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# A comparison of oral versus topical combination of glucosamine sulphate and diacerein in patients of grade 2 osteoarthritis

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## ABSTRACT

**Background:** The study aimed to compare oral versus topical combination of glucosamine sulphate and diacerein in patients of grade 2 Osteoarthritis.
**Methods:** This was a prospective study of 70 patients with grade 2 osteoarthritis knee, randomly divided into 2 groups of 35 each. The first group was given oral 1500mg of glucosamine and 100mg of diacerein per day and second group was given topical preparation of 10% w/w glucosamine sulphate and 1% w/w diacerein to be applied twice. Both the groups were followed up at 1, 3, 6 and 12 weeks. At each follow up, Visual Analog Scale (VAS) and Lequesne et al scores were used as efficacy parameters. C-Reactive Protein (CRP) level was measured in the beginning and at the end of 12 weeks.
**Results:** Both the groups showed improvement in pain and joint function as depicted by VAS score and Lequesne index however the difference was not statistically significant. The decrease in CRP value was significant in oral group (p value<0.001) but not in topical group (p value of 0.047). Paracetamol demand was slightly higher in topical group however the difference was not significant.
**Conclusions:** Glucosamine sulphate and diacerein combination are effective in improving pain, stiffness and function in patients of grade 2 osteoarthritis knee. However, the efficacy of glucosamine sulphate and diacerein combination- oral as well as topical, in improving pain and stiffness is similar- there is no superiority of one over the other.

**Keywords:** Glucosamine sulphate, Diacerein, Knee osteoarthritis

## INTRODUCTION

Musculoskeletal conditions are a diverse group with regard to pathophysiology but are linked anatomically and by their association with pain and impaired physical function. They encompass a spectrum of conditions, from those of acute onset and short duration to lifelong disorders, including osteoarthritis, rheumatoid arthritis, osteoporosis, and low back pain. The prevalence of many of these conditions increases markedly with age, and many are affected by lifestyle factors, such as obesity and lack of physical activity. The increasing number of older people and the changes in lifestyle throughout the world mean that the burden on people and society will increase dramatically. This has been recognized by the United Nations and WHO, with their endorsement of Bone and Joint Decade 2000–2010.[1] Osteoarthritis (OA) is a chronic disorder of synovial joints in which there is progressive softening and disintegration of articular cartilage accompanied by new growth of cartilage and bone at the joint margins (osteophytes), cyst formation and sclerosis in the subchondral bone, mild synovitis and capsular fibrosis. It is also known as degenerative arthritis, which commonly affects the hands, feet, spine, and large weight-bearing joints, such as the hips and knees.[2]

In India, OA is the most common musculoskeletal problem in individuals above 50 years of age. Pal et al conducted a study on epidemiology of knee osteoarthritis in India in 2016.[3] According to this study, the prevalence of knee OA was found to be 28.7%, it was higher in villages and big cities as compared to towns and small cities. OA of the knees was found to be more prevalent in females (31.6%) than in males (28.1%). Also, it was found that prevalence of OA knees increased with increase in body mass index (BMI). Knee OA prevalence was significantly lower in underweight people (28%) as compared to normal weight and obese participants (33%).

Human joints are cushioned by cartilages and lined by synovial fluid such that we can move and twist our joint freely in any direction. The principal lubricating substances in cartilage, ligaments, tendons, synovial fluid and mucous membranes are chondroitin sulphate and glycosaminoglycans (GAGs). Glucosamine is a component of GAGs that stimulates proteoglycans to produce proteoglycans and increase the production of hyaluronic acid resupply of synovial fluid to act as a lubricant, while chondroitin sulphate absorbs water into cartilage and acts as a shock absorber. The proteoglycans are subjected to continuous metabolic turnover, undergoing constant breakdown and re-synthesis. The imbalances in these processes that occur with ageing or with other medical conditions are partially responsible for arthritis. In OA, the synthesis of proteoglycans and collagen continues to rise in proportion to the severity of the lesion, leading to degenerative changes.[4]

For decades, the traditional pharmacological management for OA has been symptomatic mainly non-steroidal anti-inflammatory drugs (NSAIDs), in spite of several side effects like peptic ulcer disease, renal failure and haemorrhage. Dietary supplements like glucosamine sulphate are nowadays being used increasingly in management of OA. Glucosamine or 2-amino-2-deoxy-D-glucose is an amino monosaccharide derived principally from chitin, a compound found in exoskeleton of certain marine invertebrates. Due to its basic role in cartilage and synovial fluid synthesis, glucosamine—administered as glucosamine sulphate (GlcN·S) or hydrochloride (GlcN·HCl)—has been tested in numerous clinical OA trials and the effects have been summarized in reviews and meta-analyses. After oral administration, glucosamine reaches articular cartilage and is preferentially incorporated by the chondrocytes into the components of the glycosaminoglycan chains in intact cartilage, stimulates the synthesis of physiological proteoglycans, and decreases the activity of catabolic enzymes like matrix metalloproteinases (MMPs).[5] The glucosamine and chondroitin sulphate combination suppresses IL-1-induced gene expression of NO and PGE2, two mediators responsible for the cell death of chondrocytes and inflammatory reactions.[6] Similarly Diacerein, a drug with interleukin-1beta--inhibitory activity in vitro, is being used for treating OA. According to a study, Diacerein was shown to be an effective treatment for symptoms in patients of knee OA.[7]

Contradictory researches have been published regarding the efficacy of glucosamine and chondroitin sulphate in OA. Some researchers found that glucosamine and diacerein has a questionable value in the management of OA.[8,9] One of the studies showed that there is no role of glucosamine hydrochloride in pain management, although sulphate formulation has a moderate effect and there is no evidence that nutraceuticals or viscosupplementation influences OA's natural progression.[8] Another study compared clinical outcomes of placebo versus glucosamine, glucosamine versus NSAIDs, diacerein versus placebo, diacerein versus NSAIDs based on VAS and Lequesne scores and showed no statistically significant difference between the two.[9]

However, some of the studies show that these agents seem to reduce pain and improve function.[10-13] Studies by Braham et al and Cohen et al showed improved pain scores (VAS and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale) with oral and topical glucosamine sulphate respectively.[10,11] Brahmachari et al in his study demonstrated efficacy of diacerein in early knee osteoarthritis by highly significant reductions in VAS and WOMAC pain scores and significantly lower requirement of rescue medication.[12]

The aim of the study was to compare the efficacy between the oral and topical glucosamine and diacerein combination in patients with grade 2 knee osteoarthritis. A randomised controlled trial was planned using VAS and Lequesne et al scores as efficacy parameters and CRP as a parameter for biochemical evaluation.

## METHODS

Seventy patients (males and females) aged 40 and above, diagnosed as grade 2 OA of the knee based on Kellgren and Lawrence scale were included in the study.[14] The following exclusion criteria were considered on enrolment: rheumatologic disorders causing erosive arthritis of knee; cases with severe arthritis causing moderate or marked effusion of knee; regular requirement of analgesics for conditions other than OA; use of oral/ topical glucosamine and diacerein in previous 6 weeks; intra articular injection of steroids or hyaluronic acid in previous 6 months; patients with a history of gastrointestinal bleed or peptic ulcer disease; other grades of Osteoarthritis (grade 0, 1, 3, 4).

### *Study design*

This was a prospective randomised controlled study conducted in the Department of Orthopaedics, at Christian Medical College and Hospital, Ludhiana, Punjab, over a period of one and a half years starting from 1st December 2017 till May 2019. It was approved by institutional research and ethics committee. A total of 70 patients with

grade 2 Osteoarthritis seen at the Orthopaedic OPD during the study period were included after taking an informed consent. Clinical diagnosis was confirmed with radiography. Following radiological confirmation of OA, a detailed clinical evaluation was performed.

***Treatment protocol***

A total of 85 patients were screened out of which 15 failed to meet inclusion/ exclusion criteria. The remaining 70 were enrolled in the study and divided into 2 groups of 35 each by block randomisation of size 4. The first group was given oral 1500mg of glucosamine and 100mg of diacerein per day and second group was given topical preparation of 10% w/w glucosamine sulphate and 1% w/w diacerein to be applied twice daily. Tablet paracetamol (650 mg) BD was given as an acute pain relief for rescue mechanism. The patients were asked to keep a hard copy record of each drug intake. CRP was measured in the beginning and at the end of treatment course. Along with this, physiotherapy and lifestyle modifications were recommended to patients of both the groups. All the participants were followed up at 1 week, 3 weeks, 6 weeks and 12 weeks treatment course. At each follow up, clinical evaluation was done. Each patient was asked for any adverse event experienced since last visit. The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and declaration of Helsinki (1975), as received in 2008.

***Efficacy parameters***

Symptoms of knee joint pain were evaluated at the first visit and at all subsequent visits by Visual Analog Scale (VAS) and Lequesne et al index for severity of OA.

***Biochemical evaluation***

Estimation of CRP levels was done in the beginning and at 12 weeks to assess the anti-inflammatory effect of glucosamine sulphate and diacerein on Osteoarthritis.

***Statistical analysis***

The sample size was calculated using the mean and standard deviation of Lequesne et al score is N=35 for each group by using the formula

$$N = 2(Z1 - \alpha \div 2 + Z1 - \beta)2 \times \sigma 2 \div (\mu 1 - \mu 2)2$$

Where,

Z1-α/2=1.96, is standard normal deviate at type 1 error α=0.05,

Z1-β=0.84 is standard normal deviate at type 2 error β=0.20,

σ is standard deviation and μ1 and μ2 are the means in Group1 and Group 2 respectively.

In the descriptive analysis, continuous variables were expressed as Mean± S.D. and categorical variables were expressed as count (percentage). Chi-square was used to compare the categorical variables between groups or Fisher exact test was used when expected count was <5. Independent t-test or Mann Whitney U test was used to compare continuous variables between two groups. ANOVA for repeated measures was used to obtain the improvement between different intervals of time. The significance level was set at $p<0.05$. All statistical analysis was performed using Statistical package for social sciences (SPSS), version 21.0. Armonk, NY: IBM corp.

## RESULTS

A total of 70 patients with grade 2 osteoarthritis on Kellgren and Lawrence scale were included in the study. All the participants completed the 12 week treatment course. No significant difference was found between the two groups as regards the age, gender, body mass index and duration of symptoms (Table 1).

**Table 1: Baseline characteristics of the patients.**

| Characteristic | Oral group n=35 | Topical group n=35 | P value |
|---|---|---|---|
| **Age (years)** | 53±9.7 | 55±8.1 | 0.298 |
| **Gender (%)** | Male- 17.1<br>Female- 82.9 | Male- 31.4<br>Female- 68.6 | 0.163 |
| **Duration of symptoms (months)** | 8±4.7 | 6±4.1 | 0.118 |
| **Body mass index (kg/m2)** | 23.6±1.61 | 23.5±1.52 | 0.766 |

**Table 2: Comparison of VAS between the groups.**

| VAS | Oral | Topical | P value |
|---|---|---|---|
| **Baseline** | 5.20±0.72 | 5.23±0.84 | 0.879 |
| **1 week** | 5.11±0.80 | 5.14±0.91 | 0.889 |
| **3 weeks** | 4.23±0.73 | 4.26±0.82 | 0.878 |
| **6 weeks** | 3.94±0.77 | 4.06±0.84 | 0.553 |
| **12 weeks** | 3.49±0.56 | 3.60±0.85 | 0.508 |

***Change in VAS scores***

Visual analog scale was used for comparing symptomatic pain relief in patients enrolled in the study. VAS score was calculated in the beginning and at each subsequent visit (Table 2).

***Change in Lequesne et al scores***

Lequesne et al score was used as an efficacy parameter. The mean Lequesne et al score in the beginning of treatment was 6.40 in oral group and 6.33 in topical group (Table 3).

**Table 3: Comparison of Lequesne scores between the groups.**

| Lequesne score | Oral | Topical | P value |
|---|---|---|---|
| **Baseline** | 6.40±0.77 | 6.33±0.95 | 0.732 |
| **1 week** | 6.36±0.76 | 6.34±0.75 | 0.937 |
| **3 weeks** | 5.89±0.80 | 5.81±0.77 | 0.704 |
| **6 weeks** | 5.79±0.82 | 5.66±0.75 | 0.494 |
| **12 weeks** | 5.47±0.77 | 5.43±0.77 | 0.816 |

**Table 4: Efficacy parameters before and after treatment.**

| Characteristic | Knee OA patients according to treatment groups | | | | | |
|---|---|---|---|---|---|---|
| | Oral group | | | Topical group | | |
| | Base line | 12 week | P | Base line | 12 week | P |
| **VAS score** | 5.2± 0.72 | 3.4± 0.56 | <0. 001 | 5.2± 0.84 | 3.6± 0.85 | <0. 001 |
| **Lequesne et al acore** | 6.4± 0.77 | 5.4± 0.77 | <0. 001 | 6.3± 0.95 | 5.4± 0.77 | <0. 001 |

**Table 5: CRP value before and after treatment.**

| | Oral group | | Topical group | |
|---|---|---|---|---|
| | Median (IQR) | P value | Median (IQR) | P value |
| **Baseline** | 4.3 (2.3-6.5) | <0.001 | 3.2 (2.3-4.7) | 0.047 |
| **At week 12** | 4.2 (2.1-6.4) | | 3.0 (2.3-4.7) | |

**Table 6: Comparison of total dose of paracetamol between the groups.**

| | Oral (Mean±SD) | Topical (Mean±SD) | P value |
|---|---|---|---|
| **Total dose (gms)** | 9.9±1.31 | 10.6±1.85 | 0.086 |

Both the efficacy parameters were then compared before and after treatment (Table 4).

***Change in CRP***

Serum CRP levels were measured in the beginning and at the end of treatment for comparing the efficacy of oral and topical drugs. A significant decrease was found in oral group whereas no significant reduction was found in topical group (Table 5).

***Paracetamol dose requirement in two groups***

No significant difference was found in paracetamol dose requirement in the two groups. The total paracetamol requirement in oral group was 9.91 grams during the course of treatment while it was 10.58 grams in topical group. (p value of 0.086) (Table 6).

*Adverse effects*

There were no adverse events noted by the patients.

## DISCUSSION

The present study was carried out to compare oral versus topical combination of glucosamine sulphate and diacerein in patients of grade 2 osteoarthritis. It was a prospective study that included 70 patients with a follow up of 12 weeks. The included patients were randomly divided into 2 groups, each of 35 patients. One group took oral and the second group took topical combination of glucosamine sulphate and diacerein for 12 weeks. The study focused on outcome following administration of the drugs measuring pain status by VAS score and Lequesne et al index. Also, the biochemical evaluation was done by measuring CRP levels in the beginning and at the end of the treatment to assess the anti-inflammatory effect of the drugs on osteoarthritis process.

In our study, we prescribed 1500 mg of glucosamine and 100mg of diacerein per day for oral group and a topical preparation of 10% w/w glucosamine sulphate and 1% w/w diacerein to be applied twice daily for topical group. Most currently available glucosamine based drugs and supplements are taken at a dosage of 1500 mg daily. Similarly an emulsion of Glucosamine is available. According to a study, a 10% (w/w) Glucosamine is able to provide enzymes with a sufficient amount of substrate for their cartilage regeneration and rehabilitation processes.[15] Taking into account both efficacy and safety, the optimal daily dosage of diacerein for patients with knee OA is 100 mg/day (50 mg twice daily).[7]

The mean VAS score in our study was 5.2 in oral as well as topical group in the beginning of treatment. Both the groups showed a decrease in VAS pain score at the end of treatment. It decreased to 3.49 in oral group and 3.60 in topical group. A study by Hammad et al also observed a decrease in VAS score in oral as well as topical groups.[13] Other studies where glucosamine and diacerein have been compared with other drugs also show a decrease in VAS pain score at the end of treatment.[16-18]

Also, a decrease in Lequesne et al index was found in oral as well as topical group. The mean score in the beginning of treatment was 6.40 in oral group and 6.33 in topical group. This score decreased to 5.47 in oral and 5.43 in topical group at the end of treatment. Similar studies also show a decrease in Lequesne et al score after the use of glucosamine and diacerein.[19,20] A randomized, double-blind, placebo-controlled study using acetaminophen as a comparator by Herrero-Beaumont et al on glucosamine sulphate in the treatment of knee osteoarthritis symptoms measured 6 month change in Lequesne index as the

primary outcome.[19] There was a change of almost -2 with placebo treatment, but the change was -3.1 with glucosamine sulphate (p=0.032 versus placebo). Similarly, a double blind randomised controlled study was done by Louthrenoo et al on efficacy, safety and carry-over effect of diacerein in treatment of painful knee osteoarthritis.[20] The study concluded that diacerein was as effective as piroxicam in reducing pain and improving function but, unlike piroxicam, displayed a carry-over effect and a better safety profile.

The study results show that glucosamine sulphate and diacerein combination are effective in improving pain, stiffness and function in patients of grade 2 osteoarthritis knee. The efficacy of glucosamine sulphate and diacerein combination- oral as well as topical, in improving pain and stiffness is similar.

Previous studies have demonstrated relation between osteoarthritis progression and inflammation as demonstrated by raised CRP levels.[21,22] Levels of CRP were significantly associated with pain and decreased physical function.[23] Our study showed a decrease in CRP values in both oral (4.3 to 4.2) as well as topical (3.2 to 3.0) group. The decrease in CRP value in oral group was significant (p<0.001). A study by Hammad et al compared CRP levels in patients before and after starting oral and topical combination of glucosamine sulphate and chondroitin sulphate, showing a decrease in CRP values in oral as well as topical group.[13]

Although the study shows that glucosamine sulphate and diacerein are effective in improving pain, stiffness and function, there were few limitations of the study. It was a single centre study with small sample size and a short follow up. A larger study with long term follow up may lower Lequesne et al scores further and improve health status.

## CONCLUSION

Glucosamine sulphate and diacerein combination are effective in improving pain, stiffness and function in patients of grade 2 osteoarthritis knee. The efficacy of glucosamine sulphate and diacerein combination- oral as well as topical, in improving pain and stiffness is similar- there is no superiority of one over the other. Although the oral drug has shown slightly better effect in reducing serum CRP levels and thus inflammation in patients with knee osteoarthritis, there was no difference between the two groups on the basis of pain scores.

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