

EFFECTIVENESS OF GENICULAR NERVES RADIOFREQUENCY NEUROABLATION FOR PAIN SYNDROME MANAGEMENT IN PATIENTS WITH KNEE ARTHRITIS.

Abstract. Most people in age above 65 years with knee arthritis suffer from pain syndrome. Traditionally, this pain is nociceptive and an important part of knee osteoarthritis treatment is pain management. Radiofrequency neuroablation was proposed as a long-term and effective method of the pain syndrome treatment that induces the nociceptive mechanism in the structures that conduct pain impulses.

Objectives: analyze the effectiveness of pain syndrome treatment with radiofrequency neuroablation in patients with knee arthritis for 6 months after the procedure.

Material and methods: this single-blind controlled study includes analysis of the treatment of patients with knee arthritis of the 3-rd stage with intensive pain syndrome. The number of patients included in the study is 42. Patients were divided into two groups: the study group (n = 21) in which patients additionally had RFNA of the superior medial, superior lateral and inferior medial genicular nerves to basis therapy for the treatment of knee joint pain; and the comparison group (n = 21) in which patients had only basis therapy. The intensity of the pain syndrome was measured with VAS. The functional status and quality of patients' life were measured using the WOMAC questionnaire in terms of 2 weeks, 1, 3 and 6 months from the beginning of the treatment.

Results. This study established that the main complaint of patients with knee arthritis is intensive pain (VAS in study group is 9.0 (7.0; 10.0) and in comparison group is 8.5 points (7.0; 10.0)) which affects to the functional activity (the total WOMAC index - 87.0 (85.0; 91.0) points in study group and 87.0 (82.0; 91.0) points in comparison group). Estimation of the pain intensity dynamics, functional activity and quality of life revealed positive changes in both groups of patients. The more pronounced effect of the treatment was admitted in a group of patients who underwent radiofrequency neuroablation procedure of the genicular nerves in combination with basis conservative treatment (decreasing values regard to the VAS is 4.5 (3.0; 6.0) points and the total WOMAC index is 47.0 (44.0; 49.0).

Conclusion: radiofrequency neuroablation of the genicular nerves in combination with conservative therapy is an effective method of pain syndrome management in patients with knee arthritis, which increases patients' functional activity and quality of life.

Keywords: pain syndrome, knee osteoarthritis, radiofrequency neuroablation.

Introduction

Pain syndrome is one of the most frequent reasons for an appeal to a physician of elderly patients with knee arthritis [1]. Most people in age above 65 years have radiographic signs of knee arthritis, and about 11% of people aged over 60 have clinical symptoms [2]. The analysis showed that women suffer from knee arthritis more often than men, and this difference increased with age over 55 years [5]. Clinical manifestations of the disease begin with the constant pain, fatigue, sleep disturbances, limitations of functionality in everyday life (walking, lifting stairs and even getting out of bed) in people of middle ages.

Traditionally, the pain is nociceptive and associated with local tissue damage and concomitant inflammation that causes the stimulation of the pain receptors [3, 4]. Nociceptive stimuli are perceived by C-fibers contained in all structures of the joint except for articular cartilage [6]. Therefore, it is rational in the treatment of knee joint osteoarthritis to use a meaningful effect on the structure that produces pain.

Nonsteroidal anti-inflammatory drugs (NSAID) that do not affect the development of basic pathological process and central neurophysiological mechanisms of pain development are widely used for the treatment of pain. They only decrease the intensity of pain syndrome and inflammation, but also have side effects and warnings. The main adverse effect of NSAIDs prolonged use is an injury to the gastric mucosa, which

is less pronounced in the selective COX-2 inhibitors. However high doses and prolonged use of new COX-2 inhibitors lead to a higher risk of cardiovascular diseases [7].

Radiofrequency neuroablation (RFNA) was proposed as a durable and effective treatment method of pain in diseases such as trigeminal neuralgia, spinal pain and oncological pain [9, 10, 11, 14]. RFNA affects to the nociceptive mechanisms in the structures that provide pain impulses [15]. The procedure is based on the targeted thermal effects on nerve structures which causes their local denaturation leads to Wallerian degeneration of the distal part of axons, leads to the disintegration of the myelin sheath, but due to saved endoneurium, perineurium and epineurium leaves the possibility of axonal regeneration and remyelination [8]. Functional restoration of the sensory axon is observed from several weeks to a year, depending on the extent of the axon lesion and its capacity for regeneration [13].

Objectives. To evaluate the effectiveness of radiofrequency neuroablation in the treatment of pain syndrome in patients with knee arthritis.

Materials and methods

A single-blind randomized controlled trial conducted at the clinical bases of the Department of Traumatology and Orthopedics of Zaporizhzhya State Medical University in accordance with ICH / GCP rules, Helsinki Declaration of Human Rights, 2002,

Council of Europe Convention on Human Rights and Biomedicine, 1977, International Guidelines principles on ethics in conducting to human researches and the law of Ukraine. Treatment results of 42 patients (6 male and 36 female) aged from 54 to 72 years who received treatment from September 2018 to December 2018. All patients were examined clinically, had a one- or two-sided knee joint osteoarthritis with pain dominance of one knee. According to the X-ray classification of J.H. Kellgren and J.S. Lawrence, all patients had 3-rd stage of the knee osteoarthritis. Patients were randomly divided into two groups: the study group (n = 22) and

the comparison group (n = 22). Patients in both groups for the treatment of the knee joint osteoarthritis received basic conservative therapy (glucosamine sulphate and chondroitin sulphate, paracetamol 500 mg once a day in the evening and meloxicam 15 mg during 14 days); locally applied gel which contains diclofenac - 3 times a day, and omeprazole 40 mg once a day every morning). Patients underwent the course of physical therapy and massage of the lower extremities. The more detailed description of groups according to age, sex, BMI, prevalence and duration of disease is presented in Table 1.

Table 1

General characteristics of the patient groups represented in the study, M ± m.

| Characteristic | Study group (n = 21) | Comparison group (n = 21) |
|--|-------------------------|------------------------------|
| 1. Age, years | 64.36 ± 1.13 | 63.18 ± 1.20 |
| 2. Gender (m / f) | 4/17 | 2/19 |
| 3. BMI, kg/m ² | 28.21 ± 0.33 | 28.1 ± 0.39 |
| 4. Joint affected with knee arthritis: | | |
| a. Bilateral | 14 (66.67%) | 12 (57.14%) |
| b. Right-side | 5 (23.81%) | 6 (28.57%) |
| c. Left-side | 2 (9.52%) | 3 (14.29%) |
| 5. Disease duration, years | 9.01 ± 0.82 | 8.5 ± 0.95 |

The study group consisted of 21 persons (4 male and 17 female), the average age was 64.36±1.13 years, with overweight (BMI - 28.21±0.33 kg/m²), with bilateral knee arthritis in 14 patients (66.67%) which disturbed them for more than 9.01±0.92 years. Patients in the study group for the treatment of knee joint pain received the treatment described above. Additionally, they had RFNA of the upper medial, upper lateral and lower medial genicular nerves.

The comparison group consisted of 21 persons (gender distribution - 2 male and 19 female) in age 63.1±1.10 years. Patients also had problems with overweight (BMI was 28.1±0.39 kg/m²), with a predominance of bilateral knee arthritis - 12 patients (57.14%), which had disturbed them more than 8.5±0.95 years. Patients in this group held only course of medication and physical therapy for two weeks, as the patients in the study group, without performing RFA of the genicular nerves.

Exclusion criteria: intra-articular injection of steroids or hyaluronic acid during the previous three months; knee injury in the last month; surgical treatment of the knee joint in history; presence of generalized infection or local inflammation of the skin at the site of the procedure; the presence of systemic diseases of the connective tissues, which can affect the knee joints, mental illnesses.

RFNA of the genicular nerves performed under complete aseptic conditions, using portable ultrasound equipment. The patient's position was on the back, the knee flexion angle was 30-40° (there was rolled pillow under the knee). Previously, a series of tests was performed to determine the amount of active and passive movements at the knee and the intensity of pain. Under ultrasound control, vascular nerve bundles were identified using an ultrasound scanner (Athrex

Synergy MSK™ Ultrasound) with color Doppler imaging (*a., v., n. genicularis superioris medialis, superioris lateralis, inferioris medialis*), that are available for visualization near the periosteum. Conducted blunt cannula for radiofrequency ablation 20G 10 cm with active tip 10 mm positioned in the area of femur and tibia periosteum, then inserted active electrode. For verifying the cannula position used sensory stimulation with electrical impulses at a frequency of 50 Hz and voltage of 0.4 V. The positive result of the test is the appearance of paresthesia, an increase of pain sensitivity in the area of the knee joint that innervated with a certain nerve. The next step was motor stimulation at a frequency of 2 Hz and a voltage of 1.4 V to prevent damage to the motor nerves. After determining the final position of the electrode and verification under ultrasound guidance, via cannula was injected 2 ml of 0.5% bupivacaine solution. After 2-3 minutes and injection of local anesthetic was provided radiofrequency lesioning of the genicular nerves to 70-90°C for 90 seconds.

Subjective assessment of the intensity of pain was performed with VAS. Assessment of functional status and quality of patients' life with knee joint osteoarthritis was performed using the WOMAC questionnaire, which was evaluated by the following clinical parameters: pain, mobility impairment, and difficulty in performing daily activities. [12] The outcome measurement of pain intensity and functional status was performed before treatment, in 2 weeks, 1, 3 and 6 months.

For statistical analysis of the obtained results was used a computer and license packages «Microsoft Office Excel 2010» and «Statistica» version 13 (Copyright 1384-2018 TIBCO Software Inc.). Methods of parametric and non-parametric variation statistics (calculation of parameters and their errors) were used

in the analysis. The results reliability was determined by the Student's t-test (for data distributed for normal law) and Mann-Whitney (for the data the distribution of which differed from normal). The differences were considered statistically significant at $p < 0.05$.

Results

Assessment of pain intensity according to VAS

Changes in the subjective sensation of pain intensity before treatment, after 2 weeks, 1, 3 and 6 months was determined with a VAS score and shown in Fig. 1.

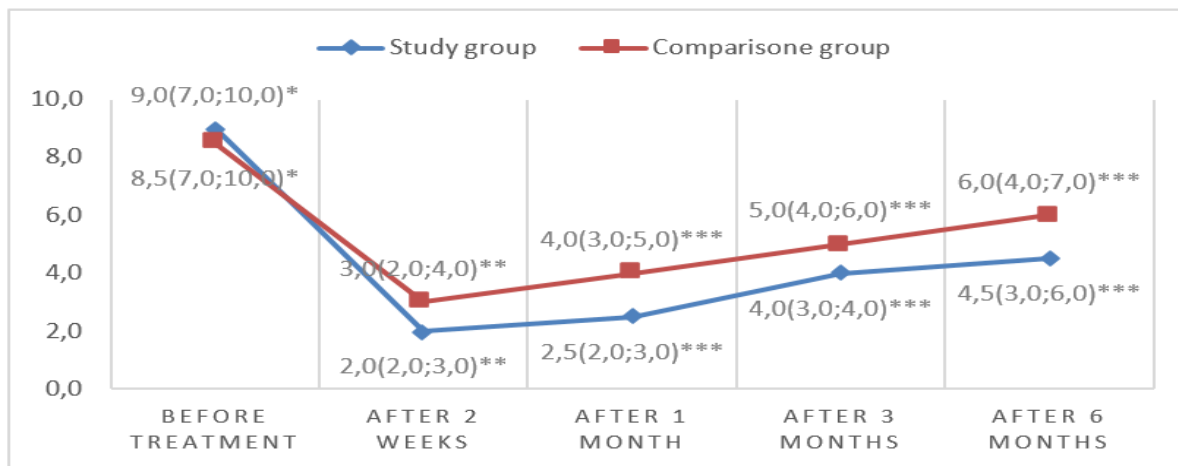


Fig. 1. Dynamics of the pain intensity changes (VAS, points) Me (Q25; Q75).

(* - $p > 0,05$, ** - $p < 0,05$, *** - $p < 0,01$)

Analysis of the results obtained with VAS (Fig.1) marked decreasing of the pain intensity in both groups: 2.0 (2.0; 3.0) points in the study group and in the comparison group - 3.0 (2, 0; 4.0) points in comparison to the basal values - 9.0 (7.0; 10.0) and 8.5 points (7.0; 10.0) points after 2 weeks from the start of the treatment. The values were significantly lower from baseline during the study period (examination after 1 month - 2.5 (2.0; 3.0) points, 3 months - 4.0 (3.0; 4.0) points and 6 months - 4.5 (3.0; 6.0) points) in the study group of patients who underwent RFNA procedure. In the comparison group of patients who had only the conservative treatment, also was noted reducing of the pain intensity after 2 weeks - 3.0 (2.0; 4.0) points from the beginning of treatment and recovery of pain almost to the initial level at the control examination in 6 months - 6.0 (4.0; 7.0) points. A comparison of both groups revealed a more pronounced reduction in the intensity of pain and more stable long-term effect among patients who underwent RFNA in combination with the conservative treatment. There was a tendency for recovering of the pain syndrome in both groups. The more pronounced tendency was admitted among patients who received only the conservative treatment course.

Assessment of patients' functional status and quality of life using the WOMAC questionnaire

Assessment of patients' functional status and the impact of knee pain on the quality of everyday life using the WOMAC questionnaire revealed significant differences between the two groups.

Analysis of the results of the WOMAC questionnaire, in the section corresponding to the "Pain" criterion (5 questions) showed a high level of intensity of pain before treatment in both groups of patients and amounted to 17.5 (16.0; 20.0) points in the study group, and 17.0 (16.0; 18.0) points in the comparison group. A more pronounced and persistent decreasing of pain was observed in the study group during the control period: after 2 weeks - 3.0 (2.0; 4.0) points, after 1 month - 4.0 (4.0; 5.0) points, after 3 months - 6.0 (6.0; 8.0) points, after 6 months - 8.0 (6.0; 9.0) points. In the comparison group also was noted a decrease in pain intensity within 2 weeks from the start of treatment to 4.0 (3.0; 4.0) points. In both groups, there was a tendency of pain recovering at the control at 6 months, and in the comparison group it was almost at the initial level - 15.0 (13.0; 17.0) points (Table 2).

Table 2

Functional status assessment of patients with knee osteoarthritis using the WOMAC questionnaire (“Pain”), Me (Q25; Q75)

| | Before treatment | After 2 weeks | After 1 month | After 3 months | After 6 months |
|---------------------------|----------------------|-------------------|-------------------|----------------------|----------------------|
| Study group (n = 21) | 17.5 (16.0; 20.0) | 3.0 (2.0; 4.0) | 4.0 (4.0; 5.0) | 6.0 (6.0; 8.0) | 8.0 (6.0; 9.0) |
| Comparison group (n = 21) | 17.0 (16.0; 18.0) | 4.0 (3.0; 4.0) | 7.0 (6.0; 8.0) | 12.0 (11.0; 14.0) | 15.0 (13.0; 17.0) |
| p | > 0.05 | <0.05 | <0.05 | <0.05 | <0.05 |

Analysis of a section of the questionnaire reflecting the subjective feeling of "Stiffness" (2 questions) showed improvement of treatment results in both groups of patients: study group - after 2 weeks - 3.0 (3.0; 4.0) points, after 1 month - 3.0 (3.0; 4.0) points, after 3 months - 3.5 (3.0; 5.0) points and after 3

months - 4.0 (3.0; 5.0). The results of the comparison group were in 2 weeks - 6.0 (5.0; 6.0) points, in 1 month - 6.0 (5.0; 7.0) points, in 3 and 6 months - 7.0 (6.0; 8.0). The baseline scores: 7.0 (6.0; 8.0) points in the study group and 7.0 (7.0; 8.0) points in the comparison group (Table 3).

Table 3

Functional status assessment of patients with knee osteoarthritis using the WOMAC questionnaire (“Stiffness”), Me (Q25; Q75)

| | Before treatment | After 2 weeks | After 1 month | After 3 months | After 6 months |
|---------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Study group (n = 21) | 7.0 (7.0; 8.0) | 3.0 (3.0; 4.0) | 3.0 (3.0; 4.0) | 2.5 (2.0; 3.0) | 4.0 (3.0; 5.0) |
| Comparison group (n = 21) | 7.0 (6.0; 8.0) | 6.0 (5.0; 6.0) | 6.0 (5.0; 7.0) | 7.0 (6.0; 8.0) | 7.0 (6.0; 8.0) |
| p | p > 0.05 | p < 0.05 | p < 0.05 | p < 0.05 | p < 0.05 |

The analysis of the section corresponding to the criterion for the evaluation of "Difficulties in daily activities" (17 questions) showed a high degree of limitation of physical activity of patients in both groups of patients before treatment: 62.0 (59.0; 66.0) points in the study group and 65.0 (58.0; 67.0) points in the comparison group. Within 2 weeks from the beginning of treatment, there was a decrease in scores: in the study

group - 21.0 (19.0; 21.0) points, after 1 month - 21.0 (19.0; 22.0) points, 3 months - 24.0 (22.0; 25.0) points and 6 months - 35.0 (30.0; 39.0) points; in the comparison group - 22.0 (21.0; 24.0) points, after 1 month 28.0 (27.0; 29.0) points, 3 months - 41.5 (39.0; 43.0) points and 6 months - 48.5 (42.0; 51.0) points (Table 4).

Table 4

Functional status assessment of patients with knee osteoarthritis using the WOMAC questionnaire (“Difficulties in daily activities”), Me (Q25; Q75)

| | Before treatment | After 2 weeks | After 1 month | After 3 months | After 6 months |
|---------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Study group (n = 21) | 62.0 (59.0; 66.0) | 21.0 (19.0; 21.0) | 21.0 (19.0; 22.0) | 24.0 (22.0; 25.0) | 35.0 (30.0; 39.0) |
| Comparison group (n = 21) | 65.0 (58.0; 67.0) | 22.0 (21.0; 24.0) | 28.0 (27.0; 29.0) | 41.5 (39.0; 43.0) | 48.5 (42.0; 51.0) |
| p | p > 0.05 | p < 0.05 | p < 0.05 | p < 0.05 | p < 0.05 |

The total WOMAC index provides an opportunity to evaluate the functional status of patients and its impact on quality of life in patients with knee arthritis (Table 5). More pronounced improvement in treatment outcomes was observed in the group of patients who underwent conservative treatment in combination with RFNA and was 26.5 (25.0; 28.0) points at 2 weeks after initiation of treatment, 28.0 (26.0; 30.0) points after 1 month and 47.0 (44.0; 49.0) points after 6 months, in

compare to the initial level of 87.0 (85.0; 91.0). In the group of patients who underwent only a course of conservative treatment, there was also an improvement in functional status within 2 weeks from the start of treatment - 32.5 (30.0; 34.0) points, but with a less long-lasting effect and restoration of almost a previous condition when interviewed after 6 months - 70.0 (69.0; 73.0) points in compare to the initial level of 87.0 (82.0; 91.0) points.

Table 5

Functional status assessment of patients with knee osteoarthritis by determining the total WOMAC index, Me (Q25; Q75)

| | Before treatment | After 2 weeks | After 1 month | After 3 months | After 6 months |
|---------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Study group (n = 21) | 87.0 (85.0; 91.0) | 26.5 (25.0; 28.0) | 28.0 (26.0; 30.0) | 33.0 (32.0; 34.0) | 47.0 (44.0; 49.0) |
| Comparison group (n = 21) | 87.0 (82.0; 91.0) | 32.5 (30.0; 34.0) | 40.5 (40.0; 42.0) | 61.0 (57.0; 63.0) | 70.0 (69.0; 73.0) |
| p | p > 0.05 | p < 0.05 | p < 0.05 | p < 0.05 | p < 0.05 |

Thus, this study revealed a high level of intensity of pain in patients with third stage knee arthritis (intensity on VAS - 9.0 (7.0; 10.0) points and 8.5 (7.0; 10.0) points in the groups of patients). The main complaint of patients with osteoarthritis of the knees was a pain, which contributes to the limitation of functional activity (WOMAC total index is 87.0 (85.0; 91.0) points and 87.0 (82.0; 91.0) points), therefore, a necessary measure of treatment for this pathology is the reduction of pain syndrome. Assessment of the dynamics of pain intensity, functional status, and quality of life revealed positive changes in both groups of patients. The more pronounced and long-lasting effect of the treatment was obtained in the group of patients who underwent RFNA of the genicular nerves in combination with conservative treatment (decreasing of the VAS score to 4.5 (3.0; 6.0) points and WOMAC total index to 47.0 (44.0; 49.0) points) in comparison to the group of patients who received only conservative treatment (decreasing of the VAS score to 6.0 (4.0; 7.0) points and total WOMAC index to 70.0 (69.0; 73.0) points).

Discussion

The results of this study showed that patients with severe knee osteoarthritis suffer from intense pain syndrome and have limitations of the functional activity in everyday life. Adequate conservative therapy of knee arthritis showed an improvement that can be obtained in pain intensity level and daily function in both groups of the patients. The more pronounced and long-termed improvement had been obtained in the study group of the patients which additionally underwent the radiofrequency neuroablation procedure.

Application of the RFNA in the treatment of chronic pain syndrome in the orthopedic practice is modern and gaining popularity method of the pain management described only a decade ago.

Radiofrequency is a type of alternate current that created heating the target tissues by providing friction between the molecules, thus, a thermal lesion is formed by the heat generated from the current. In our study, the targeted structures were sensory branches that innervate the knee joint.

In the present study, during the RFNA procedure, we used standard technique and targeted genicular nerves were specified as superior medial, superior lateral and inferior medial which influence on knee innervation was confirmed in various studies [10, 11, 13, 14, 15].

The study published in 2011 by Choi et al. [13] was designed to compare genicular nerve RFNA to sham RFNA. The results showed that RFNA significantly lowered the VAS at all time periods compared to sham, but both groups showed similar improvement at 1 week, suggesting a temporary improvement with a local anesthetic nerve block.

Kirdemir et al. [17] in 2017 published the study investigated the short-term effectiveness of genicular nerve RFNA applied in patients with chronic knee pain due to osteoarthritis. They showed results only after the procedure and admitted significant pain reduction and functional improvement.

The 2018 trial by Davis et al. [16] is the largest study and was also the first to employ RFNA. Similar to the Choi trial and our study, the same genicular nerves were targeted. Pain relief after the procedure was higher to that obtained with intra-articular steroids injections at all time periods, and at 6 month follow-up. Function and global perception were also higher in the RFNA group.

In our opinion, the most significant problem to achieve success in denervation is the identification of these genicular nerves. We performed RFNA under ultrasound guidance and use genicular arteries as landmarks identified by color Doppler visualization in the area of the femur and tibia periosteum. It has advantages over fluoroscopically guided knee denervation: direct soft tissue structures imagining, neurovascular bundles identification and absence of ionizing radiation.

Reducing the pain intensity after the procedure in combination with conservative therapy improves functional activity and quality of the patients' life. But this study showed increasing of the pain score to baseline values after 6 months after treatment which proves the temporary effect of the RFNA and nerves remyelination.

Conclusions

1. The pain syndrome in patients with knee arthritis makes limitations of the functional activity, so the reduction of the pain intensity is a necessary measure of treatment for this pathology, which may improve the quality of life of patients.

2. RFNA of the genicular nerves, as an additional method of treatment of pain syndrome, in combination with conservative therapy in patients with knee arthritis is an effective way to reduce the pain intensity and improves functional activity and quality of life of patients.

Prospects for further research: usage of radiofrequency neuroablation for reducing the intensity of pain syndrome in patients with joint diseases

Conflict of interest: authors have no conflict of interest to declare.

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