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ORIGINAL ARTICLE

The evaluation of the effectiveness of intra-articular steroid, tenoxicam, and combined steroid–tenoxicam injections in the treatment of patients with knee osteoarthritis

Ebru Yilmaz[1]

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Abstract

Objective Although intra-articular corticosteroid injections are widely applied in the treatment of knee osteoarthritis (OA), its effect is short term. Additionally, apart from oral use, tenoxicam is also applied as an intra-articular treatment option to minimize gastrointestinal side effects of NSAIDs. Clinical evidence suggests that the combined use of NSAIDs and corticosteroids is synergistic (especially macular edema after cataract surgery in ophthalmology). Therefore, the aim of this study is to determine whether the combination of intra-articular steroid and tenoxicam was more effective for a long period rather than only tenoxicam and steroid injection alone in OA treatment.

Methods Ninety patients were randomly divided into three groups (30 patients per group): group 1, group 2, and group 3 were treated by intra-articular injection of tenoxicam, triamcinolone hexacetonide, and triamcinolone hexacetonide plus tenoxicam, respectively. Visual analog scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) were enrolled at baseline and 1, 3, and 6 months post-injection.

Results The mean age of patients was 68.07 ± 8.08, 65.83 ± 10.13, and 67.07 ± 6.01 in group 1, group 2, and group 3, respectively. In tenoxicam group, median pre- and post-treatment (at 1, 3, and 6 months) VAS/WOMAC scores were 7.30 ± 0.53/32.50 ± 3.79, 2.27 ± 0.98/10.83 ± 2.61, 6.73 ± 1.14/30.33 ± 5.93, and 7.03 ± 0.80/31.37 ± 4.38, respectively. In steroid group, median pre- and post-treatment VAS/WOMAC scores were 7.60 ± 0.49/34.33 ± 3.40, 1.37 ± 1.21/8.83 ± 2.70, 6.87 ± 1.35/30.80 ± 7.70, and 7.27 ± 0.86/32.83 ± 4.87, respectively. In steroid plus tenoxicam group, median pre- and post-treatment VAS/WOMAC scores were 7.57 ± 0.50/33.20 ± 3.66, 0.33 ± 0.47/6.67 ± 0.95, 0.93 ± 0.98/7.87 ± 1.96, and 1.97 ± 1.12/10.43 ± 3.70, respectively. VAS and WOMAC scores in 1 month after the injection significantly decreased in both groups compared to baseline ($p < 0.01$). Steroid plus tenoxicam group showed significantly improved VAS and WOMAC scores when compared to only steroid and tenoxicam group at follow-up 3 and 6 months ($p < 0.01$).

Conclusion The combined therapy seems to produce a more effective result for a long period than monotherapy in reducing pain and improving functional recovery.

Key points

• There is an evidence of short-term effects of intra-articular corticosteroid injection in treatment of knee OA; however, there is no consensus for the long-term benefit of this treatment yet.

• Apart from oral use, tenoxicam is also applied as an intra-articular treatment option to minimize gastrointestinal side effects of NSAIDs.

• Clinical evidence suggests that the combined use of NSAIDs and corticosteroids is synergistic (especially macular edema after cataract surgery in ophthalmology).

• The combined therapy seems to produce a more effective result for a long period than alone therapy.

✉ Ebru Yilmaz
dr.ozcanebru@gmail.com

[1] Department of Physical and Rehabilitation Medicine, Kocaeli Government Hospital, Kocaeli, Turkey

Keywords Combined therapy · Intra-articular steroid injection · Intra-articular steroid plus tenoxicam injection · Intra-articular tenoxicam injection · Knee osteoarthritis

Introduction

Osteoarthritis (OA) is a non-inflammatory chronic degenerative disease characterized by progressive cartilage destruction, osteophyte formation, and subchondral sclerosis generally in the weight-bearing joints. Clinical features include pain, joint stiffness, joint hypertrophy, crepitation, limitation of movement, muscle weakness, local tenderness, deformity, and loss of function [1, 2]. The etiology of OA is multifactorial. It results from a physiological imbalance between the ability of joint-supporting structures such as cartilage, bone, and soft tissues to absorb and distributed loadings on the joint. The predisposing and leading factors for the development of OA include age, sex, obesity, abnormal joint loading, trauma, previous joint injuries, and deformities [3]. OA can occur in any joint, but the most commonly affected sites are the knees, hips, spine, and the small joints of the hands [4].

The main purpose in the treatment of OA located on knee is to reduce pain, to remove restriction of joint motion, to reduce secondary functional insufficiency, and to improve quality of life. Treatment modalities for knee OA include patient education, rest, preventive measures, slimming of overweight patients, analgesics (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy agents, and intra-articular injections (steroids, tenoxicam, hyaluronic acid). Various surgical procedures can be performed if patients do not benefit from these treatments [4].

Intra-articular corticosteroid injections have long been used with the aim of reducing local inflammation and pain [5]. Intra-articular corticosteroid injections have been reported by the American College of Rheumatology (ACR) as an application supporting the treatment of knee OA [6]. Several studies evaluated the beneficial effect of intra-articular corticosteroid injections on reducing chronic pain as well as acute exacerbations in patients with knee OA [7].

Tenoxicam is an effective analgesic and anti-inflammatory drug for symptomatic treatment of OA. It is thought that it has a chondroprotective effect. Additionally, apart from oral use, tenoxicam is also applied as an intra-articular treatment option to minimize gastrointestinal side effects of NSAIDs [8].

There is an evidence of short-term effects of intra-articular corticosteroid injection (up to 3–4 weeks); however, there is no consensus for the long-term benefit of this treatment yet [9]. Moreover, previous studies compared the effectivity of oral and intra-articular tenoxicam in OA treatment. They suggested that intra-articular tenoxicam is as effective as oral tenoxicam and could be thought as an alternative treatment in knee OA [8, 15]. Clinical evidence suggests that the combined use of NSAIDs and corticosteroids is synergistic (especially macular edema after cataract surgery in ophthalmology) [10]. Therefore, the aim of this study is to determine whether the combination of intra-articular corticosteroid and tenoxicam may be more effective for a long period rather than only tenoxicam and corticosteroid injection alone in knee OA treatment.

Material and methods

This prospective, randomized study was conducted at the Department of Physical Therapy and Rehabilitation, Physical Therapy and Rehabilitation Hospital, Kastamonu, Turkey, between January 2016 and June 2016. The study protocol was approved by the Ethical Committee of Kocaeli University (Trial registration: KU GOKAEK 2017/106). Written informed consent was obtained from all patients.

Ninety patients (56 female, 34 male) were included in this study. Knee OA was diagnosed based on criteria of American College of Rheumatology (ACR) for patients. Radiographic imaging (X-rays) were performed all patients and the severity of knee OA based on the Kellgren–Lawrence classification of radiological changes (Table 4). Inclusion criteria were grade 1 and grade 2 with OA by Kellgren–Lawrence scale (based on radiologist's report). Exclusion criteria were inflammatory joint disease (e.g., rheumatoid arthritis, reactive arthritis, crystal arthropathies), the patients with history of systemic disease (e.g., cardiovascular disease, diabetes mellitus), metabolic bone disease, any active infection or wound of the knee, history of any knee articular injection, previous knee surgery, and grade 3 or grade 4 with OA patients by Kellgren–Lawrence scale.

Data collected include age, sex, symptom duration, body mass index, the stage of disease, and affected side. The estimation of the severity of pain by the visual analog scale (VAS) was enrolled at baseline and 1, 3, and 6 months post-injection. The pain VAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 10) [11]. Additionally, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used to determine the outcome measures of pain, stiffness, and physical functioning at baseline and 1, 3, and 6 months post-injection.

All patients were randomly assigned to three groups (30 patients per group): group 1: intra-articular tenoxicam; group 2: intra-articular corticosteroid; and group 3: the combination of intra-articular corticosteroid with tenoxicam. All injections

were performed by the same physician through random allocation using a computer-generated random number (EY). VAS and WOMAC scores were recorded by a nurse. Group 1 was treated by intra-articular injection of 2 ml of 20 mg tenoxicam. Group 2 was treated by intra-articular injection of 1 ml of 20 mg triamcinolone hexacetonide. Group 3 was treated by intra-articular injection of 1 ml of 20 mg triamcinolone hexacetonide combined with 2 ml of 20 mg tenoxicam. The joint was cleaned with povidone–iodine solution, and sterilized gloves were worn during the injection. The injections were performed at an injection site above the tibial plateau and lateral to the patellar tendon with the knee flexed at about 90° and without ultrasound or fluoroscopy guidance (Figs. 1 and 2). In a previous study with yttrium-90, which used radiation synovectomy, injection in refractory synovitis recommended that 3-day immobilization and rest after the injection were essential in order to optimize the effect and to prevent leakage from the knee joint [12]. Therefore, considering the lives of the patients, they were advised to rest or immobilize and avoid any kind of weight loadings on the injected knee at least the next 24 h. Additionally, patients were advised to take a simple analgesic drug (e.g., acetaminophen) or apply cold compresses if it is required. There were no major complications after injections in all groups. The number of acetaminophen pills taken by patients was not exceeded 3 tablets per a week.

Statistical analysis

A sample size and power calculation determined that 22 patients in each group were sufficient power (power of 0.80, $\alpha = 0.05$, and $\beta = 0.20$). Power calculation was based on VAS.

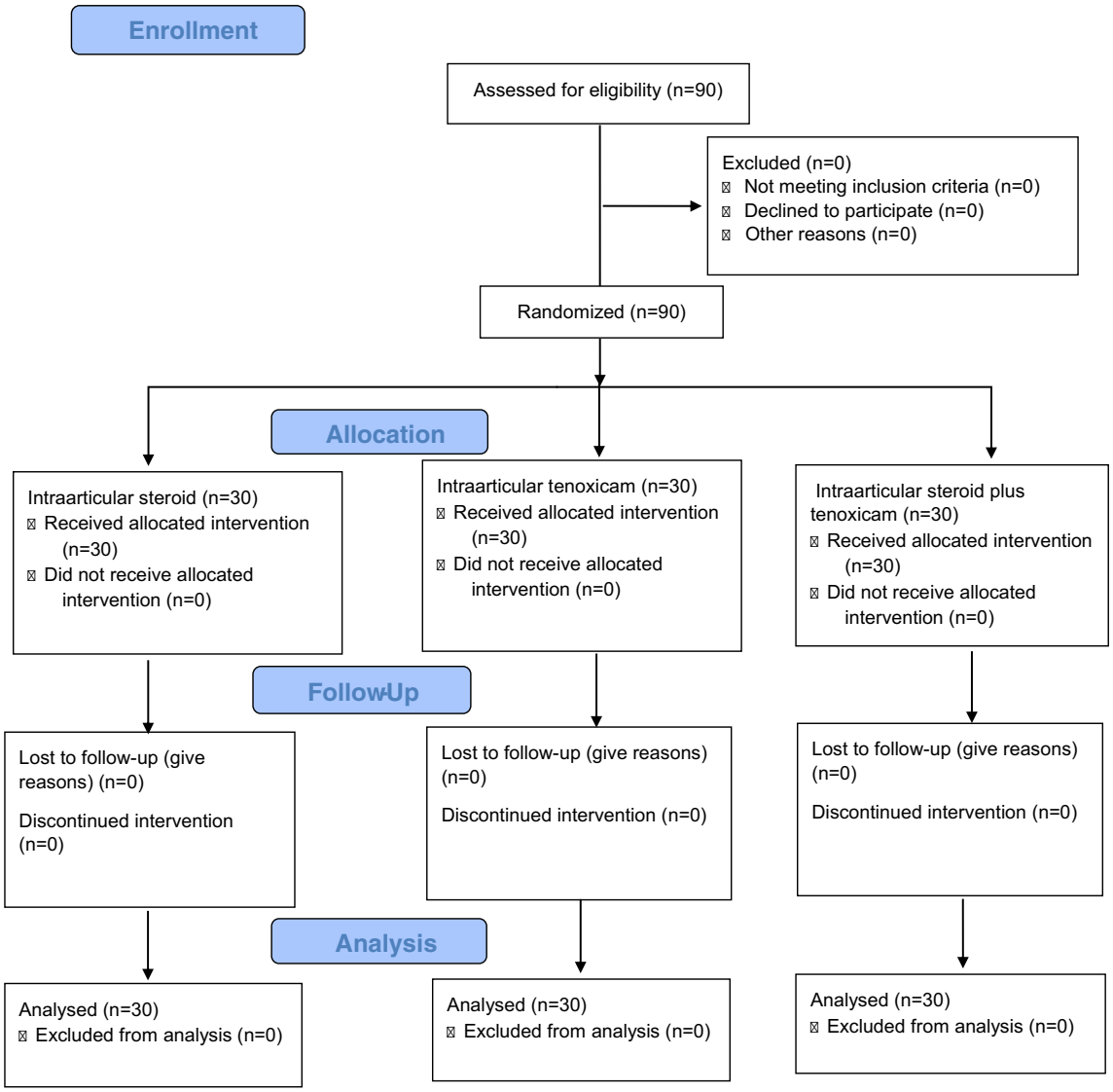

Fig. 1 Flow diagram for a randomized trial comparing intra-articular corticosteroid injection, intra-articular tenoxicam injection, and the combination of intra-articular corticosteroid with tenoxicam injection for treating patients with knee osteoarthritis

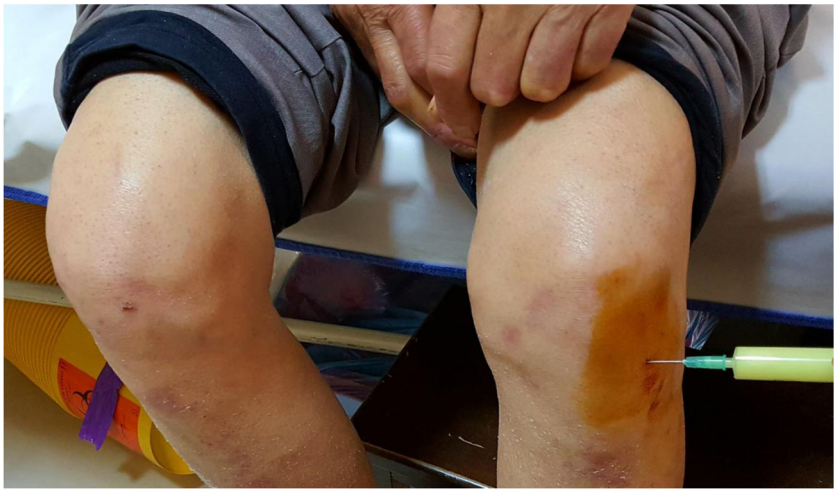

Fig. 2 The injection technique used for intra-articular corticosteroid and tenoxicam (left side)

Statistical analyses were performed using the Statistical Package for the Social Sciences version 24 (SPSS, Chicago, IL, USA). For continuous data (age, symptom duration, body mass index, VAS, and WOMAC score), descriptive statistics were expressed as mean ± standard deviation (SD). Four categorical data (sex, occupation, affected side, Kellgren–Lawrence scale) were expressed as frequency and percentage. Kolmogorov–Smirnov tests were used to determine whether or not the variables were normally distributed. Normal distributions of continuous variables were assessed by Student's *t* test. Non-normally distributed metric variables were analyzed by Mann–Whitney *U* tests. Repeated non-normal VAS and WOMAC scores were compared using Friedman two-way ANOVA (VAS and WOMAC scores are non-normal variables). p values < 0.05 were considered statistically significant.

Results

The demographic characteristics of patients including age, sex, occupation, duration of symptoms, body mass index (BMI), affected side, and the stage of disease are presented in Table 1. The mean age of patients was 68.07 ± 8.08, 65.83 ± 10.13, and 67.07 ± 6.01 in group 1, group 2, and group 3, respectively. In group 1, 63.3% ($n = 19$) was female and 36.7% ($n = 11$) was male. In group 2, 73.3% ($n = 22$) was female and 26.7% ($n = 8$) was male. In group 3, 50.0% ($n = 15$) was female and 50.0% ($n = 15$) was male. Mean duration of symptoms was 51.03 ± 49.29, 57.67 ± 61.69, and 50.80 ± 40.68 months in group 1, group 2, and group 3, respectively. BMI was 29.50 ± 5.56, 29.06 ± 4.05, and 32.40 ± 5.79 in group 1, group 2, and group 3, respectively. In tenoxicam group, median pre- and post-treatment (at 1, 3, and 6 months) VAS/WOMAC scores were 77.30 ± 0.53/32.50 ± 3.79, 2.27 ± 0.98/10.83 ± 2.61, 6.73 ± 1.14/30.33 ± 5.93, and 7.03 ± 0.80/31.37 ± 4.38, respectively (Fig. 3). In steroid group, median pre- and post-treatment (at 1, 3 and 6 months) VAS/WOMAC scores were7.60 ± 0.49/34.33 ± 3.40, 1.37 ± 1.21/8.83 ± 2.70, 6.87 ± 1.35/30.80 ± 7.70, and 7.27 ± 0.86/32.83 ± 4.87, respectively. In steroid plus tenoxicam group, median pre- and post-treatment (at 1, 3, and 6 months) VAS/WOMAC scores were 7.57 ± 0.50/33.20 ± 3.66, 0.33 ± 0.47/6.67 ± 0.95, 0.93 ± 0.98/7.87 ± 1.96, and 1.97 ± 1.12/10.43 ± 3.70, respectively. There is no significant difference between groups in terms of age, sex, occupation, duration of symptoms, body mass index (BMI), affected side, and the stage of disease ($p > 0.05$). The change in VAS and WOMAC scores compared with the initial evaluation is shown in Tables 2 and 3. VAS and WOMAC scores in 1 month after the injection significantly decreased in both groups compared to baseline ($p < 0.01$). However, there was a pronounced improvement in only steroid plus tenoxicam group at 3 and 6 months post-injection ($p < 0.01$). Steroid plus tenoxicam group showed significantly improved VAS and WOMAC scores when compared to only steroid and tenoxicam group at follow-up 3 and 6 months ($p < 0.01$) (Fig. 4a, b).

Discussion

Knee OA is the most common cause of pain and disability, especially in the elderly population. There is no curative therapy to stop the articular cartilage degeneration for the time being. All the current methods are symptomatic treatments. The main symptom of knee OA is pain; therefore, the main goal of its treatment should be relief of pain. Moreover, the improvement in function and disability, and finally, disease modification must be provided [13]. OARSI (Osteoarthritis Research Society International) recommends for the non-surgical management of knee OA are divided into four groups: (1) Appropriate treatments for all individuals: biomechanical interventions (knee

Table 1 Patients characteristics

Variables	Group 1 ($n = 30$)	Group 2 ($n = 30$)	Group 3 ($n = 30$)	p
Age (year)	68.07 ± 8.08	65.83 ± 10.13	67.07 ± 6.01	N.S.
Sex				
Female	19 (63.3%)	22 (73.3%)	15 (50.0%)	N.S.
Male	11 (36.7%)	8 (26.7%)	15 (50.0%)	
Duration of symptoms (months)	51.03 ± 49.29	57.67 ± 61.69	50.80 ± 40.68	N.S.
Occupation				
Housewife	19 (63.3%)	21 (70.0%)	15 (50.0%)	N.S.
Farmer	7 (23.3%)	4 (13.3%)	5 (16.7%)	
Worker	1 (3.3%)	1 (3.3%)	5 (16.7%)	
Cook	1 (3.3%)	2 (6.7%)	0 (0.0%)	
Officer	1 (3.3%)	2 (6.7%)	4 (13.3%)	
Driver	1 (3.3%)	0 (0.0%)	1 (3.3%)	
Body mass index (BMI)	29.50 ± 5.56	29.06 ± 4.05	32.40 ± 5.79	N.S.
Affected side				
Right	3 (10.0%)	5 (16.7%)	3 (10.0%)	N.S.
Left	4 (13.3%)	1 (3.3%)	2 (6.7%)	
Bilateral	23 (76.7%)	24 (80.0%)	25 (83.3%)	
Kellgren–Lawrence scale				
Stage 1	17 (56.7%)	16 (53.3%)	17 (56.7%)	N.S.
Stage 2	13 (43.3%)	14 (46.7%)	13 (43.3%)	

All values are expressed as mean ± SD, number, and percentage

N.S. no significance

braces, knee sleeves, foot orthoses and lateral wedge insoles), intra-articular corticosteroids, exercise (land-based and water-based), self-management and education, strength training and weight management; (2) appropriate treatments for specific clinical subphenotypes: acetaminophen (paracetamol), balneotherapy, capsaicin, cane (walking stick), duloxetine, oral NSAIDs (COX-2 selective and non-selective), and topical NSAIDs; (3) uncertain treatments for specific clinical subphenotypes: acupuncture, avocado soybean unsaponfiables, chondroitin, crutches, diacerein, glucosamine, intra-articular hyaluronic acid, opioids (oral and transdermal), rosehip, transcutaneous electrical nerve stimulation, and ultrasound; (4) inappropriate treatments: risedronate and electrotherapy (neuromuscular electrical stimulation) [14].

Intra-articular corticosteroid injections obtain clinical improvement in patients with symptomatic knee OA; however, this effect is short term. There is some evidence that multiple corticosteroid injections increase cartilage protein synthesis and cartilage destruction, and it is recommended that no more than 4 injections are administered into a single joint within 1 year [15]. Additionally, NSAIDs must achieve a certain concentration in the blood to emerge their anti-inflammatory

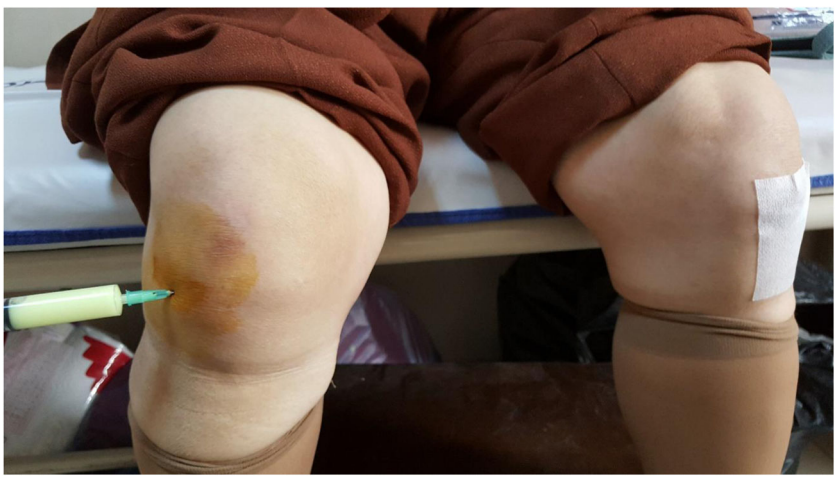

Fig. 3 The injection technique used for intra-articular corticosteroid and tenoxicam (right side)

Table 2 Changes in VAS in before injection and 1.3 and 6 months after the injection in groups 1, 2, and 3

Variables	Group 1 ($n = 30$) Intra-articular tenoxicam injection	Group 2 ($n = 30$) Intra-articular corticosteroid injection	Group 3 ($n = 30$) Intra-articular tenoxicam plus corticosteroid injection
Before injection	7.30 ± 0.53	7.60 ± 0.49	7.57 ± 0.50
1 Month after the injection	2.27 ± 0.98	1.37 ± 1.21	0.33 ± 0.47
3 Months after the injection	6.73 ± 1.14	6.87 ± 1.35	0.93 ± 0.98
6 Months after the injection	7.03 ± 0.80	7.27 ± 0.86	1.97 ± 1.12
p	< 0.001[a]	< 0.001[a]	< 0.001[a,b,c,e,f]

All values are expressed as mean ± SD

[a] There are differences between before injection and 1 month after injection

[b] There are differences between before injection and 3 months after injection

[c] There are differences between before injection and 6 months after injection

[d] There are differences between 1 month after injection and 3 months after injection

[e] There are differences between 1 month after injection and 6 months after injection

[f] There are differences between 3 months after injection and 6 months after injection

effects. However, the effective dose concentration could not be obtained because of limiting their long-term use due to systemic side effects [16]. Therefore, this study hypothesized that the combination of intra-articular corticosteroid and tenoxicam, which acts at different points in the inflammatory cascade, may increase the duration of symptomatic effectivity in knee OA treatment. Additionally, this study may also contribute to the literature in term of comparing the effectiveness of intra-articular administration of these treatments and their combination. According to the results of this study, both therapy and their combination seem to be effective in pain relief and functional improvement at 1 month post-injection. Although their effects alone discontinued at follow-up 3 and 6 months, their combination provided a pronounced improvement.

In the osteoarthritic process, overweight or obesity is a well-known and modifiable risk factor in OA [17]. In this study, BMI was over 25 in all groups. The mechanical stress loaded onto the chondrocyte causes the production of oxygen free radicals, and these molecules play a key role in the pathogenesis of OA via leading to the destruction of articular cartilage. The changes observed in articular cartilage are as follows: (1) an increase in cytokine and matrix metalloproteinase levels, (2) a decline in growth factors, (3) a reduction in the production of extracellular matrix (especially aggrecan and type II collagen produced by chondrocyte which are responsible for cartilage homeostasis), and (4) chondrocyte death [18, 19]. IL-1β especially plays a crucial role in the local pathogenesis of OA leading to the release of cartilage-degrading enzymes, such as metalloproteinases and aggrecanases from chondrocytes and inhibiting the production of the extracellular matrix [20]. Therefore, the focus of pharmacologic treatment of OA should be included targets from the cell and cytokine level to larger joint components such as cartilage, bone, innervations, and vascular supply.

Intra-articular steroid injections act through its anti-inflammatory effects by inhibiting prostaglandin and cytokine synthesis, and thus, it controls local inflammation by suppressing the activity of collagenase and other destructive enzymes [21]. A systematic review compared betamethasone and methylprednisolone with triamcinolone in patients with osteoarthritis found that triamcinolone is more effective than betamethasone and methylprednisolone (1B+ level) (Table 4). In addition, studies that compared triamcinolone hexacetonide and triamcinolone acetonide injections in the treatment of

Table 3 Changes in WOMAC in before injection and 1, 3 and 6 months after the injection in group 1, 2 and 3

Variables	Group 1 ($n = 30$) Intra-articular tenoxicam injection	Group 2 ($n = 30$) Intra-articular corticosteroid injection	Group 3 ($n = 30$) Intra-articular tenoxicam plus corticosteroid injection
Before injection	32.50 ± 3.79	34.33 ± 3.40	33.20 ± 3.66
1 Month after the injection	10.83 ± 2.61	8.83 ± 2.70	6.67 ± 0.95
3 Months after the injection	30.33 ± 5.93	30.80 ± 7.70	7.87 ± 1.96
6 Months after the injection	31.37 ± 4.38	32.83 ± 4.87	10.43 ± 3.70
p	< 0.001[a]	< 0.001[a]	< 0.001[a,b,c,e,f]

All values are expressed as mean ± SD

[a] There are differences between before injection and 1 month after injection

[b] There are differences between before injection and 3 months after injection

[c] There are differences between before injection and 6 months after injection

[d] There are differences between 1 month after injection and 3 months after injection

[e] There are differences between 1 month after injection and 6 months after injection

[f] There are differences between 3 months after injection and 6 months after injection

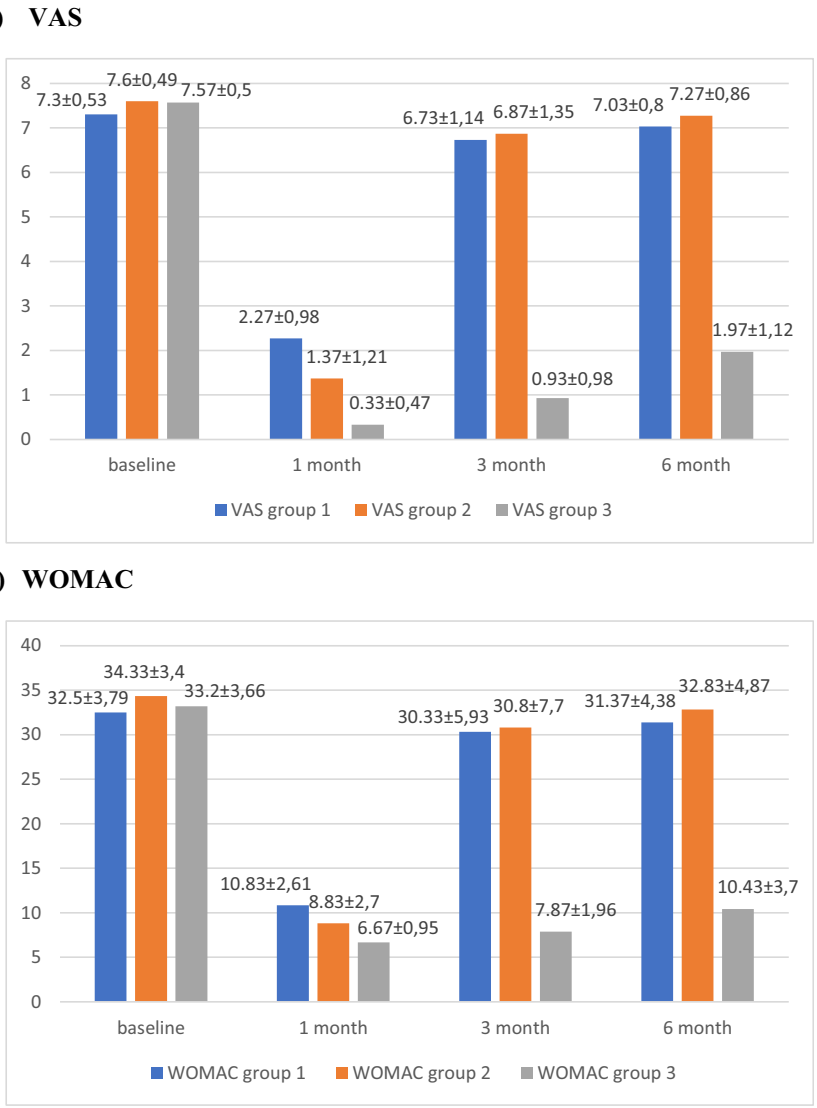

Fig. 4 **a**, **b** The median changes of VAS and quick DASH scores in tenoxicam group (group 1), steroid group (group 2), and steroid plus tenoxicam group (group 3)

juvenile rheumatoid arthritis suggested that triamcinolone hexacetonide was more favorable and preferred as an intra-articular steroid (2B+ level) [22]. The systematic review including only randomized controlled trials conducted by Garg et al. evaluated the efficacy of different intra-articular and soft tissue corticosteroids injections, and it was reported that triamcinolone hexacetonide provides a faster reduction of pain within 3 weeks compared to methylprednisolone in the knee OA. In fact, several studies demonstrated that because of its advantages, triamcinolone hexacetonide is preferable when compared to other corticosteroids [23]. Under the light of this information, it was preferred to use only triamcinolone hexacetonide as a corticosteroid in this study.

NSAIDs have both analgesic and anti-inflammatory properties. Therefore, they are considered as the first-line agents in the treatment of OA. They inhibit the cyclooxygenase (COX) enzymes converting arachidonic acid into prostaglandins, a major mediator of inflammation; thus, they must be carefully used because of the gastrointestinal and cardiovascular toxicities [15]. The type of solvent used in the injectable formulation has prevented the intra-articular administration of NSAIDs in OA because of problems associated with local tolerability. Since tenoxicam is water soluble and does not require a solubilizing agent unlike most injectable NSAID preparations, it is especially appropriate for intra-articular injection. Tenoxicam is an NSAID with a long half-life and rapidly becomes penetrating into the synovial fluid of patients with OA [3]. Although it was demonstrated that many NSAID drugs reduce chondrocyte biosynthesis on human and animal cartilage and result in cartilage destruction in vivo and in vitro studies, it was expressed that tenoxicam does not only suppress chondro-formative process in human OA cartilage in vitro studies but also has beneficial effects. In addition, tenoxicam concentrates in the synovial fluid rather than cartilage. Additionally, tenoxicam is also used intra-articularly for postartoscopic analgesia. In a randomize study compared oral

Table 4 Kellgren–Lawrence scale

Kellgren–Lawrence scale	Grade comments
0	No radiographic findings of osteoarthritis
1	Minute osteophytes of doubtful clinical significance
2	Definite osteophytes with unimpaired joint space
3	Definite osteophytes with moderate joint space narrowing
4	Definite osteophytes with severe joint space narrowing and subchondral sclerosis

tenoxicam and intra-articular tenoxicam for pain and physical functioning in OA of the knee, Unlu et al. indicated that treatment of knee OA with intra-articular tenoxicam is as effective as that with oral tenoxicam. In addition, they suggested that intra-articular administration of NSAIDs can be preferred to oral therapy to minimize their potential side effects such as gastrointestinal and cardiovascular toxicity [24]. A study conducted by Erbas et al. to compare the effectivity of oral and intra-articular administration of tenoxicam in OA treatment found results similar to those of Unlu et al. [16]. An experimental study produced OA in rats with anterior cruciate ligament transection and medial meniscectomy; Ozkan et al. reported that the effect of tenoxicam is similar to hyaluronic acid to protect cartilage structure and proteoglycan content [25]. The efficacy of intra-articular tenoxicam lasted for 6 months in the study conducted by Unlu et al. and 3 months in the study conducted by Erbas et al. This long-lasting beneficial effect may be caused by the application of intra-articular tenoxicam performing once a week for 3 weeks in these studies. However, in this study, this effect continued for up to 1 month just like the other study conducted by Evcik et al. because only one injection was performed due to the possibility of deleterious effects of repetitive injections on cartilage.

There is a little study in the literature to compare intra-articular tenoxicam and corticosteroid efficacy in knee OA. An experimental study in healthy rats conducted by Orak et al. investigated the effect of chronic intra-articular methylprednisolone, diclofenac, and tenoxicam on the knee joint and gastric mucosa, and it was reported that diclofenac and tenoxicam increase fibrosis and fibroblast production, although the use of chronic methylprednisolone has no negative effects on synovium and cartilage [26]. This study may also contribute to the literature in term of comparing the effect of intra-articular corticosteroid, tenoxicam, and corticosteroid plus tenoxicam in patients with knee OA. However, placebo-controlled studies are required.

The systematic review including only randomized controlled trials conducted by Godwin et al. demonstrated that intra-articular corticosteroid injections in patients with knee OA provide clinically and statistically significantly pain reduction in the first week, but its beneficial effect was terminated within 3–4 weeks and completely disappeared in 6–8 weeks [27]. A meta-analysis conducted by Arroll et al. supported that intra-articular corticosteroid injections were effective in the short term (up to 2 weeks) and long-term efficacy of intra-articular corticosteroid injections lasted from 16 to 24 weeks [28]. The review conducted by Rozental et al. demonstrated that corticosteroid injections especially combined with NSAID drugs, rest, and physical therapy provide a significant pain relief [29]. In a randomized study compared oral NSAID and intra-articular steroid injection in patients with congestive knee OA, Dieu-Donne et al. demonstrated that corticosteroid injections have a shorter effect than NSAIDs. In addition, although intra-articular corticosteroid injection is an effective method, the effect of intra-articular corticosteroid injection did not proceed for more than 2 or 3 weeks. For this reason, they proposed that both treatment methods could be used together [30].

Additionally, corticosteroids and NSAIDs are the most important drugs used to manage ocular inflammation. Although drugs from both classes can provide effective inflammation control, they act by very different molecular and cellular mechanisms. Corticosteroids act primarily on the cytosolic glucocorticoid receptor alpha, which is expressed in almost all cells and intercedes effects across multiple signaling pathways, and mediate their broad therapeutic effects through both genomic and non-genomic mechanism. They also block the inflammatory cascade at the upstream level of phospholipase A2. All NSAIDs inhibit both COX1 and COX2 with varying degrees of specificity. By inhibiting the COX2 enzyme, NSAIDs reduce the production of prostaglandins. They do not affect the other arm of the inflammatory cascade, which is catalyzed by lipooxygenase to produce leukotrienes. A number of clinical trials have reported a synergistic effect when NSAIDs and corticosteroids are administered together [31, 32]. Although this clinical impression of synergy remains unproven, the mechanism of action can be explained by an additive effect of a second anti-inflammatory agent [33]. Under the light of this information, corticosteroid was combined with tenoxicam to increase the duration of symptomatic efficacy in this study. The results of the study support the hypothesis. In point of drug interaction, the combined use of corticosteroids and NSAIDs may increase the potential for serious gastrointestinal toxicity. Therefore, a limited non-clinical study suggests that an ulcerogenic potential of NSAIDs in combination with corticosteroids was seen only with a COX-1, but not a COX-2, inhibitor [34]. In this study, no gastrointestinal side effects were observed in patients.

Study limitations

Some limitations of the present study include the following: (1) sample size; (2) no control group; (3) no oral NSAIDs group; (4) no long-term consequences of the combination of tenoxicam and corticosteroid injection therapy, tenoxicam therapy, and corticosteroid therapy. Even if it has some limitations (especially not a controlled double-blind trial and small number of patients), the findings of the study suggest that the combined therapies could be more effective rather than monotherapy. Moreover, the results of this study may provide a perspective to consider the use of combined therapies in practice and may lead to future studies.

Conclusion

The combination of intra-articular corticosteroid and tenoxicam seems to produce a more effective result than monotherapy in reducing pain and improving functional recovery.

Compliance with ethical standards The study protocol was approved by the Ethical Committee of Kocaeli University (Trial registration: KU GOKAEK 2017/106). Written informed consent was obtained from all patients.

Disclosures None.

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