Drug Corner

A Pilot Observational Study of Topical Glucosamine and Chondroitin Sulfate in Patients with Knee Osteoarthritis

Moazzam Jah[1], Anish Desai[2]

Objective : To determine the efficacy and safety of topical glucosamine and chondroitin sulfate in the treatment of knee Osteoarthritis (OA).

Materials and Methods : Thirty-three patients diagnosed with knee OA were included in the study. Subjects received topical application of glucosamine and chondroitin sulfate on the affected knee two times a day for four weeks. 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. The patients were assessed before the treatment and four weeks after the initiation of the treatment.

Results : The WOMAC scores for pain, stiffness, and function, as well as the VAS score, were significantly improved (P<0.01) in subjects at week four compared to the baseline. There was a 44.02% improvement in the total WOMAC scores and a 51.11% improvement in the VAS scores with glucosamine and chondroitin sulfate topical gel after four weeks.

Conclusion : Topical glucosamine and chondroitin sulfate are safe and effective in improving knee pain, stiffness, and physical function in knee OA.

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Key words **: Glucosamine, Chondroitin, Topical, Osteoarthritis.**

Osteoarthritis (OA) is a common joint condition characterized by the degradation of joint cartilage. Moreover, OA is one of the causes of morbidity, which significantly impairs the individual's daily activities and social performance. According to global estimates, 9.6% of men and 18% of women over 60 have symptomatic OA. Oral treatments for patients with mild to moderate OA pain include paracetamol, diclofenac, and other NSAIDs.NSAIDs have been shown to be effective in OA patients. Nonetheless, they are linked to dose–duration- and age-related risks of gastrointestinal, cardiovascular, renal, hematological, and hepatic side effects and other drug interactions[1]. To avoid these complications, the National Institute of Health and Clinical Excellence (NICE) guidelines for managing OA and the American Geriatrics Society guidelines for managing chronic pain in the elderly advocate avoiding oral NSAIDs as much as possible.There has been increased interest in localized treatments for OA, ie, therapies administered to the joint or in the region of the joint such as topical treatment.NSAID exposure can be reduced by topical NSAIDs, or NSAIDs can be entirely avoided by topical salicylates or capsaicin. However, clinical trial data suggest that topical NSAIDs act locally at the application site rather than through systemic absorption and distribution.Analgesic effects of diclofenac gel in the knee are probably a product of enhanced concentrations in skin and subcutaneous tissues at the application site. Therapeutic concentrations in synovial tissue and fluid of the knee are not achieved with diclofenac gel or patch[2,3]. Preclinical data suggest that topical NSAIDs, including diclofenac and piroxicam, penetrate to a depth of 3-4 cm, which might not be adequate to reach the synovial structures of the knee. In the absence of significant tissue penetration or a significant anti-inflammatory effect, capsaicin has shown less efficacy than either topical NSAIDs or salicylates and is associated with application site pain and nerve damage[4].

It has been demonstrated that glucosamine and chondroitin sulfate reduces pain and stiffness associated with OA. Glucosamine and chondroitin sulfate, the structural components of joint cartilage, have an essential role in the continuity and repair of

[1]MS (Ortho), Consultant Orthopaedic surgeon, Arthroscopy and sports injury clinic, Nishat Hospital, Lucknow

[2]MD, FCP, PGDHEP, Clinical Pharmacologist & Nutraceutical, Physician, Founder & CEO, IntelliMed Healthcare Solutions, Mumbai

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the cartilage. The glucosamine and chondroitin sulfate combination suppress Interleukin-1 (IL-1) induced gene expression of nitric oxide synthase(NOS), cyclooxygenase-2 (COX- 2), and Nuclear factor-κB (NF-κB) in cartilage explants. This leads to reduced production of NO and Prostaglandin-E2 (PGE2), two mediators that are responsible for the cell death of chondrocytes and inflammatory reactions. Inhibition of the IL-1 beta-induced NF-κB pathway by glucosamine sulfate results in reduced synthesis of the COX-2 enzyme (Fig 1). Chondroitin sulfate diminishes the nuclear translocation of NF-κB, which reduces the formation of proinflammatory cytokines IL- 1beta and TNF-alpha and proinflammatory enzymes such as COX-2and NOS-2[5].Glucosamine sulfate possesses antioxidant properties, thereby suppressing high concentrations of Reactive Oxygen Species (ROS), which cause the breakdown of cartilage due to the presence of free radicals and pro-oxidants. Increased synovial fluid IL-1ß, IL-6, and TNF-α levels are essential findings of inflammation in the development of osteoarthritis. Glucosamine-chondroitin combination significantly decreases the synovial fluid IL-1β and IL-6 levels. The decrease in the levels of these mediators in the synovial fluids indicates the anti-inflammatory effect of glucosamine-chondroitin sulfate[6,7].

In accordance with the recommendations of the European League of Associations for Rheumatology and The Osteoarthritis Research Society International on the treatment of knee OA, glucosamine and chondroitin can be used as symptomatic slow-acting drugs for OA. Only a small percentage is available to the joint when administered orally, glucosamine and chondroitin sulfate daily. With the topical route, rapid onset of action is achieved due to the absorption of glucosamine and chondroitin sulfate into the bloodstream and direct uptake into localjoint tissue. Moreover, a high and sustainable level of glucosamine in the blood is achieved through skin delivery and can provide means for cartilage regeneration in OA[8-10]. Studies have shown an adequate amount of glucosamine in the subject's synovial fluid by skin absorption in one to three hours after application. Furthermore, themean glucosamine concentration was100.56ng/ml in the synovial fluid[11]. Fig 2 shows the penetration of glucosamine and chondroitin sulfate in the knee's synovial fluid with OA.The study aimed to determine the efficacy and safety of topical emulgel containing glucosamine and chondroitin sulfate in the treatment of knee OA.

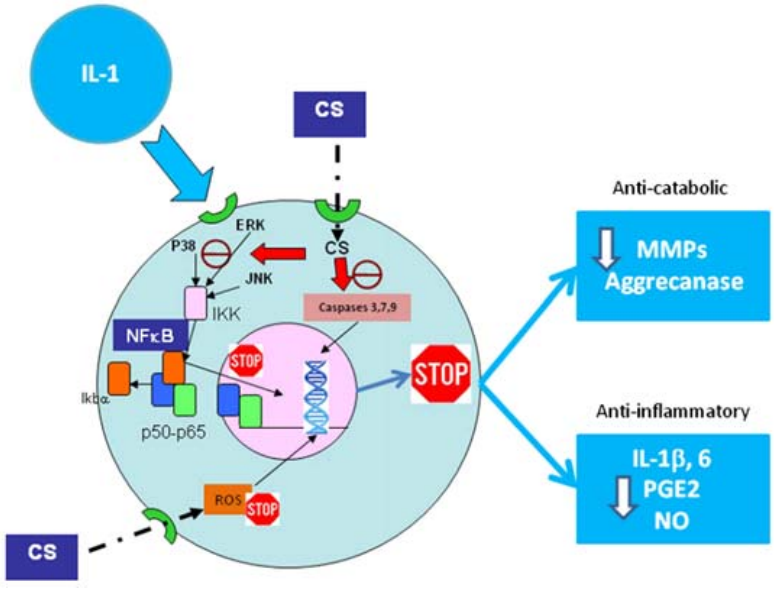

Fig 1 — Schematic representation of the cellular mechanisms of action of chondroitin sulfate (CS). ERK, extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinases; IKK, IκB kinase; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cell; ROS, reactive oxygen species; MMP, matrix metalloproteases; IL, interleukin; PGE2, prostaglandin E2; NO, nitric oxide[12]

Materials and Methods

Study Design :

The Suraksha Institutional Ethics Committee approved the study protocol and related materials in compliance with ICMR (Indian Council of Medical Research), New Drugs and Clinical Trials Rules, 2019, ICH GCP, and the declaration of Helsinki. The present study was designed as a pilot observational study involving volunteers with OA of the knee. Thirty-three patients diagnosed with knee OA as per the American College of Rheumatology (ACR) criteria were included in the study. Participants recruited were

men and women from 19 to 75 years of age who had been diagnosed with knee OA and had a history of mild to moderate pain in the knee during the painful knee movement during the last month. Pregnant or lactating women or subjects with uncontrolled diabetes and hypertension; any severe cardiac, renal, and hepatic disease or end-organ damage were not included in the study. Exclusion criteria included a history of allergy to herbal products or NSAIDs and acute knee joint trauma. Written informed consent was obtained from all participants before the commencement of the study.

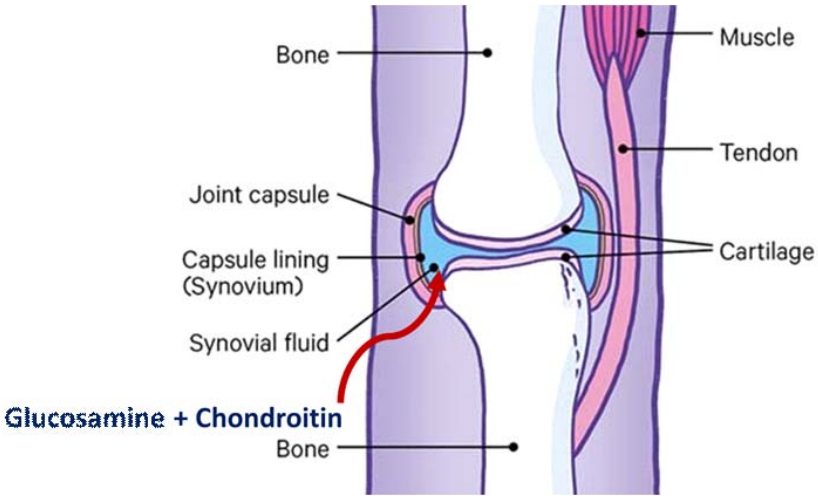

Fig 2 — Penetration of glucosamine + chondroitin into the synovial fluid of OA knee

Study Intervention

An aqueous gel containing Glucosamine Sulfate 0.05 mg, Chondroitin sulfate 2mg, Curcumin (Curcuma longa) 0.02 mg, Guggul (Boswellia serrata) 1.5 mg, Ginger (Zingiber officinale) 0.1 mg, Oil of wintergreen 50 mg, and Menthol 10 mg which was developed and supplied by Stabicon Life Sciences Pvt Ltd and marketed by Universal NutriScience.The emulgel was developed using VesiFuzeEmulgel^{TM*} technology which consists of an aqueous gel containing tiny lipid vesicles in which drugs are embedded and is designed to pass through the skin into the joint with a permeability enhancer.Subjects were asked to use the topical application (2 g single dose treatment) on the affected knee two times a day for four weeks.

Outcome measures

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. The patients were assessed before the treatment and four weeks after the initiation of the treatment.

Statistical Analysis

A primary database was created in validated Microsoft Excel spreadsheets while processing registration forms received from the study sites. The data were analyzed using statistical software SAS® version 9.1 Inc, CARY, USA. Outcomes were assessed using an unpaired Student t-test. Two-tailed P-values <0.01 were considered statistically significant. All deviations from the final version of the

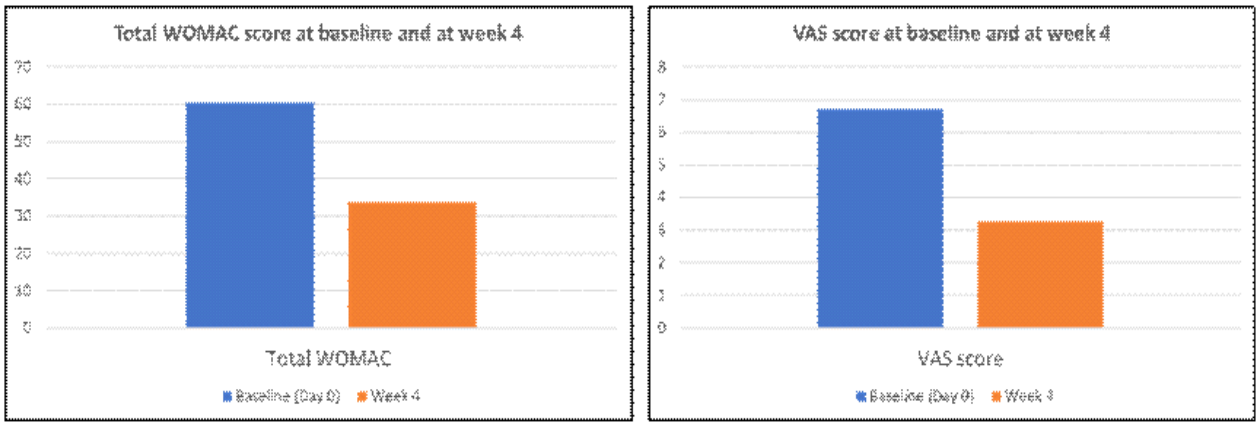

Fig 3 — Improvement in the WOMAC and VAS scores at baseline and at week 4.

statistical analysis plan were described and substantiated in the final manuscript. Descriptive statistics were presented for all continuous efficacy and safety indicators obtained during the study, and frequency distribution was presented for all categorical variables available in the data.

Results

The subjects comprised 45.45% females and 54.54% males, with a mean age of 57±8.59 years old. The clinical assessment proved that all the included patients suffered knee pain.There was a significant improvement (P< 0.01) in the WOMAC scores for pain, stiffness, and physical function and VAS scores at four weeks when compared to baseline (day 0) with Glucosamine sulfate and Chondroitin sulfate. At baseline,WOMAC for pain averaged 11.96 ± 0.73, whereas post-4-week treatment averaged 6.03 ± 0.57. The percent improvement in the WOMAC score for pain was 49.58% (P< 0.01). The average WOMAC score for stiffness at baseline was 5.57 ± 0.36, and at four weeks was 3.03 + 0.29, which shows a 45.60% (P< 0.01) change in the scores.The average WOMAC score for physical function at baseline was 43.30 + 2.46, whereas at four weeks was 22.78 + 2.08, which shows a 47.39% (P< 0.01)improvement in the scores. The total WOMAC scores at baseline were observed to be 60.46 + 2.95, and at four weeks,33.84 + 2.76, which shows a 44.02% (P< 0.01) improvement in the total scores. At baseline,the VAS score was found to be 6.71± 0.34, and at four weeks was 3.28 ± 0.35, which is a 51.11% (P< 0.01)improvement in the scores. WOMAC scores and the VAS scores at the start and end of the treatment at four weeks of the topical gel are presented in Fig 3. The subjects reported no allergic or adverse reactions during or after the topical application.

Discussion

OA of the knee joint is a disorder characterized by multiple symptoms. This study evaluated the efficacy and safety of topical glucosamine and chondroitin sulfate in treating knee OA.The study focused on the outcome following the administration of the topical formulation by VAS score and WOMAC scores. Post four weeks after the treatment, there was a significant improvement of 49.58% in the WOMAC for pain, 45.60%improvement in the WOMAC for stiffness, 47.39% improvement in the WOMAC for physical function, and overall 44.02% improvement in the total WOMAC scores. In contrast, the VAS score improved by 51.11%. The percentage of improvement in the VAS and WOMAC scores is comparable with other studies. A study conducted by Tandon et al. showed similar results, with a significant decrease in the VAS score for pain at the end of treatment[13].

Similarly, a study by Erhan, Belgin, *et al* showed significant improvement in the WOMAC scores at four weeks with the group receiving topical glucosamine sulfate[14]. Hammad YH, *et al* showed that overall response and joint stiffness were better in the locally treated group compared to the orally treated group, which suggests that topical application of glucosamine and chondroitin sulfate is more effective than the oral route of administration in improving stiffness and function of the joint[15]. Moreover, topical administration's benefits include maximizing the drug's bioavailability, optimizing therapeutic efficacy, and minimizing side effects.Furthermore, a combination of glucosamine and chondroitin provides efficient pain relief at a similar level as tramadol, which is an analgesic.

The WOMAC subscale scores improved 42.9% for pain, 40.5% for stiffness, 39.3% for physical function, after four weeks of treatment for knee OA with topical diclofenac[16]. Moreover, one placebo-controlled trial investigating 2 weeks of treatment of knee OA with a topical diclofenac gel was conducted with the use of the WOMAC and found reductions in pain, stiffness and physical function of 37%, 17% and 26% respectively[17]. The percentage improvement in WOMAC subscale scores observed with topical diclofenac therapy (39.3% to 44.4%) are similar to those reported for oral diclofenac treatment (35% to 40%), whereas other trials of topical diclofenac showed 42% to 45% reductions in VAS pain intensity in OA[18]. Subsequently, the percentage improvement in WOMAC and VAS scores was found to be better in our study at week 4 with topical glucosamine and chondroitin sulfate treatment. However, long-term studies on larger samples should be conducted to investigate the efficacy of topical glucosamine and chondroitin treatment in OA.

Conclusion

In conclusion, this study showed topical glucosamine and chondroitin sulfate effectively improves pain, stiffness, and physical function in knee

OA. Moreover, this topical application can substantially benefit the management of OA symptomsin the knee. This formulation can benefit patients who cannot tolerate analgesics or NSAIDs to manage their symptoms. This study adds to the body of evidence that topical chondroitin sulfate and glucosamine sulfate should be positively considered for the symptomatic management of OA.

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Conflict of interest : The authors declare no conflict of interest.

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References

1 Sinusas K — Osteoarthritis: Diagnosis and Treatment. *Am Fam Physician* 2012; **85:** 49-56.
2 Altman RD, Barthel HR — Topical therapies for osteoarthritis. *Drugs* 2011; **71:** 1259-79.
3 Karrar S, Mackworth-Young C, Karrar S — Local Therapies for Osteoarthritis — An Update and a Review of the Literature. *Osteoarthr - Prog Basic Res Treat*. Epub ahead of print 1 July 2015. DOI: 10.5772/60557.
4 Fendrick AM, Greenberg BP — A review of the benefits and risks of nonsteroidal anti-inflammatory drugs in the management of mild-to-moderate osteoarthritis. *Osteopath Med Prim Care* 2009; **3:** 1.
5 Jerosch J. Effects of Glucosamine and Chondroitin Sulfate on Cartilage Metabolism in OA: Outlook on Other Nutrient Partners Especially Omega-3 Fatty Acids. *Int J Rheumatol* 2011; **2011:** 17.
6 Damlar Ý, Esen E, Tatli U — Effects of glucosamine-chondroitin combination on synovial fluid IL-1β, IL-6, TNF-α and PGE2 levels in internal derangements of temporomandibular joint. *Med Oral Patol Oral Cir Bucal* 2015; **20:** e278.
7 Teslim OA, Daniel AO, Nesto T — Comparative Effects of a Single Treatment Session Using Glucosamine Sulphate and Methyl Salicylate on Pain and Hamstring Flexibility of Patients with Knee Osteoarthritis. *http://www.sciencepublishinggroup.com* 2014; **2:** 40.
8 Reginster JY, Neuprez A, Lecart MP — Role of glucosamine in the treatment for osteoarthritis. *Rheumatol Int* 2012; **32:** 2959.
9 Roman-Blas JA, Castañeda S, Sánchez-Pernaute O — Combined Treatment With Chondroitin Sulfate and Glucosamine Sulfate Shows No Superiority Over Placebo for Reduction of Joint Pain and Functional Impairment in Patients With Knee Osteoarthritis: A Six-Month Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Arthritis Rheumatol* 2017; **69:** 77-85.
10 Theodosakis J, Grove ML, Cohen M — A Randomized, Double Blind, Placebo Controlled Trial of a Topical Cream Containing Glucosamine Sulfate, Chondroitin Sulfate, and Camphor for Osteoarthritis of the Knee [5] (multiple letters). *J Rheumatol* 2004; **31:** 826-7.
11 Kong M, Hashim KB, Lin P — Penetration of Topical Glucosamine Sulfate into the Synovial Fluid of Patients with Knee Osteoarthritis: A Nonrandomized, Open-Label, Single Dose, Bioavailability Study. *J Biosci Med* 2019; **07:** 76-90.
12 Henrotin Y, Lambert C — Chondroitin and Glucosamine in the Management of Osteoarthritis: An Update. *Curr Rheumatol Reports 2013 1510* 2013; **15:** 1-9.
13 Tandon N, Paul R, Kwatra G — A comparison of oral versus topical combination of glucosamine sulphate and diacerein in patients of grade 2 osteoarthritis. *Int J Res Orthop* 2021; **7:** 1104.
14 Medicine IP, Hospital RT, Medicine P — Sulfate in Knee Osteoarthritis Treated With Physical Placebo-Controlled Study. 2012; 194-9.
15 Hammad YH, Magid HR, Sobhy MM. Clinical and biochemical study of the comparative efficacy of topical versus oral glucosamine/chondroitin sulfate on osteoarthritis of the knee. *Egypt Rheumatol* 2015; **37:** 85-91.
16 Bookman AAM, Williams KSA, Shainhouse JZ — Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *CMAJ* 2004; **171:** 333-8.
17 Grace D, Rogers J, Skeith K — Topical diclofenac versus placebo: A double blind, randomized clinical trial in patients with osteoarthritis of the knee. *J Rheumatol* 1999; **26:** 2659-63.
18 Altman RD, Barkin RL — Topical therapy for osteoarthritis: Clinical and pharmacologic perspectives. *Postgrad Med* 2009; **121:** 139-47.