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Original Article

Clinical observation of pulsed radiofrequency in treatment of knee osteoarthritis

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Abstract: Objective: To investigate the clinical effect of intra-articular pulsed radiofrequency on the pain caused by refractory knee osteoarthritis. Methods: 42 cases of patients (totally 67 knees) suffering the pain caused by severe knee osteoarthritis were randomly divided into two groups: group C and group R. Group C was treated with intra-articular injection of compound betamethasone; Group R was treated with intra-articular pulsed RF. Visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC index), clinical effect and recurrence rate during follow-up, adverse reactions as well as the changes of tumor necrosis factor (TNF-α), matrix metalloproteinase-3 (MMP-3) and interleukin-1 (IL-1) in synovial fluid of both groups were recorded at pre-treatment and 1, 4, 8, 12, 24 weeks after treatment respectively. All collected data were analyzed by SPSS 11.5 software. Results: Comparing with pre-treatment scores, the VAS and WOMAC scores at 1, 4, 8, 12 and 24 weeks after treatment were decreased significantly in both groups with group C significantly higher than group R; The total effective rate was 95.5% in group R comparing with 85.5% in group C, and there was significant difference between the two groups. After treatment, the recurrence rate of group C was significantly higher than that of group R, with statistical difference. No obvious adverse reactions occurred in all patients. After treatment, the content of TNF-α, MMP-3 and IL-1 in the synovial was significantly reduced in the patients of group R, and the reduced volume was significantly higher than that of group C, with significant difference. Conclusion: the effect of intra-articular pulsed RF treatment is obviously superior to the traditional compound betamethasone injection group in the treatment for refractory knee osteoarthritis; pulsed RF could obviously alleviate the clinical symptoms and decrease the content of TNF-α, MMP-3 and IL-1 in the synovial, in addition, it is safe and reliable, all of these make it an effective method for senile refractory knee osteoarthritis.

Keywords: Knee osteoarthritis, knee joint cavity, pulsed radiofrequency

Introduction

Knee osteoarthritis, as a common chronic disease in the elderly, is a serious public health problem in the world. Studies have showed that people over 65 years old with symptomatic knee osteoarthritis accounts for 20-30% of the elderly population [1]. The main clinical symptoms are chronic articular pain on knee, dysfunction, depression mood, and decreased quality of life. The conventional conservative treatments of knee osteoarthritis include physical therapy, medication, intra-articular corticosteroid injections (IACIs), and intra-articular injection of hyaluronic acid etc. Although conservative treatment is effective in most patients with arthritis, the effects are not ideal in some patients with refractory osteoarthritis. Total knee arthroplasty is an effective treatment for refractory knee osteoarthritis [2]. However, some elderly patients with many other complications couldn't or do not want to accept the high risks of surgery. Exploring a more appropriate treatment to alleviate the pain of those patients is the goal of our study. Pulsed RF, as a commonly used technique for clinical treatment of painful diseases, has been reported to be used in the treatment of intra-articular pain disorders in recent years [3, 4]. Karaman et al. [5] using intra-articular pulsed radiofrequency to treat 31 patients with knee osteoarthritis was proved to be effective, however, since then there was no report on the treatment of intra-articular pulsed radiofrequency. Due to the high safety of pulsed RF and easy operation of knee joint, this study further explored the efficacy of

pulsed radiofrequency in the treatment of refractory pain in knee osteoarthritis.

Methods

General information

42 patients diagnosed of chronic osteoarthritis were selected in this study, including 14 males and 28 females. The patients aged from 56 to 81 years old (average age was 68±9.5 years old) and weighted from 47 to 87 kg (average weight was 62.5±15.3 kg); there were 17 cases of unilateral knee joint pain and 25 cases of bilateral knee pain, and the duration of disease was more than 3 months; the VAS of patients ranged from 4 to 8 points (7.16±1.38 points for average). Patients were treated with non steroidal anti-inflammatory drugs (NSAIDs), however, the therapeutic effect was poor, and some patients even couldn't tolerate, that seriously influenced the quality of life. Patients with acute pain, connective tissue disease, severe cardiopulmonary insufficiency or neurological and psychiatric disease were excluded. No patients had abnormal coagulation or peripatellar tissue infection, or treated with intra-/extra-articular corticosteroid injection within 3 months. Patients were randomly divided into two groups: compound betamethasone injection group (Group C, 20 cases, 32 joints), and pulsed radiofrequency treatment group (Group R, 22 cases, 35 joints).

Treatment methods

Patients in group C were treated with injection of compound betamethasone at the point EX-LE 4 (neixiyan) and point ST35 (waixiyan). Compound mixture: 2 ml 2% lidocaine and 0.5 ml compound betamethasone were diluted by physiological saline to 4 ml; 2 ml for each injection point.

Pulsed RF was used in group R. Patients were in supine position with knee flexed to approximately 120°, and pillows were used to support the flex position; point EX-LE 4 (neixiyan) and point ST35 (waixiyan) were chosen as puncture points. After routine disinfection, appropriate amount of 0.5 ml 1% lidocaine was used for local anesthesia, then a 10 cm No.22 RF needle with 1 cm working end was used to puncture at point ST35 (waixiyan), the puncture depth was approximately 3-4 cm into the articular cavity, and then 2 ml physiological saline was injected to confirm the entering of articular cavity if there was no resistance. Connect the RF needle to radio frequency instrument, set temperature at 42°C; pulsed RF with 2 Hz and pulse width of 20 ms was applied for 120 seconds * 3 cycles, a total of 6 minutes, then pull out the needle. Repeat the above procedures on point EX-LE 4 (neixiyan). All patients did not take other analgesic drugs.

Observation indicators

VAS, WOMAC index and adverse reactions of patients were recorded at pre-treatment and 1, 4, 8, 12 and 24 weeks after treatment.

VAS score: the pain level was scaled from 0-10 points, Patients pointed out the picture of facial expression while they suffering from the pain, and the physician recorded the relevant scores behind the picture. 0 point for pain free and 10 points for unbearable pain; 1-4: mild pain, 5-7: moderate pain, 8-10: severe pain.

Western Ontario and McMaster Universities Oste-oarthritis Index, also named as WOMAC index: [6]: it includes 24 questions, among them, 5 relate with arthralgia, 2 relate with anchylosis, and 17 relate with joint physiologic function. Each question has five levels with 0~4 points, 0 = none, 1 = mild, 2 = moderate, 3 = serious and 4 = very serious. Each symptom was comprehensively evaluated at pre-treatment and 1, 4, 8, 12 and 24 weeks after treatment.

Criteria for judging therapeutic effect

The criteria for the evaluation of therapeutic effect: clinical cure: no pain on knee joint, range of motion of knee joint was basically normal, no tenderness reaction, the total WOMAC score ranged 0-1; significant effectiveness: symptoms of knee osteoarthritis basically disappeared or significantly relieved, range of motion was increased significantly, no tenderness reaction, total WOMAC score decreased ≥ 2/3; effectiveness: symptoms of knee osteoarthritis was partially relieved, range of motion was increased, tenderness reaction was weakly positive, and total WOMAC score decreased ≥ 1/3; invalid: relief of symptoms and signs were not in the criteria mentioned above, the total score of the WOMAC decreased < 1/3. After 3 months, all patients (except invalid) were followed-up.

Table 1. Comparison of general information between two groups

	Cases	Gender (male/female)	Age	Duration of disease (month)	Diseased region			VAS	WOMAC index
					Left	Right	Both		
Group C	20	7/13	67.4±10.3	38.3±9.2	4	4	12	5.6±1.4	54.1±10.4
Group R	22	7/15	69.9±11.1	41.6±8.4	5	4	13	5.9±1.1	52.1±11.9

Table 2. Comparison of total curative effect between two groups after treatment

Groups	Cases	Clinical cure	Significant effectiveness	Effectiveness	Invalid	The total effective rate
Group R	22	1	7	13	1	95.5%
Group C	20	0	3	14	3	85.0%

Detection of cytokines in synovial fluid

At pre-treatment and 1 week after the treatment, 1 ml synovial fluid of two groups of patients were extracted and stored in sterile EP tube at -20°C. The content of TNF-α, MMP-3 and IL-1 in the synovial fluid samples was measured strictly according to the steps in the operation manual.

Statistical analysis

Data were analyzed using SPSS 11.5 statistical software. Measurement data were expressed with mean ± standard deviation ($\bar{X}$ ± SD); comparison of WOMAC, VAS scores in two groups of patients before and after treatment was analyzed by t test. Ridit analysis was used to compare the ranked data. Enumeration data were expressed with percentage and compared by chi-square test. $P < 0.05$ indicates statistically significant difference.

Results

General information

Two groups of patients (20 cases in group C and 22 cases in group R) showed no statistically significant differences in age, body weight, gender, duration of disease, and pre-treatment VAS score and WOMAC score (P > 0.05), see **Table 1**.

Comparison of total therapeutic effect between two groups

The overall effective rate in group R was significantly higher than that of group C. The clinical effect of the two groups was analyzed by Ridit, showing that there were significant differences ($u = 2.05$, $P = 0.03 < 0.05$), from which we can see that the curative effect of two groups in improving the total symptoms is significantly different, see **Table 2**.

Comparison of the VAS and WOMAC score between two groups

The comparison of pre-treatment VAS and WOMAC score between two groups had no significant differences; compared with pre-treatment values, the VAS score and WOMAC score at 1, 4, 8, and 12, 24 weeks after treatment was decreased significantly in both two groups, the differences were statistically significant. VAS and WOMAC scores in group R decreased more obviously than group C, and comparison between the two groups at the same time point was significantly different. (P < 0.05), as shown in **Table 3**.

Comparison of follow-up results between two groups

After 3 months' follow-up of the patients in two groups (except the patients with invalid effect), the results showed that there were 7 cases and 10 cases of recurrence in group R and group C, respectively. The difference between the two groups in recurrence rate had statistical significance ($\chi^2 = 11.812$, $P < 0.05$), see **Table 4**.

Complications of adverse reactions

Knee joint dropsy in patients of group R (3.72± 1.23 ml) within 2 weeks after the treatment was less than that of group C (15.68±3.15 ml) ($t = 17.42$, $P < 0.05$). No obvious puncture infection, sensory disturbance of lower extremities and other serious complications were observed in two groups of patients.

Detection of cytokines in synovial fluid between two groups

The content of TNF-α, MMP-3 and IL-1 was compared between the two groups at pre-treatment

Table 3. Comparison of the VAS and WOMAC scores between two groups before and after treatment

	Groups	Before treatment	1 week after treatment	4 weeks after treatment	8 weeks after treatment	12 weeks after treatment	24 weeks after treatment
VAS	group C	5.6±1.4	3.4±1.3*	3.6±1.6*	3.8±1.4*	3.3±1.7*	3.5±1.5*
	group R	5.9±1.1	2.3±1.3**,#	2.1±1.4**,#	2.4±1.2**,#	2.6±1.4**,#	2.3±1.6*,#
WOMAC	group C	54.1±10.4	40.1±9.7*	41.3±11.2*	42.1±10.4*	39.8±11.7*	41.0±9.4*
	group R	52.1±11.9	31.1±10.6**,##	30.4±10.3**,##	32.5±11.2**,##	33.4±9.9**,##	31.6±10.3**,##

*P < 0.05, **P < 0.01, *VS.* pre-treatment; #P < 0.05, ##P < 0.01, comparison between two groups at the same time-point.

Table 4. Comparison of the recurrence between two groups during follow up

Groups	Total number of observed patients (no.)	Recurrence (no.)	Without recurrence (no.)	Recurrence rate
Group R	21	7	14	33.3%
Group C	17	10	7	58.5%

Table 5. Comparison of cytokines in synovial fluid between two groups

Groups	Cytokines	Before treatment (ug)	After treatment (ug)	Content difference (ug)
Group R	TNF-α	1.31±0.18	1.07±0.12*	0.24±0.19#
	MMP-3	85.78±19.2	67.58±18.87*	18.2±3.32#
	IL-1	101.68±29.05	81.21±28.79*	20.47±6.35#
Group C	TNF-α	1.28±0.15	1.13±0.07*	0.15±0.10
	MMP-3	82.74±18.95	72.68±17.63*	9.06±6.27
	IL-1	97.42±21.92	79.73±20.81*	18.69±7.12

Note: *P < 0.05, compared with pre-treatment; #P < 0.05, compared group C.

($P > 0.05$), the result showed that the two groups were comparable with no statistically significant differences. After the treatment, the content of 3 cytokines mentioned above was significantly decreased in both groups ($P < 0.05$). The content of the 3 cytokines in group R decreased more sharply than that of group C with statistical significance. Visibly, both two treatments have clinical efficacy on knee osteoarthritis, but pulsed RF was significantly better than compound betamethasone injection, as shown in **Table 5**.

Discussion

Among the conservative treatments for knee osteoarthritis, drug treatment is the foundation, and the intra-articular injection of compound betamethasone is an internationally recognized traditional treatment for patients refractory to medical therapy [7, 8]. So, this study used the intra-articular injection of compound betamethasone as the control group to observe the curative effect.

Radio frequency has been widely used in analgesia. There are many reports about the use of standard radiofrequency to damage the peripheral nerves of knee both in domestic and abroad [9, 10]. But the method is tedious in the process, the peripheral nerve branch of knee are so many and not fixed, the failure rate is high in finding the nerves, moreover, partial loss of sensation after neural damage leads to the discomfort of the patient. The major source of the pain caused by knee osteoarthritis is unknown, therefore, there is no reliable study to confirm that the pain on knee could be completely eliminated after damaging the knee peripheral nerves; the intra-articular structures, including synovial membrane, capsule, and ligament, may have considerable responsibility for the pain caused by knee osteoarthritis [11-13]. Compared with the standard RF, the electric current of pulsed RF is generated in the pulsed mode, the maximum temperature of therapeutic electrode does not exceed 42°C; it retains the integrity of structure and function of Aδ nerve fiber under the circumstance of blocking nociceptive impulses of Aδ and C fiber. There are a lot of reports on pulsed radiofrequency in treating all kinds of joint cavities [14, 15], at present, there are some articles and case reports on using pulsed RF in the intra-articular treatment at abroad [16, 17]. Based on previous studies, our department compared pulsed RF with the traditional method to verify its effectiveness.

Inflammation may be an important feature in the process of knee osteoarthritis. Pain associ-

ated with pro-inflammatory cytokines (such as local P substance and cytokines) and the occurrence of osteoarthritis is closely related to cartilage destruction and inflammation of subchondral bone and synovitis; the inflammatory factors secreted in the process are the key mediators that relate to pathophysiology of osteoarthritis, especially IL-1, TNF-α and MMP-3, they are the key cytokines that control the degeneration of articular cartilage matrix and become the main targets in therapy [18-20]. Other cytokines such as IL-6, IL-15, IL-17, IL-18, IL-21, leukemia inhibitory factor, and IL-8 are also likely to be the targets of OA therapy. There is study showed that pulsed radiofrequency might achieve the purpose of analgesia by two ways [3]: First, by inhibiting the local excitatory C- fiber to affect synaptic transmission, which can block the pathway of pain. This could explain the immediate analgesic effect of the RF, and we found that the pain in patients with severe knee osteoarthritis can be significantly relieved immediately after treatment. Second: the effect on immune response by inhibiting the release of immune cells and pro-inflammatory cytokines (interleukin-1β, IL-6, etc.). By regulating these cytokines, pulsed RF stimulates a greater level of cascade reaction-stop amplification of inflammatory reaction and avoid vicious circles, which as a mechanism, has a better possibility in the application in big joint, such as the treatment of knee joint cavity in this study. It can explain the mechanisms of long-term pain mitigation after using pulsed RF.

The results of this randomized control study were consistent with the results of the retrospective study of Karaman [5] and further confirmed the efficacy of pulsed radiofrequency in the treatment of knee osteoarthritis. The next step for us is to explore the optimal time of treatment and the possible mechanisms by experimental studies.

In summary, this study found intra-articular pulsed RF treatment, is worthy to be popularized in clinical treatment for patients suffering the pain caused by refractory chronic knee osteoarthritis; the treatment is safe and easy to control, more importantly, the curative effect is remarkable and can sustain for a long time.

Disclosure of conflict of interest

None.

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References

[1] Mannoni A, Briganti MP, Di Bari M, Ferrucci L, Costanzo S, Serni U, Masotti G and Marchionni N. Epidemiological profile of symptomatic osteoarthritis in older adults: a population based study in Dicomano, Italy. Ann Rheum Dis 2003; 62: 576-578.

[2] Ikeuchi M, Izumi M, Aso K, Sugimura N and Tani T. Clinical characteristics of pain originating from intra-articular structures of the knee joint in patients with medial knee osteoarthritis. Springerplus 2013; 2: 628.

[3] Sluijter ME, Teixeira A, Serra V, Balogh S and Schianchi P. Intra-articular application of pulsed radiofrequency for arthrogenic pain--report of six cases. Pain Pract 2008; 8: 57-61.

[4] Halim W, Chua NH and Vissers KC. Long-term pain relief in patients with cervicogenic headaches after pulsed radiofrequency application into the lateral atlantoaxial (C1-2) joint using an anterolateral approach. Pain Pract 2010; 10: 267-271.

[5] Karaman H, Tufek A, Kavak GO, Yildirim ZB, Uysal E, Celik F and Kaya S. Intra-articularly applied pulsed radiofrequency can reduce chronic knee pain in patients with osteoarthritis. J Chin Med Assoc 2011; 74: 336-340.

[6] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J and Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-1840.

[7] Huleatt JB, Campbell KJ and Laprade RF. Nonoperative treatment approach to knee osteoarthritis in the master athlete. Sports Health 2014; 6: 56-62.

[8] Ayhan E, Kesmezacar H and Akgun I. Intra-articular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop 2014; 5: 351-361.

[9] Choi WJ, Hwang SJ, Song JG, Leem JG, Kang YU, Park PH and Shin JW. Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double-blind randomized controlled trial. Pain 2011; 152: 481-487.

[10] Ikeuchi M, Ushida T, Izumi M and Tani T. Percutaneous radiofrequency treatment for refractory anteromedial pain of osteoarthritic knees. Pain Med 2011; 12: 546-551.

[11] Masala S, Fiori R, Raguso M, Calabria E, Cuzzolino A, Fusco A and Simonetti G. Pulse-

dose radiofrequency can reduce chronic pain in trapezio-metacarpal osteoarthritis: A mini-invasive therapeutic approach. Int J Rheum Dis 2015; [Epub ahead of print].
[12] Schianchi PM. A new technique to treat facet joint pain with pulsed radiofrequency. Anesth Pain Med 2015; 5: e21061.
[13] Masala S, Fiori R, Raguso M, Morini M, Calabria E and Simonetti G. Pulse-dose radiofrequency for knee osteoartrithis. Cardiovasc Intervent Radiol 2014; 37: 482-487.
[14] Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP and Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 2011; 7: 33-42.
[15] Colini-Baldeschi G. Evaluation of pulsed radiofrequency denervation in the treatment of chronic facetjoint pain: an observational study. Anesth Pain Med 2012; 1: 168-173.
[16] Lakemeier S, Lind M, Schultz W, Fuchs-Winkelmann S, Timmesfeld N, Foelsch C and Peterlein CD. A comparison of intraarticular lumbar facet joint steroid injections and lumbar facet joint radiofrequency denervation in the treatment of low back pain: a randomized, controlled, double-blind trial. Anesth Analg 2013; 117: 228-235.
[17] Falco FJ, Manchikanti L, Datta S, Sehgal N, Geffert S, Onyewu O, Zhu J, Coubarous S, Hameed M, Ward SP, Sharma M, Hameed H, Singh V and Boswell MV. An update of the effectiveness of therapeutic lumbar facet joint interventions. Pain Physician 2012; 15: E909-953.
[18] Hansen H, Manchikanti L, Simopoulos TT, Christo PJ, Gupta S, Smith HS, Hameed H and Cohen SP. A systematic evaluation of the therapeutic effectiveness of sacroiliac joint interventions. Pain Physician 2012; 15: E247-278.
[19] Mikeladze G, Espinal R, Finnegan R, Routon J and Martin D. Pulsed radiofrequency application in treatment of chronic zygapophyseal joint pain. Spine J 2003; 3: 360-362.
[20] Tekin I, Mirzai H, Ok G, Erbuyun K and Vatansever D. A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. Clin J Pain 2007; 23: 524-529.