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The Efficacy of Topical Glucosamine Sulfate-Chondroitin Sulfate in Knee Osteoarthritis Treated With Physical Therapy: A Randomized, Double-Blind, Placebo-Controlled Study

Fizik Tedavi Uygulanan Diz Osteoartritli Hastalarda Topikal Glukozamin Sülfat-Kondroitin Sülfatın Etkinliği: Randomize Çift Kör Plasebo Kontrollü Bir Çalışma

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Summary

Objective: To determine the efficacy of topical glucosamine on pain and functional status in patients receiving physical therapy for knee osteoarthritis (OA).

Materials and Methods: Forty-nine patients with knee OA were randomized into two groups. The first group consisted of 27 patients receiving physical therapy and topical glucosamine and the second group consisted of 22 patients receiving physical therapy and placebo, for 4 weeks. The patients and the physician were blinded to the treatment. The patients were evaluated before the treatment and at 1, 4, and 12 weeks. Demographic features, pain duration and radiological findings (Kellgren-Lawrence) were recorded; joint stiffness and physical function were evaluated by the Western Ontario and McMaster Osteoarthritis Index (WOMAC).

Results: The WOMAC scores for pain, stiffness, and function were significantly improved in both groups at 1 and 4 weeks as compared to the pre-treatment period (P<0.05), however, no difference was determined between pre-treatment and 12 weeks in any of the WOMAC scores. No significant difference was demonstrated between the two groups in WOMAC scores for pain, stiffness, and function at any evaluation (P>0.05).

Conclusion: In this study, it was shown that topical glucosamine treatment combined with physical therapy in patients with knee OA had no superiority over placebo. T*urk J Phys Med Rehab 2012;58:194-8.*

Key Words: Glucosamine; knee osteoarthritis; physical therapy; WOMAC

Özet

Amaç: Fizik tedavi gören Diz Osteoartritli (OA) hastalarda, topikal glukozamin uygulamasının ağrı ve fonksiyonel durum üzerine etkinliğini ve güvenirliliğini belirlemek.

Gereç ve Yöntem: Diz OA'lı 49 hasta yazı tura yöntemi ile randomize edilerek iki gruba ayrıldı. Birinci gruba fizik tedavi modaliteleri (FT) ve topikal glukozamin, ikinci gruba FT ve topikal plasebo ilaç 4 hafta boyunca uygulandı. Hastaları değerlendiren hekim ve hastalar kör idi. Hastalar tedavi öncesi, 1. hafta, 4. hafta ve 12. haftada değerlendirildi. Hastaların demografik özellikleri, ağrı süresi, radyolojik bulguları (Kellgren -Lawrence) kaydedildi; Western Ontario and McMaster Universities Arthritis Index (WOMAC) skalası ile ağrı, eklem sertliği ve fiziksel fonksiyonlar değerlendirildi.

Bulgular: Her iki grupta WOMAC ağrı, tutukluk ve fonksiyon skorları birinci hafta ve dördüncü haftada tedavi öncesine göre anlamlı olarak düzelmişti (p<0,05); fakat tedavi öncesi ile 12. hafta arasında WOMAC skorlarının tüm parametreleri arasında fark olmadığı saptandı. İki grup arasında WOMAC ağrı, tutukluk ve fonksiyon skorları arasında anlamlı bir fark saptanmadı (p>0,05).

Sonuç: Çalışmamızda fizik tedavi modaliteleri yanında topikal glukozamin uygulamasının plaseboya göre üstünlüğü bulunmamıştır. *Türk Fiz Tıp Rehab Derg 2012;58:194-8.*

Anahtar Kelimeler: Glukozamin; diz osteoartriti; fizik tedavi; WOMAC

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Introduction

Osteoarthritis (OA) is a highly prevalent joint disease characterized by joint cartilage degeneration (1). Moreover, OA is one of the causes of morbidity which significantly impairs the daily activities and social performance of the individual. Although primary alterations in OA involve the cartilage, all the joint tissues are affected by this clinical entity (2). Therefore, the entire biomechanics of the joint is altered and functional loss occurs. The most frequently affected joint is the knee (3); it usually presents as a monoarticular disease, and then, the signs slowly begin to appear in the contralateral joint. The prevalence of symptomatic knee OA increases up to 50% in those over 60 years of age (4).

Transcutaneous Electrical Nerve Stimulation (TENS) and ultrasound are non-pharmacologic physical therapy modalities recommended by the European League of Associations for Rheumatology (EULAR) for the treatment of OA (5). Physical therapy modalities are used either alone or in combination with other rehabilitation techniques, and drug therapies to reduce pain and to improve function.

It has been demonstrated that glucosamine and chondroitin sulfate are low-toxicity agents that reduce pain and stiffness associated with OA (6,7). Glucosamine and chondroitin sulfate, which are the structural components of joint cartilage, have an essential role in the continuity and repair of the cartilage. In animal studies, it has been demonstrated that glucosamine slows the destruction of cartilage (8). In accordance with the recommendations of the EULAR and The Osteoarthritis Research Society International (OARSI) on the treatment of knee OA, glucosamine and chondroidin can be used as symptomatic slow-acting drugs for OA (5,9). It has been determined that the effective in vivo level obtained after receiving standard oral doses of glucosamine is quite low (10). Although glucosamine can also be applied by intramuscular injection, it may provide a more concentrated effect with topical application (10). Despite the low gastrointestinal bioavailability of chondroitin sulfate, it reduces pain in OA and enhances the pain-reducing effect of glucosamine (11-13).

The aim of the present study was to determine the efficacy and safety of topical glucosamine application in relieving pain and improving functional status in patients with bilateral knee OA who were treated with physical therapy.

Materials and Methods

The study was conducted in a rehabilitation hospital between November 2006 and March 2007.

Participants: Sixty female patients diagnosed with bilateral knee OA in accordance with the criteria of the American College of Rheumatology (ACR) were included in the study. Exclusion criteria included a history of inflammatory arthritis, fibromyalgia, knee surgery or knee injections, trauma, intra-articular intervention or physical therapy applied to the knees within the last 6 months, oral or topical glucosamine use within the last 6 weeks, paresis or neuropathy, intra-articular neoplasms, osteonecrosis, and mental disorders. Since the number of male patients was limited, they were not included in the study. Three patients who did not use the medication properly (2 in the drug, 1 in placebo group) and eight patients who did not attend follow-up visits regularly (4 from each group) were excluded; thus, a total of 49 patients were evaluated (Figure 1).

The present study was designed as a randomized, double-blind, placebo-controlled study. Both the patients and the physician who evaluated the patients were blinded to the treatment. The demographic characteristics of the patients and the duration of pain and medical history were recorded. Radiological findings were graded according to the Kellgren-Lawrence scale (14). Pain, joint stiffness, and physical functions were evaluated by the Western Ontario and McMaster Osteoarthritis Index (WOMAC). A Visual Analog Scale (VAS) was used to evaluate the severity of the initial pain.

Written consent of all patients concerning their approval to participate in the study and the approval of the local ethics committee were obtained.

The patients were randomized into two groups by a coin toss method. Physical therapy and topical glucosamine were applied for 4 weeks in the first group; the second group received applications of topical placebo in addition to physical therapy for 4 weeks. Physical therapy modalities for both groups included conventional TENS (20 min) for 12 sessions, infrared (15 min), and short-wave diathermy with condenser (20 min). All patients were taught to perform isometric quadriceps strengthening and range-of-motion exercises.

Topical glucosamine-chondroitin cream includes 1500 mg of glucosamine sulfate, 1200 mg of chondroitin sulfate, and aromatic oils (mint, daphnia, ginger, fennel, orange, eucalyptus, and lavender) per 75 mL. The placebo drug was produced to be the same color with the same odor, and was contained in the same package. Patients were asked to apply the cream for 4 weeks by massaging it around the knee 3 times a day. Each patient was asked to use 4 tubes of topical cream (approximately 215 mg/day of glucosamine sulfate and 170 mg/day of chondroitin sulfate) in the course of the therapy. As a medical therapy, the patients were also administered oral paracetamol, not exceeding 1500 mg/day, as required. The patients were evaluated before the treatment, and 1, 4, and 12 weeks after initiation of the treatment.

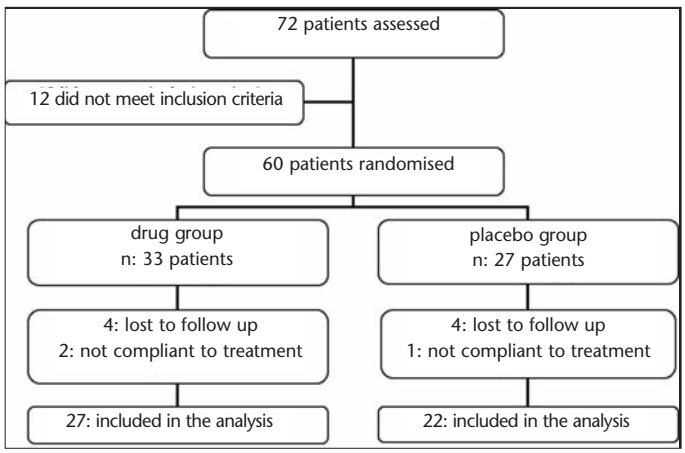

Figure 1. The flow diagram of the patients.

Statistical analysis was performed using SPSS 10.0 for Windows. The Friedman and Wilcoxon tests were used for intra-group comparisons, and the Mann-Whitney U test was used for inter-group comparisons. A p value of less than 0.05 was considered significant.

Results

Twenty-seven patients were included in the drug group and 22 patients were included in the placebo group. The demographic and clinical characteristics of the patients are presented in Table 1. There was no significant difference between the groups regarding demographic characteristics, VAS scores, or pre-treatment WOMAC scores (p>0.05; Table 1).

There was a significant decrease in the WOMAC scores for pain, stiffness, and physical function when evaluations at 1 and 4 weeks were compared with pre-treatment in the group who received topical glucosamine; there was no difference between pre-treatment and 12 weeks in WOMAC scores for any of the three parameters (Table 2).

In the placebo group also, a significant improvement was observed in the WOMAC scores for pain, stiffness, and physical function at 1 and 4 weeks as compared with pre-treatment, whereas no significant difference was seen at 12 weeks compared to pre-treatment values (Table 3).

Table 1. Demographic and radiologic characteristics of both groups and their pre-treatment WOMAC scores.

	Drug group (n=27)	Placebo group (n=22)	P
Age (years) (Median (range))	58 (46-77)	61.5 (49-82)	0.27
Pain duration (Median (range))	35.6 (46-77)	36.0 (49-82)	0.42
Radiologic stage (Median (range))	2.8 (2-3)	2.7 (2-3)	0.32
VAS (0-10) (Median (range))	6 (4-9)	6 (5-8)	0.52
BMI (kg/m2) (Median (range))	32.3 (22-35)	31.7 (21-32)	0.56
WOMAC pain (Median (range))	15.0 (9-22)	15 (8-21)	0.67
WOMAC stiffness (Median (range))	5 (2-9)	5.5 (2-10)	0.57
WOMAC physical function (Median (range))	50 (35-70)	57.5 (38-74)	0.62

VAS: Visual Analogue Scale, BMI: Body Mass Index, WOMAC: Western Ontario and McMaster Osteoarthritis Index.

Table 2. WOMAC scores of placebo group and P values at 1, 4, and 12 weeks compared to pre-treatment values.

	Pre-treatment	1 week	4 weeks	12 weeks
WOMAC pain	15 (9-22)	11 (6-22)	10 (5-25)	14 (8-21)
P		<0.001	<0.001	0.168
WOMAC stiffness	5 (2-9)	4 (2-7)	3 (2-7)	5 (2-8)
P		0.014	<0.001	0.078
WOMAC physical function	50 (35-70)	43 (21-74)	38 (17-75)	53 (42-74)
P		<0.001	<0.001	0.380

WOMAC: Western Ontario and McMaster Osteoarthritis Index.
Friedman and Wilcoxon tests were used for intra-group comparisons.

Table 3. WOMAC scores of placebo group and P values at 1, 4, and 12 weeks compared to pre-treatment values.

	Pre-treatment	1 week	4 weeks	12 weeks
WOMAC pain	15 (8-21)	11 (6-17)	11 (5-18)	14.5 (8-25)
P		<0.001	0.001	0.824
WOMAC stiffness	5 (2-10)	3 (2-10)	4 (2-8)	5 (2-9)
P		0.001	0.008	0.310
WOMAC physical function	57.5 (38-74)	43.5 (25-78)	44 (18-76)	57.5 (36-74)
P		0.001	<0.001	0.382

WOMAC: Western Ontario and McMaster Osteoarthritis Index.
Friedman and Wilcoxon tests were used for intra-group comparisons.

When the topical glucosamine and placebo groups were compared, no significant difference was shown between the two groups regarding the WOMAC scores for pain, stiffness, and physical function in any of the evaluations (Table 4).

In terms of side effects of the drug, one of the patients complained about temporary erythema that did not affect the patient's participation in the study.

Discussion

Chondroitin and glucosamine sulfate, which are the structural components of joint cartilage, have an essential role in the continuity and repair of the cartilage. In animal studies, it has been demonstrated that glucosamine sulfate slows down cartilage destruction by means of stimulating production of glucosamine and proteoglycans, as well as causing inhibition of proteolytic enzymes (15). There are various studies which have shown that oral glucosamine sulfate slows down cartilage destruction in patients with OA. In a study conducted by Reginster et al. (16), 1500 mg of glucosamine was applied to 212 patients with OA, and significantly less joint space narrowing as compared to placebo was shown. Glucosamine sulfate can provide symptomatic improvement in patients with OA. The Glucosamine Unum In Die Efficacy (GUIDE) study was independently carried out in thirteen centers throughout Europe; glucosamine therapy was applied to 318 patients with OA with a dose of 1500 mg/day, and its efficacy in relieving pain and improving functional status was found to be superior to acetaminophen and placebo (17), also in the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) study the results were similar to placebo (18). In another study (19), it was concluded that glucosamine sulfate and chondroitin sulfate combination may be effective in a subgroup of patients with moderate to severe pain. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended in many guidelines regarding the management of mild to moderate OA of the knee or hand, particularly in patients with few affected joints and/or a history of sensitivity to oral NSAIDs (20). On the other hand, there are a limited number of studies about topical glucosamine sulfate for the treatment of OA. To the best of our knowledge, there is only one study in the literature reporting a significant decrease in VAS scores in both placebo and treatment groups from the first day of treatment, and this decrease was more pronounced in the treatment group (21). A significant decrease on the first day of treatment indicates that topical application has a more rapid effect. This rapid improvement in pain was attributed to the analgesic effect of mint and camphor in the topical drug. In the same study, significant improvement was observed in the glucosamine sulfate group as compared to the placebo group after 8 weeks of topical application.

In the present study, topical glucosamine-chondroitin sulfate was not superior to placebo. Significant improvement was observed both in the group who received topical glucosamine sulfate and in the placebo group regarding the WOMAC scores at 1 and 4 weeks compared to pre-treatment. However, this improvement was not observed at 12 weeks.

In this study, the patients were applied physical therapy at the same time. Hence, physical therapy and also the analgesic effect of aromatic oils included in the topical preparation as well as the placebo effect of massaging can be effective in the improvement. The lack of a difference between the drug group and the placebo group regarding the WOMAC scores may indicate the inefficacy of topical glucosamine sulfate application.

The limitations of the present study were as follows: the simultaneous physical therapy application to the patients, which might have concealed the drug effect; the effect of aromatic oils and massage effect of the cream; and the limited number of study subjects. In addition, drug concentration after topical application was not determined.

In conclusion, in the present study, we determined that topical glucosamine-chondroitin sulfate concomitantly applied with physical therapy in the treatment of knee OA is not superior to placebo. Long-term studies on larger samples should be conducted to investigate the efficacy of topical glucosamine application.

Conflict of Interest:

Authors reported no conflicts of interest.

Table 4. Comparison of WOMAC scores and P values between two groups.

	Drug	Placebo	P
WOMAC pain 1 week	11.41±3.3	10.86±3.09	0.56
WOMAC stiffness 1 week	4.22±1.5	3.68±1.96	0.28
WOMAC physical function 1 week	43.44±12.0	45.23±12.3	0.61
WOMAC pain 4 weeks	11.11±4.8	10.68±3.99	0.74
WOMAC stiffness 4 weeks	3.52±1.4	3.77±1.71	0.58
WOMAC physical function 4 weeks	41.44±12.0	43.73±13.6	0.54
WOMAC pain 12 weeks	14.17±3.2	15.36±4.79	0.37
WOMAC stiffness 12 weeks	4.48±1.6	4.79±2.25	0.63
WOMAC physical function 12 weeks	54.30±8.6	56.43±10.33	0.50

WOMAC: Western Ontario and McMaster Osteoarthritis Index.
Mann-Whitney U test was used.

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