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ORIGINAL ARTICLE

The effectiveness of intra-articular pulsed radiofrequency in patients with painful knee osteoarthritis: A randomized controlled trial

Burak Erken, Duygu Gizem Karali Bingül

Department of Algology, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye

SUMMARY

Objectives: This study aimed to compare the effects of intra-articular steroid injection (IASI) and IASI combined with intra-articular pulsed radiofrequency (IAPRF) on pain and functional activities in stage II–III knee osteoarthritis.

Methods: This randomized controlled trial included patients with knee pain persisting for more than 3 months. The participants were randomized into two groups: IAPRF + steroid injection (Group 1) and steroid injection only (Group 2). The injections were administered under fluoroscopic guidance, and the needle was advanced to the midline of the tibiofemoral joint. Group 1 received 8 mg of intra-articular dexamethasone after IAPRF application for 360 s at 45 V, with the temperature not exceeding 42°C. Group 2 received 8 mg of intra-articular dexamethasone only. Pain intensity and participation in daily activities were evaluated using the Numerical Rating Scale and the Western Ontario and McMaster Universities Arthritis Index, respectively, before the procedure and 1, 4, and 12 weeks after the procedure.

Results: A total of 54 patients were included in the study. Demographic data, baseline pain levels, and functional activities did not differ between the groups. Pain intensity at 4 and 12 weeks after the procedure was lower in Group 1. Participation in daily living activities was significantly higher in Group 1 at 12 weeks after the procedure.

Conclusion: IAPRF combined with intra-articular steroid significantly improves pain during the early-to-mid period and participation in daily living activities in the mid-term in stage II–III knee osteoarthritis.

Keywords: Intra-articular injection; knee osteoarthritis; pain management; pulsed radiofrequency treatment.

Introduction

Osteoarthritis (OA) of the knee, a leading cause of disability in the elderly population, is characterized by pain, stiffness, and limitations in the activities of daily living.[1,2] Several conservative methods have been introduced for the management of OA of the knee, such as symptomatic pain medications, physical therapy modalities, intra-articular steroid injections, platelet-rich plasma injections, visco-supplementation, and genicular nerve ablation methods. Surgical options, such as knee replacement, may also be considered in patients who do not benefit from conservative treatment, especially those with advanced OA.[2]

Radiofrequency ablation of the genicular nerves is widely performed by pain specialists, as pain signals in the knee are transmitted via the genicular nerves. The free nerve endings in the joint capsules have become a target for treatment in recent years. The application of intra-articular pulsed radiofrequency (IAPRF) to the knee joint was first reported in 2008,[3] with subsequent studies reporting promising results.[4–6] IAPRF is an easy-to-apply method with a low risk of side effects and complications. However, its mechanism of action remains to be clarified.

PRF is assumed to alter the transmission of pain through the pericapsular nerve endings, thereby reducing the severity of pain; however, further re-

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Correspondence: Dr. Burak Erken. Sağlık Bilimleri Üniversitesi, Başakşehir Çam ve Sakura Şehir Hastanesi, Algoloji Kliniği, İstanbul, Türkiye.
Phone: +90 - 212 - 909 60 00 **e-mail:** drburakerken@gmail.com

search is required to confirm its effectiveness. Therefore, this study aimed to investigate the additional effect of IAPRF on pain and functional activities in patients with grade II and III knee OA.

Materials and Methods

This single-center, single-blinded, randomized prospective trial received approval from the Ethics Committee of Başakşehir Çam and Sakura City Hospital and was conducted in accordance with the Declaration of Helsinki. The study was carried out between May and September 2022. After receiving ethical approval, 62 patients who were assessed for eligibility were referred to the Pain Medicine Outpatient Clinic of Başakşehir Çam and Sakura City Hospital. Among these 62 patients, six were excluded as they did not meet the inclusion criteria, and two declined participation. Thus, 54 patients were enrolled in the study after providing written and verbal consent.

The enrolled patients were randomized into two groups: Group 1 (IAPRF+steroid injection) and Group 2 (steroid injection only) (Fig. 1). Randomization was performed using a computerized program. Randomization, pre-injection assessments, and enrollment were carried out by the clinic nurse. Due to differences between the methods applied in the two groups, the operator and nurses were not blinded. However, post-injection assessments were performed by a blinded evaluator.

The inclusion criteria were as follows: (1) age over 18 years, (2) knee pain persisting for more than 3 months due to knee OA, (3) Kellgren–Lawrence Classification grades II and III OA, and (4) provision of written and verbal informed consent. Exclusion criteria included: (1) history of knee surgery and/or intra-articular knee injection within the previous 6 months, (2) local or systemic infections or a coagulation disorder, or (3) refusal to participate in the study.

All procedures were performed by a practitioner with more than 5 years of experience in an operating room under blood pressure and peripheral oxygen saturation monitoring. Patients were placed in the supine position with knees slightly flexed. For local anesthesia, 1–2 mL of 1% lidocaine was administered.

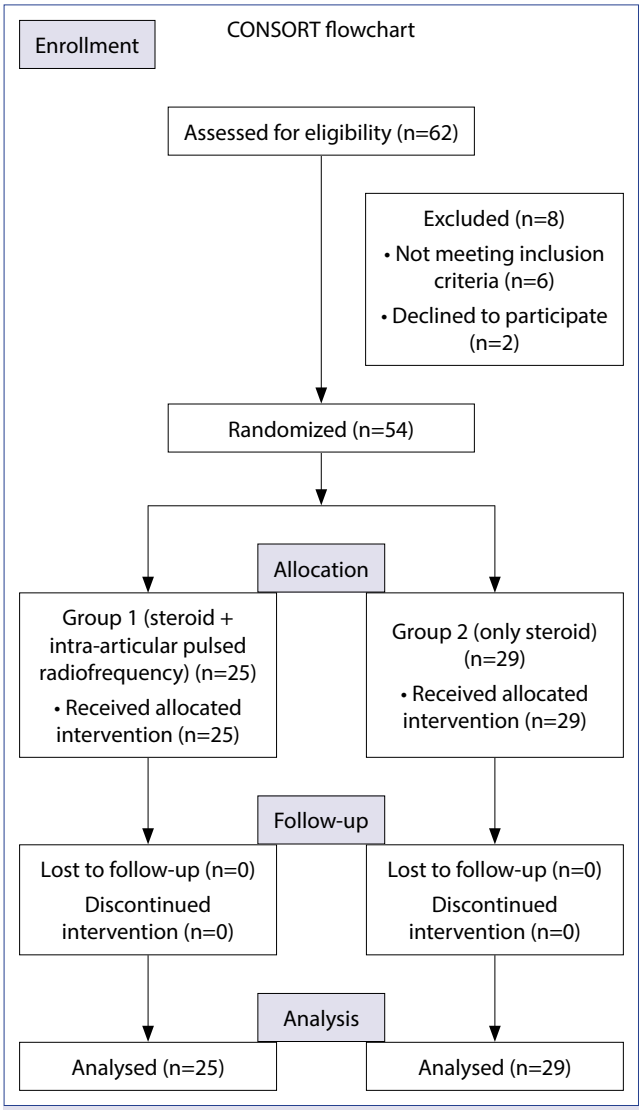

Figure 1. Flow diagram.

In Group 1, a 22-G 10-cm radiofrequency cannula with a 10-mm active tip was advanced to the mid-tibiofemoral joint under fluoroscopic guidance (Fig. 2). After needle insertion, paresthesia-pain and motor stimulation tests were performed using sensory (50 Hz) and motor (2 Hz, 1 V) stimulation to confirm the absence of stimulation. PRF was applied at 45 V with a 20-ms pulse width for 360 s, followed by a 480-ms silent phase. The tissue temperature was kept below 42°C. After confirmation of intra-articular contrast injection, 8 mg of dexamethasone was administered.

In Group 2, a 22-G needle was advanced to the mid-tibiofemoral joint, and 8 mg of dexamethasone was administered under fluoroscopic guidance.

Outcomes

Pre-injection evaluation and demographic data

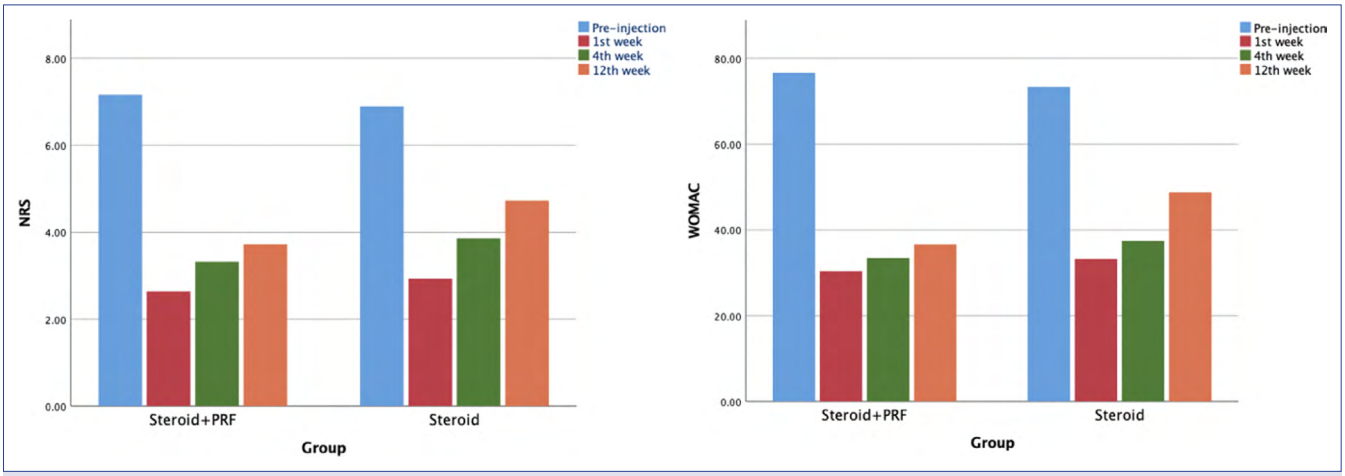

Figure 2. Numeric rating scale (NRS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) score graphs of patients.

collection were performed by the operator before randomization. Post-injection evaluations were performed by the patients under the guidance of a blinded evaluator at 1, 4, and 12 weeks after treatment.

Numeric Rating Scale

Knee pain was assessed using the numeric rating scale (NRS) at all evaluation points. Patients were instructed to score their pain intensity on a scale of 0 to 10, where 0 represents "no pain at all" and 10 represents "worst pain ever possible."

Western Ontario and McMaster Universities Arthritis Index

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used to assess daily living activities at all evaluation points. The WOMAC consists of 24 items across three subscales: pain, stiffness, and physical function. All items were scored on a scale of 0 to 4, where 0 represents none, 1 represents mild, 2 represents moderate, 3 represents severe, and 4 represents extreme. The total score ranges from 0 to 96, with a higher score indicating poorer function in daily living activities.

Sample Size

The sample size was calculated using G*Power V.3.1.7 (University of Kiel, Kiel, Germany) based on data from Yuan et al.[7] According to their visual analog scale scores 4 weeks after treatment (corticosteroid group: 3.6±1.6, radiofrequency group: 2.1±1.4), with a power (β error)=0.95 and α error=0.05, the minimum sample size was calculated as 23 for each group, with an estimated drop-out of 10%. Thus, a minimum of 51 patients were planned to be enrolled in the study.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics for Mac Version 25 (IBM, Armonk, NY). The Shapiro–Wilk test, histograms, and normality plots were used to evaluate the distribution of values. Descriptive statistics are presented as mean (standard deviation). Some data were not normally distributed; therefore, non-parametric tests were used to evaluate between- and within-group changes. Between-group comparisons were performed using the Mann–Whitney U test, within-group changes were evaluated using the Friedman test, and pairwise comparisons were performed using the Wilcoxon test with Bonferroni correction. Statistical significance was set at $p<0.05$.

Results

A total of 54 patients (44 females and 10 males) were included in the study. The mean age was 62.9 years in Group 1 and 61.9 years in Group 2. No significant differences were observed between the patient demographics, such as age, sex, weight, height, and body mass index (BMI), in the two groups (Table 1).

The baseline pain intensity measured using NRS (7.16±0.85; 6.9±0.9; p=0.242, respectively) and the functional level in daily living activities measured using the WOMAC scores (76.64±8.47; 73.31±8.46; p=0.124, respectively) were similar between the two groups (Table 2).

Table 1. Patient demographics

	Steroid+IAPRF group (n=25)	Steroid group (n=29)	p
Age (years)			0.531[a]
Mean±SD	62.9± 8	61.9±8.8	
Min–Max	45–79	46–78	
Sex (female/male)	21/4	23/6	0.658[b]
Height (cm)			0.074 [a]
Mean±SD	161.5±6.8	163.3±5.6	
Min–Max	152–180	156–180	
Weight (kg)			0.23[a]
Mean±SD	81.8±17.6	75.5±9.2	
Min–Max	57–135	58–95	
BMI (kg/m^2)			0.071[a]
Mean±SD	31.4±6.84	28.3±3.1	
Min–Max	22.8–54.1	23.8–35.9	
Side (Right/Left)	15/10	13/16	0.266[b]
Radiological grade			0.266[b]
Grade II	10	16	
Grade III	15	13	

IAPRF: Intra-articular pulsed radiofrequency; SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body Mass Index; a: Mann–Whitney U test; b: Chi-Squared Test.

A significant decrease in pain levels and an increase in daily functionality were observed in both groups during follow-up. In addition, a substantial difference was observed between baseline and later evaluation timepoints, as well as between the first and 12th weeks. Compared with Group 2, pain levels were lower at 4 and 12 weeks in Group 1, while daily function was better only at the 12th week (Table 2, Fig. 3).

In patients who received steroid+IAPRF, 10 were grade II and 15 were grade III. Mann–Whitney U analysis was used to examine the effect of radiological stage of osteoarthritis on pain and functional level in patients who received pulsed RF treatment. No statistically significant difference was found between stage II and III in baseline, 1st, 4th, and 12th week VAS scores (p=0.182, 0.928, 0.951, 0.859, respectively). Similarly, no statistically significant difference was found between stage II and III in WOMAC values at baseline, 1st, 4th, and 12th week follow-ups (p=0.781, 0.824, 0.632, 0.889, respectively).

Table 2. Mean NRS and WOMAC scores before and 1, 4, 12 weeks after procedure in both groups

	Steroid+IAPRF group (n=25) Mean±SD	Steroid group (n=29) Mean±SD	p*
NRS			
Pre-injection	7.16±0.85	6.9±0.9	0.242
1st week	2.64±0.76	2.93±0.75	0.136
4th week	3.32±0.69	3.86±0.74	**0.004**
12th week	3.72±0.46	4.72±0.59	**<0.001**
p-value**	**<0.001**	**<0.001**	
p-value[a]	<0.001	<0.001	
p-value[b]	<0.001	<0.001	
p-value[c]	0.001	0.004	
WOMAC			
Pre-injection	76.64±8.47	73.31±8.46	0.124
1st week	30.36±6.81	33.2±6.79	0.125
4th week	33.48±6.65	37.41±8.15	0.054
12th week	36.64±5.63	48.76±7.79	**<0.001**
p-value**	**<0.001**	**<0.001**	
p-value[a]	<0.001	<0.001	
p-value[b]	<0.001	<0.001	
p-value[c]	0.001	0.006	

IAPRF: Intra-articular pulsed radiofrequency; SD: Standard deviation; NRS: Numeric Rating Scale; WOMAC,: Western Ontario and McMaster Universities Arthritis Index; *: Comparison between groups by Mann–Whitney U Test; **: Comparison within Groups by Friedman Test; a: Pre-injection to 1st week; b: Pre-injection to 4th week; c: Pre-injection to 12th week.

Discussion

Previous studies have demonstrated positive results regarding the effectiveness of IAPRF in recent years. However, few prospective randomized controlled studies have been conducted in this field. To the best of our knowledge, this is the first study to investigate the efficacy of IAPRF combined with steroids in patients with knee OA.

Various theories have been proposed regarding the mechanisms of action of IAPRF. According to Sluijter et al.,[3] pain is modulated by a dual effect. The PRF waves may affect the pericapsular nerve endings and suppress the excitatory C-fiber response, thereby reducing pain by regulating synaptic transmission when applied intra-articularly.[4] A second effect

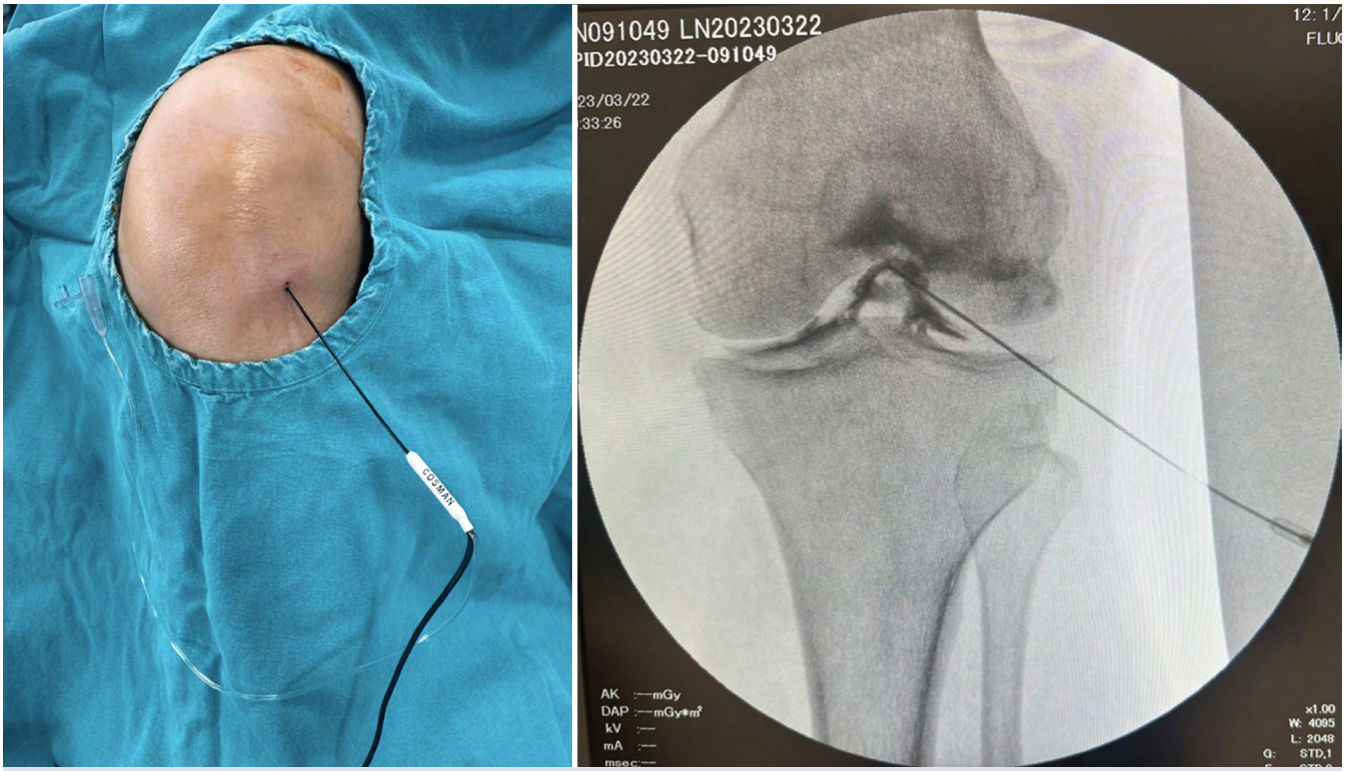

Figure 3. Fluoroscopic images of needle placement.

on the immune response has also been suggested. Tissue studies have shown that single and repetitive PRF applications decreased the concentrations of inflammatory mediators such as COX-2, IL-1B, IL-6, IL-10, and TNF-α (with enzyme-linked immunosorbent assays and western blots) in the synovial membrane and synovial fluid of the inflamed knee, resulting in decreased pain and improved function.[8,9]

The clinical effects of IAPRF on knee joint pain have been studied over the past decade. Karaman et al.[10] investigated the effect of IAPRF in 31 patients with early-stage gonarthrosis (Kellgren–Lawrence Classification grades 1–3) and reported a 32.8% reduction in pain levels for up to 6 months. Another study, which included patients with late-stage OA (grades 3–4) who received IAPRF, reported significantly lower pain levels for up to 12 months.[4] Papa et al.[6] retrospectively analyzed 129 patients who received IAPRF in 2021 and reported a significant reduction in pain at 1, 3, and 4 months after the procedure. However, these studies lacked control groups and were conducted retrospectively.

Another study investigating the effectiveness of IAPRF compared with intra-articular steroid injection, with 22 patients in the IAPRF group and 20 in the steroid group, was published by Yuan et al.[7] IAPRF was applied at a temperature of 42°C and a frequency of 2 Hz for 6 min in that study. Although both groups showed remarkable improvements, significantly lower pain levels and better WOMAC scores were observed in the IAPRF group at weeks 1, 4, 8, 12, and 24. A synovial fluid analysis revealed that pro-inflammatory cytokine levels such as TNF-α, MMP-3, and IL-1 decreased in both groups, with a significantly greater reduction in the IAPRF group.

In our study, consistent with previous reports, both the steroid and IAPRF + steroid groups showed improvements in pain levels and function within groups at all timepoints. Both groups showed a trend of increasing pain and worsening function after the first week but at different magnitudes. When the groups were compared across timepoints, pain levels were significantly lower in Group 1 at the first and third months, and WOMAC scores were significantly lower at the third month. Statistically insignificant differences at earlier timepoints may be attributed to the fact that both groups received steroid injections.

The appropriate duration and parameters for PRF application remain debated. Application times vary from 6 to 15 min in different studies, along with dif-

ferences in pulse duration and voltage. Moreover, the duration of effect remains unclear. Although positive effects were observed for up to 3 months in the short- and mid-term results, some studies with longer follow-up periods have shown improvements lasting up to 12 months. In the present study, IAPRF in combination with steroid injections was effective for up to 3 months.

Gulec et al.[11] studied the effects of unipolar and bipolar IAPRF in knee OA and reported a significant reduction in pain at 1, 4, and 12 weeks in both groups. At least 50% pain relief was observed in 84% of patients in the bipolar group and in 50% of patients in the unipolar group. Pain reduction and WOMAC scores were significantly higher in the bipolar PRF group, indicating that the application of a wider electromagnetic field may yield better clinical results.

Hong et al.[12] retrospectively analyzed 57 patients, among whom 29 received high-voltage IAPRF treatment and 28 received low-voltage IAPRF treatment. The NRS scores in the high-voltage group were significantly lower than those in the low-voltage group from the first week to 6 months. High-voltage PRF has been widely studied for the treatment of various chronic pain syndromes and pathologies in recent years.[13,14]

Hong et al.[15] retrospectively compared radiofrequency thermocoagulation of the genicular nerves (RFTC-GN), IAPRF, and intra-articular steroid injections. Post-treatment results were better than pre-treatment results in all three groups. Although pain scores were lower in the RFTC-GN group at baseline, there was no significant difference between the long-term results of RFTC-GN and IAPRF (3 and 6 months).[15] IAPRF is preferred over RFTC-GN, as it is not an ablative method, has a low risk of complications, and shows no significant difference in efficacy at long-term follow-up.

No major complications were observed in the present study. A short-term increase in pain occurred in some patients during the first 1–2 days after the procedure. These patients were advised to apply ice and take paracetamol if needed. IAPRF application has been found to be safe in the literature, and no major complications have been reported in previous studies.[7,10,15,16]

Limitations

The randomized controlled design of the present study, which evaluated the efficacy of IAPRF in combination with intra-articular steroid injection for the treatment of knee pain resistant to medical therapy, contributes to the literature. However, the absence of a true placebo/sham group due to ethical reasons is among its limitations. Patients were advised to continue the same analgesic treatments, and their analgesic prescriptions were not changed during the study. However, concomitant analgesic medication data were not collected during the trial, which may also represent a limitation. Further studies with longer follow-up periods and tissue or synovial fluid analyses will contribute to the literature.

Conclusion

Based on our findings, in stage II–III knee OA, IAPRF application in combination with intra-articular steroid may improve knee pain and participation in daily living activities during the early-to-mid period and is considered a safe method.

Ethics Committee Approval: The Başakşehir Çam and Sakura City Hospital Ethics Committee granted approval for this study (date: 01.04.2022, number: 2022.03.89).

Informed Consent: Written and verbal informed consent was obtained from all patients.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – BE, DGKB; Design – BE; Supervision – BE; Resources – BE; Data collection and/or processing – BE; Analysis and/or interpretation – BE, DGKB; Literature search – BE, DGKB; Writing – BE, DGKB; Critical review – BE, DGKB.

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