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Efficacy of Topical 5% Doxepin Cream Compared with Diclofenac Gel and Placebo for Knee Osteoarthritis: A Randomized Double-Blind Clinical Trial

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Research Article

Keywords: Knee Osteoarthritis, Doxepin, Topical Administration, Diclofenac, Pain Management, Randomized Controlled Trial

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11091898/v1

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Additional Declarations: No competing interests reported.

Abstract

Background and purpose

Osteoarthritis is the most common type of arthritis, and knee osteoarthritis is one of the most important forms, causing symptoms such as knee pain and stiffness, followed by reduced physical performance and a decreased quality of life. Among complementary treatments of interest are new and optimal drugs that can reduce pain and discomfort in patients with fewer side effects. This study aimed to evaluate the efficacy and safety of topical 5% doxepin cream.

Methods

In this double-blind clinical trial, 60 patients with knee osteoarthritis were selected and randomly assigned to 3 groups of 20. The first group used placebo cream twice daily, the second group used 5% doxepin cream twice daily, and the third group used 1% diclofenac topical gel twice daily. All three groups also took 250–500 mg of naproxen tablets orally daily. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Visual Analogue Scale (VAS) questionnaires were administered at baseline and at six weeks after treatment initiation. Improvement in physical function and reduction in pain were considered a response to treatment.

Results

This study showed that after the doxepin intervention, in the second group, there was a significant difference in knee pain ($P < 0.005$), daytime stiffness ($P < 0.05$), morning stiffness ($P < 0.05$), and physical performance ($P < 0.05$) between the groups. In the two groups receiving doxepin cream and diclofenac gel, there was a significant reduction in symptoms (pain and stiffness of the knee) and an improvement in physical performance.

Conclusion

Topical 5% doxepin cream significantly improved pain, stiffness, and physical function in patients with primary knee osteoarthritis. Although diclofenac demonstrated greater improvement in overall knee pain, topical doxepin also showed clinically meaningful benefits and may represent a promising adjunctive treatment option for symptom management in knee osteoarthritis. Larger randomized controlled trials are warranted to confirm these findings.

Introduction

Osteoarthritis is currently recognized as a multifactorial whole-joint disease rather than a simple consequence of aging. Its pathogenesis involves complex interactions among genetic susceptibility,

mechanical loading, low-grade inflammation, metabolic alterations, and cellular and molecular signaling pathways affecting cartilage, subchondral bone, synovium, and other joint tissues [1]. Osteoarthritis is usually seen in people over 40 years old. Osteoarthritis is characterized by persistent joint pain, stiffness, reduced physical function, and progressive structural joint damage. Pain is typically aggravated by physical activity and relieved by rest during the early stages of the disease; however, as osteoarthritis progresses, pain may occur during minimal activity, at rest, and even during the night, substantially impairing quality of life and functional independence [2]. The goal of treatment in osteoarthritis is to reduce pain, swelling, and disability and increase the quality of life of patients because a definitive treatment for this disease has not yet been discovered [3]. Lifestyle changes[4], drug treatments[5], herbal treatments[6], physical treatments[7], and finally surgery [8] are among the treatment solutions used for knee osteoarthritis. In recent years, special attention has been paid to topical products in the treatment of knee arthritis, among which topical non-steroidal anti-inflammatory drugs can be mentioned that have much fewer side effects than the oral form [9, 10]. However, dry skin, contact dermatitis, rash, and itching have been reported as a result of using these compounds[11, 12]. Doxepin is a tricyclic antidepressant (TCAs) that blocks the reuptake of serotonin and norepinephrine[13]. Doxepin has shown analgesic properties such as amitriptyline[14–16], desimipramine [17–19], clomipramine[20, 21] and imipramine[22]. It has been found that the topical use of doxepin has analgesic effects[23]. In this regard, Mika et al. reported that doxepin and amitriptyline reduced neuropathic pain symptoms in rats subjected to chronic contractile injury[24]. In addition, the results of another study showed that doxepin was effective in reducing thermal hyperalgesia and mechanical allodynia[25]. In a study done by McCleane, it was found that topical application of doxepin has an analgesic effect in neuropathic pain and that compared with oral administration, side effects are less common. He stated that topical application of 3.3% doxepin, 0.025% capsaicin, and 3.3% doxepin/0.025% capsaicin produces analgesia of similar magnitude. The combination produces more rapid analgesia. Despite the proven efficacy of oral TCAs in neuropathic pain, side effects are experienced by almost one in three patients [23].

Since there is no definitive treatment for OA, complementary treatments are one of the most important treatment strategies for these patients, along with NSAIDs, which help reduce the pain of patients and are safe for clinical use over long periods. Therefore, this study aims to investigate the effectiveness of doxepin topical cream on improving physical performance and reducing pain in patients with grade 2 to 3 knee osteoarthritis.

Methods

This study was conducted as a double-blind clinical trial on patients with grade 2 and 3 knee osteoarthritis in the age group of 45–75 years who were referred to the orthopedic clinic of Rasoul Akram Hospital of Iran University of Medical Sciences.

Ethical considerations

The study design complies with the ethical principles of the Helsinki Declaration. This study protocol was approved at the Behavioral Sciences Ethics Committee of Iran University of Medical Sciences (ethics code IR: IR.IUMS.REC.1400.1247) and then in the Iranian clinical trial registration center (IRCT) with code: **IRCT20161204031229N7**. Registration Date 2022-04-14. The informed consent form was taken from patients participating in the study.

Inclusion criteria

The age range of 75 – 45 years and definitive diagnosis of osteoarthritis grade 2 and 3 based on diagnostic criteria by a specialist doctor and radiological evidence of OA in one or both knee joints.

Exclusion criteria

The presence of simultaneous severe diseases such as metabolic and digestive diseases, taking tricyclic antidepressants and duloxetine, people with rheumatological diseases involving the joint, as well as patients with a history of intra-knee injections with hyaluronic acid and glucocorticoid and a history of joint platelet-Rich Plasma (PRP) in the past six months, consumption of other local and oral painkillers, severe infection or local infections, the occurrence of drug sensitivity, pregnancy and breastfeeding, disturbed liver tests, history of old fractures or surgery in the knee, and suffering from rheumatoid arthritis and arthropathy seronegative and seropositive, not agreeing to continue participating in the study and taking any type of painkiller at the same time that may cause disturbances in the results.

Sample size and sampling method

An a priori sample size calculation was performed using G*Power software (version 3.1; Heinrich Heine University, Düsseldorf, Germany) for a one-way analysis of variance (ANOVA). Based on a two-sided significance level of 0.05, a statistical power of 90%, and an anticipated effect size derived from previous clinical studies of topical interventions for osteoarthritis, together with clinical judgment, the required sample size was estimated to be 60 participants, with 20 participants allocated to each study group [26].

Preparation of doxepin cream and investigation of physicochemical properties

To prepare doxepin cream, first, the oily phase of the formulation including cetyl alcohol, isopropyl myristate, wax, glycerin monostearate, and vaseline was heated to 70°C to melt. Then, the aqueous phase of the formulation, including doxepin dissolved in water, titanium dioxide dispersed in glycerin, and other aqueous phase materials (benzyl alcohol, sorbitol, glycerin, and Bridge 35), is all mixed and heated to 75°C in a bain marie and slowly mixed with the oil phase. After making doxepin cream, physicochemical evaluations were done on it. To perform physical tests, the uniformity and absence of

creaming and coalescence as well as the appearance of the product, were examined. The viscosity and pH of doxepin cream were measured with a viscometer and pH meter, respectively. Also, thermal stability tests (at temperatures of 4–8°C and 45–60°C after 24 hours, one week, one month, and three months) and heating and cooling tests (for 48 hours at 45–50°C) were done. The amount of drug released from the cream base was also studied using the dialysis bag.

Intervention

Patients with osteoarthritis were divided into three groups of 20 people. The first group uses 5% doxepin cream 2 times a day, the second group uses placebo cream 2 times a day, and the third group uses 1% diclofenac topical gel, the same amount as the doxepin group, 2 times a day. Patients in each group were instructed to apply a volume of cream equal to the size of a grain of rice to the painful area twice daily over the six-week study period. Patients were told not to douche for two hours after taking it. The selection of the 5% concentration of doxepin was based on a previous study that conclude that topical doxepin hydrochloride 5% has an analgesic effect in neuropathic pain and its use is not commonly complicated by side effects [23]. All three groups should use 250–500 mg naproxen tablets orally daily. All patients were informed about the nature and the aim of the study.

Primary outcome

The primary outcome was the change in knee pain intensity from baseline (visit 1) to 6 weeks (visit 2). after treatment, assessed using the Visual Analog Scale (VAS) and the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

The WOMAC questionnaire is an international and standardized questionnaire to evaluate the treatment outcomes of patients with knee osteoarthritis. 3 criteria of pain (5 questions), joint stiffness (2 questions), and physical function (17 questions) are quantitatively evaluated in this tool. There are five options for each question, and the answers are scored from 0 to 4, and the total score is from 0 to 100. The number zero indicates the absence of a problem and the number 100 indicates the maximum problem. A decrease in the WOMAC score is a sign of improvement. The result obtained in each subgroup is expressed as a quantitative value in five WOMAC subgroups [27].

The VAS questionnaire is a visual scale for measuring pain intensity in the form of a 10 cm ruler, with the word "no pain" written at the left end and the most severe state of pain written at the right end. According to the level of pain in the last 48 hours, the person marks on the continuum. Note that they mark only one point [28].

Secondary outcomes

Secondary outcomes included changes in physical function, morning stiffness, right and left knee pain scores, daytime stiffness, and overall WOMAC score. Safety outcomes included the incidence of adverse

events and treatment tolerability.

Randomization and blinding

In this double-blind study, a simple randomization method was used. First, the randomization sequence was determined by the researchers, and then sampling was done. There were 2 vases, in the first vase there were numbers from 1 to 63, and in the second vase, there were 63 non-transparent envelopes, in which the desired treatment type was inserted. First, a number was randomly selected from the first vase and an envelope was randomly selected from the second vase and placed in a box. The number drawn from the first pot will take the treatment that was drawn from the second pot. In fact, the treatment assigned to the numbers is not known until the person comes and the envelope is opened for him, and secondly, the names of the treatments will not be clear inside the envelopes, and the names of the treatments will be A, B, and C, and only the study designer knows the type of treatment.

Assessment of adverse effects

All patients were asked at each visit for evaluation of the adverse effects of medications. The type and severity of possible adverse effects experienced by the patients during the treatment, such as itching, skin rash, burning, erythema, and drowsiness were recorded.

Statistical analysis

Statistical data were analyzed with the SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). The results for quantitative variables are expressed as mean and standard deviation (mean ± SD) and for categorical qualitative variables as percentages. To compare the quantitative variables between the three studied groups, if the condition of normality is established, a one-way analysis of variance will be used, otherwise, the Kruskal-Wallis test will be used. In order to compare qualitative variables between the three groups, the chi-square test or Fisher's exact test will be used. A significance level of $P < 0.05$ is considered.

Results

Determination of the Characteristics of Doxepin Cream

The physicochemical evaluation demonstrated that the formulated 5% doxepin cream remained stable throughout the 3-month study period. No changes were observed in the color, odor, appearance, or overall physical stability of the formulation. The detailed physicochemical characteristics are presented in Table 1. In addition, the in vitro drug release study showed a gradual release profile, with approximately 70% of the drug being released within 6 hours, indicating favorable release characteristics for topical administration (Fig. 1).

Table 1
Physicochemical properties of doxepin cream.

Time Analysis type		48 h (Mean ± SD)	1 week (Mean ± SD)	4 week (Mean ± SD)	12 week (Mean ± SD)
Uniformity		Stable	Stable	Stable	Stable
Creaming and coalescence		No hard clots, no turbidity	No hard clots, no turbidity	No hard clots, no turbidity	No hard clots Relatively invisible turbidity
Temperature changes	4–6°C	Stable color, odor, viscosity, and uniformity	Stable color, odor, viscosity, and uniformity	Stable color, odor, viscosity, and uniformity	Stable color, odor, viscosity, and uniformity
	25°C	Stable color, odor, viscosity, and uniformity	Stable color, odor, viscosity, and uniformity	Stable color and smell Relatively stable viscosity and uniformity	Stable color and smell Relatively stable viscosity and uniformity
	45–50°C	Stable color, odor, viscosity, and uniformity	Stable color, odor, viscosity, and uniformity	Stable color and smell, relatively stable viscosity and uniformity	Stable color and smell, relatively stable viscosity and uniformity
Stability against cold and heat	48 hours at -15 to -25°C	Stable	Stable	Stable	Stable
	48 hours at 45–50°C	Stable	Stable	Relatively stable	Relatively stable
Viscosity	0.3 rpm	378.2 ± 0.03	391.8 ± 0.49	398.2 ± 0.02	390.5 ± 0.05
	0.6 rpm	146.5 ± 0.33	150.3 ± 0.01	154.7 ± 0.05	152.1 ± 0.7
	3 rpm	11 ± 0.21	11.6 ± 0.18	12.65 ± 0.01	11.85 ± 0.01
	6 rpm	4.62 ± 0.01	4.84 ± 0.01	4.4 ± 0.02	4.93 ± 0.00
	60 rpm	0.82 ± 0.00	0.8 ± 0.00	0.8 ± 0.00	0.7 ± 0.00
pH		5.16 ± 0.02	5.18 ± 0.01	5.23 ± 0.03	5.27 ± 0.05

Baseline Demographic Characteristics

The participant flow diagram is presented in Fig. 2. A total of 105 patients were assessed for eligibility. Of these, 45 patients were excluded, including 17 who did not meet the inclusion criteria, 10 who declined to participate, and 18 who were excluded for other reasons. The remaining 60 eligible participants were randomly assigned in a 1:1:1 ratio to receive topical 5% doxepin cream (n = 20), placebo cream (n = 20), or 1% diclofenac gel (n = 20). All randomized participants completed the 6-week follow-up and were included in the final analysis. The mean age of the participants was 58.28 ± 8.43 years. The mean ages were 57.65 ± 8.62 years in the doxepin group, 58.80 ± 9.25 years in the placebo group, and 58.40 ± 7.74 years in the diclofenac group, with no statistically significant difference among the groups (P > 0.05). Overall, 40% of the participants were male and 60% were female. The distribution of sex was comparable across the three groups, with no statistically significant difference observed (P > 0.05).

As shown in Table 2, no significant difference in WOMAC knee pain scores was observed among the three groups at baseline (P > 0.05). However, after 6 weeks of treatment, a statistically significant difference was detected (P < 0.05). Patients receiving topical doxepin cream and diclofenac gel demonstrated greater reductions in knee pain than those receiving placebo (Fig. 3).

Table 2
Average knee pain index in osteoarthritis patients in 3 groups in 2 follow-up intervals.

Follow-up	Diclofenac (n = 20)	Placebo(n = 20)	Doxepin (n = 20)	*P value*
Day 1	**2.04 ± 0.68**	1.84 ± 0.93	**1.94 ± 0.82**	**0.094**
Week 6	**0.92 ± 0.60**	1.59 ± 0.85	**1.07 ± 0.68**	**< 0.001**
Data are presented as mean ± SD. Comparisons among the three groups were performed using one-way ANOVA. Statistically significant P values are shown in bold.				

Table 3 presents the WOMAC scores for right and left knee pain separately. No significant differences were observed among the three groups at baseline for either knee (P > 0.05). At week 6, significant between-group differences were identified (P < 0.05), with greater improvements observed in the doxepin and diclofenac groups than in the placebo group (Figs. 4 and 5).

Table 3
Average right and left knee pain index in osteoarthritis patients in 3 groups in 2 follow-up intervals.

Outcome	Follow-up	Doxepin (n = 20) Mean ± SD	Diclofenac (n = 20) Mean ± SD	Placebo (n = 20) Mean ± SD	P value
Right knee pain	Baseline	1.85 ± 1.09	2.05 ± 1.05	2.00 ± 1.21	0.247
	Week 6	0.95 ± 0.76	1.20 ± 0.89	1.80 ± 1.15	**< 0.001**
Left knee pain	Baseline	1.90 ± 1.21	1.80 ± 0.95	2.00 ± 1.26	0.742
	Week 6	1.05 ± 0.83	1.00 ± 0.92	1.95 ± 1.10	**< 0.001**

Data are presented as mean ± SD. Comparisons among groups were performed using one-way ANOVA. Statistically significant P values are shown in bold.

Similarly, morning stiffness and daytime stiffness did not differ significantly among the study groups at baseline ($P > 0.05$). After 6 weeks of treatment, both outcomes showed statistically significant differences among the groups ($P < 0.05$), favoring the doxepin and diclofenac treatment groups (Table 4; Figs. 6 and 7).

Table 4
The mean index of daytime stiffness and morning stiffness in osteoarthritis patients in 3 groups in 2 follow-up intervals.

Outcome	Follow-up	Doxepin (n = 20) Mean ± SD	Diclofenac (n = 20) Mean ± SD	Placebo (n = 20) Mean ± SD	P value
Morning stiffness	Baseline	2.25 ± 0.91	1.95 ± 0.76	2.30 ± 1.03	0.159
	Week 6	1.10 ± 0.79	1.45 ± 0.83	2.10 ± 0.97	**0.001**
Daytime stiffness	Baseline	1.60 ± 0.68	1.90 ± 0.72	1.70 ± 0.80	0.484
	Week 6	0.65 ± 0.49	1.65 ± 0.75	1.50 ± 0.76	**< 0.001**

Data are presented as mean ± SD. Group comparisons were performed using one-way ANOVA. Statistically significant P values are shown in bold.

The physical function results are summarized in Table 5. No significant between-group difference was observed at baseline ($P > 0.05$). However, after 6 weeks, physical function improved significantly, with a statistically significant difference among the three groups ($P < 0.05$). Greater improvements were observed in the doxepin and diclofenac groups than in the placebo group (Fig. 8).

Table 5
Mean Physical Performance Index of Patients with Knee Osteoarthritis in the Three Study Groups at Two Follow-up Time Points

Follow-up Time	Diclofenac (n = 20) Mean ± SD	Placebo (n = 20) Mean ± SD	Doxepin (n = 20) Mean ± SD	Total (n = 60) Mean ± SD	*P*-value
First day after treatment	1.83 ± 0.847	1.71 ± 0.907	1.78 ± 0.868	1.78 ± 0.879	0.084
Sixth week after treatment	1.17 ± 0.688	1.64 ± 0.863	1.26 ± 0.697	1.35 ± 0.781	**0.026***

Data are presented as mean ± SD. Group comparisons were performed using one-way ANOVA. Statistically significant P values are shown in bold.

VAS pain scores are presented in Table 6. Baseline VAS scores were comparable among the three groups ($P > 0.05$). Following 6 weeks of treatment, a significant between-group difference was observed ($P < 0.001$). Both topical doxepin cream and diclofenac gel significantly reduced pain intensity compared with placebo, with the diclofenac group showing the lowest mean VAS score at the final follow-up (Fig. 9).

Table 6
Mean Visual Analog Scale (VAS) Pain Scores of Patients with Knee Osteoarthritis in the Three Study Groups at Two Follow-up Time Points

Follow-up Time	Diclofenac (n = 20) Mean ± SD	Placebo (n = 20) Mean ± SD	Doxepin (n = 20) Mean ± SD	Total (n = 60) Mean ± SD	*P*-value
First day after treatment	4.50 ± 1.960	4.45 ± 2.523	4.95 ± 2.564	4.63 ± 2.336	0.229
Sixth week after treatment	2.90 ± 1.944	4.20 ± 2.441	3.40 ± 2.186	3.50 ± 2.228	**< 0.001***

Data are presented as mean ± SD. Group comparisons were performed using one-way ANOVA. Statistically significant P values are shown in bold.

Table 7
Between-group effect sizes (Hedges' g) for clinical outcomes at Week 6.

Outcome	Diclofenac vs. Placebo Hedges' g (95% CI)	Doxepin vs. Placebo Hedges' g (95% CI)	Interpretation
Overall knee pain	0.90 (0.25–1.55)	0.66 (0.02–1.30)	Large vs. Moderate
VAS pain	0.58 (− 0.06–1.22)	0.34 (− 0.29–0.96)	Moderate vs. Small
Right knee pain	0.56 (− 0.08–1.20)	0.82 (0.17–1.46)	Moderate vs. Large
Left knee pain	0.95 (0.29–1.61)	0.89 (0.24–1.55)	Large vs. Large
Morning stiffness	0.67 (0.02–1.31)	1.10 (0.43–1.78)	Moderate vs. Large
Daytime stiffness	0.20 (− 0.42–0.82)	1.27 (0.58–1.96)	Small vs. Very large
Effect sizes were calculated as Hedges' g using pooled standard deviations because of the relatively small sample size (n = 20 per group). Values of 0.2, 0.5, and 0.8 represent small, moderate, and large effect sizes, respectively.			

Effect size analysis demonstrated clinically meaningful treatment effects for both active interventions compared with placebo. Diclofenac showed a large effect on overall knee pain (Hedges' g = 0.90) and left knee pain (g = 0.95), whereas topical doxepin demonstrated moderate-to-large effects across most WOMAC domains, including overall knee pain (g = 0.66), right knee pain (g = 0.82), left knee pain (g = 0.89), morning stiffness (g = 1.10), and daytime stiffness (g = 1.27). For VAS pain, diclofenac showed a moderate effect (g = 0.58), while doxepin showed a small effect (g = 0.34). Overall, these findings indicate that both topical treatments provided clinically meaningful improvements over placebo, with diclofenac showing a greater effect on overall pain reduction and doxepin demonstrating particularly strong effects on stiffness-related outcomes.

Assessment of Adverse Events

Topical doxepin cream was generally well tolerated. During the study, three patients in the doxepin group reported transient drowsiness and mild confusion. Two patients experienced a mild burning sensation at the application site, and two developed localized pruritus suggestive of a mild allergic reaction. In the diclofenac group, one patient reported mild application-site irritation. No serious adverse events or treatment discontinuations related to the study medications were observed.

Discussion

The effect size analysis complements the statistical significance findings by demonstrating the magnitude of the treatment effects. While both topical doxepin and diclofenac were associated with clinically meaningful improvements compared with placebo, their patterns of efficacy differed slightly. Diclofenac showed the greatest effect on overall pain reduction, whereas topical doxepin demonstrated

larger effects for stiffness-related outcomes and comparable effects for several WOMAC pain domains. These findings suggest that topical doxepin may provide meaningful symptomatic relief and may serve as a potential adjunctive treatment for patients with knee osteoarthritis, particularly in those with prominent stiffness symptoms. Osteoarthritis is a common joint disease and one of the important causes of progressive pain and disability, especially in the elderly. The existing treatments only reduce pain and have not been effective enough, and in addition, they have their side effects. Among the drugs used in this disease are NSAIDs, which have side effects such as digestive and skin complications and digestive intolerance[29]. Also, some studies have shown that non-steroidal anti-inflammatory drugs that are commonly prescribed today inhibit the synthesis of cartilage matrix in humans, which in turn increases the destruction of joint cartilage in osteoarthritis, which also applies to their local use. Researchers are trying to find a safer alternative with fewer side effects for this group of drugs. One of the alternative treatments is topical drugs, which are more acceptable to patients and have fewer side effects than oral drugs. The goal of treatment in osteoarthritis is to reduce pain, swelling, and disability and increase the quality of life of patients because no definitive treatment has been discovered for this disease yet [30]. The use of analgesic and anti-inflammatory drugs is necessary and unavoidable in clinical medicine. It is very important to use drugs other than painkillers and anti-inflammatory steroids with similar and even better effects with fewer side effects. Many studies have been conducted to investigate the effect of oral doxepin on pain, which has shown the reduction of pain with the use of this drug in various diseases [31–32]. It has been suggested in studies that TCA drugs such as doxepin, when used topically, can show analgesic effects with different mechanisms, including local anesthetic effects and central effects[23]. It has also been shown that the analgesic effects of these drugs (doxepin) can be caused by systemic absorption or chronic environmental effects (local peripheral) of doxepin or a combination of these two effects[33, 34]. It has also been shown in a study that doxepin or inhibition of sodium channels is more effective than lidocaine in the treatment of peripheral neuropathies[23]. Therefore, in this study, the effect of topical doxepin on reducing pain and improving the physical performance of patients with knee osteoarthritis was investigated.

Considering the importance of pain and inflammation and the new approach, studies have recently been conducted to investigate the effects of the drug doxepin on the process of pain and inflammation. In a study conducted by Tugwell et al in 2004 on the comparison of the effect of oral and topical diclofenac, during 12 weeks, patients mentioned side effects such as skin irritation and dryness in the applied area[35]. In another study conducted by Dingle et al. in 1999 on the effect of non-steroidal anti-inflammatory drugs on human articular cartilage matrix, they concluded that commonly prescribed non-steroidal anti-inflammatory drugs inhibit the synthesis of cartilage matrix in humans, which in turn cause the destruction of joint cartilage in osteoarthritis, and this effect also applies to their local consumption [30]. Recently, doxepin has been used as a TCA antidepressant to reduce acute and chronic pain [33, 34, 36]. Also, in another research, the effects of topical cream of doxepin hydrochloride 3.3% and capsaicin 0.025 and also the combination of these two drugs, were investigated on people who suffered from chronic pain caused by neuropathy. In this study, 200 patients were examined; some of them received a placebo, doxepin, and capsaicin, and the rest received a combination of these two drugs. The results

after 4 weeks showed that doxepin, capsaicin, and their combination all three cause a reduction of chronic pain caused by neuropathy [36]. It has also been shown in a study that doxepin is more effective than lidocaine in the treatment of peripheral neuropathies by inhibiting sodium channels. Also, in another study, it has been shown that topical doxepin has inhibitory effects on NMDA receptors, as well as inhibitory effects on noradrenaline and 5-hydroxytryptamine reuptake [36].

Conclusion

The effect size analysis indicated that both active treatments were associated with clinically relevant improvements compared with placebo. Topical doxepin demonstrated large effects for several WOMAC outcomes, particularly knee pain and stiffness, while diclofenac also showed moderate-to-large effects. Overall, the small effect sizes observed in the direct comparison between doxepin and diclofenac suggest that the two active treatments achieved broadly comparable clinical outcomes over the 6-week study period. This study demonstrated that both topical 5% doxepin cream and topical diclofenac significantly improved pain, morning stiffness, daytime stiffness, and physical function in patients with primary knee osteoarthritis compared with placebo. Effect size analysis supported these findings, demonstrating clinically meaningful treatment effects for both active interventions across most clinical outcomes. Diclofenac showed the greatest improvement in overall knee pain, whereas topical doxepin also produced substantial improvements and generally demonstrated therapeutic effects comparable to diclofenac for several WOMAC domains. Direct comparisons between the two active treatment groups yielded predominantly small effect sizes, suggesting that the differences between the two treatments were modest despite slightly greater pain reduction with diclofenac. The present study has several limitations. The relatively small sample size, single-center design, inclusion of patients with mild-to-moderate knee osteoarthritis, and the 6-week follow-up period may limit the generalizability of the findings. In addition, because all participants received concomitant naproxen therapy, the independent therapeutic effect of topical doxepin could not be completely isolated. Future multicenter randomized controlled trials with larger sample sizes, longer follow-up periods, and evaluation of topical doxepin as monotherapy are needed to confirm these findings.

Declarations

Ethical approval

The study was approved by the ethics committee of the Iran University of Medical Sciences. The study was performed following the Guidelines for Good Clinical Practice (ICH-GCP), the Declaration of Helsinki in its latest version, and international and local laws.

Consent to participate

Informed consent was obtained from all subjects involved in the study.

Consent for publication

All co-authors have reviewed and approved this manuscript for publication.

Consort Guideline

Study adheres to CONSORT guidelines

Competing interests

The authors declare no competing interests.

Research Data Policy and Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding

This study is funded by the Iran University of Medical Sciences.

Author Contribution

Azadeh Eshraghi, Neda Eslami contributed to the study conception and design. Mahnam Majmajmasanaye, Hossein Mazhari wrote the paper. Hossein Mazhari, Maryam Mehrpooya, Azadeh Eshraghi, and Neda Eslami recruited and followed up the subjects and collected the data. Hossein Mazhari, Maryam Farasatinasab and Azadeh Eshraghi analysed the data. All authors contributed to the review and revision and have seen and approved the final version of the manuscript.

Acknowledgments

The authors thank all patients for helping and participating in the study.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Tong L, Yu H, Huang X, Shen J, Xiao G, Chen L, et al. Current understanding of osteoarthritis pathogenesis and relevant new approaches. Bone Res. 2022;10:60.
2. Coaccioli S, Sarzi-Puttini P, Zis P, Rinonapoli G, Varrassi G. Osteoarthritis: New Insight on Its Pathophysiology. J Clin Med. 2022;11(20):6013. 10.3390/jcm11206013.
3. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020;72(2):149–62. 10.1002/acr.24131.
4. Masilionyte M, et al. Estimating the impact of lifestyle changes on treatment outcomes for people with knee osteoarthritis through system dynamics simulation modeling. J Oper Res Soc. 2021;72(12):2649–60.
5. Wolff DG, et al. Topical nonsteroidal anti-inflammatory drugs in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Phys Sportsmed. 2021;49(4):381–91.
6. Wang M et al. Mechanism of traditional Chinese medicine in treating knee osteoarthritis. J Pain Res, 2020: pp. 1421–9.
7. Zampogna B, et al. The role of physical activity as a conservative treatment for hip and knee osteoarthritis in older people: a systematic review and meta-analysis. J Clin Med. 2020;9(4):1167.
8. Sato M, et al. Combined surgery and chondrocyte cell-sheet transplantation improve clinical and structural outcomes in knee osteoarthritis. NPJ Regen Med. 2019;4(1):4.
9. Lin J, et al. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. BMJ. 2004;329(7461):324.
10. Honvo G, et al. Safety of topical non-steroidal anti-inflammatory drugs in osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019;36:45–64.
11. Bamrungsawad N, et al. Safety of topical non-steroidal anti-inflammatory drugs (NSAIDS) using the Thia health product vigilance center database. TBPS. 2020;15(2):59–72.
12. Matyushkin A, Ivanova E. Efficacy and Safety of Topical Dosage Forms of Non-Steroidal Anti-Inflammatory Drugs and their Pharmacokinetic Determinants. Pharm Chem J. 2021;55(5):490–3.
13. Yeung W-F, et al. Doxepin for insomnia: a systematic review of randomized placebo-controlled trials. Sleep Med Rev. 2015;19:75–83.
14. Watson C, Evans R. A comparative trial of amitriptyline and zimelidine in post-herpetic neuralgia. Pain. 1985;23(4):387–94.
15. Max M, et al. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology. 1988;38(9):1427–1427.
16. Watson CP, et al. Amitriptyline versus placebo in postherpetic neuralgia. Neurology. 1982;32(6):671–671.
17. Kishore-kumar R, et al. Desipramine relieves postherpetic neuralgia. CPT. 1990;47(3):305–12.

18. Max MB, et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain. 1991;45(1):3–9.
19. Max MB, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. NEJM. 1992;326(19):1250–6.
20. Sindrup S, et al. Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. Br J Clin Pharmacol. 1990;30(5):683–91.
21. Langohr H, Stöhr M, Petruch F. An open and double-blind cross-over study on the efficacy of clomipramine (Anafranil®) in patients with painful mono-and polyneuropathies. Eur Neurol. 1982;21(5):309–17.
22. Kvinesdal B, et al. Imipramine treatment of painful diabetic neuropathy. JAMA. 1984;251(13):1727–30.
23. McCleane GJ. Topical doxepin hydrochloride reduces neuropathic pain: a randomized, double-blind, placebo-controlled study. Pain Clin. 2000;12(1):47–50.
24. Mika J, et al. Effects of chronic doxepin and amitriptyline administration in naïve mice and in neuropathic pain mice model. Neurosci. 2015;294:38–50.
25. Wrzosek A, et al. Efficacy of tramadol in combination with doxepin or venlafaxine in inhibition of nociceptive process in the rat model of neuropathic pain: an isobolographic analysis. J Physiol Pharmacol. 2009;60(4):71–8.
26. Zeng C, Doherty M, Persson MSM, Yang Z, Sarmanova A, Wei J, et al. Comparative efficacy and safety of acetaminophen, topical and oral non-steroidal anti-inflammatory drugs for knee osteoarthritis: evidence from a network meta-analysis of randomized controlled trials and real-world data. Osteoarthritis Cartilage. 2021;29(9):1242–51.
27. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Volume 45. Arthritis Care & Research: Arthritis & Rheumatology (A&R),; 2001. pp. 453–61. 5.
28. Klimek L, et al. Visual analog scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). Allergo J Int. 2017;26:16–24.
29. Fayad N, et al. Water and alcohol extraction of Thyme plant (Thymus vulgaris) and activity study against bacteria, tumors and used as anti-oxidant in margarine manufacture. ISDE. 2013;4(1):41–51.
30. Dingle J. The effects of NSAID on the matrix of human articular cartilages. Z Rheumatol. 1999;58:125–9.
31. Epstein JB, et al. Oral doxepin rinse: the analgesic effect and duration of pain reduction in patients with oral mucositis due to cancer therapy. Anesth Analg. 2006;103(2):465–70.

32. Epstein J, et al. Oral topical doxepin rinse: analgesic effect in patients with oral mucosal pain due to cancer or cancer therapy. Oral Oncol. 2001;37(8):632–7.
33. Epstein JB, et al. Doxepin rinse for management of mucositis pain in patients with cancer: one-week follow-up of topical therapy. Spec Care Dentist. 2008;28(2):73–7.
34. Wammack R, et al. Efficacy of oral doxepin and piroxicam treatment for interstitial cystitis. Eur Urol. 2002;41(6):596–600.
35. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in the symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. J Rheumatol. 2004;31(10):2002–12.
36. McCleane G. Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. Br J Clin Pharmacol. 2000;49(6):574–9.

Figures

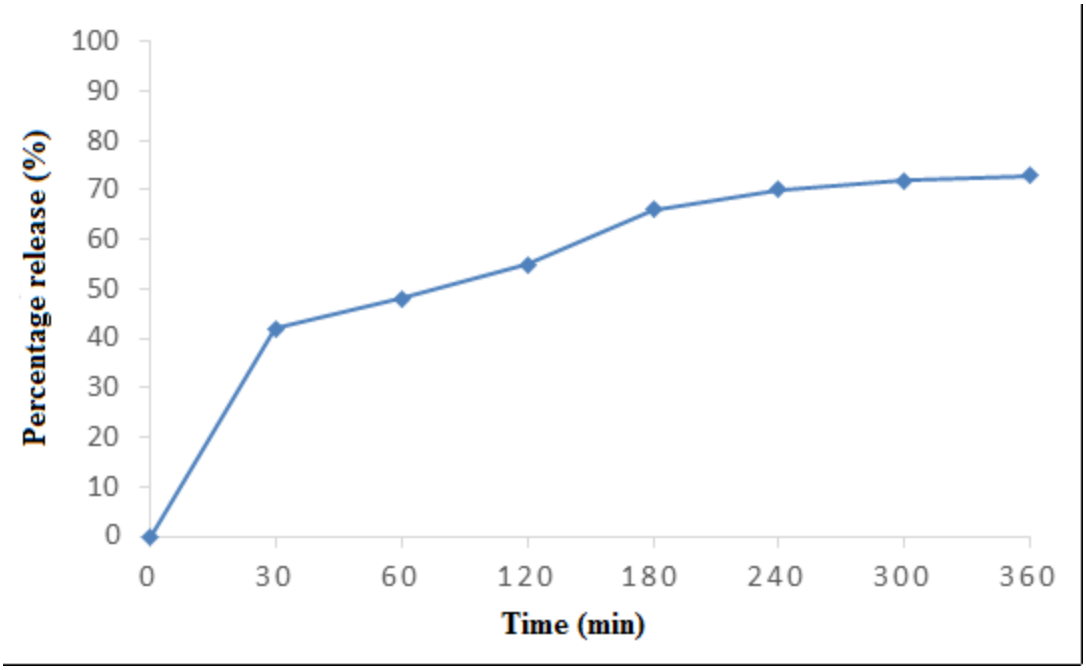


Figure 1

The amount of drug released from the cream base versus time.

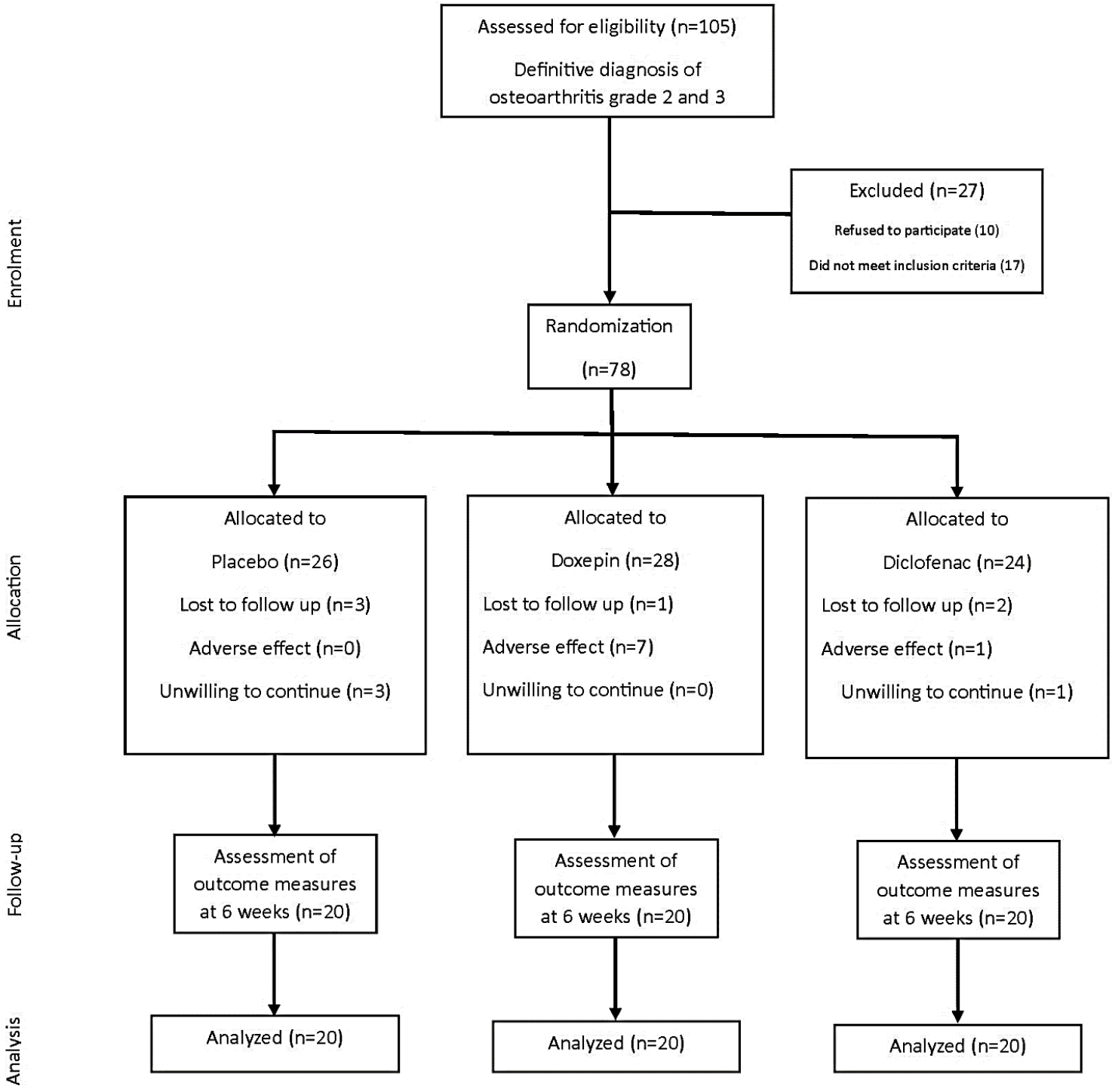


Figure 2

Flow chart depicting patient selection.

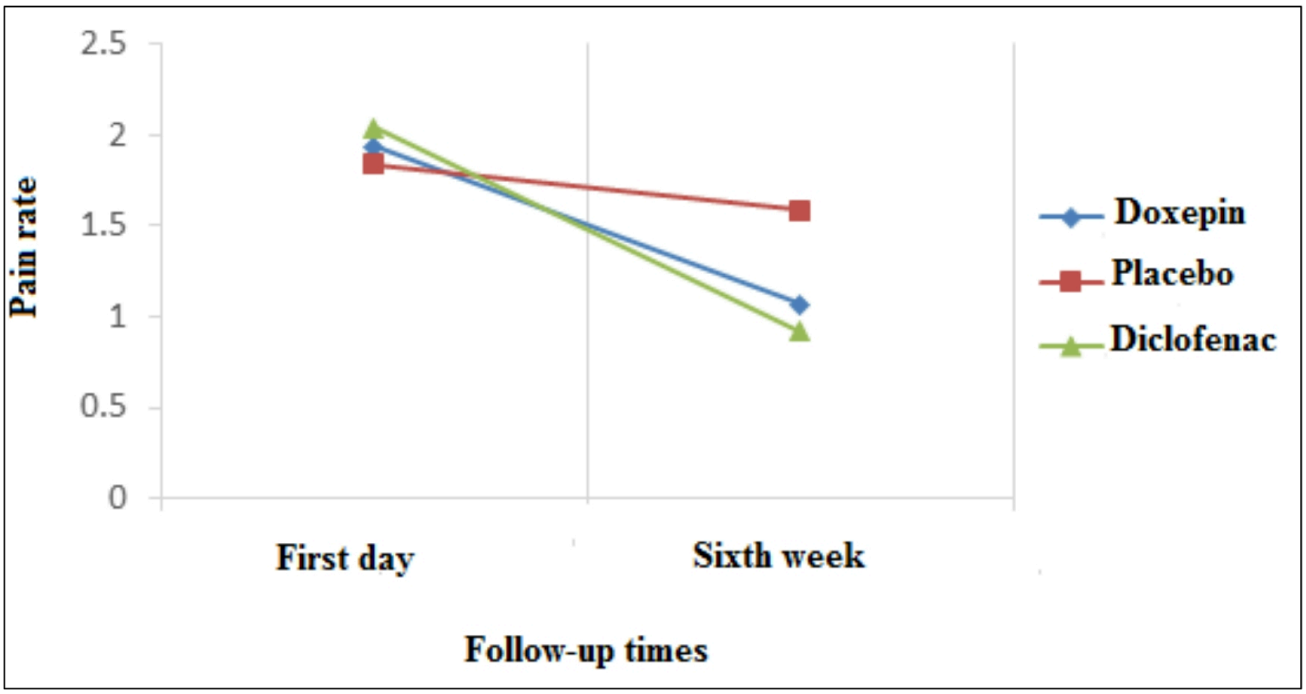


Figure 3

Comparison of knee osteoarthritis patients concerning knee pain in the 3 groups and during 6 follow-up intervals.

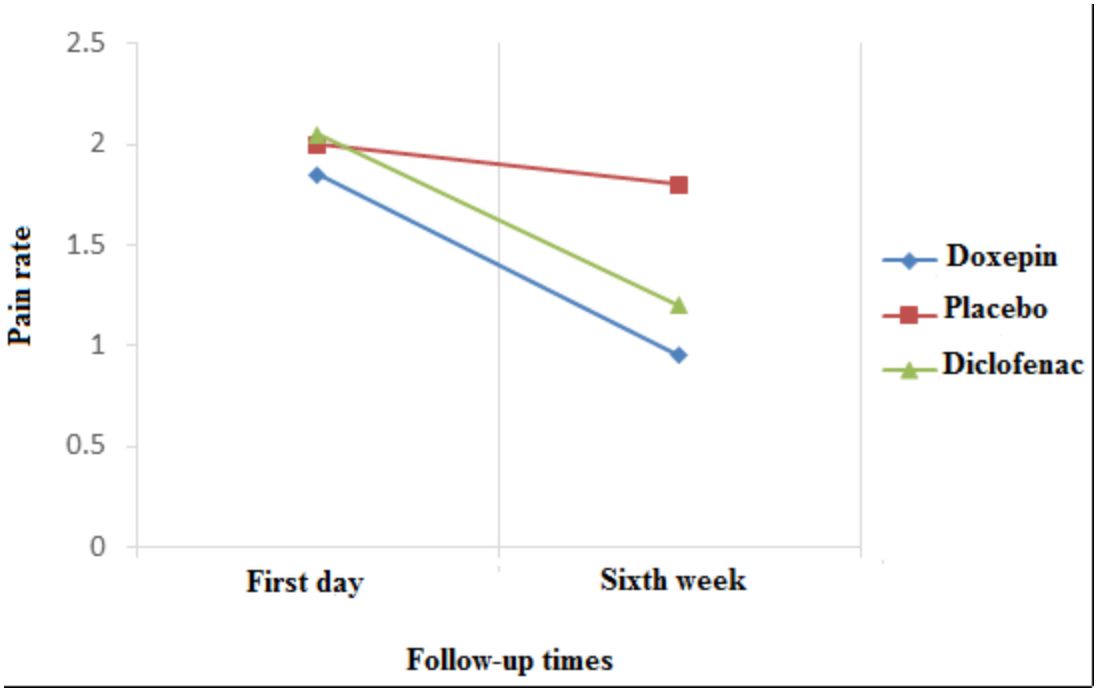


Figure 4

Comparison of knee osteoarthritis patients concerning right knee pain in the 3 groups and during 2 follow-up intervals.

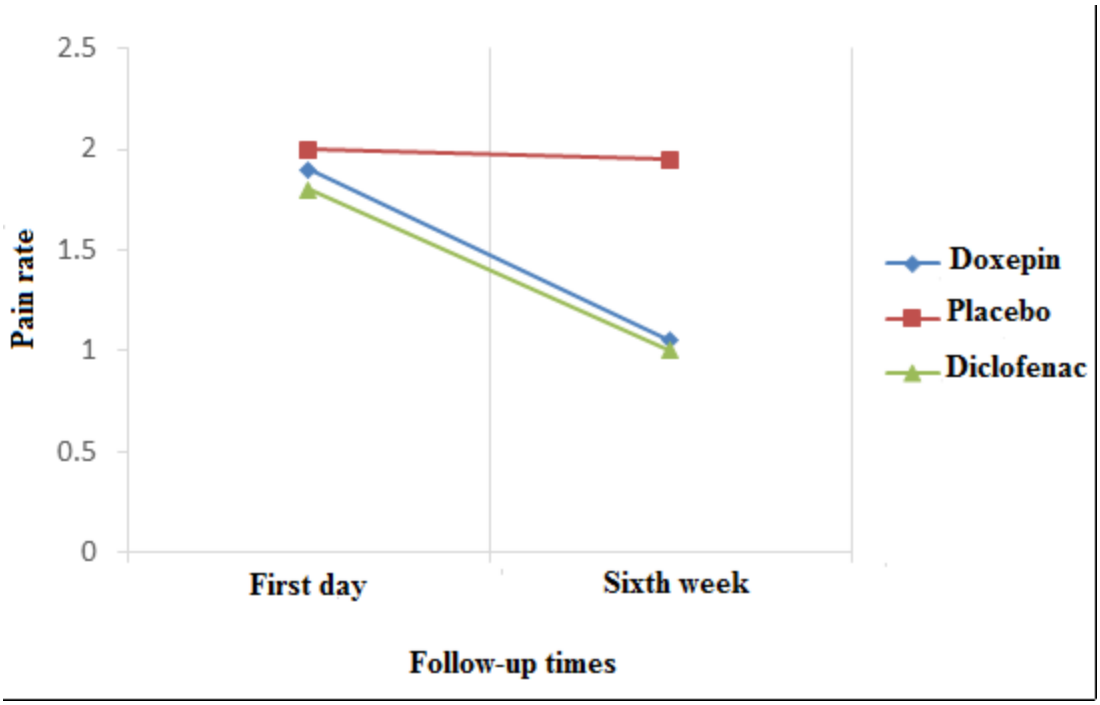


Figure 5

Comparison of knee osteoarthritis patients concerning left knee pain in the 3 groups during 2 intervals of follow-up.

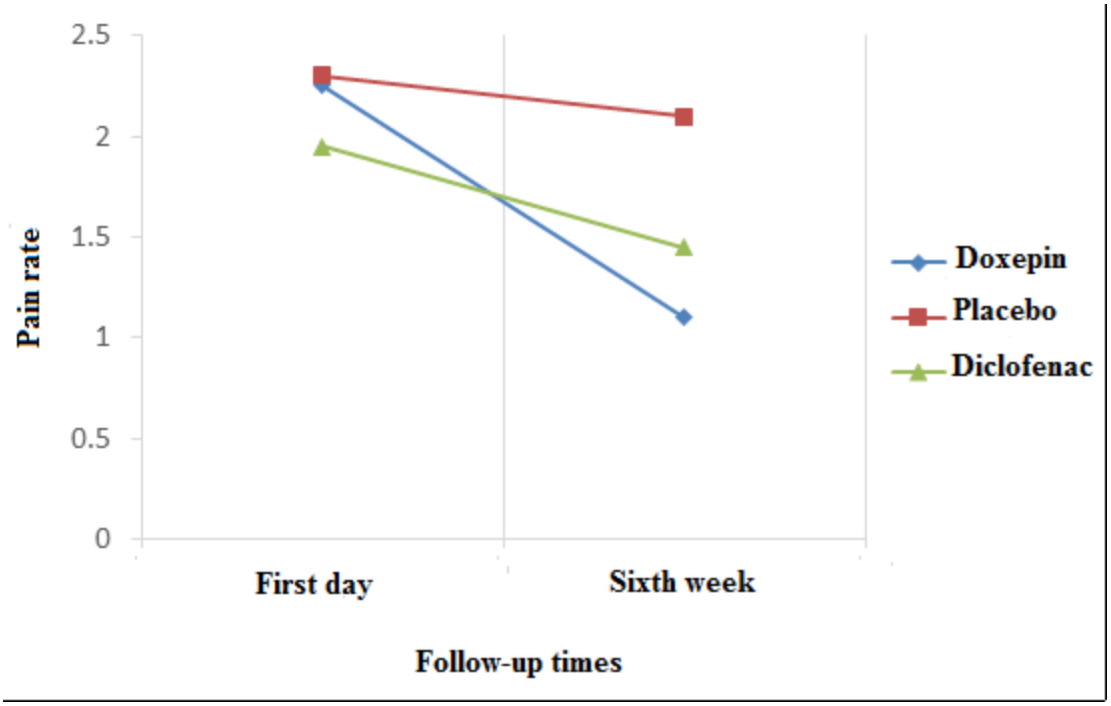


Figure 6

Comparison of knee osteoarthritis patients concerning morning stiffness in the 3 groups during 6 intervals of follow-up.

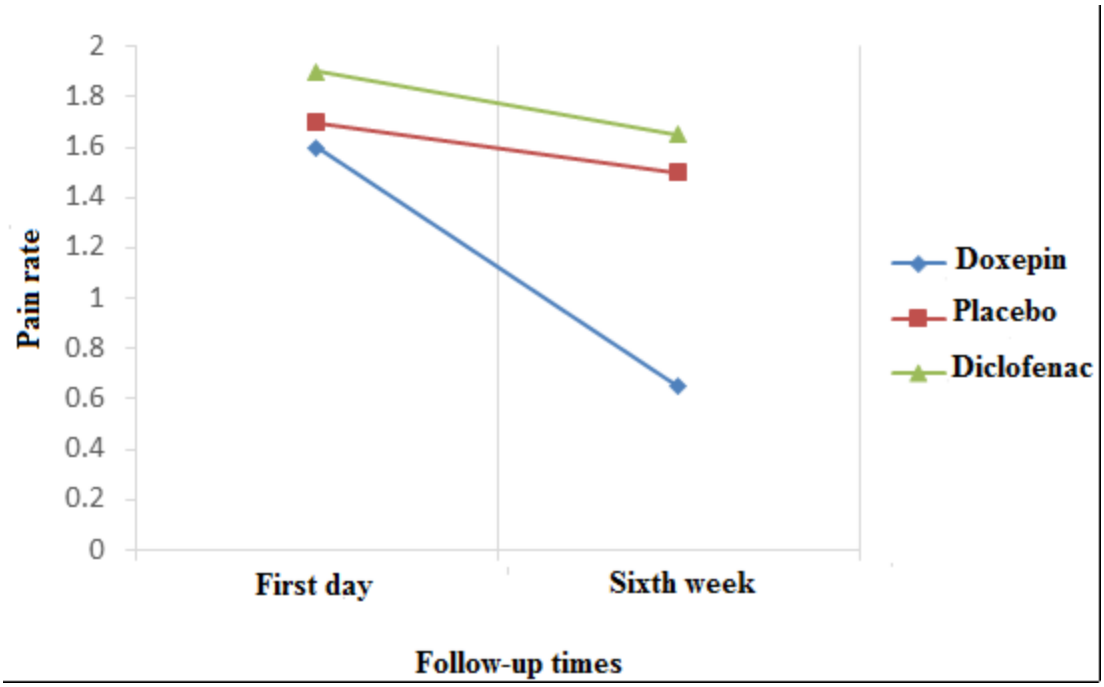


Figure 7

Comparison of knee osteoarthritis patients concerning daily stiffness rate in the 3 groups during 2 intervals of follow-up.

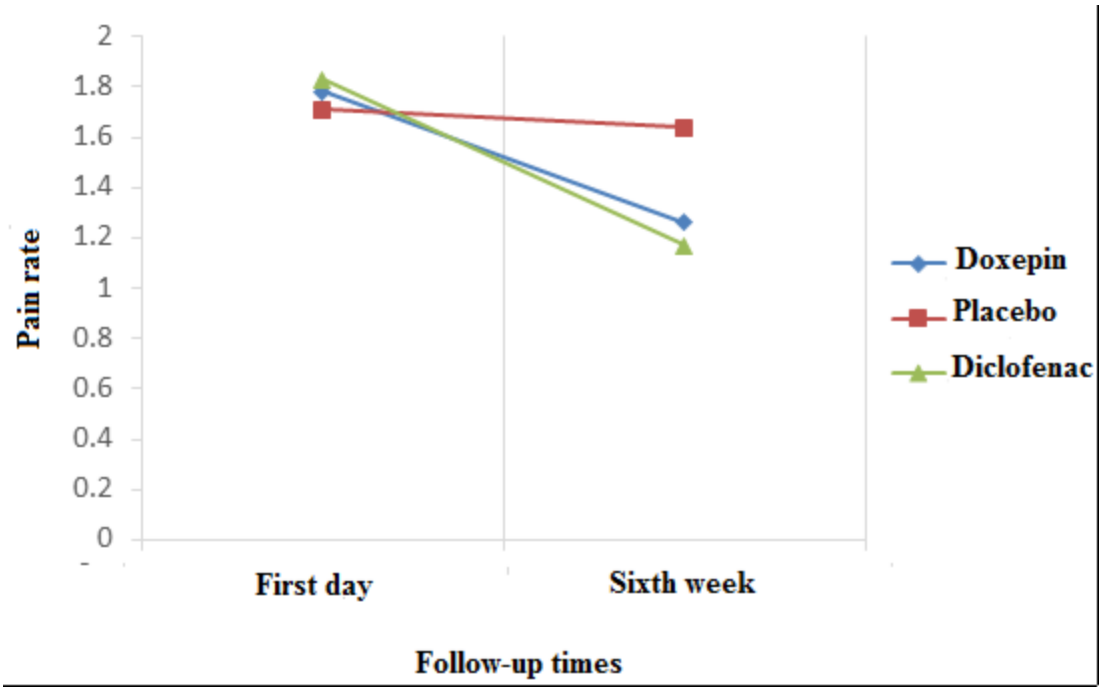


Figure 8

Comparison of knee osteoarthritis patients concerning physical performance in the 3 groups during 2 intervals of follow-up.

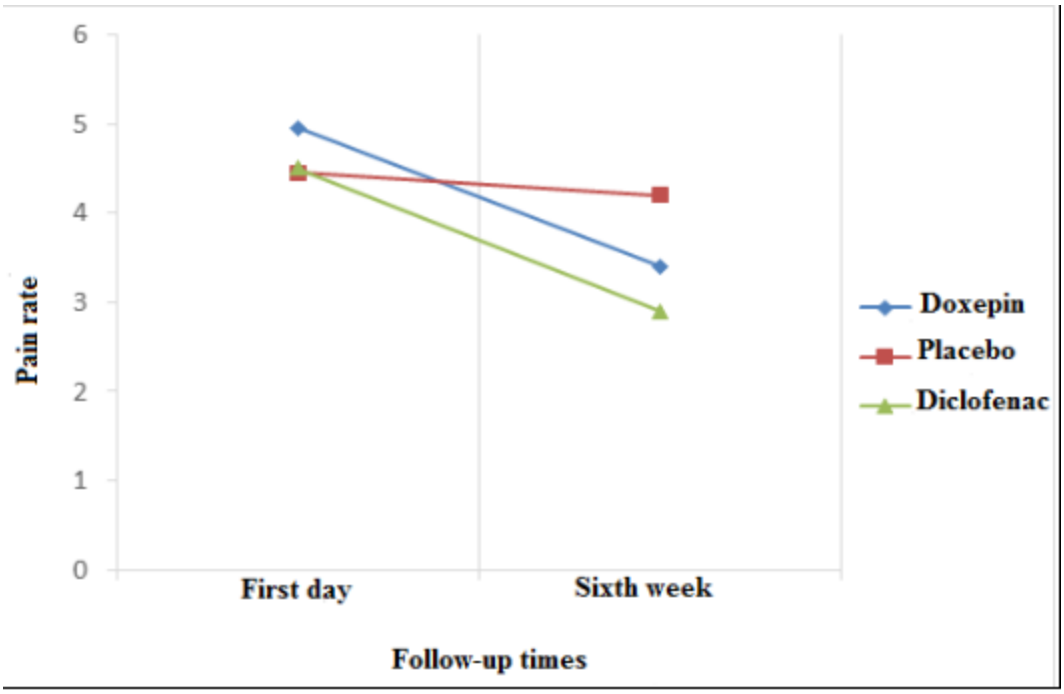


Figure 9

Comparison of knee osteoarthritis patients with respect to pain rate in the 3 groups during 2 intervals of follow-up based on VAS criterion.

Supplementary Files

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- CONSORT2025editablechecklist.docx