trigeminal ganglion for the treatment of ITN. Patients whose detailed perioperative clinical data or follow-up data were incompletely recorded were excluded from this study.

2.2. PBC Procedures

2.2.1. Preparation and Anaesthesia. C-arm is a routinely used guidance technique in PBC surgeries at both participating centers. To further improve PBC surgery, spiral-CTs were used as an alternative guidance tool. Before PBC operations, patients were explained in detail regarding the procedures of PBC surgeries with both techniques and were asked to choose which technique they preferred.

Patients were placed in supine position with their head centered on a CT scanning bed or an operating table. Blood pressure, heart rate, electrocardiography, and pulse oximetry were continuously monitored. Sufentanil (0.1 μg/kg), propofol (1.5–2 mg/kg), and cisatracurium (0.1 mg/kg) were injected for anaesthesia induction. A laryngeal mask (LMA) was then applied and connected to the circle system for ventilation. Propofol (4 mg/(kg·h)) and remifentanil (0.05–0.1 μg/(kg·minute)) were administered with an intravenous pump to maintain anaesthesia.

Puncture point and puncture path were infiltrated with local anaesthetic (0.5% lidocaine). Puncture was performed by an adapted Hartel approach using a 14 G needle with a semi-sharp stylet (CTZ-15, Qingyuan Medical Instrument, Shenzhen, China) through a stab incision targeting the FO.

2.2.2. 3D-CT-Guided Procedure. The entry point was located approximately 2.5 cm lateral to the commissure of the lips, and the other two reference points were 3 cm anterior to the external auditory meatus along the zygomatic arch, 1 cm inferior to the pupil. Based on the surgeon's clinical experience, the needle was advanced less than 7 cm, where the tip reached near the basal part of the mid-cranial fossa. Then, CT scan was performed, and 3D reconstruction of the CT images was visualized on a post-processing workstation (GE AW VolumeShare 2, version aw4.4, Wisconsin, USA) to determine the exact location of the needle and the FO. The position of the needle was adjusted according to its spatial relationship with the FO, until it was verified by a subsequent CT scan that the needle had entered the FO (Figures 1(a)–1(c)). [22] After the stylet was withdrawn, a disposable balloon catheter (QKS-1850567, Qingyuan Medical Instrument) was inserted into the needle and then into the Meckel's cave using a guide wire. When the end of the balloon catheter was 1 cm past the end of the needle and was 17–19 mm from the FO, [8] the guide wire was removed, and 0.3–0.5 ml of nonionic contrast agent (Omnipaque) was slowly injected into the balloon catheter to inflate the balloon. Another CT scan was performed and 3D images were reconstructed to check the position and shape of the balloon (Figures 1(d)–1(i)). The balloon appears to form the shape of a pear when positioned correctly into the FO. If satisfactory position or shape was not obtained, the balloon was deflated,

the catheter was withdrawn, and the needle was set back and readjusted according to the CT images, following which the balloon was reinflated, and imaging scans and evaluations were performed again [19].

2.2.3. C-Arm-Guided Procedure. C-arm image-intensified fluoroscopy was used to obtain lateral images. A needle of the same model used for the 3D-CT-guided procedure was inserted until it penetrated the FO on lateral C-arm imaging (Figure 2(a)). The same entry point and puncture direction with the CT group were used to insert the needle and identified in sagittal view as well as coronal view of the C-arm. The blunt stylet was then withdrawn, and the balloon catheter (of the same model used in the 3D-CT-guided procedure) was advanced into Meckel's cave under direct C-arm fluoroscopy (Figures 2(b) and 2(c)). The balloon was slowly inflated with nonionic contrast agent (Omnipaque) under fluoroscopic monitoring until it was proximal to the posterior fossa (Figures 2(d) and 2(e)). The shape and position of the balloon were inspected in reference to bony landmarks, such as clivus, sella turcica, and petrous bones (Figure 2(f)). If satisfactory position and pear shape was not achieved, the procedure was repeated for proper placement of the needle, by deflating the balloon, readjusting the catheter and reinflating the balloon, along with reevaluation through imaging scans.

2.2.4. Procedure for Compression. After visual confirmation that the balloon was correctly positioned, a total of 0.3–0.8 ml of contrast agent was injected to compress the nerve [8]. The compression lasted 1.5–3 minutes, depending on the operator's surgical experience [8], after which the balloon was drained and removed along with the needle. The puncture point was compressed for 5 minutes to stop the bleeding, sterile dressing was then applied, and anaesthesia was stopped. After opening their eyes and having the LMA removed, patients were sent for post-anaesthesia care.

2.3. Data Acquisition and Analysis. We collected preoperative, intraoperative, and postoperative data from patients' medical records and the follow-up databases of both hospitals. Preoperative data included gender, age, length of history before PBC, side of TN, involved branches of the trigeminal nerve, preoperative Barrow Neurological Institute (BNI) pain score, and previous surgical treatments. Intraoperative details on the PBC procedures, such as duration of FO puncture, number of needle passes during the procedure, duration of the whole operation, and intraoperative complications and side effects, were also collected. The postoperative data included the BNI pain score, the BNI facial numbness score, and other complications or side effects.

The follow-up databases of both hospitals were built for improving the quality of medical care, and to be used for scientific research after IRB approval is granted. Each patient was clinically evaluated in person before PBC procedure and before discharge. Follow-ups were conducted at 1 month, 2 months, 3 months, and 6 months postoperatively, and then every 6 to 12 months thereafter by telephone calls or even outpatient visits if necessary. Detailed information on pain relief, pain recurrence, complications, and side effects at each follow-up was recorded in the databases.

The intensity of pain was assessed using the BNI pain intensity score [23]. Initial pain relief was defined as a BNI pain score of I or II, achieved within 3 months after PBC treatment. Pain recurrence was defined as an increase in the BNI pain intensity score from class I or II to class III or higher. Numbness was graded using the BNI facial numbness score [23]. Similar to previous studies, the number of needle passes required for successful punctures was recorded and analysed [16, 24]. A needle pass during the procedure is defined as the attempt of moving the needle forward. Before satisfactory position and shape of the balloon were achieved, if a backward movement of the needle or another attempt at FO puncture was performed for any reason, it was regarded as another needle pass.

IBM SPSS Statistics version 23 was used for statistical analyses. For measurement data, if the variables followed a normal distribution, means and standard deviations were calculated, and t-test or analysis of variance was used for intergroup comparisons. Otherwise, for non-normal distributions, expressed as medians and interquartile ranges (IQRs), quartiles were calculated, and Mann–Whitney U test or Kruskal–Wallis H test was used for intergroup comparisons. For categorical data, frequencies and percentages were calculated, and chi-squared test was used for intergroup comparisons. Recurrence-free survival of both groups was estimated and compared using Kaplan–Meier method.

3. Results

3.1. Patient Population and Preoperative Conditions. A total of 294 patients were identified, among which 291 patients were included in analysis. The number of patients who underwent PBCs with C-arm and 3D-CT was 79 (27.1%) and 212 (72.9%), respectively. The patient selection procedure is shown in Figure 3(a). A summary of the patients' parameters is shown in Table 1.

3.2. Effectiveness of PBC Treatments. 4 (5.1%) patients in the C-arm group and 1 (0.5%) patient in the 3D-CT group received an incomplete PBC procedure because of failure of FO puncture despite repeated attempts during the surgery ($P = 0.020$); therefore, other therapies were sought instead. Among patients with successful attempts, 5 (2.4%) patients in the CT group and 11 (14.7%) patients in the C-arm group required more than one needle pass to achieve correct FO cannulation ($P < 0.001$). Initial pain relief was achieved in 202 (95.7%) patients in the 3D-CT group and 71 (94.7%) in the C-arm group ($P = 0.749$, Table 2).

Median time taken for FO puncture was significantly shorter with the guidance of 3D-CT than with C-arm (3 minutes [IQR: 3 minutes–7 minutes] vs 12 minutes [IQR: 2 minutes–22 minutes], $P < 0.001$). In particular, the maximum time taken for FO puncture was higher in C-arm

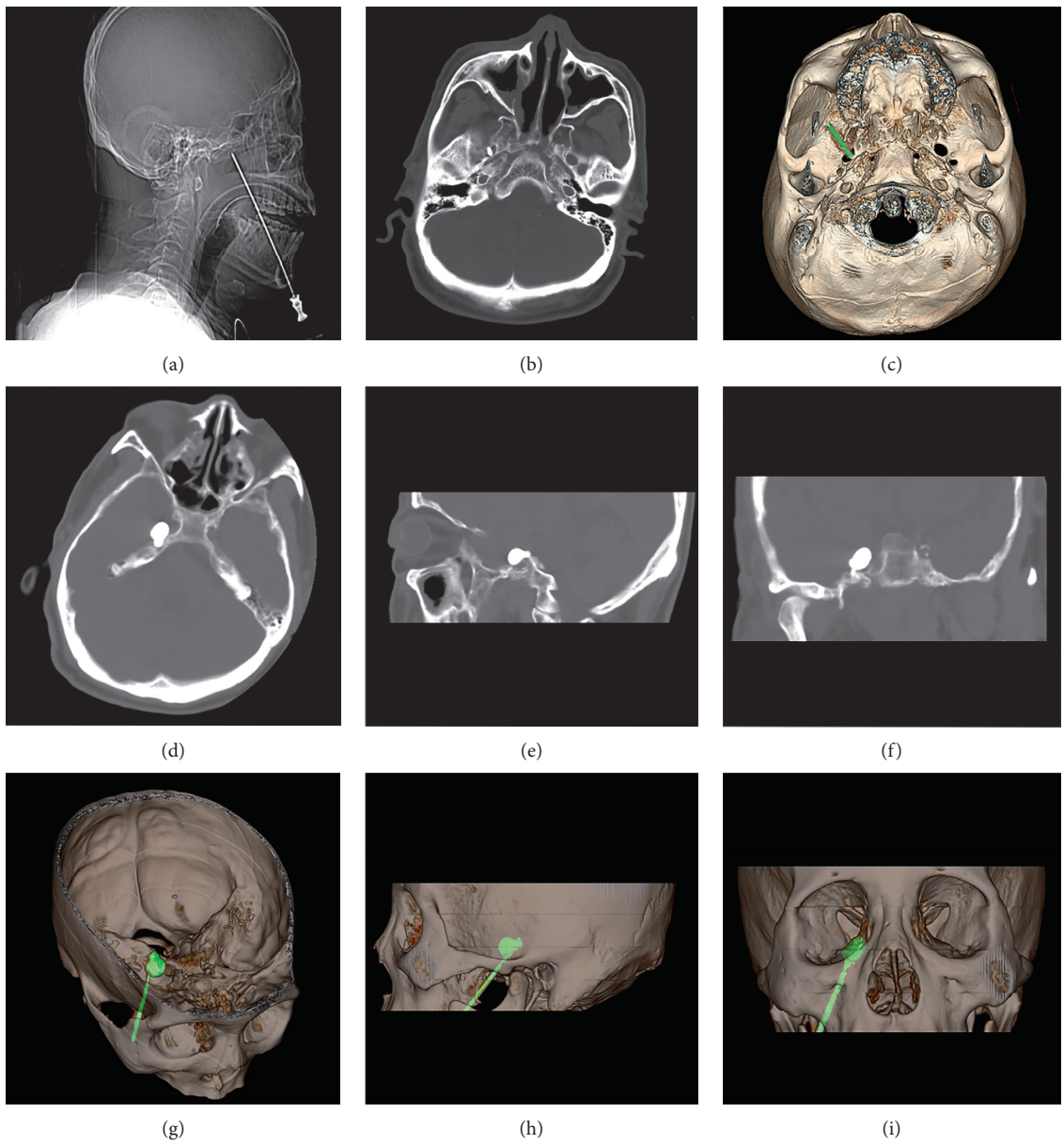

Figure 1: 2D images and reconstructed 3D-CT images during FO puncture. (a) Scout image of spiral CT during FO puncture; (b), (c) 2D and reconstructed 3D images of spiral CT showing the spatial relationship between the needle and the targeted FO; (d-f) axial, sagittal, and coronal views of the pear-shaped balloon; (g-i) reconstructed 3D-CT images provided confirmation of the position and shape of the balloon.

group than in 3D-CT group (40 minutes vs 16 minutes). With the guidance of 3D-CT, the median whole duration of PBC operations was also shorter (19 minutes [IQR: 16 minutes–24 minutes] vs 28 minutes [IQR: 17 minutes–38 minutes], $P < 0.001$). Additionally, the maximum time taken for the whole operation was higher in C-arm group (70 minutes VS 40 minutes). Related results are shown in Figure 3(b).

Among patients who showed initial pain relief after PBCs, the length of follow-up ranged from 8 months to 36 months, with a median of 22 months. 2 patients (2.8%) in the C-arm group and 5 patients (2.5%) in the CT group were lost to follow-up by the time of data acquisition. Five patients (7.0%) in the C-arm group and 15 (7.4%) in the CT group suffered from pain recurrences during follow-ups. Survival analysis revealed no significant difference in recurrence-free survival between groups ($P = 0.839$, Figure 3(c)).

3.3. Safety of PBC Treatments. No puncture-related complications were observed among all included patients. Among patients with successful attempts, common compression-related complications showed no significant difference in incidence between groups (Table 2).

4. Discussion

In this study, we found that both the failure rate of FO puncture and the proportion of patients who need more

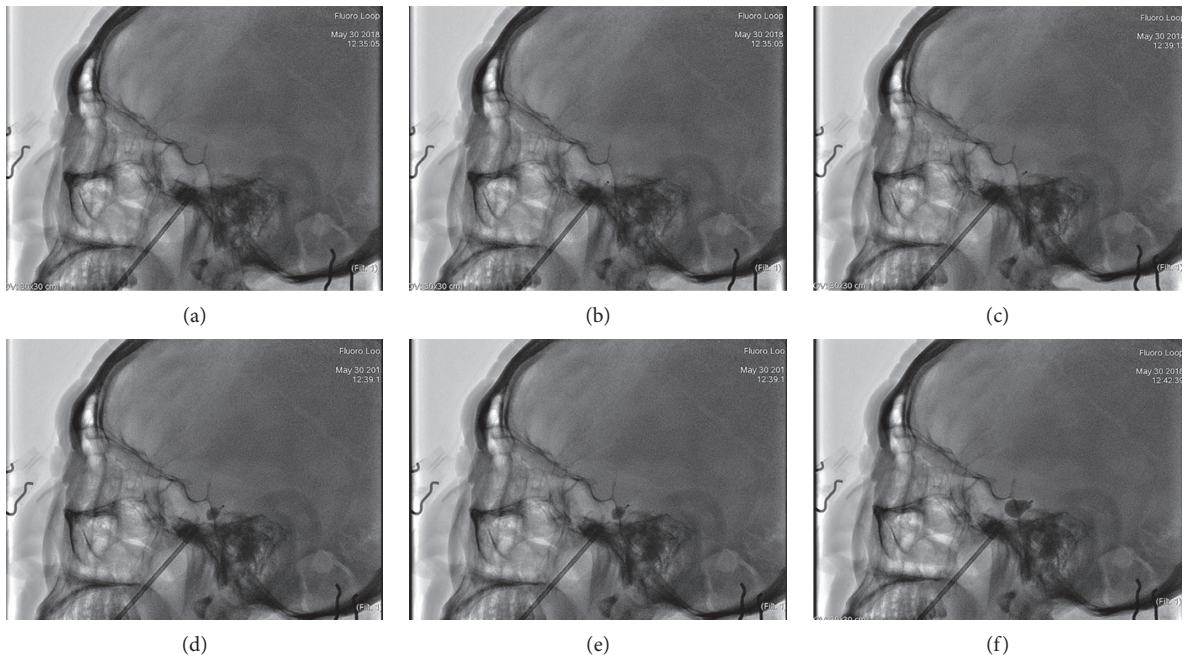

Figure 2: C-arm-guided FO puncture. (a) The needle penetrated the foramen ovale under lateral C-arm imaging; (b), (c) the balloon catheter was advanced into Meckel's cave under direct C-arm fluoroscopy; (d, e) the balloon was slowly inflated with nonionic contrast agent (omnipaque) under fluoroscopic monitoring; (f) the shape of the balloon was confirmed to be pear-like on lateral C-arm imaging.

than one needle pass to get successful attempts were higher in the C-arm group than in the 3D-CT group. Also, the C-arm group needed more time for FO puncture and the whole PBC operation. However, once the FO was punctured successfully and the PBC was performed, the two groups shared similar rates of initial pain relief, similar recurrence-free survival during follow-ups, and similar incidences of postoperative compression-related complications. Upon these findings, we conclude that 3D-CT can facilitate FO puncture and increase the success rate and time efficiency of the procedure compared to the common image-guided method, C-arm.

Time consumption of FO punctures and the entire PBC surgeries was significantly higher in the C-arm group. The increased efficiency might be attributable to the 3D visualizations reconstructed from the thin-of images acquired by CT scans. They provide intuitive, clear and accurate observations of the spatial relationship between the needle and the targeted FO. Quantitative distances and angles can also be measured. None of these benefits can be obtained through the 2D images provided by C-arm imaging, which involves repeated adjustment of the scanning arm and multi-angle 2D scans. Consequently, physicians were able to adjust the needle swiftly and accurately on the CT group, thereby saving time. Furthermore, the length of the procedure was shorter than the values reported in previous studies with other guidance techniques [13, 24]. These previous findings further support the time efficiency of 3D-CT as an image guiding tool for PBC.

In this study, we did not compare 3D-CT with other 3D visual methods, such as Dyna-CT and neuronavigation, because the devices for these imaging techniques were not available in either of the participating centers. Although 3D-CT can provide only semi-real-time guidance, the high success rate of FO puncture was significantly different from the rates in previous reports, which stated that only 18% of neurosurgeons in training felt they would be able to perform the FO cannulation independently and FO cannulation with x-ray imaging alone could have a failure rate as high as 15%, indicating that correction of the needle after a CT scan facilitated FO puncture [12, 25]. The results concerning puncture were in accordance with previous studies on spiral CT-assisted radiofrequency treatment for TN [18, 22]. Thus, it is our opinion that 3D-CT scans are very helpful in validating and correcting needle position during PBC, making them a useful guiding technology for PBC. Meanwhile, as the C-arm is now a common tool to facilitate the FO procedure and 3D-CT showed better assistive performance, we believe that, with the assistance of 3D-CT, FO puncture is easier, and PBCs may show more potential in clinical practice. Recently, 3D C-arm, which could provide both 3D images and real-time guidance, was reported to be used in spinal operations and showed its potential [26]. However, 3D C-arm was not a common tool yet and rarely reported in TN operations. The potential of 3D C-arm will be investigated in the future if the devices are available in our sites.

We observed similar rate of initial pain relief and recurrence-free survival between the two groups. Additionally, our results were consistent with other studies concluding that the PBC method inevitably carries a high risk of facial numbness and masseter weakness [15, 27, 28]. Some researchers believe that reduced compression time can decrease the incidence of complications; however, insufficient compression time could result in unrelieved pain or pain

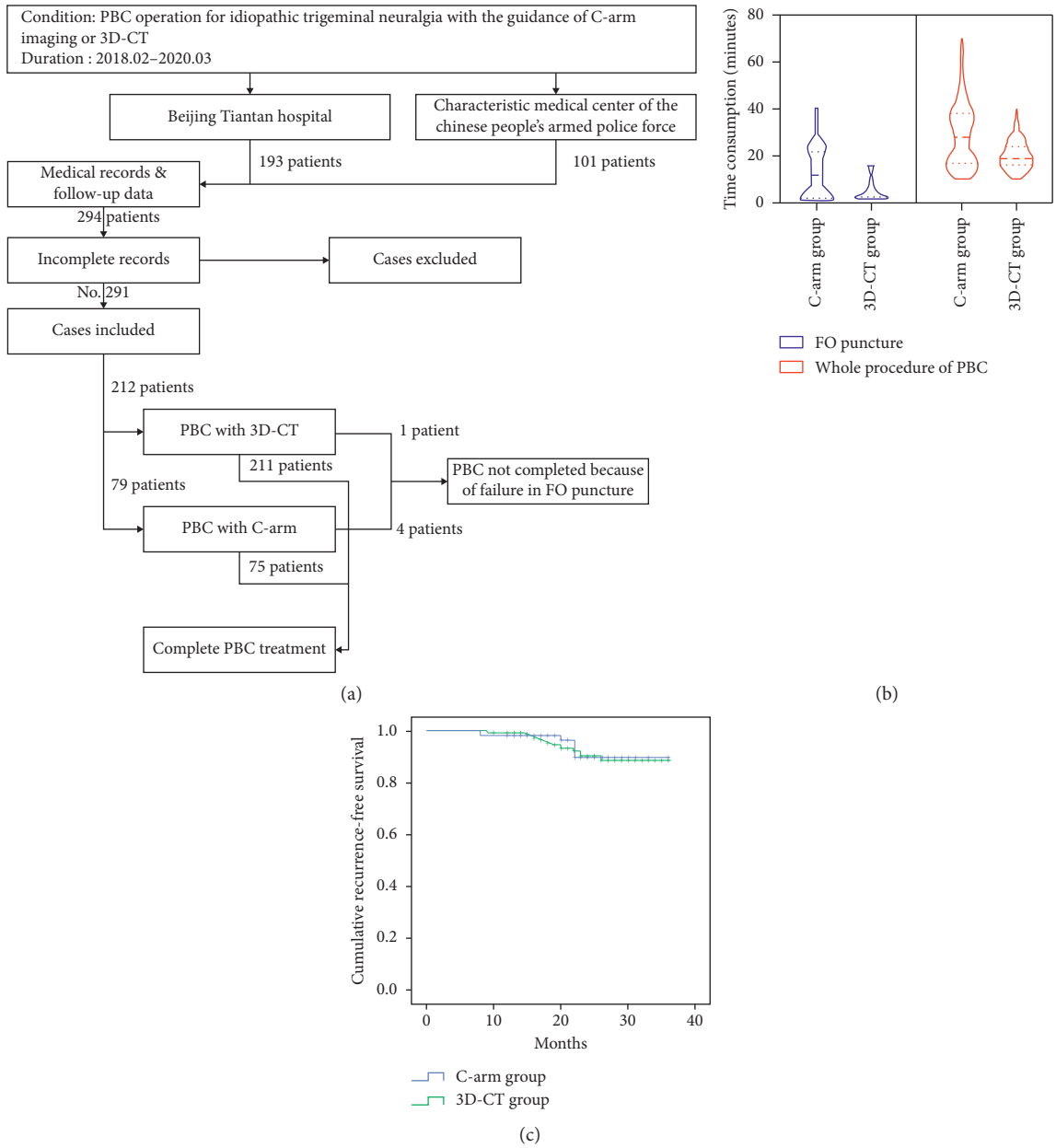

Figure 3: Summary of study results. (a) Plot of patient selection procedure; (b) time consumption of FO puncture and whole procedure of PBC; (c) Kaplan–Meier curves of recurrence-free survival of both groups.

recurrence [11]. To date, there is no consensus on the proper duration of compression or the proper volume of balloon inflation for PBC operations [24, 29, 30]. Given the retrospective nature of this study, there were no pre-set standards for compression time, and the length of compression was determined by the physicians according to their clinical experience. Furthermore, the compression settings could not be completely extracted from medical records, making it impossible to analyse whether similar safety and effectiveness was the result of imbalanced distribution of these settings among groups. Prospective controlled studies aiming at investigating the influences of both different settings and image-guided techniques are in progress.

Except PBC, other microinvasive approaches, such as gamma knife radiotherapy, glycerol rhizotomy, and radiofrequency thermocoagulation, were also reported to be useful in treatment of ITN [1, 6–9]. A recently published meta-analysis concerning TN showed that glycerol rhizotomy showed similar rate of immediate pain relief and pain recurrence with PBC but showed lower incidences of numbness and diplopia, while the incidences of other complications were similar in both groups [9]. Also, PBC showed similar rate of immediate pain relief, pain recurrence, and incidences of complications with radiofrequency thermocoagulation [9]. The reports on comparison between radiotherapy and PBC in the condition of ITN were lacking;

Table 1: Demographic data and preoperative conditions of the included patients.

Variables	Total	C-arm	3D-CT	*P* value
N	291	79	212	
Age (years old)	63.0 (53.9, 68.0)	63.0 (56.3, 66.9)	62.4 (53.7, 69.1)	0.882
Gender (female/male)	182/109	55/24	127/85	0.136
Preoperative disease duration (months)	47.8 ± 18.5	50.2 ± 14.6	46.9 ± 19.7	0.170
Left/right-sided lesion (n)	77/214	15/64	62/150	0.100
Branches affected (n)				0.237
I	15	5	10	
II	39	15	24	
III	36	10	26	
I + II	55	17	38	
I + III	19	6	13	
II + III	77	19	58	
I + II + III	50	7	43	
Preoperative BNI *(n)*				0.270
I	0	0	0	
II	0	0	0	
III	32	12	20	
IV	199	49	150	
V	60	18	42	
Patients with previous surgeries/interventions (n)	113	26	87	0.225
Radiotherapy	71	17	54	—
Radiofrequency	67	26	41	—
PBC	14	3	11	

Table 2: Summary of immediate effectiveness and postoperative complications.

	C-arm ($N = 75$)	3D-CT ($N = 211$)	*P* value
Immediate pain relief (*n*)	71	202	0.749
Postoperative BNI *pain score (n)*			0.266
I	43	141	
II	28	61	
III	0	1	
IV	3	8	
V	1	0	
Complications (n)			
Facial numbness	55	162	0.535
Hypoaesthesia	45	144	0.204
Masseter weakness	14	29	0.347
Herpes	21	65	0.770
Paraesthesia	8	15	0.330
Dysaesthesia	6	15	0.799
Diplopia	3	3	0.187
Keratitis	4	6	0.296
Postoperative BNI *facial numbness score (n)*			0.853
I	20	49	
II	12	36	
III	27	86	
IV	16	40	

however the reported time to pain relief was considered longer than percutaneous approaches [31]. Thus, these approaches are considered to be an option for ITN with their own potential.

This research has some limitations. First, this was a retrospective study performed in only two centers. Due to the retrospective nature of this study, patients were not assigned randomly; therefore the results may have been biased. Second, the duration of follow-up was relatively short compared to that of other published studies. Third, some valuable variables, such as the pressure of the balloon, were unavailable due to the retrospective nature of this study. To address these problems, prospective randomized studies on the effectiveness and safety of PBC with a variety of

parameters for the treatment of TN must be performed in the future. In the meantime, the results of a longer follow-up of this study will be published in the next few years.

5. Conclusions

3D-CT facilitates FO puncture and improves the success rate of PBC procedures. The overall time efficiency of PBC is also increased with 3D-CT. Thus, 3D-CT is an image guidance technology with potential for PBCs on ITN.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request via e-mail.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Fang Luo and Hongtao Sun correspond to this work equally.

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Research Article

Intra-Articular Application of Sluijter-Teixera Poisson Pulsed Radiofrequency in Symptomatic Patients with Knee Osteoarthritis: Focus upon Clinical Efficacy and Safety

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Purpose. To retrospectively evaluate the effectiveness of intra-articular application of Sluijter-Teixera Poisson pulsed radiofrequency (STP PRF) in knee osteoarthritis symptomatic patients with chronic pain refractory to conservative therapies. *Materials and Methods*. Institutional database research of two centers identified 39 cases of knee osteoarthritis patients treated with intra-articular STP PRF. Pain prior and one-week and one-, three-, six-, and twelve-month post-STP PRF was compared by means of a numeric visual scale (NVS) questionnaire. Cardiovascular and Interventional Radiological Society of Europe (CIRSE) classification system was used for complications reporting. Mean patient age was 71.59 ± 11.99 years, mean body mass index was 30.23 ± 4.69, and male/female ratio was 9/30. *Results*. Mean baseline pain score was 8.31 ± 1.70 NVS units. This was reduced to a mean value of 0.90 ± 1.50 NVS units one-week post-RF, 1.08 ± 1.53 at one month, 1.54 ± 1.88 at three months, 2.33 ± 2.17 at six months, and 3.23 ± 2.23 at 12 months of follow-up ($p < 0.01$). Pain decrease of more than 4 NVS units was noticed in 35/39 knees (89.7%) at first week, 36/39 knees (92.3%) at first month, 35/39 knees (89.7%) at three months, 32/39 knees (82.1%) at six months, and 25/39 knees (64.1%) at one year. There was no recurrence during the follow-up. No complication was observed. *Conclusions*. Percutaneous, intra-articular application of STP PRF is an effective and safe technique for chronic pain reduction in patients with knee osteoarthritis. Results seem to be reproducible and long lasting with significant patient satisfaction at 12-month follow-up.

1. Introduction

The most common cause of chronic knee pain is degenerative osteoarthritis most commonly affecting middle-aged and elderly patients resulting in significant functional capacity reduction [1, 2]. Therapeutic armamentarium includes physical and oral pharmacologic therapy, intra-articular injections, neurolytic or neuromodulatory techniques, transcatheter arterial embolization, minimally invasive arthroscopic treatment, and partial or total knee arthroplasty [3–6]. Intra-articular application of pulsed radiofrequency with or without viscosupplementation has been reported in different studies as a safe and efficacious technique for pain reduction and mobility improvement in symptomatic patients suffering from degenerative knee osteoarthritis [7–9]. Pulsed mode of radiofrequency energy (PRF) deposition is characterized by long silent phases (480 milliseconds) which between the short bursts of energy application (10–20 milliseconds) contribute to maintaining tissue temperature under 42°C which is below the irreversible tissue damage threshold; this results in much less (if any) neurodestructive potential [10, 11]. PRF creates a neuromodulatory effect, suppressing both excitatory C-fibers activation and the spread of pain impulse at the synaptic junction, in addition to a modulatory effect on proinflammatory cytokines [6, 9].

A variety of pulsed radiofrequency mode utilizes the Poisson curve for energy distribution (Sluijter-Teixera Poisson radiofrequency) (STP) aiming to provide pulses which are meticulously spread in order to achieve highest treatment result with the lowest heat development [12–14]. STP mode of pulsed radiofrequency provides a short pulse width for minimal destructive effect and a higher coefficient of variance for better treatment effectiveness. This variation in pulsed mode has been applied inside the intervertebral discs for discogenic pain and intra-articularly for arthrogenic pain with preliminary results reporting significant efficacy rates on terms of pain reduction and mobility improvement [12–14]. Combining intra-articular application of pulsed radiofrequency to genicular nerve pulsed neuromodulation seems to result in improved WOMAC (Western Ontario and McMaster Universities Arthritis Index) scores at 3 months after the treatment with a longer period of efficacy when compared to extra-articular application alone; however, in this first clinical comparative study of different approaches for pulsed radiofrequency in knee osteoarthritis, both arms were effective in reducing pain at 3 and 6 months follow-up [15]. Intra-articular application of RF in the knee joint is related to the action of electric fields on immune cells rather than on deflection of the current by bony surfaces and therefore could work as a stand-alone approach.

The purpose of this study is to retrospectively evaluate the effectiveness of intra-articular application of Sluijter-Teixera Poisson pulsed radiofrequency in patients with knee osteoarthritis suffering from chronic pain refractory to conservative therapies.

2. Materials and Methods

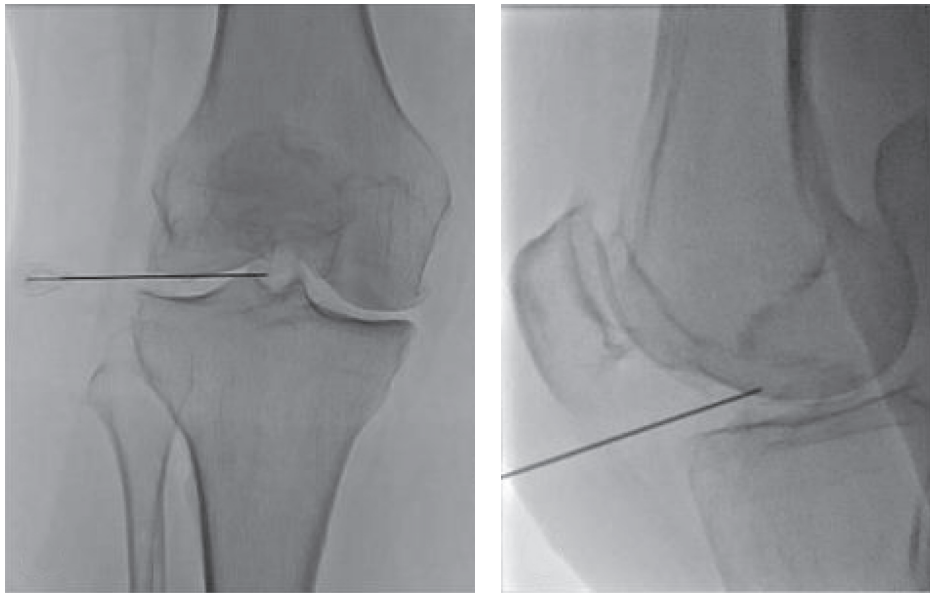
2.1. Patient Selection and Evaluation. Institutional database research of two centers from 01/12/2018 to 01/08/2020 identified 39 symptomatic patients with knee osteoarthritis who underwent intra-articular application of STP PRF. Inclusion criteria included adult patients with symptomatic knee osteoarthritis diagnosed with X-rays and classified as grade II to IV according to the Kellgren–Lawrence (KL) classification; pain in all patients was located at the level of the knee joint with no neurologic signs and was refractory to conservative therapies (analgesics and nonsteroidal anti-inflammatory drugs as well as physiotherapy) in the past six months without success. At the time of treatment, all patients had discontinued all drug therapy for at least two weeks. All included patients and lesions should have been evaluable for the 12-month follow-up. The diagnosis was made by an interventional radiologist with 11 years of experience or the referring orthopaedic surgeon who identified the potential participants and verified their eligibility. Preoperational evaluation included imaging with knee X-rays on anterior-posterior and lateral views used to evaluate patients according the Kellgren–Lawrence (KL) classification along with clinical evaluation; from the 39 patients included in the present study, 7 were classified as grade 2 (KL-2), 18 as grade 3 (KL-3), and 14 as grade 4 (KL-4). Exclusion criteria for the procedure included untreatable coagulopathy, active, systemic, or local infections and patient unwilling to consent to the procedure and the study.

2.2. Technique. Under extensive local sterility and fluoroscopic guidance, selection of the entrance skin point was performed and local anesthesia (3–5 ml of lidocaine hydrochloric 2%) was applied. No preoperative antibiosis was intravenously administered. A 20 gauge/10 cm RF cannula was percutaneously inserted from the anterolateral region of the knee joint. The final position of the RF cannula inside the joint (midline and in an equidistant level between tibial and femoral bones) was fluoroscopically verified in face and lateral projections (Figure 1). Coaxially, a RF electrode with a 10 mm "active tip" (EQUIP MEDIKEY BV, Gouda Netherlands) was introduced, and a 10-minute neurolysis session was performed with PRF (1,200 pulses at 50 V with 10 ms duration followed by a 480 ms silent phase). Each patient remained in the hospital for 30–45 minutes (only for observation) and was then discharged with suggestions of 1-day rest and then being free to engage in normal activities.

2.3. Statistical Analysis. Continuous variables are presented as mean ± SD, whereas categorical variables are presented as absolute frequencies. Pain prior and one-week and 1-, 3-, 6-, and 12-month post-STP PRF was compared by means of a numeric visual scale (NVS) questionnaire [16]. To evaluate differences from baseline to post-RF follow-up, a 3×5 (osteoarthritis group by time) mixed model analysis of variance (mixed model ANOVA) was conducted (with osteoarthritis group as the between-group factor and time as the within-group factor). Significant main effects for time were followed by dependent t-tests between baseline and follow-up timepoints. Statistically significant group by time interactions was further explored using pairwise comparisons. Pain improvement and recurrences were defined according to previous study [9]. Specifically, improvement was defined as any pain decrease of more than 4 NVS units after the treatment. Recurrence during the follow-up was defined as any pain increase lower than the score before treatment despite initial improvement. The association between the percentage of cases with improvement/no change/recurrence and osteoarthritis groups was examined using chi-square (χ^2). The statistical threshold was set at $p < 0.05$, with Bonferroni correction for multiple comparisons. All analyses were conducted with SPSS v. 22.0 (IBM Corp, Armonk, NY). The definition of complications was assigned according to the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) classification system [17].

3. Results

Table 1 presents demographic and patient-related characteristics for the total sample of 39 cases. Descriptive measures (mean, SD, and Min-Max) for NVS were calculated both at baseline before RF and different follow-up



(a) (b)

Figure 1: (a) Face fluoroscopy view illustrating the final position of the trocar at the level of the tibial crest. (b) Lateral fluoroscopy view illustrating the final position of the trocar anteriorly to the tibial crest.

Table 1: Demographic characteristics of the total group of cases ($N = 39$).

Variables	Statistics			
	Mean	SD	Min	Max
Age (yrs)	71.59	11.99	37	93
Gender (M/F)		9/30		
Weight (kg)	81.66	15.72	45	140
Height (cm)	164.10	6.95	150	185
BMI	30.23	4.69	15.57	44.69

Note. SD = standard deviation; Min = minimum; Max = maximum; yrs = -years; M/F = male/female; kg = kilograms; cm = centimeters. Continuous variables (age, weight, and height) are presenting as mean ± SD (min-max). Gender is presenting in absolute frequency.

timepoints. The profile of mean NVS score at baseline and follow-up timepoints is shown in Figure 2. Mean pain score prior to RF was 8.31 ± 1.70 NVS units. This baseline score was reduced to a mean value of 0.90 ± 1.50 NVS units one-week post-RF, 1.08 ± 1.53 NVS units at one month, 1.54 ± 1.88 NVS units at three months, 2.33 ± 2.17 NVS units at six months, and 3.23 ± 2.23 NVS units at 12 months of follow-up (Table 2).

A 3 × 5 mixed model ANOVA with Greenhouse–Geisser correction showed a significant main effect of time [F (3.017, 108.613) = 179.577; $p < 0.001$, partial eta^2 = 0.833)], osteoarthritis group [F (2, 36) = 12.947; $p < 0.001$; partial eta^2 = 0.418], and osteoarthritis group by time interaction [F (6.034, 108,613) = 4.116; $p = 0.001$; partial eta^2 = 0.186]. Paired samples t-tests with Bonferroni correction were used to examine post hoc comparisons on NVS between different follow-up timepoints across all osteoarthritis groups (Figure 2). We found significant differences between baseline

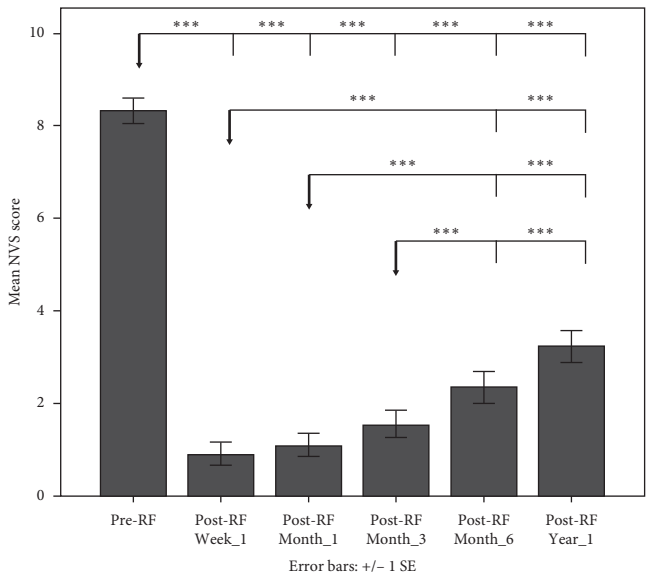


Figure 2: Bar chart illustrating mean NVS scores and standard error (1SE) prior and during the follow-up period across all groups (note: the reference point for each comparison is indicated with a grey arrow; *** $p < 0.005$, ** $p < 0.01$, and * $p < 0.05$ after Bonferroni correction).

and (a) week_1 NVS (mean difference = 7.271; $p < 0.001$), (b) month_1 NVS (mean difference = 7.051; $p < 0.001$), (c) month_3 NVS (mean difference = 6.630; $p < 0.001$), (d) month_6 NVS (mean difference = 5.973; $p < 0.001$), and (e) year_1 NVS (mean difference = 5.264; $p < 0.001$). Of note, post-RF NVS score started to increase after week_1 and until the end of the 12-month period, yet the differences were not

Table 2: Descriptive statistics of NVS questionnaire in the total group of 39 cases at different timepoints.

Timepoints	Statistics			
	Mean	SD	Min	Max
Pre-RF				
Baseline	8.31	1.70	5	10
Post-RF				
Week_1	0.90	1.50	0	6
Month_1	1.08	1.53	0	5
Months_3	1.54	1.88	0	7
Months_6	2.33	2.17	0	7
Year_1	3.23	2.23	0	7

Note. NVS = numeric visual scale; RF = radiofrequency; SD = standard deviation; Min = minimum; Max = maximum.

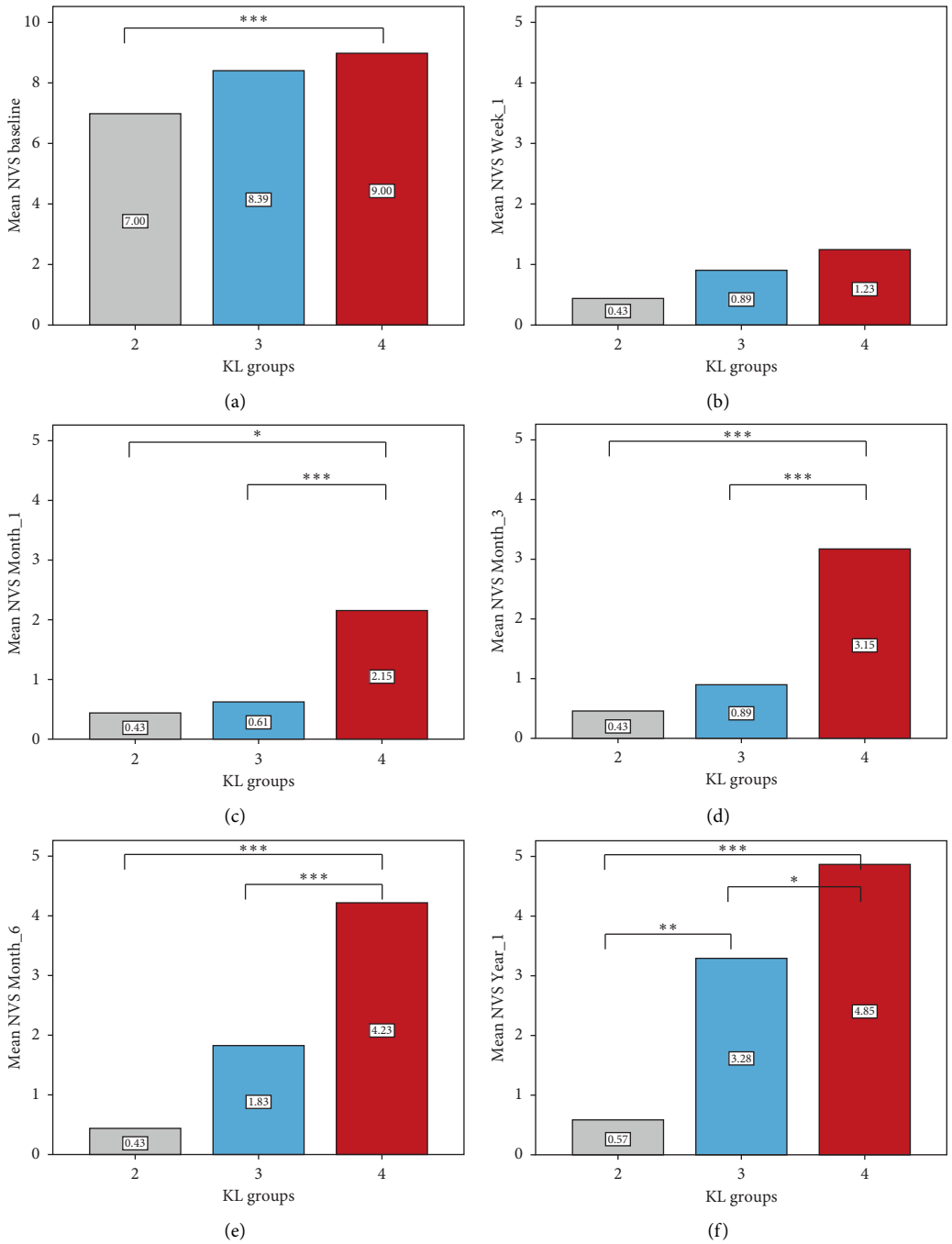


Figure 3: Bar chart illustrating mean NVS scores prior and during the follow-up period across the three osteoarthritis groups (KL-2, KL-3, and KL-4) (note: *** $p < 0.005$, ** $p < 0.01$, and * $p < 0.05$ after Bonferroni correction).

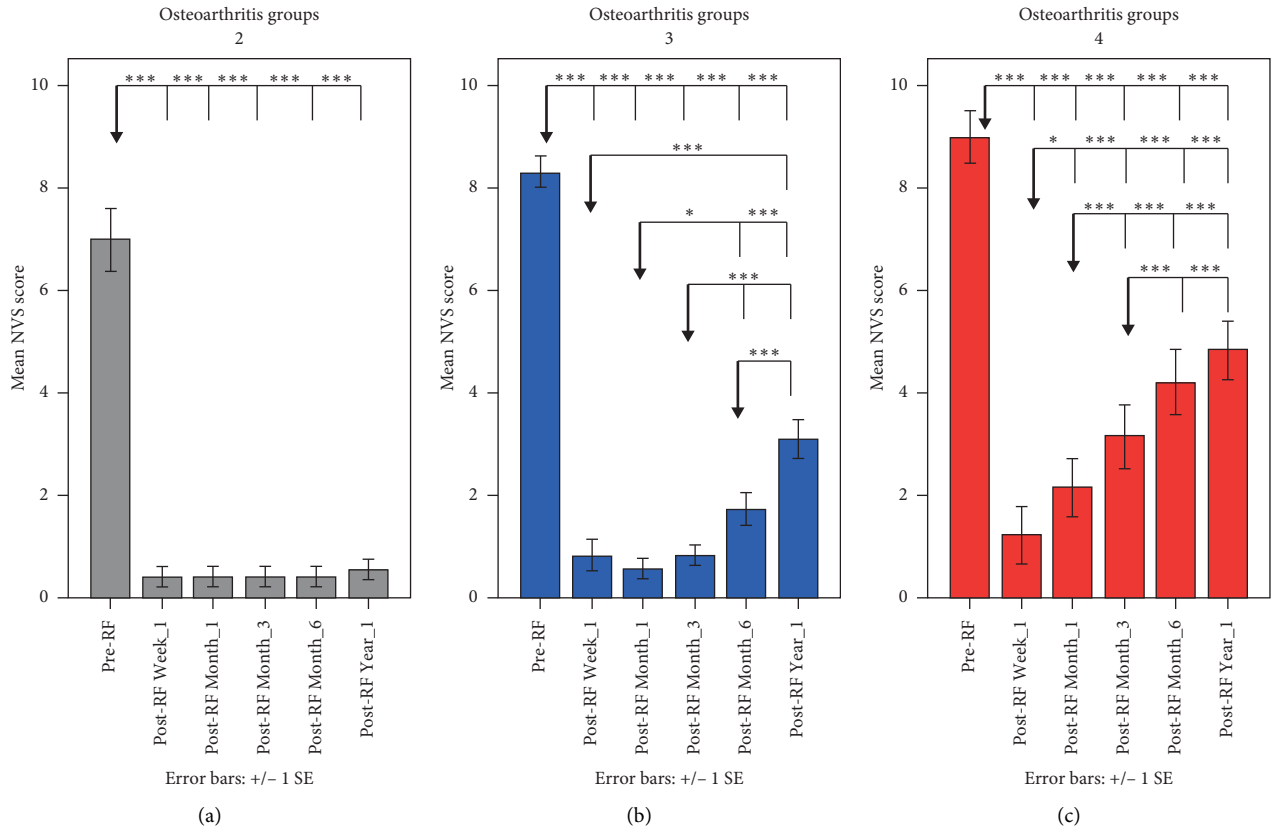


Figure 4: Bar charts illustrating mean NVS scores and standard error (1SE) prior and during the follow-up period within each osteoarthritis group (note: the reference point for each comparison is indicated with a grey arrow; $^{***}p < 0.005$, $^{**}p < 0.01$, and $^{*}p < 0.05$ after Bonferroni correction).

significant within the first three months (week_1, month_1, and month_3), and only comparisons of these three post-RF NVS scores with month_6 and year_1 were significant ($p < 0.05$, Bonferroni correction).

Based on the significant group by time interaction, pairwise comparisons were further examined (Figures 3 and 4). We found significant differences on NVS score between KL-2 and KL-4 at baseline ($p = 0.034$), month_1 ($p = 0.030$), month_3 ($p = 0.001$), month_6 ($p < 0.001$), and year_1 ($p < 0.001$). Osteoarthritis groups KL-3 and KL-4 differed on NVS score in month_1 ($p = 0.008$), month_3 ($p < 0.001$), month_6 ($p = 0.001$), and year_1 ($p = 0.023$). Furthermore, groups KL-2 and KL-3 differed on NVS score only in year_1 ($p = 0.006$). There were no significant differences between KL-2, KL-3, and KL-4 in week_1 ($p > 0.05$). Figure 4 depicts the profile of NVS scores across time separately for each osteoarthritis group (KL-2, KL-3, and KL-4) as well as between different timepoint comparisons within each group. Improvement (pain decrease of more than 4 NVS units during follow-up) was noticed in 35/39 knees (89.7%) at first week, 36/39 knees (92.3%) at first month, 35/39 knees (89.7%) at three months, 32/39 knees (82.1%) at six months, and 25/39 knees (64.1%) at one year. There was no recurrence (pain increase) during the follow-up. The percentage of cases with no changes or improvement in follow-up compared to baseline is shown in Figure 4. There was not any significant association between improvement/no change and osteoarthritis group (chi-square, $p > 0.05$).

Mean pain score prior to RF was 8.31 ± 1.70 NVS units. This baseline score was reduced to a mean value of 0.90 ± 1.50 NVS units one-week post-RF, 1.08 ± 1.53 at one month, 1.54 ± 1.88 at three months, 2.33 ± 2.17 at six months, and 3.23 ± 2.23 at 12 months of follow-up (Table 2 and Figure 2). A repeated measures ANOVA with Greenhouse–Geisser correction showed that mean NVS differed significantly between timepoints F (2.979, 113.189) = 190.026; $p < 0.001$, partial eta2 = 0.833). Paired samples t-tests with Bonferroni correction were used to examine post hoc comparisons between baseline NVS and NVS at different follow-up timepoints. We found significant differences between baseline and (a) week_1 NVS (mean difference = 7.410; $p < 0.001$), (b) month_1 NVS (mean difference = 7.231; $p < 0.001$), (c) month_3 NVS (mean difference = 6.769; $p < 0.001$), (d) month_6 NVS (mean difference = 5.974; $p < 0.001$), and (e) year_1 NVS (mean difference = 5.077; $p < 0.001$).

Improvement (pain decrease of more than 4 NVS units during follow-up) was noticed in 35/39 knees (89.7%) at first week, 36/39 knees (92.3%) at first month, 35/39 knees

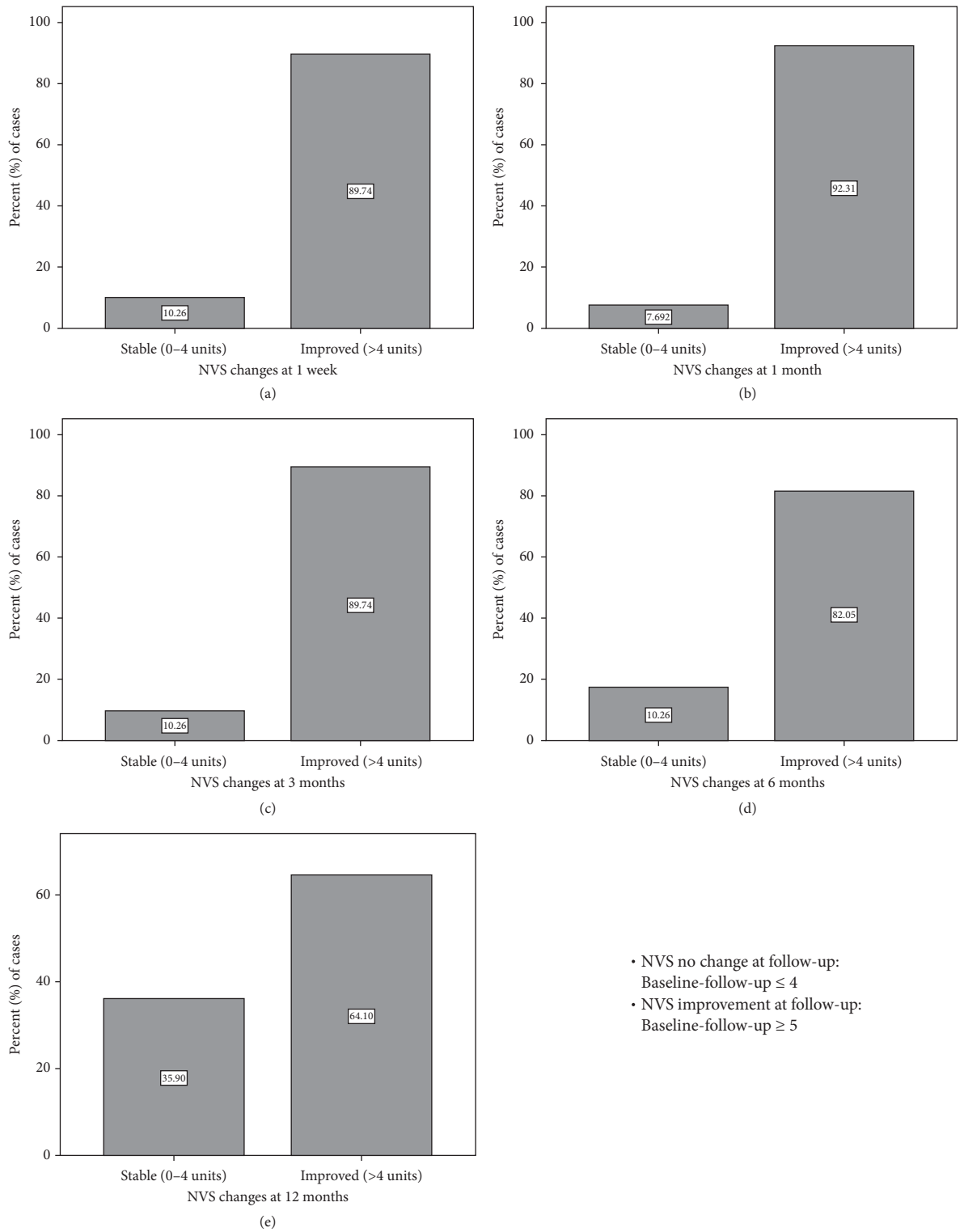


Figure 5: Percentage of cases with no change or improvement of pain based on the comparison between baseline (before RF) and follow-up (post-RF) NVS scores.

(89.7%) at three months, 32/39 knees (82.1%) at six months, and 25/39 knees (64.1%) at one year. There was no recurrence (pain increase) during the follow-up. The percentage of cases with no changes or improvement in follow-up compared to baseline is shown in Figure 5.

4. Discussion

The present study adds to the growing number of case series showing that intra-articular application of PRF is an efficacious and safe technique in terms of achieving pain

reduction [7–9, 15]. Similar to other studies, in the present case series, the treatment of pain due to knee osteoarthritis with intra-articular application of PRF was successful and well tolerated [7–9, 15]. One major difference of the present study is that all patients were treated with STP PRF as a stand-alone therapy, resulting however in no significant differences concerning the efficacy and safety rates [7–9, 15]. Another major difference is that although towards the end of the 12-month period, there is a tendency for pain increase and this is significantly lower than the baseline requiring no new therapeutic session for further symptom improvement [7–9, 15].

Although the pathophysiology and action mechanism of intra-articular PRF is not entirely clear, potential explanations include modulation of inflammatory response especially associated with cytokine production along with the effect upon peripheral osseous nerve endings which are related to pain perception; this effect upon nerve fibers seems to be amplified whenever a low-energy electric field is applied within a closed joint [18–20]. There is no doubt that peri- and postprocedural pain is limited during PRF in comparison to continuous RF neurolysis, thus enabling the procedure to be held under local anesthesia. When compared to continuous RF neurolysis of genicular nerves, intra-articular application of STP PRF is a less complex procedure with shorter intraprocedural duration since only one electrode is necessary to be placed inside the joint instead of three placed at the level upper and lower medial and upper lateral genicular nerves.

Kellgrene and Lawrence scale classifies osteoarthritis based upon the severity of radiographic findings [21]. The results of the present study are in accordance with those of other paper reporting that higher grades in KL scale (more severe osteoarthritis) are related to less and of shorter duration pain reduction [7, 9]. Although in the 1st week and 1st month, there is no significant difference between KL grades 2, 3, and 4 later in the follow-up period at 6th and 12th month of follow-up and there is a clear difference between patients with severe osteoarthritis (grade 4) versus those with moderate (grade 3) or mild (grade 2). Similar differences at the same follow-up timepoints are reported between KL-2 and KL-3 grades (moderate versus mild). Possibly other therapies including either neurolysis of genicular nerves or transarterial embolization may be proven more efficient in more severe osteoarthritis; however, at the moment, there are no data available to support such a hypothesis.

Limitations of our study include that this is a retrospective study lacking a control group which will consist of patients undergoing either a sham procedure or any other local therapy. Furthermore, there was no direct comparison of intra-articular application of STP PRF either to other pulsed modes or to the extra-articular neurolysis of the genicular nerves by means of continuous RF.

Percutaneous, intra-articular application of STP PRF is an effective and safe technique for chronic pain reduction in patients with knee osteoarthritis. Results seem to be reproducible and long lasting with significant patient satisfaction at 12-month follow-up. The results of the present study do not show a clear need of repeating the session at 1 year. Further evaluation of the technique against sham trial and/or other local therapies is warranted.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent

Informed consent was obtained from all individual participants included in the study. Consent for publication was obtained for every individual person's data included in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Efficacy and Safety of Ultrasound-Guided Radiofrequency Treatment for Chronic Pain in Patients with Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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Background. Knee osteoarthritis (KOA) is a common degenerative disease associated with joint dysfunction and pain. Ultrasound-guided radiofrequency (RF) may be a promising therapy in the treatment of chronic pain for KOA patients. *Objective*. To evaluate the efficacy and safety of ultrasound-guided RF treatment for chronic pain in patients with KOA. *Design*. A systematic review was conducted, and a meta-analysis was carried out when possible. *Setting*. We examined the studies evaluating the clinical efficiency of ultrasound-guided RF on chronic pain in KOA population. *Method*. A systematic review for the efficacy and safety of ultrasound-guided RF treatment for pain management of KOA patients was carried out in PubMed, EMBASE, Cochrane Library, Web of Science, Wanfang Data, and China National Knowledge Infrastructure (CNKI) from the date of inception to February 2020, and a meta-analysis was conducted. The primary outcomes of pain intensity (visual analogue scale or numerical rating scale) and knee function [the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)] were evaluated from baseline to various follow-up times by random-effects model. Heterogeneity was assessed by I^2 statistic and the potential sources of heterogeneity by subgroup and metaregression analyses, respectively. *Results*. Eight publications with 256 patients were included in the meta-analysis. RF could relieve pain with −4.196 of pooled mean difference and improve knee function by decreasing 23.155 points in WOMAC. Three patients had ecchymosis, two with hypoesthesia and one with numbness after the procedure, and improved within 6 months. Furthermore, study design and treatment target were the sources of heterogeneity by subgroup and metaregression analyses, accounting for 37% and 74% of variances, respectively. Target of genicular nerve achieved better pain relief than intra-articular or sciatic nerve. Sensitivity analysis showed that removal of any single study was unlikely to overturn the findings. *Limitations*. There were some limitations in the study. Firstly, the small number of relevant studies limited the confidence level of the meta-analysis. Also, the significant heterogeneity may not be explained due to the limited data. Secondly, the direct comparison of two different guidance methods (ultrasound vs. fluoroscopy) for RF therapy is lacking. In addition, the outcomes were blindly assessed in the meta-analysis from all studies according to evaluation of bias, which could affect the reality of the data. Finally, most of the studies only provided short follow-up times, so we could not analyze the long-term effectiveness of ultrasound-guided RF in the treatment of patients with KOA. *Conclusions*. Ultrasonography is an effective, safe, nonradiative, and easily applicable guidance method for RF in pain relief and functional improvement in KOA patients.

1. Introduction

Knee osteoarthritis (KOA) is a very common joint disease and associated with diverse factors including age, obesity, metabolic bone diseases, acute or chronic joint injuries, etc. [1]. The prevalence of KOA ranges from 4.2% to 15.5% and gradually increases with age. Approximately 80% of KOA patients could be diagnosed by imaging at the age of 65 years or older, while only 60% of patients have shown clinical manifestations [2, 3]. Pain and disabilities are the major consequences of KOA, with 25% of patients suffering from severe arthralgia. Furthermore, KOA was ranked 11th among the 291 disabling illnesses worldwide [4]. It is currently believed that failure of chondrocytes to maintain homeostasis between synthesis and degradation of extracellular matrix and subchondral bone leads to osteoarthritis [5–8]. Treatments of KOA include noninvasive therapies such as medication, physical therapy, and rehabilitation as well as minimally invasive strategies from intra- or periarticular injections to radiofrequency (RF) [9]. Multiple studies have shown that postoperative RF therapy could accelerate the early rehabilitation of the joints in patients with late stage of KOA after joint replacement surgery [10, 11].

Recently, minimally invasive RF has been extensively used in the treatment of different stages of KOA and has achieved convincing therapeutic benefits. However, conventional RF is routinely guided by X-rays, so it may increase the risk of radiation exposure to the patients and health care providers [12]. Thus, musculoskeletal ultrasonography has become a potential guidance method for RF instead of fluoroscopy in chronic pain management due to its unique advantages [13, 14]. For example, ultrasound guidance is very accurate in peripheral or paraspinal nerve blocks to avoid injury of blood vessels and pleura [15, 16]. The efficacy of ultrasound-guided intervention is associated with many factors such as the settings of ultrasound device, preoperative administration of diagnostic nerve block (DNB), the location of targeted site, the skill of physician, etc. [17]. In recent years, more studies have demonstrated its therapeutic effects on the improvements of soreness, pain, and functional impairments induced by KOA, including case reports, retrospective and prospective uncontrolled studies, and randomized controlled trials (RCTs). However, confounding factors from these studies such as sample size, different methods or procedures may affect the outcomes. Meanwhile, there is no systematic analysis for evaluating the efficacy and safety of ultrasound-guided RF in the treatment of chronic pain in KOA patients. Therefore, we searched several databases from relevant literature to perform a systematic review and meta-analysis to evaluate the efficacy and safety of ultrasound-guided RF for providing preliminary scientific evidence for its clinical application in the treatment of patients with KOA.

2. Methods

2.1. Design. A systematic review was conducted, and a meta-analysis was carried out when possible.

2.2. Search Strategy. We systematically searched several electronic databases including PubMed, Excerpta Medica Database (EMBASE), Cochrane Library, Web of Science, Wanfang Data, and China National Knowledge Infrastructure (CNKI) via strategies developed using the appropriate Medical Subject Headings (MeSH) terms from the date of inception to February 2020. Keywords such as "knee osteoarthritis," "ultrasound guided," "radiofrequency therapy," "genicular nerve," "intra-articular," and "chronic knee pain" were used. No date, language, or country limitations were applied to the searching.

2.3. Inclusion Criteria. The inclusion criteria for the meta-analysis were as follows: (1) human clinical trials with or without control groups and cointervention were allowed if the trial was performed equally to both arms; (2) patients were diagnosed with KOA and suffered from chronic pain without satisfying pain relief by conservative therapies; (3) patients received RF therapy such as pulsed radiofrequency (PRF) or radiofrequency ablation (RFA); (4) minimally invasive procedure was completed under the guidance of ultrasound; and (5) necessary evaluation index was provided before and after RF therapy, for pain intensity and knee function including visual analogue scale (VAS), numerical rating scale (NRS), Oxford Knee Score (OKS), or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and for quality of life including 36-Item Short-Form Health Survey (SF-36).

2.4. Exclusion Criteria. The exclusion criteria for the meta-analysis were as follows: (1) full text is not available; (2) patients received total knee arthroplasty (TKA) or other knee surgery; (3) case report; (4) studies with insufficient data or uncompleted RCT; and (5) studies with doubtful data such as illogical outcomes without reasonable explanation.

2.5. Study Selection. After targeted publications were found from different databases, the duplicates were removed first by two experienced investigators independently. Next, irrelevant studies were excluded by further scanning the title and abstract of publication by the inclusion criteria, and then the full text of remaining study was carefully screened to identify eligibility according to the exclusion criteria. Any uncertainty or disagreements were finally resolved via discussion between the two investigators and consulted with the third investigator to reach consensus.

2.6. Data Extraction. Two investigators independently extracted relevant data from each study including the first and corresponding authors, year of publication, country, study design, sample size, demographic characteristics (age and gender), grade of radiologic KOA (Kellgren–Lawrence grading system), follow-up time, type of RF, ultrasound transducer parameter, treatment targets and controls, primary outcomes such as the scores of pain intensity (VAS or NRS) and knee function (WOMAC or Lysholm knee scoring

scale) at baseline and available follow-up times, complications or adverse effects, conclusion, and limitations. We contacted the first and/or corresponding authors of study to verify any unclear information and data by e-mails, and the data were considered to be irretrievable without a reply from the authors. All the information was recorded in a prepared spreadsheet, and data were fully analyzed after collection.

2.7. Quality Assessment. The quality and risk of bias for each study were independently assessed by at least two examiners. Additional investigators were consulted when discrepancies were present. RCTs were assessed by the criteria from the Cochrane Handbook for Systematic Reviews of Interventions [18]. The potential sources of bias include random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias were judged as "low risk," "high risk," or "unclear risk," respectively. For nonrandomized studies, different biases were determined by the criteria according to "Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions" [19]. This specific form contains 9 questions, and each question represents a potential source of bias. Positive answer indicates low risk of bias, while negative answer means high risk of bias. Newcastle-Ottawa Scale (NOS) criteria were also used for reference [20].

2.8. Statistical Analysis. One of the primary outcomes from the studies was the pain intensity of patients as reported as the VAS (0–10 or 0–100 mm) or NRS (0–10) in different studies. To standardize the pain scale, the VAS (0–10 cm) was equivalent to the NRS (0–10) and transformed the scale from 0–10 cm to 0–100 mm. The 95% confidence interval (CI) for the difference in means was used to measure the scores of pain and knee function (WOMAC). For each analysis, the heterogeneity test was performed with I^2 statistics to measure the degree of data inconsistency as $I^2 > 50\%$ being statistically significant between studies. Data were also analyzed with the random-effects model for high heterogeneity. Subgroup analysis was conducted for study design (RCT vs. prospective vs. retrospective study), treatment target (intra-articular vs. genicular vs. sciatic nerve), the performance of DNB, and follow-up period (0 vs. 4, 12, or 24 weeks). Metaregression analyses were performed to evaluate the sources of heterogeneity based on all the covariates including age and gender in subgroup analysis. Sensitivity analysis was conducted to evaluate the impact of every single study on the pooled mean difference (MD). In addition, the publication bias was evaluated by Begg and Mazumdar rank correlation test and Egger's regression test [21, 22]. Comprehensive meta-analysis (CMA version 3.0, Biostat, Englewood, NJ, USA) was used to analyze the pooled data.

3. Results

3.1. Study Selection. A total of 157 publications were identified from six electronic databases and 117 studies for further screening after removing 40 duplicates. Eighty-four irrelevant studies were removed through screening the titles and abstracts of publications, and 25 additional studies were excluded by exclusion criteria via full-text screening. Finally, eight eligible publications were included in the study of meta-analysis including 3 RCTs, 3 prospective trials, and 2 retrospective studies [23–30]. The screening method and results of the relevant studies are illustrated in Figure 1.

3.2. Study Characteristics. The included studies were conducted in five countries including Spain 3, Turkey 2, Egypt 1, India 1, and China 1, and the published date was from 2013 to 2019. The studies had 256 patients in total, with 61 males and 195 females, and the mean ages ranged from 60.0 to 72.5 years. The characteristics of studies were presented in Table 1. For RF therapy, PRF was used in 4 and RFA in 3 studies, while the combination of PRF and RFA was used in one study [25]. Most studies of RF therapy were focused on sciatic nerve or genicular nerve, but two studies applied intra-articular procedure [24, 27]. Furthermore, DNB was used to confirm the source of pain and positioning targets of RF therapy in 2 studies [27, 30]. VAS/NRS scores were available to compare the changes of pain intensity before and after RF therapy in 7 studies. In addition, WOMAC and Lysholm scores were available to evaluate the functional improvement from baseline to various follow-up times in 7 studies. The most of follow-up times were up to half year (0, 4, 12, and 24 weeks), and only one study was followed up to one year (0, 4, 12, 24, and 48 weeks). The ultrasound transducer parameter, complication or adverse effect, conclusion and limitation of studies are presented in Tables 2 and 3.

3.3. Clinical Outcomes. The primary clinical outcomes for ultrasound-guided RF therapy were pain relief and functional improvement in patients with OA, and the results are shown in Figures 2 and 3. Significant pain relief was achieved by the treatment of ultrasound-guided RF in 7 studies [23, 24, 26–30], and the pooled mean difference of pain score was −4.196 (SE: 0.324; 95% CI: −4.832 to −3.560; $P < 0.001$; I^2: 97.894%) compared to that of pretreatment (baseline) in patients with OA (Figure 2).

As shown in in Figure 3, knee function was also significantly improved after the treatment of ultrasound-guided RF in patients with OA in six studies [23, 25, 27–30]. WOMAC was decreased by 23.155 points (SE: 3.776; 95% CI: −30.556 to −15.753; $P < 0.001$; I^2: 97.302%) after the treatment of ultrasound-guided RF compared to that of baseline in patients with OA.

3.4. Adverse Effect. Ultrasound-guided RF induced adverse events were uncommon and not serious; 3 patients were reported with ecchymosis at the site of procedure in the study by Santana Pineda et al. [28] and two patients with hypoesthesia and one patient with numbness in the study by Ahmed and Arora [30] after the therapy, and all the symptoms were improved by more than 50% within 6

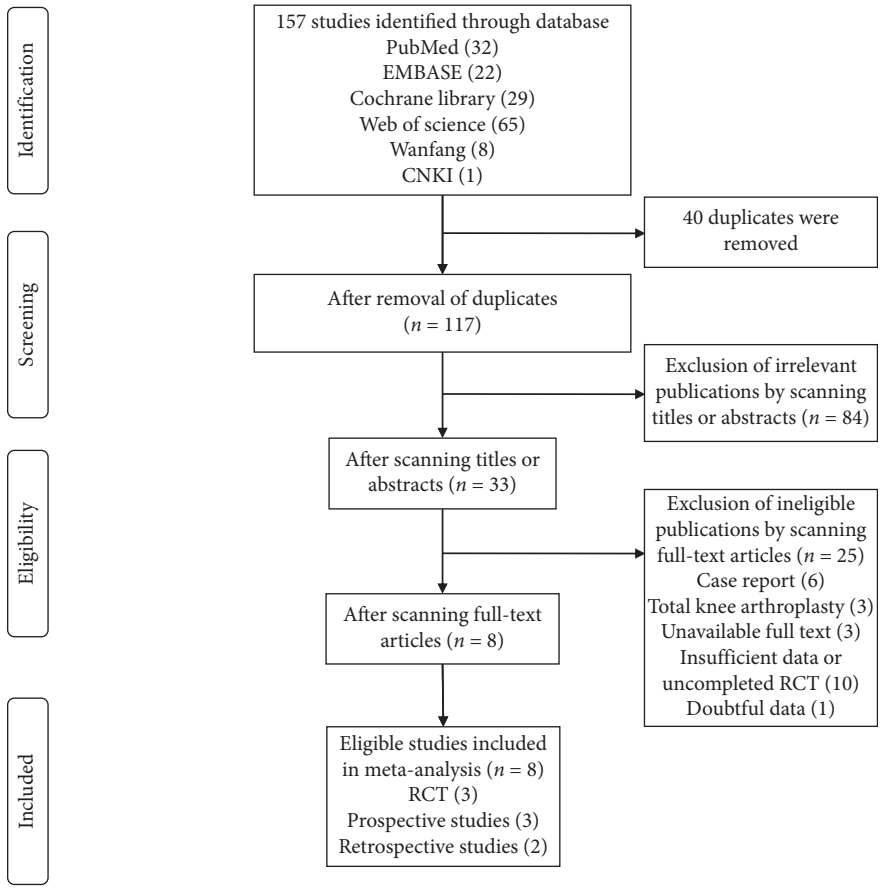


Figure 1: Flowchart of study selection.

Table 1: Included studies.

Study	Country	Type of study	Sample size	Gender (M/F)	Age mean (SD) (intervention/control)	K-L grade	Follow-up time (week)
Sari et al. [23]	Turkey	RCT	50	6/44	66.08 (10.52)/65.92 (8.71)	2-4	4, 12
Xie et al. [24]	China	RCT	54	23/31	60 (6)/59 (6)	2-3	4, 24
Monerris et al. [25]	Spain	RCT	25	7/18	75.2 (9.1)	3-4	4, 12, 24
Djibilian Fucci et al. [26]	Spain	Prospective study	47	6/41	70.6 (9.7)	—	4
Ibrahim Aly et al. [27]	Egypt	Prospective study	30	6/24	60.8 (7.1)	2-3	1, 4, 12
Santana Pineda et al. [28]	Spain	Prospective study	25	3/22	72.5 (9)	3-4	4, 24, 48
Erdem and Sir [29]	Turkey	Retrospective study	17	5/12	69.75 (11.82)	3-4	3, 12
Ahmed and Arora [30]	India	Retrospective study	8	5/3	65.75 (6.96)	3-4	4, 24

K-L grade: Kellgren–Lawrence grading system; RCT: randomized controlled trial.

months of treatment. No other complications have been reported in the patients with ultrasound-guided RF therapy. No adverse event was even reported in other 6 studies.

3.5. Risk of Bias. As mentioned previously, two different methods were used to evaluate the risk of bias. For RCTs, the risks of selection, performance, attrition, report, detection, and other bias were determined by the criteria from the Cochrane Handbook for Systematic Reviews of Interventions [19]. The risks of allocation concealment (selection bias) and blinding of outcome assessment (detection bias) were unclear in all three RCTs. However, the study by Monerris and colleagues [25] had 3 potential sources of bias, indicating at high risk. The risks of biases are summarized in Figures 4 and 5 for RCTs. For nonrandomized clinical trials, a design-specific form containing nine questions was used to determine bias according to "Assessing the Risk of Bias of

Table 2: Details of intervention, evaluation criterion, adverse effect, conclusion, and limitation of the 3 RCTs.

Study	Intervention	Control	RF mode	Target location	Ultrasound transducer parameter	Diagnostic nerve block	Evaluation criterion	Reported adverse effect	Conclusion	Limitation
Sari et al. [23]	Ultrasound-guided RF	Fluoroscopic-guided RF	RFA	SM, SL, IM genicular nerves	8–14 MHz	No	VAS; WOMAC	None	Ultrasound-guided RF achieved same clinical efficacy but easily applicable, safe, dynamic, and no radiation compared to fluoroscopic-guided RF	Small sample size; short follow-up time
Xie et al. [24]	Acupotomy combined with RF	Acupotomy	PRF	Intra-articular	7–12 MHz	No	VAS; Lysholm; SF-36	None	Ultrasound-guided PRF combined with acupotomy has better clinical efficacy than acupotomy alone	Small sample size
Monerris et al. [25]	Ultrasound-guided RF	Sham RF treatment	PRF + RFA	PFA: saphenous nerve; RFA: SL, IL, IM genicular nerves	6–13 MHz	No	VAS; WOMAC; PGIC; SF-12	None	The combination of PRF and RFA did not achieve better therapeutic efficacy on knee pain and function compared to control	Small sample size; imperfect study design and data presentation

RF: radiofrequency; RFA: radiofrequency ablation; PRF: pulsed radiofrequency; SM: superior medial; SL: superior lateral; IM: inferior medial; IL: inferior lateral; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SF-36: 36-Item Short-Form Health Survey; PGIC: Patients' Global Impression of Change questionnaire; and SF-12: 12-Item Short-Form Health Survey.

Table 3: Details of intervention, evaluation criterion, adverse effects, conclusion, and limitation of the nonrandomized studies.

First author (year)	RF mode	Target location	Ultrasound transducer parameter	Diagnostic nerve block	Evaluation criterion	Reported adverse effects	Conclusion	Limitation
Djibilian Fucci et al. [26]	PRF	Sciatic nerve	3–6 MHz	No	VAS	None	Ultrasound-guided PRF on sciatic nerve significantly relieved pain and may become a novel therapeutic approach for chronic knee pain	Lack of control group; small sample size; short follow-up time; lack of evaluation for knee function
Ibrahim Aly et al. [27]	PRF	Intra-articular	6–13 MHz	Yes	NRS; WOMAC	Ecchymosis at the site of injection (3/30)	Intra-articular PRF was safe and beneficial for pain relief in patients with KOA	Lack of control ; small sample size
Santana Pineda et al. [28]	RFA	SL, SM, IM genicular nerve	5–10 MHz	No	VAS; WOMAC	None	Ultrasound-guided RFA of genicular nerve was a safe, effective, minimally invasive treatment for chronic pain and disability induced by KOA	Lack of control group; small sample size
Erdem and Sir [29]	PRF	SL, SM, IM genicular nerve	6–15 MHz	No	VAS; WOMAC	None	Ultrasound-guided PRF targeting genicular nerves was a safe and minimally invasive procedure that significantly alleviated pain and disability in patients with severe KOA	Lack of control; small sample size; short follow-up time
Ahmed and Arora [30]	RFA	SM, SL, M, IM, IL, P genicular nerve; LRN	6–13 MHz	YES	NRS; OKS; WOMAC; SF-36	Hypoesthesia (2/8); numbness (1/8)	Ultrasound-guided RFA targeting genicular nerves was safe and effective for significantly improving pain, disability and quality of life in patients with severe KOA	Lack of control; small sample size

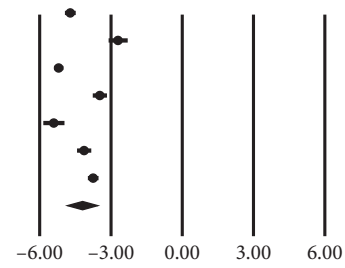
RF: radiofrequency; RFA: radiofrequency ablation; PRF: pulsed radiofrequency; SM: superior medial; SL: superior lateral; IM: inferior medial; IL: inferior lateral; M: middle; P: posterior; LRN: lateral retinacular nerve; VAS: visual analogue scale; NRS: numerical rating scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; OKS: Oxford Knee Score; and SF-36: 36-Item Short-Form Health Survey.

Individual Studies in Systematic Reviews of Health Care Interventions" [20]. Particularly, there was not enough information for evaluating blinding of outcome assessment in most of nonrandomized trials. The detailed risks of bias in each study are presented in Table 4.

3.6. Publication Bias. No publication bias was found for the primary outcomes (pain relief and functional improvement) of RF therapy in patients with OA. The results showed $P = 0.332$ and $P = 0.274$ for pain relief and $P = 0.245$ and $P = 0.226$ for functional improvement (by Egger's regression test and Begg and Mazumdar rank correlation test, resp.).

3.7. Subgroup Analysis and Metaregression Analysis. Subgroup analysis was performed to confirm the sources of heterogeneity for pain intensity associated with study design (RCTs vs. prospective vs. retrospective studies), treatment targets (intra-articular vs. genicular vs. sciatic nerves), administration of DNB before treatment (applied vs. unapplied DNB), and time of follow-up (0 vs. 4, 12, or 24 weeks), and the results are presented in Table 5. The data from subgroup analysis showed that study design (RCTs MD: −3.926, 95% CI: −4.296 to −3.557; prospective MD: −3.853; 95% CI −5.241 to −2.464; and retrospective MD: −4.959; 95% CI: −5.440 to −4.447) and treatment targets (intra-articular MD: −3.626; 95% CI: −3.900 to −3.352; genicular nerve MD: −4.851; 95% CI: −5.350 to −4.452; and sciatic nerve MD:

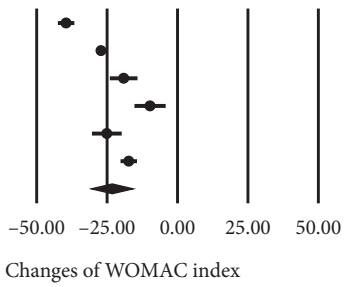
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Ahmed and Arora (2018)	−4.710	0.102	0.010	−4.910	−4.510	−46.164	0.000
Djibilian Fucci et al. (2013)	−2.700	0.191	0.036	−3.074	−2.326	−14.139	0.000
Erdem and Sir (2019)	−5.202	0.087	0.008	−5.373	−5.030	−59.484	0.000
Ibrahim Aly et al. (2018)	−3.468	0.139	0.019	−3.741	−3.196	−24.947	0.000
Santana Pineda et al. (2017)	−5.403	0.213	0.046	−5.822	−4.985	−25.321	0.000
Sari et al. (2016)	−4.128	0.140	0.019	−4.401	−3.854	−29.570	0.000
Xie et al. (2019)	−3.750	0.100	0.010	−3.946	−3.554	−37.500	0.000
	−4.196	0.324	0.105	−4.832	−3.560	−12.934	0.000



Heterogeneity	Q-value	df (Q)	p-value	I^2
	284.959	6	0.000	97.894

Figure 2: Summary of different biases in the randomized controlled trials (RCTs) of ultrasound-guided radiofrequency (RF) in the treatment of patients with knee osteoarthritis (KOA).

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Ahmed and Arora (2018)	−39.565	1.368	1.870	−42.246	−36.884	−28.929	0.000
Erdem and Sir (2019)	−27.150	0.713	0.508	−28.547	−25.753	−38.086	0.000
Ibrahim Aly et al. (2018)	−19.100	2.378	5.657	−23.762	−14.438	−8.030	0.000
Monerris et al. (2019)	−9.750	2.712	7.356	−15.066	−4.434	−3.595	0.000
Santana Pineda et al. (2017)	−25.100	2.582	6.669	−30.161	−20.039	−9.720	0.000
Sari et al. (2016)	−17.300	1.369	1.873	−19.983	−14.617	−12.640	0.000
	−23.155	3.776	14.260	−30.556	−15.753	−6.132	0.000



Heterogeneity	Q-valuve	df (Q)	p-value	I^2
	185.327	5	0.000	97.302

Figure 3: Percentage (%) of the risk of bias in the randomized controlled trials (RCTs) of ultrasound-guided radiofrequency (RF) in the treatment of patients with knee osteoarthritis (KOA).

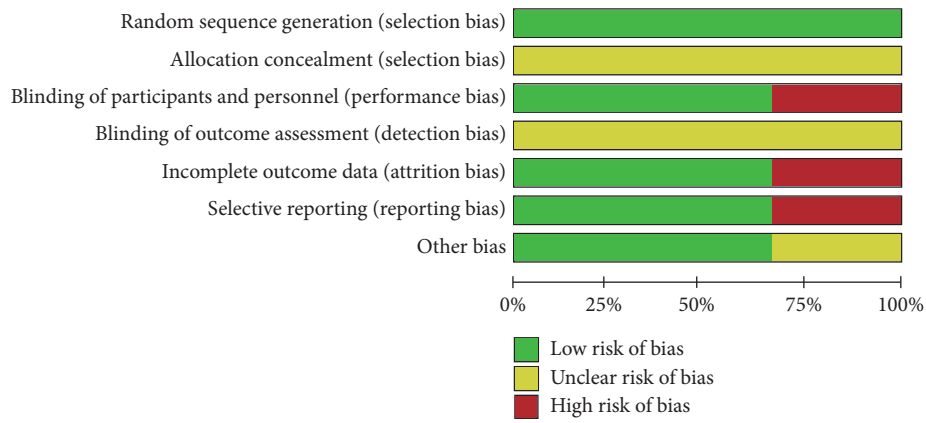


Figure 4: Effect of ultrasound-guided radiofrequency (RF) on the pain scores in patients with knee osteoarthritis (KOA). VAS: visual analogue scale; NRS: numerical rating scale.

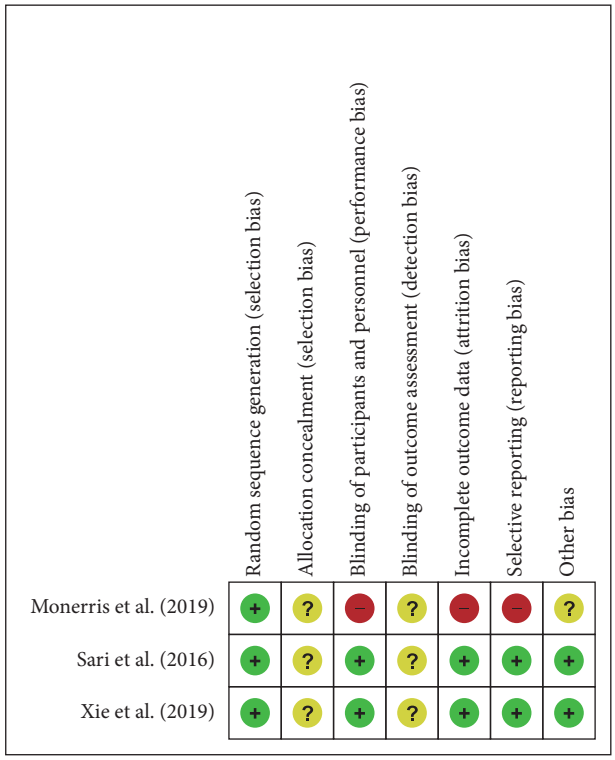


Figure 5: Effect of ultrasound-guided radiofrequency (RF) on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

−2.700; 95% CI −3.074 to −2.326) were the potential sources of heterogeneity ($P < 0.01$ and $P < 0.001$, resp.). However, there was no significant difference in pain relief whether DNB was administrated or not before RF therapy and among different follow-up periods ($P > 0.05$).

Furthermore, we also performed a metaregression analysis based on all the covariates in subgroup analysis including age and gender to verify the sources of heterogeneity, and the results are shown in Table 6 and Figure 6. The data revealed that different study designs accounted for 37% and different treatment targets for 74% in pain relief between-study variance. Target of genicular nerve (GN) achieved best pain relief while sciatic nerve was the least effective target among the 3 nerves. However, other covariates may not account for any heterogeneity according to the analysis.

3.8. Sensitivity Analysis and Other Evaluation Indices. The results in Figure 7 exhibited the stability of pooled effect size via sensitivity analysis of pain scores. The data showed that the conclusion of meta-analysis could not be overturned by removing any single study; besides, the names of studies were recalculated with pooled MD after removal of each study.

Moreover, the total time spent on the procedure for ultrasound-guided RF was recorded and compared to that of fluoroscopy-guided RF in the study by Sarı and colleagues [23]. The duration was 20.2 ± 6.4 min for ultrasonography and 25.0 ± 4.8 min for fluoroscopy, respectively. The data

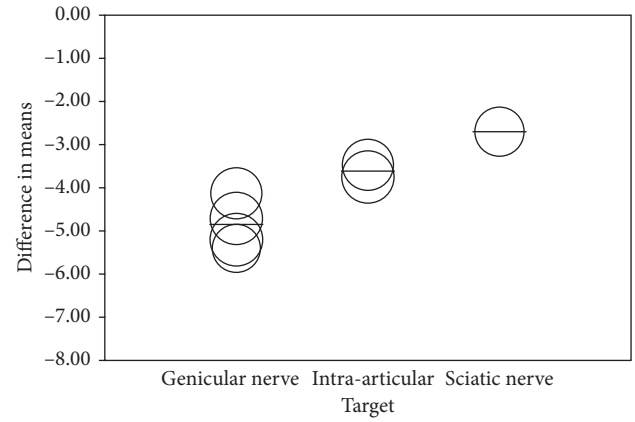


Figure 6: The correlation between treatment target and the pain scores in patients with knee osteoarthritis (KOA) by metaregression.

indicate that performance of ultrasound-guided RF requires much less time than that of fluoroscopy-guided RF. For knee functional improvement, Xie et al. reported that the Lysholm scores were increased from pretreatment of 53 ± 9 (baseline) to 79 ± 7 (4 weeks) and 70 ± 8 (24 weeks) after RF therapy, and SF-36 scores were also improved from pretreatment of 407 ± 91 (baseline) to 597 ± 102 (4 weeks) and 541 ± 95 (24 weeks), respectively; there were statistically significant differences ($P < 0.01$) before and after RF therapy for both Lysholm and SF-36 scores [22]. In addition, Likert scale was used to assess patient's satisfaction in the studies by Santana Pineda et al. and Erdem and Sir [29, 30]. Santana Pineda et al. reported that the scores were poor in 2 (2/25), average in 1 (1/25), good in 5 (5/25), and very good in 16 (16/25) in total of 25 patients after 24 weeks of RF therapy. In the study by Erdem and Sir, the outcomes of ultrasound-guided RF therapy were uncertain in 3 (3/17), good in 3 (3/17), and very good in 11 (11/17) in total of 17 treated patients. Both studies indicate that most of the patients were significantly improved by ultrasound-guided RF therapy. Furthermore, the study by Ahmed and Arora also reported significant improvement in pain intensity and the quality of life after RF therapy ($P < 0.05$) [4]. The OKS and WOMAC were improved from 7.75 ± 1.25 and 77.75 ± 4.34 at baseline to 28.88 ± 2.53 and 38.38 ± 5.82 at 4 weeks, 28.13 ± 1.80 and 39.25 ± 5.12 at 24 weeks of therapy, respectively.

4. Discussion

KOA is a very common disease and has become a huge economic burden on our society [1, 4]. Patients with KOA suffer intractable pain with high risk of disability. Pain management plays a major role in the treatment of KOA for pain relief and knee function improvement [31]. Different treatments are applied to different patients based on the severity of KOA. Generally, conservative therapies and TKA are commonly used treatments for KOA. However, some patients are unwilling to or could not tolerate TKA while conservative therapies could not achieve satisfying pain

Table 4: Evaluation of bias for nonrandomized studies.

Risk of bias criterion	Criterion	Djibilian Fucci et al. [26]	Ibrahim Aly et al. [27]	Santana Pineda et al. [28]	Erdem et al. [29]	Ahmed and Arora [30]
Selection bias	Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?	✗	✓	✓	✓	✓
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	✓	✓	✓	✗	✗
	Did the study maintain fidelity to the intervention protocol?	✓	✓	✓	✓	✓
Attrition bias	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?	✓	✓	✓	✓	✓
Detection bias	Were the outcome assessors blinded to the intervention or exposure status of participants?	—	—	—	✗	✗
	Were interventions/exposures assessed/defined using valid and reliable measures implemented consistently across all study participants?	✓	✓	✓	✓	✓
	Were outcomes assessed/defined using valid and reliable measures implemented consistently across all study participants?	✓	✓	✓	✓	✓
	Were confounding variables assessed using valid and reliable measures implemented consistently across all study participants?	✗	✓	✓	✓	✓
Reporting bias	Were the potential outcomes prespecified by the researchers? Were all prespecified outcomes reported?	✓	✓	✓	✓	✓

relief. Therefore, more effective and safe therapeutic strategy is urgently needed for pain relief in the patients with KOA.

Recently, RF has been widely used to relieve intractable pain in KOA patients as a novel minimal invasion technique [32, 33]. Choi et al. first reported the efficacy of RF to relieve pain by targeting genicular nerve in patients with chronic KOA from a double-blind, randomized controlled trial [12]. Fluoroscopy is the most used method to guide RF currently. However, more and more cases were registered for clinical trials with ultrasound-guided RF therapy in patients with OA recently [34], indicating that ultrasound may have some unique advantages and could be a potential guidance method in place of fluoroscopy.

4.1. Summary of the Main Results. In the study of meta-analysis, 8 articles with a total of 256 patients were analyzed to evaluate the effect of ultrasound-guided RF on pain relief and knee functional recovery in patients with KOA. The main results revealed that all the patients suffered from intractable knee pain before treatment, and pain intensity and knee function were significantly improved from baseline (pretreatment) to different follow-up times after RF therapy. In an RCT for comparison of the efficacy of ultrasound- and fluoroscopy-guided RF in KOA patients by Sari et al. [23], ultrasound-guided RF achieved the same therapeutic effects as those of fluoroscopy-guided RF for pain relief and functional improvement, but the procedure time was significantly less than that of fluoroscopy. Furthermore, the incidence of adverse events is very low (2.33%) after ultrasound-guided RF therapy, and only 6 patients experienced adverse events in 3 patients with ecchymosis at the site of procedure [28], two patients with hypoesthesia [30], and one patient with numbness [30] from 256 treated patients, and these symptoms were significantly improved or disappeared in the next 6 months. No adverse event was even reported in other 6 studies.

For the meta-analysis, the patients with previous TKA used only as control were excluded from the calculation according to our exclusion criteria in the study by Erdem and Sir [29]. In the subgroup analysis, we studied the changes of pain intensity with different study design (RCT vs. prospective vs. retrospective), treatment targets (intra-articular vs. genicular vs. sciatic nerves), with or without DNB, and duration of follow-up (0 vs. 4, 12, or 24 weeks). The results from metaregression analysis revealed that study design and treatment target would account for the major sources of heterogeneity as 37% and 74%, respectively. Furthermore, significant difference of pain relief was observed with different treatment targets by subgroup analysis, which showed that target of genicular nerves achieved better effect on pain relief than targeting intra-articular and sciatic

Table 5: The potential sources of heterogeneity on pain intensity by subgroup analysis.

Subgroup	Study number	Mean difference (95% CI)	I^2	P value
Study design				
RCT	2	−3.926 (−4.296 to −3.557)	79.334	
Retrospective	2	−4.959 (−5.440 to −4.447)	92.529	0.003
Prospective	3	−3.853 (−5.241 to −2.464)	97.870	
Treatment target				
IA	2	−3.626 (−3.900 to −3.352)	63.051	
GN	4	−4.851 (−5.350 to −4.352)	94.158	<0.001
SN	1	−2.700 (−3.074 to −2.326)	0	
Diagnosis nerve block (DNB)				
DNB	2	−4.093 (−5.309 to −2.876)	98.071	0.850
No DNB	5	−4.237 (−5.104 to −3.370)	98.272	
Follow-up time (week)				
4	7	−4.378 (−5.149 to −3.607)	97.484	
12	3	−4.115 (−5.093 to −3.138)	96.229	0.820
24	3	−4.172 (−4.728 to −3.617)	82.941	

IA: intra-articular; GN: genicular nerve; and SN: sciatic nerve.

Table 6: The sources of between-study heterogeneity on pain intensity by metaregression analysis.

Subgroup	Q-value	df	P value	Proportion of variance by covariate
Age	0.68	1	0.411	0.02
Gender (ratio)	0.30	1	0.586	0
Study design	3.59	2	0.166	0.37
Treatment target	21.82	2	<0.001	0.74
Diagnosis nerve block (DNB)	0.03	1	0.857	0
Follow-up time	0.19	2	0.911	0

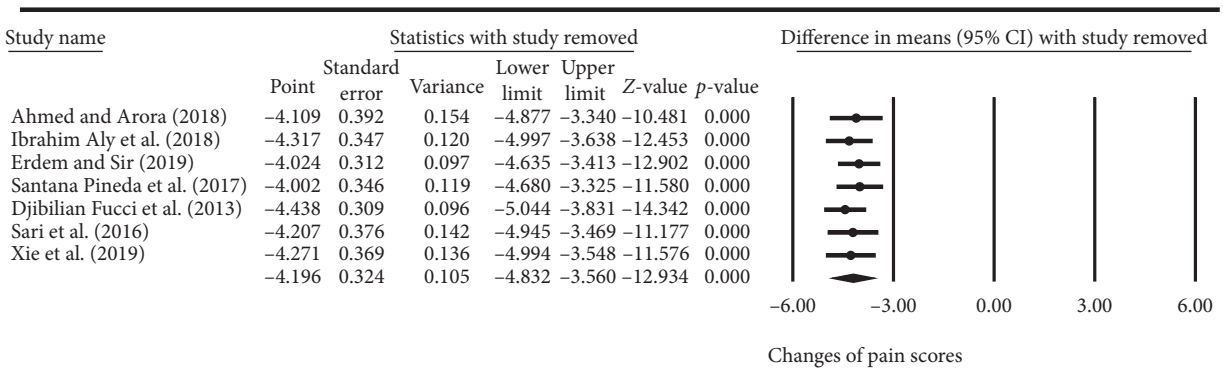


Figure 7: Effect of ultrasound-guided radiofrequency (RF) on pain scores by sensitivity analysis.

nerves. The result suggests that genicular nerve is a preferable target in ultrasound-guided RF therapy in KOA patients. No significant difference of pain relief was observed with DNB and duration of follow-up by subgroup analysis (Table 6). However, pain scores were decreased in all of follow-up ties, indicating that the efficacy of ultrasound-guided RF therapy on KOA patients would maintain for at least 24 weeks. The data suggest that ultrasound-guided RF as a minimally invasive procedure could significantly relieve pain and improve knee function and it is effective, safe, and time-saving in the treatment of patients with KOA.

4.2. Ultrasound-Guided Therapy. The application of ultrasonography is rapidly increased for guidance of RF in pain management and knee function improvement in KOA patients. Over the last few years, more and more patients with KOA have used ultrasonography instead of fluoroscopy

in RF therapy. Perrine et al. found that ultrasound- and fluoroscopy-guided RF therapy achieved the same effects on pain relief and functional improvement in KOA patients [32]. Kim et al. reported that ultrasound- and fluoroscopy-guided genicular nerve block also had similar effects on pain relief, functional improvement, and safety in patients with chronic KOA [35]. These studies suggested that RF could reach accurate localization of genicular nerve by ultrasonic guidance as by fluoroscopy. The sources of sensory nerve played the key role in knee pain and could help the operator to identify the appropriate branches of nerve for RF therapy with anatomic landmarks [36–38]. The studies by Ergonenc and Beyaz [39] and Wu et al. [40]. have reported the effect of ultrasound-guided RF therapy on targeting suprascapular nerve for the treatment of chronic shoulder pain, indicating that ultrasound-guided RF therapy could also be applied to treat other diseases such as musculoskeletal pain. Narouze reviewed the role of ultrasonography in spine interventional procedures in pain management from evidence-based studies [41] and demonstrated the effectiveness and safety of ultrasonography in RF therapy. Ultrasonography has several advantages over fluoroscopy. Firstly, ultrasonic guidance can be performed as a dynamic examination, and various tissues and arteries can be directly visualized under ultrasonography to help identifying the nerves and real-time needle advancement. In addition, the machine of ultrasound is more affordable and moveable than a fluoroscopy. Furthermore, the most important advantage of ultrasonography is radiation free, and prolonged or repeated exposure to radiation is harmful to the health care providers and patients [42]. Therefore, ultrasonography is apparently a better choice than fluoroscopy in RF therapy.

4.3. Limitations. There were some limitations in the study. First of all, we have only 8 enrolled studies with 256 patients for the meta-analysis. The small number of relevant studies and enrolled patients limited the confidence level of the meta-analysis. Secondly, another major problem is lacking high-quality RCTs to directly compare the two different guidance methods (ultrasound vs. fluoroscopy) for RF therapy in patients with KOA. Thirdly, high heterogeneity was observed in the studies. For example, study design and treatment targets were of the major between-study variances as accounted for 37% and 74% of variances, respectively; and I^2 was more than 50 by subgroup analysis and metaregression analysis for potential sources of heterogeneity. In addition, the outcomes were blindly assessed in the meta-analysis from all studies according to evaluation of bias, which could affect the reality of the data. Finally, most of the studies only provided short follow-up times, so we could not analyze the long-term effectiveness of ultrasound-guided RF in the treatment of patients with KOA.

5. Conclusion

Although there were some limitations in the studies, the results still provided clear evidence that ultrasound-guided RF therapy was effective and safe in the treatment of KOA patients for pain relief and knee function improvement. Numerous uncompleted RCTs related to the meta-analysis were found from the Cochrane Library, indicating that researchers and physicians have paid more attention to the application of this novel technique. However, there are still some questions needed to be answered. Ultrasound-guided RF therapy to target genicular nerve has only been widely used in recent few years. There are no detailed criteria or recommendations for this procedure such as RF type and treatment targets currently. The long-term effectiveness of ultrasound-guided RF in the treatment of KOA is still needed to be defined due to limited data. Nevertheless, ultrasonography is an effective, safe, dynamic, easily applicable, and nonradiative guidance method for RF therapy to achieve satisfying pain relief and functional improvement in KOA patients who failed conservative treatment. However, the efficacy and safety of ultrasound-guided RF in the treatment of KOA requires further investigation for clinical validation by high-quality multicentric, randomized controlled trials with large sample size.

Data Availability

There were no data used other than the original one collected for the objective of this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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