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Radiofrequency treatment relieves chronic knee osteoarthritis pain: A double-blind randomized controlled trial

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ABSTRACT

Chronic osteoarthritis (OA) pain of the knee is often not effectively managed with current non-pharmacological or pharmacological treatments. Radiofrequency (RF) neurotomy is a therapeutic alternative for chronic pain. We investigated whether RF neurotomy applied to articular nerve branches (genicular nerves) was effective in relieving chronic OA knee joint pain. The study involved 38 elderly patients with (a) severe knee OA pain lasting more than 3 months, (b) positive response to a diagnostic genicular nerve block and (c) no response to conservative treatments. Patients were randomly assigned to receive percutaneous RF genicular neurotomy under fluoroscopic guidance (RF group; $n = 19$) or the same procedure without effective neurotomy (control group; $n = 19$). Visual analogue scale (VAS), Oxford knee scores, and global perceived effect on a 7-point scale were measured at baseline and at 1, 4, and 12 weeks post-procedure. VAS scores showed that the RF group had less knee joint pain at 4 ($p < 0.001$) and 12 ($p < 0.001$) weeks compared with the control group. Oxford knee scores showed similar findings ($p < 0.001$). In the RF group, 10/17 (59%), 11/17 (65%) and 10/17 (59%) achieved at least 50% knee pain relief at 1, 4, and 12 weeks, respectively. No patient reported a post-procedure adverse event during the follow-up period. RF neurotomy of genicular nerves leads to significant pain reduction and functional improvement in a subset of elderly chronic knee OA pain, and thus may be an effective treatment in such cases. Further trials with larger sample size and longer follow-up are warranted.

1. Introduction

Chronic knee osteoarthritis (OA) is one of the most common diseases of advanced age [8,11]. OA often results in clinical consequences such as pain, restricted movement, sleep disturbance, and psychosocial disability [14,16,20,24].

Pharmacological therapy is often of limited benefit for OA pain. Moreover, the use of non-steroidal anti-inflammatory drugs is associated with serious side-effects, such as bleeding and gastrointestinal ulcers [2,12]. Non-surgical interventions, including intraarticular injection with steroids or hyaluronic acids, acupuncture and periosteal stimulation therapy, are often used as complementary therapies [3,5,10,21–23], but are not sufficient to control chronic severe knee OA pain. Although surgery is generally effective for patients with advanced disease [1], older individuals with limiting comorbidities may not be appropriate surgical candidates. In those cases, radiofrequency (RF) neurotomy might be a successful alternative treatment with few complications. This procedure is based on the theory that cutting the nerve supply to a painful structure may alleviate pain and restore function.

The knee joint is innervated by the articular branches of various nerves, including the femoral, common peroneal, saphenous, tibial and obturator nerves [13,18]. These articular branches around the knee joint are known as genicular nerves. Several genicular nerves can be easily approached percutaneously under fluoroscopic guidance.

No study has determined whether RF genicular neurotomy can relieve chronic knee OA pain. The present randomized study examined the effect of RF genicular neurotomy on chronic knee pain and knee function in elderly OA patients.

2. Methods

2.1. Patients

This randomized, double-blind, sham lesion-controlled study was conducted at the Pain Clinic of Asan Medical Center in Seoul,

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Korea. All participants provided written informed consent, and the study was approved by the Institutional Ethics Committee of Asan Medical Center (AMC IRB). Between May 2007 and June 2009, patients 50–80 years of age and with knee pain were examined to ascertain their eligibility. After clinical and radiologic assessment, the study subjects comprised elderly patients with chronic knee pain (i.e., knee pain of moderate intensity or greater on most or all days for $\geqslant$3 months) and radiologic tibiofemoral OA (Kellgren–Lawrence grade 2–4, evaluated by a radiologist) [17]. These patients conditions did not respond to other treatments including physiotherapy, oral analgesics, and intraarticular injection with hyaluronic acids or steroids.

The exclusion criteria included acute knee pain, prior knee surgery, other connective tissue diseases affecting the knee, serious neurologic or psychiatric disorders, injection with steroids or hyaluronic acids during the previous 3 months, sciatic pain, anticoagulant medications, pacemakers, and prior electroacupuncture treatment.

2.2. Diagnostic nerve blocks

The eligible patients underwent diagnostic genicular nerve blocks with local anesthetic, which were performed under fluoroscopic guidance. Genicular nerves consist of the superior lateral (SL), middle, superior medial (SM), inferior lateral (IL), inferior medial (IM), and recurrent tibial genicular nerve [4,15]. The targets included the SL, SM and IM genicular nerves which pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. Lidocaine (2 mL of 2%) was injected at each target site. Responses were recorded as positive if the participant experienced a decrease in numeric pain scores of at least 50% for more than 24 h. Patients with a positive response were included in the RF neurotomy procedures.

2.3. Procedures

Patients were randomly assigned to receive percutaneous RF genicular neurotomy (RF group, $n = 19$) or the same procedure without effective neurotomy (control group, $n = 19$) using a computer-generated randomization schedule. The randomization sequence was concealed throughout the study from both the study patients and the investigator who was an independent physician from the Outpatient Pain Clinic.

Under sterile conditions, the patient was placed in a supine position on a fluoroscopy table with a pillow under the popliteal fossa to alleviate discomfort. The true AP fluoroscopic view of the tibiofemoral joint was obtained and showed an open tibiofemoral joint space with equal width interspaces on both sides. Skin and soft tissues were anesthetized with 1 mL 1% lidocaine. A 10 cm 22-gauge RF cannula with a 10 mm active tip (NeuroTherm™, Medipoint® GmbH, Hamburg, Germany) was employed for the technique. Under fluoroscopic guidance, the cannula was advanced percutaneously towards areas connecting the shaft to the epicondyle, the so-called ''tunnel technique'', until bone contact was made (Fig. 2). Sensory stimulation at 50 Hz was performed to identify the nerve position. The sensory stimulation threshold was required to be less than 0.6 V. In order to avoid inactivating motor nerves, the nerve was tested for the absence of fasciculation in the corresponding area of the lower extremity on stimulation of 2.0 V at 2 Hz. Lidocaine (2 mL of 2%) was injected before activation of the RF generator (NeuroTherm™, Morgan automation LTD, Liss, UK). The RF electrode was then inserted through the canula, and the electrode tip temperature was raised to 70 °C for 90 s. One RF lesion was made for each genicular nerve. Control patients underwent the same procedure without activation of the RF generator, and the temperature of the electrode tip was not raised.

After the procedure, all patients were advised to continue medications which had been previously prescribed for other degenerative diseases, as well as those for knee OA. These patients were prohibited from making any alterations to their medications and physiotheraphy during the 12 weeks post-procedure. All procedures were performed by one operator. These patients were not aware of the type of treatment received.

2.4. Evaluations

All preoperative baseline and post-procedure outcome measurements at 1, 4, and 12 weeks were performed by an independent physician who was blinded for the type of treatment the patients had undergone in the Outpatient Pain Clinic. Baseline characteristics were collected for all participants. Weight-bearing radiographs were reviewed at baseline to grade the degree of OA using the Kellgren–Lawrence system. Outcome measures were assessed according to hospital visits at baseline and at 1, 4, and 12 weeks after the procedure. Prior to the procedure, participants were instructed in the use of a 100 mm visual analogue scale (VAS) (no pain to unbearable pain) and Oxford knee scores to obtain baseline values. Oxford knee scores were 12-item joint-specific self-administered questionnaires. Each question was scored from 1 to 5, with 1 representing the best outcome/least symptoms. The scores from each question were then added so that the overall figure was between 12 and 60, with 12 being the best outcome [7]. At 1, 4, and 12 weeks post-procedure, patients completed a written questionnaire requesting estimation of these measurements. In addition, the questionnaires assessed global perceived effect on a 7-point scale (1 = worst ever, 2 = much worse, 3 = worse, 4 = not improved but not worse, 5 = improved, 6 = much improved, 7 = best ever). Pain data were expressed as absolute values and as the proportion of patients who achieved at least 50% pain relief at follow-up.

The primary outcomes were the mean changes from baseline knee pain as measured by VAS at 1, 4, and 12 weeks and the proportion of patients achieving at least 50% knee pain relief at 12 weeks. Secondary outcomes were functional changes, patient satisfaction with treatment and the incidence of adverse effects. Patients were requested to report any adverse effects to the physician at each visit. They also could report by telephone at any other time for further advice and management. All adverse effects (e.g., abnormal proprioception, numbness, paresthesia, neuralgia, and motor weakness) were recorded.

2.5. Statistical analysis

The sample size was calculated following a two-arm pilot study which was performed with 10 patients in each group. That pilot study found that 60% of the RF group achieved the primary outcome versus 10% of the control group. Based on a power of 80% and a two-tailed alpha of 0.05, the sample size required for the present study was 17 per group for a total of 34 patients. The final sample required was 38 patients to accommodate an attrition rate of 10%. All scale variables were tested for normality using the Kolmogorov–Smirnov test. Two-way repeated measures analysis of variance (ANOVA) with Tukey tests for multiple comparisons was used to compare the changes from baseline VAS pain scores and Oxford knee scores among baseline, post-procedure 1, 4, and 12 weeks. To compare the differences of VAS pain scores and satisfaction between groups, the Mann–Whitney U test was used at each time point. To compare the differences of Oxford knee scores between groups, the unpaired t-test was used at baseline. The Mann–Whitney U test was used at post-procedure 1, 4, and 12 weeks. To compare patients' characteristics variables, the Fisher's exact test was used for sex, treatment sites. The chi-square test

was used for Kellgren–Lawrence grade. The unpaired *t*-test was used for body weight, height, body mass index, duration. Data analysis was performed using SPSS 11.0 for window (SPSS Inc, Chicago, IL, USA) on a personal computer. Values were estimated as mean ± standard deviation. A *P* value of <0.05 was taken to indicate a significant difference.

3. Results

3.1. Study population

Of 176 patients with knee pain screened, 113 failed the study selection criteria. The excluded patients consist of 31 refused to participate, 32 with radiculopathy, 20 with osteoarthritis (Kellgren–Lawrence grade 1), 16 with history of injection with steroid or hyaluronic acid within 3 months, nine with acute knee pain, four with prior knee surgery, one with rheumatoid arthritis. 63 fulfilled the study selection criteria. All underwent a diagnostic nerve block of the genicular nerves. After diagnostic block, 52 of them had a positive response. 38 entered the protocol and were randomized. The remaining fourteen patients did not enter the study for the following reasons: 10 of 14 patients did not want to take part in a trial, two owing to their anxiety regarding RF neurotomy, eight for personal reasons, and four of 14 patients reported no pain at all after the diagnostic nerve block (Fig. 1).

Data from two RF patients were incomplete and were thus not used in the analysis. One of these RF patients fell in the bathroom at three weeks post-procedure, thus preventing collection of the 4-week data. Her right knee pain improved more than 50% at one week post-procedure. However, as her symptoms were aggravated after the fall, she underwent a second RF neurotomy procedure which relieved her knee pain. The other patient experienced hemarthrosis from walking up a hill, thus preventing collection of the 12-week data. Because this patient's knee VAS pain score and the Oxford knee score were reduced at four weeks post-procedure, she planned to continue walking up the hill near her house. One day after resuming her walking, her left knee was swollen and was therefore immediately treated by an orthopedic surgeon. Additional hemarthrosis was not developed. Knee swelling was reduced by conservative therapy. These two RF patients did not have any detectable muscle weakness, paresthesia or abnormal proprioception. Data from one control patient were not used because the 12-week questionnaire was not completed. This patient had no reduction of knee pain after the procedure and lived too far from our hospital to complete the study. Thus, data from 35 participants (17 RF and 18 control) were analyzed for the study. Both groups showed similar baseline characteristics (Table 1).

3.2. Primary outcomes

There was a significant interaction between group and time for the mean changes of the VAS pain scores ($p < 0.001$). In the RF group, VAS knee pain scores were lower at all post-procedure assessment points compared with baseline ($p < 0.001$). By contrast, in the control group the VAS pain scores were only lower than baseline at 1 week (Fig. 3). When comparing knee pain improvement from baseline, the RF group showed superior improvement compared with the control group at both 4 ($p < 0.001$) and 12 ($p < 0.001$) weeks (Table 2). Ten participants in the RF group (59%) achieved a primary outcome of at least 50% knee pain relief at 12 weeks, whereas no participants in the control group achieved this primary outcome (Fig. 4).

3.3. Secondary outcomes

There is a significant interaction between group and time for the mean changes of the Oxford knee scores ($p < 0.001$). In the RF group, Oxford knee scores improved at all assessment points

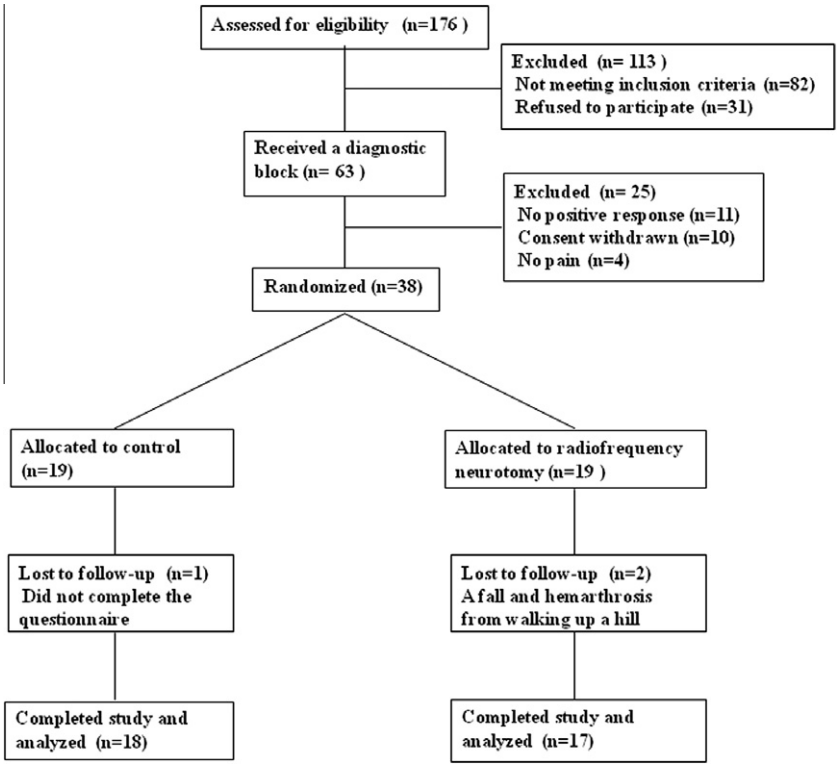

Fig. 1. Flow of patients through the trial. Out of 176 patients assessed, 38 patients were randomized to RF ($n = 19$) or control ($n = 19$). At 12 weeks post-procedure, 17 and 18 patients remained in each group, respectively.

Table 1
Baseline characteristics of patients with chronic knee pain randomly assigned to receive Radiofrequency (RF) neurotomy or lidocaine (control).

Characteristics	Control (n = 18)	RF (n = 17)	P-values
Age (yrs), mean ± SD	66.5 ± 4.8	67.9 ± 7.1	0.559
Sex (M/F)	3/15	2/15	1.0
Height (cm), mean ± SD	155.3 ± 7.5	151.9 ± 6.2	0.182
Weight (kg), mean ± SD	63.1 ± 5.1	61.6 ± 9.0	0.204
Body mass index, mean ± SD	26.5 ± 2.1	26.2 ± 3.3	0.567
Duration (years), mean ± SD	7.4 ± 4.0	6.3 ± 3.9	0.404
Treatment sites (right/left)	10/8	8/9	0.740
Visual analogue pain scale (0–100 mm), mean ± SD	77.2 ± 7.5	78.2 ± 13.8	0.942
Oxford knee score (12–60 points), mean ± SD	39.2 ± 4.4	39.8 ± 6.5	0.486
Radiographic disease severity (Kellgren–Lawrence grade)			
2	4	3	
3	7	8	0.879
4	7	6	

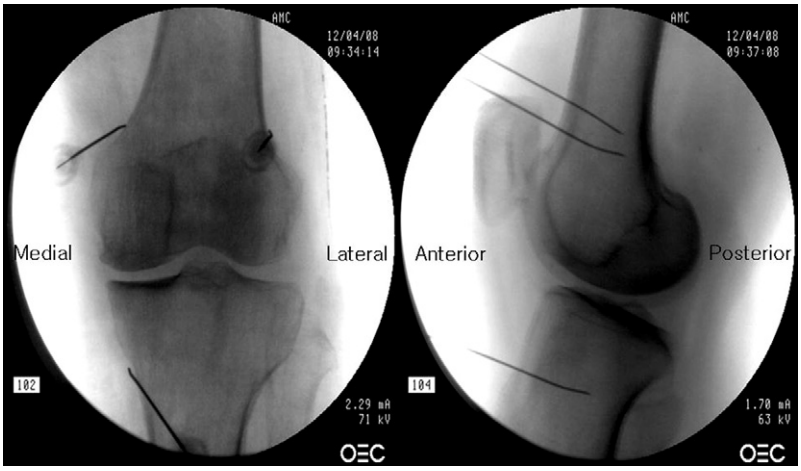

Fig. 2. Fluoroscopic image of anteroposterior and lateral views of the left knee joint. RF electrode tips were placed on periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. Superior medial, superior lateral and inferior medial genicular nerves run down these areas.

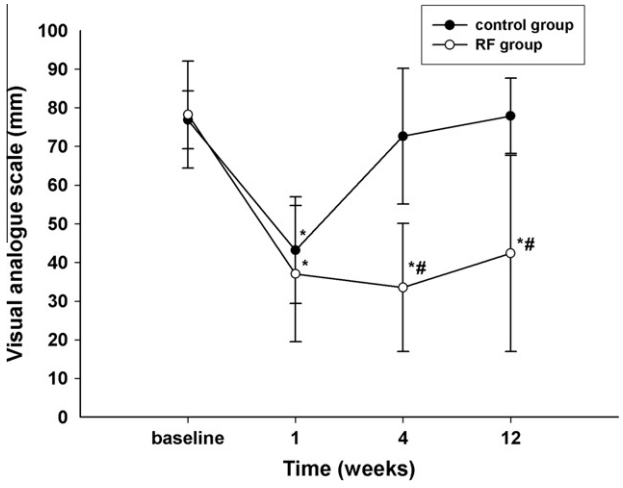

Fig. 3. Visual analogue scale pain scores in patients receiving radiofrequency (RF) neurotomy or lidocaine (control). Values represent mean and standard deviation. $^{*}p < 0.05$ vs. baseline. $^{\#}p < 0.05$ vs. control group.

compared with baseline ($p < 0.001$). The RF group Oxford knee scores were better than control group scores at 4 ($p < 0.001$) and 12 ($p < 0.001$) weeks. The RF group patient satisfaction was better than the control group satisfaction at 4 ($p < 0.001$) and 12 ($p < 0.001$) weeks, and was highest at 4 weeks in the RF group (Table 2).

3.4. Adverse events

Although several participants experienced temporary periosteum touch pain from the RF canula during the procedure, the pain was tolerable and required no medication. Otherwise, no participant reported a post-procedure adverse event during the follow-up period, and there were no withdrawals from the study owing to an adverse event. Most of patients had rescue analgesics for breakthrough pain in previously prescribed medications. If their medication was not enough to relieve pain, patients were requested to call or visit to our investigator, physician. In this study, no participant needed the changes to their analgesic medications during the follow-up period.

4. Discussion

This is the first small randomized study showing the clinical efficacy of RF genicular neurotomy for chronic knee OA. This study found that RF genicular neurotomy induced potent analgesia in elderly patients with chronic knee OA pain. Although the follow-up period was only three months, these patients also experienced significant functional improvement and treatment satisfaction. Furthermore, RF neurotomy for knee OA relieved the knee pain

Table 2
Clinical and Functional Outcomes after Radiofrequency (RF) Neurotomy and Changes from Baseline Values.

Post-procedure time	Control (n = 18)	RF (n = 17)	Changes from baseline		p-value
			Control	RF	
VAS (0–100 mm)					
1 week	43.2 ± 13.7	37.1 ± 17.6	33.7 ± 13.8	41.2 ± 18.3	0.194
4 weeks	72.6 ± 17.6	33.5 ± 16.6	4.2 ± 16.1	44.7 ± 17.7*	<0.001
12 weeks	77.9 ± 9.8	42.4 ± 25.4	-1.1 ± 6.5	35.9 ± 23.2*	<0.001
OKS (12–60 points)					
1 week	26.8 ± 4.5	23.6 ± 7.5	12.4 ± 4.3	16.2 ± 9.5	0.296
4 weeks	36.9 ± 3.5	25.8 ± 8.0	2.3 ± 4.8	14.1 ± 9.7*	<0.001
12 weeks	38.9 ± 4.9	27.4 ± 10.2	0.3 ± 1.3	12.4 ± 10.7*	<0.001
Patient satisfaction with GPE†					
1 week	5.3 ± 0.8	5.5 ± 0.7			0.457
4 weeks	4.3 ± 0.8	5.9 ± 0.9‡			<0.001
12 weeks	3.7 ± 0.5	5.5 ± 1.1‡			<0.001

All data values are means ±SD. VAS: visual analogue scale; OKS: Oxford knee score.
* $p < 0.05$ compared to the change from baseline in the control group.
† Global perceived effect (GPE) with 7-point scale (1 = worst ever, 2 = much worse, 3 = worse, 4 = not improved not worse, 5 = improved, 6 = much improved, 7 = best ever).
‡ $p < 0.05$ compared to control group.

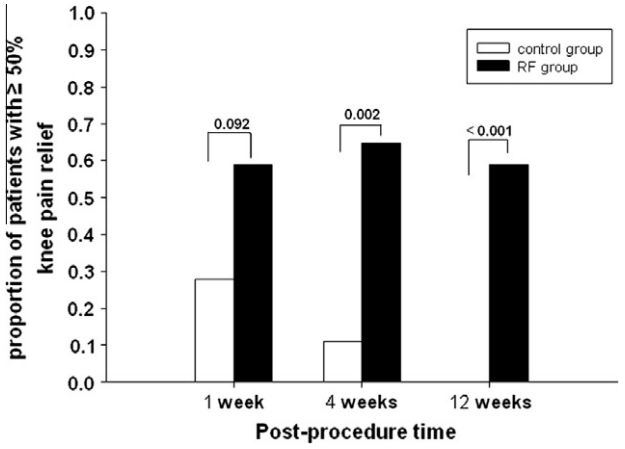

Fig. 4. Proportion of patients achieving at least 50% knee pain relief at follow-up. At 12 weeks post-procedure, ⩾50% knee pain relief was observed in 10 radiofrequency (RF) neurotomy patients (59%) and in no control patients.

without any adverse event, as well as its being accessible and acceptable to elderly patients. However, as this procedure is more invasive than other treatments, RF neurotomy should preferably be used for knee OA patients without response to conservative treatments and with a positive response to diagnostic block.

The use of RF for chronic knee OA pain requires the identification of anatomic landmarks for nerves innervating the knee joint. The sciatic nerve separates into the tibial and common peroneal nerves in the popliteal area. Subsequently, the tibial nerve projects articular branches at the popliteal fossa. These articular branches include the SM, middle and IM genicular nerves. The common peroneal nerve also projects articular branches, specifically the SL, IL, and recurrent tibial genicular nerve. The SL, SM and IM genicular nerves accompanying genicular vessels pass close to epicondyles of the femur and tibia; except the IL genicular nerve, which runs laterally above the head of the fibula, and does not pass near the lateral epicondyle of the tibia [4,15]. Therefore, the SL, SM and IM genicular nerves with relatively precise anatomic aspects were applied for the RF current. Using fresh two cadavers, although these anatomic findings were not published, we confirmed that these genicular nerves pass periosteal areas connecting the shaft to the epicondyle (Fig. 5). Therefore, the target points for RF neurotomy included periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. We identified genicular nerves at these points with sensory stimulation, and were able to generate RF lesions. The main principle of RF neurotomy also includes a correct placement of the electrode parallel to the target nerve [6]. At our institution, this was precisely performed because we could effectively place the electrode tip parallel to the genicular nerve next to the periosteum of target sites.

In the present study, two patients in the RF group (12%) achieved poor or no response to RF neurotomy throughout the study period. Several articular branches innervate the knee joint. Kennedy et al. [18] reported that articular branches of the femoral, common peroneal, saphenous, tibial and obturator nerves are distributed to the human knee. Although genicular nerves are the main innervating articular branches for the knee joint, other articular branches may also be present. For this reason, pain of the knee joint may not be completely relieved, resulting in poor response to RF neurotomy.

During the procedure, some patients transiently felt unbearable pain when the RF cannula was in contact with their periosteum. This may be attributed to stimulation of pain-sensitive structures such as the periosteum and ligament insertion sites in chronic knee OA [9,25]. Although no patients in this study withdrew from the procedure, some patients can refuse RF neurotomy because of pain caused by cannulation. Premedication with analgesics can help to reduce this pain.

Two RF patients were lost due to accidents in the study. These patients were assessed muscle tone, proprioception, balance, and gait after accidents. Proprioception and other measures of functional status were not impaired, and there had been no reduction of functional capacity after RF neurotomy. We therefore assumed that these two accidents were not adverse events related to their procedure. In this study, no patients showed postural sway or gait disturbance after RF neurotomy.

According to our assessment, the two, lost RF patients had good responses regarding the RF procedure at one and four weeks post-procedure, respectively. However, we could not analyze data which were not completed in the questionnaire at 12 weeks as the study data were analyzed using two-way repeated measures ANOVA. If these two RF patients had been included in the analysis, our results would have been better.

The potential limitations of this trial require consideration. First, we did not perform RF neurotomy for all articular branches innervating the knee joint; only three main articular branches originating in the sciatic nerve were denervated. Denervation of other articular branches would possibly give different results. Second,

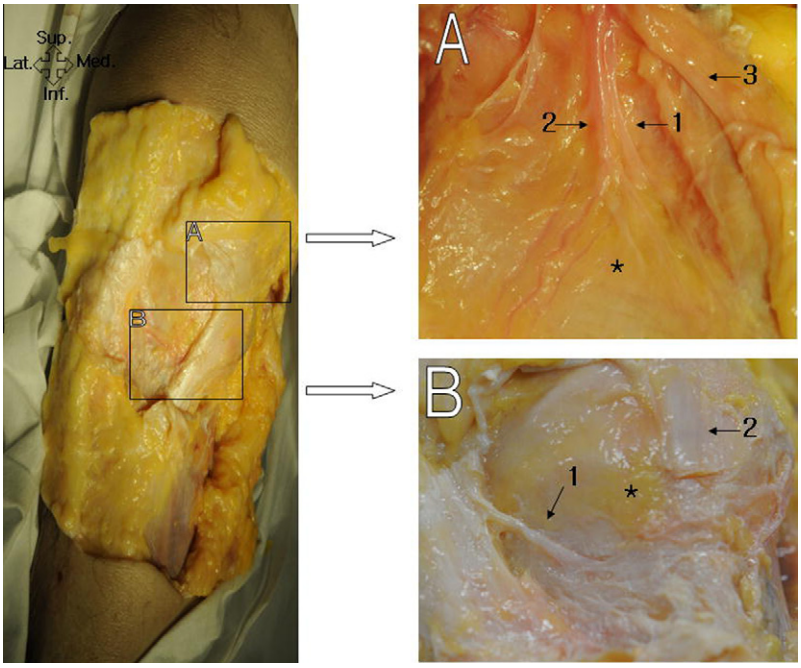

Fig. 5. Anteromedial view of the right knee joint. (A) The superior medial genicular nerve (1) runs down the upper part of the medial epicondyle (asterisk) of the femur with genicular vessels (2). The adductor magnus (3) which is inserted into the adductor tubercle on the medial condyle of the femur. (B) The inferior medial genicular nerve (1) passes the lower parts of the medial epicondyle (asterisk) of the tibia. The tibial collateral ligament (2) which is attached to the medial condyle of the tibia.

because most of the patients had degenerative joint pain including shoulder, back, and neck pain, we were not able to select the patients with only knee OA pain. And as they had taken medication consisting of various analgesics or topical products over a prolonged period of time, we could not precisely evaluate their consumption of analgesics for knee pain. Therefore, the participants continued to take medication without alterations to doses and physiotherapy during the 12 weeks post-procedure. Third, variations in the genicular nerves remain to be established, and such anatomic problems should be considered in future trials.

In the systemic review of RF neurotomy for neck and back pain [19], previous randomized controlled trials (RCTs) provided limited or conflicting evidence regarding the short-term effect of RF lesioning for pain and disability. Furthermore, RCTs are needed in non-spinal indications where RF neurotomy is currently used without any scientific evidence of its efficacy. Although this RCT had positive findings regarding the short-term effect of RF genicular neurotomy, further high-quality RCTs are needed with larger patient samples and data regarding long-term effects as the current evidence are inconclusive.

This study was not designed to provide strong evidence regarding the safety of RF genicular neurotomy, and adverse effects were relatively infrequently reported during the short-term follow-up period. However, there is still a need for further studies using large samples from other medical centers, with longer follow-up periods, and using validated checklists for gathering information about any adverse effects.

In conclusion, RF neurotomy of genicular nerves seems to be a safe, effective, and minimally invasive therapeutic procedure for chronic knee OA patients with a positive response to diagnostic block. RF neurotomy can also be repeated if necessary in order to provide further relief. This technique may be a useful treatment for chronic severe OA pain refractory to other conservative treatments, although further, large-scale studies, and longer follow-up periods are needed not only in order to demonstrate the efficacy of RF genicular neurotomy but also to track any long-term adverse effects.

Conflict of Interest

None declared.

References

[1] American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905–15.
[2] Bjordal JM, Ljunggren AE, Klovning A, Slørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 2004;329:1317.
[3] Brandt KD, Smith Jr GN, Simon LS. Intraarticular injection of hyaluronan as treatment for knee osteoarthritis: what is the evidence? Arthritis Rheum 2000;43:1192–203.
[4] Clemente CD. Anatomy of the human body by Henry Gray. Philadelphia: Lea & Febiger; 1985. p. 1239–41.
[5] Dieppe PA, Sathapatayavongs B, Jones HE, Bacon PA, Ring EF. Intra-articular steroids in osteoarthritis. Rheumatol Rehabil 1980;19:212–7.
[6] Dreyfuss P, Halbrook B, Pauza K, Joshi A, McLarty J, Bogduk N. Efficacy and validity of radiofrequency neurotomy for chronic lumbar zygapophysial joint pain. Spine 2000;25:1270–7.
[7] Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. J Bone Joint Surg Br 1998;80:63–9.
[8] Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. Radiol Clin North Am 2004;42:1–9.
[9] Felson DT. The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 2005;17:624–8.
[10] Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis: hope, hype, and hard truths. Arch Intern Med 2002;162:245–7.
[11] Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. Am J Phys Med Rehabil 2006;85:S2–S14.
[12] Gutthann SP, Garcia Rodriguez LA, Raiford DS. Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. Epidemiology 1997;8:18–24.
[13] Hirasawa Y, Okajima S, Ohta M, Tokioka T. Nerve distribution to the human knee joint: anatomical and immunohistochemical study. Int Orthop 2000;24:1–4.
[14] Hopman-Rock M, Odding E, Hofman A, Kraaimaat FW, Bijlsma JW. Physical and psychosocial disability in elderly subjects in relation to pain in the hip and/or knee. J Rheumatol 1996;23:1037–44.
[15] Horner G, Dellon AL. Innervation of the human knee joint and implications for surgery. Clin Orthop Relat Res 1994:221–6.
[16] Jinks C, Jordan K, Croft P. Measuring the population impact of knee pain and disability with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Pain 2002;100:55–64.

[17] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
[18] Kennedy JC, Alexander IJ, Hayes KC. Nerve supply of the human knee and its functional importance. Am J Sports Med 1982;10:329–35.
[19] Niemistö L, Kalso E, Malmivaara A, Seitsalo S, Hurri H. Radiofrequency denervation for neck and back pain: a systematic review within the framework of the cochrane collaboration back review group. Spine 2003;28:1877–88.
[20] Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001;60:91–7.
[21] Raynauld JP, Buckland-Wright C, Ward R, Choquette D, Haraoui B, Martel-Pelletier J, Uthman I, Khy V, Tremblay JL, Bertrand C, Pelletier JP. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2003;48:370–7.
[22] Weiner DK, Rudy TE, Morone N, Glick R, Kwoh CK. Efficacy of periosteal stimulation therapy for the treatment of osteoarthritis-associated chronic knee pain: an initial controlled clinical trial. J Am Geriatr Soc 2007;55:1541–7.
[23] White A, Foster NE, Cummings M, Barlas P. Acupuncture treatment for chronic knee pain: a systematic review. Rheumatology (Oxford) 2007;46:384–90.
[24] Wilcox S, Brenes GA, Levine D, Sevick MA, Shumaker SA, Craven T. Factors related to sleep disturbance in older adults experiencing knee pain or knee pain with radiographic evidence of knee osteoarthritis. J Am Geriatr Soc 2000;48:1241–51.
[25] Wojtys EM, Beaman DN, Glover RA, Janda D. Innervation of the human knee joint by substance-P fibers. Arthroscopy 1990;6:254–63.