# Effects of glucosamine sulfate on primary knee osteoarthritis

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**Abstrac**t: Osteoarthritis, a degenerated joint disease, is the commonest condition to affect the joints, paracetamol and NSAID$^{s}$ are widely used. These drugs do not improve the underlying pathology of the disease. Glucosamine sulfate a chondroprotective agent is now used frequently with contradictory efficacy.Randomized, double blind, parallel, placebo controlled study of oral glucosamine sulphate (500mg) three times daily in total 44 patients with knee osteoarthritis for 6 weeks. Clinical parameters for pain, swelling, mobility and Lequesne's index were recorded. Occurrence of side-effects, compliance and use of rescue medicine (paracetamol tablets) were noted. Analysis of the data shows glucosamine sulfate significantly decreased pain; swelling as compared to placebo.There was a significant improvement in joint mobility and decrease in Lequesne's index from the basal value at the end of 6 weeks in glucosamine sulfate group. Except for mild GIT upset glucosamine sulfate was well tolerated, there was a decrease use of paracetamol tablets (rescue medicine) at the end of 6 weeks in glucosamine group. Oral administration of glucosamine sulfate was found to be significantly effective in controlling pain, swelling and improving the mobility in osteoarthritis of knee.
**Keywords:** Osteoarthritis, glucosamine sulfate, knee joint.

## Introduction

Osteoarthritis is the most common joint disease and is the major cause of morbidity and disability in the elderly. The degenerated process first affects the articular cartilage[1]. In osteoarthritis histopathological changes are obvious but not appropriate for living subjects and surveys rely on radiographic features for definition and assessment of severity, of the various radiographic criteria the most widely employed are those of kellgren and Lawrence [2]. Epidemiological studies using radiographic assessment of osteoarthritis indicate that by the midlife (55yrs) approximately 80% of male and female population will be affected [3]

No cure exists for osteoarthritis at present, treatment is aimed at reducing pain, maintaining mobility and minimizing disability, various NSAID$^{S}$ are widely used, there is limited evidence that they actually improve the underline pathology of the disease and they are associate with side-effects. A number of pharmacological agents have been shown to reduce proteolytic cartilage breakdown and/or stimulates matrix repair inanimal models of osteoarthritis, such agents are called "chondroprotective drugs" [4]. Glucosamine sulfate is one of the chondroprotective agent used now a days in the management of osteoarthritis [5]. Some studies have shown no efficacy of glucosamine [6], while others found to be beneficial [7], so this randomized, double blind placebo controlled parallel study undertaken to see the effect of glucosamine sulfate in osteoarthritis of knee.

 

## Materials and Methods

*Patients***:** Forty four patients of either sex, age group of 40 – 70years having osteoarthritis of knee are included, diagnosis of osteoarthritis of the knee was made using the Clinical category of American College of Rheumatology. All patients had knee pain of at least 6 months and radiological evidence of Osteoarthritis (Kellgren and Lawrence grade 2 and 3)[8] ,and not on any NSAID$^s$ over past 2 weeks and Lequesne's ndex[9], score not less than 4 points, patients were excluded if they had severe symptoms of osteoarthritis or using any other drug from alternative system of medicine The radiological evaluation grades of O A.

Grade 0 = Normal
Grade 1 = Minimal osteophytes normal joint space
Grade 2 = Definite osteophytes and possible joint space narrowing
Grade 3 = Definite osteophytes and joint space narrowing
Grade 4 = Definite osteophytes and joint space narrowing with sclerosis and abnormal joint contour.

At enrollment physical medical examination was done for all patients to rule out any systemic diseases. The institutional review board approved the study, written informed consent was taken from every patient after explaining the study protocol.

*Treatment Regimens***:** Eligible patients were randomized to receive either glucosamine sulfate 500mg or identical looking placebo thrice daily for 6 weeks as per prior randomized schedule. Patients were evaluated at 0 (before drug administration) then 2, 4 and 6 weeks after drug administration for efficacy and safety parameters. Tablet paracetamol (500mg) was give along with the drug and allowed to be used as rescue medicine in case of unbearable pain. The patient was instructed to record the number of paracetamol tablets consumed every day in the diary card which was reviewed at each visit.

*Assessments***:** The following parameters were considered for evaluation of efficacy. VAS (100mm visual analog scale) on which higher score indicate more pain, Swelling Index, 15meter walking time(seconds),degree of flexion measured by goniometer, knee circumference(mm)Lequesne's index which range from(0-24) higher value the severe the disease and consumption of rescue medicine(Paracetamol tablets).All outcome measures were assessed at each study visit.

*Statistical analysis*: the minimum level of significance was set at 0.05 with 95% confidence interval at 80% power and student 't'test used to assess the significant difference between the two treatment.

## Results

In the present double blind, randomized study I have compared the efficacy of glucosamine sulfate against placebo in the management of osteoarthritis of knee. Out of 44 patients who are enrolled 23 patients randomized to placebo group and 21 to glucosamine sulfate group. Demographic characteristics of patients are shown in Table1.There was no statistically significant difference in the demographic between placebo and treatment group. Treatment with glucosamine sulfate group provided good pain relief compared to placebo as seen in VAS reading. As compared to placebo glucosamine group shows significant decrease VAS from 65.4 ± 12.52(0 week) to 57.36 ± 12.9, 48.82 ± 12.77 and 37.94 ± 14.16mm at the end of $2^{nd}$,$4^{th}$ and $6^{th}$ week respectively. These differences compared to baseline and placebo was found to be significant(Table 2).The swelling index significantly decrease from base line 1.24 ±0.6 to 1.15 ± 0.58, 0.88±0.47 and 0.59 ± 0.49 at the end of $2^{nd}$, $4^{th}$ and $6^{th}$ week in glucose sulfate while there was no similar reduction in swelling index in placebo group (Table 2).

**Table 1**
Characteristics of the Patient Population

| **Parameter** | | **Placebo** | **Glucosamine sulfate** | **Significance** |
|---|---|---|---|---|
| NO OF PATIENTS | | 23 | 21 | N.S |
| Age (yrs) | **Mean** | 52.04 | 54.19 | N.S |
| | **S.D.** | 7.28 | 9.45 | |
| | **S.E.** | 1.51 | 2.06 | |
| Sex | | M 10 F 13 | M 7 F 14 | |
| Height(Cms) | **Mean** | 154.6 | 157.43 | N.S |
| | **S.D.** | 8.92 | 7.94 | |
| | **S.E.** | 1.86 | 1.73 | |
| Weight(Kgs) | **Mean** | 59.69 | 64.76 | N.S |
| | **S.D.** | 10 | 12.5 | |
| | **S.E.** | 2.08 | 2.73 | |
| Duration of Complaints (Months) | **Mean** | 30.65 | 28.76 | N.S |
| | **S.D.** | 17.81 | 18.90 | |
| | **S.E.** | 4.76 | 4.12 | |
| Previous treatment out come | | E – 16, NE – 7 | E – 14, NE - 7 | N.S |

E = Effective, NE = Not Effective, N.S. = Non Significant

**Table 2**
Effect of Glucosamine Sulphate on VAS **a**nd Swelling Index

| | **Placebo** | | | | **Glucosamine sulfate** | | | |
|---|---|---|---|---|---|---|---|---|
| Parameters | 0 weeks n=23 | 2 weeks n=22 | 4 weeks n=21 | 6 weeks n=21 | 0 weeks n=21 | 2 weeks n=19 | 4 weeks n=17 | 6 weeks n=17 |
| **VAS** (Visual Analog Scale in mm) | | | | | | | | |
| Mean | 67.6 | 64.77 | 64.04 | 65.71 | 65.45 | 57.36** | 48.82*** | 37.94*** $$ |
| S.D. | 12.58 | 13.4 | 10.42 | 10.72 | 12.52 | 12.91 | 12.77 | 14.14 |
| S.E | 2.62 | 2.81 | 2.22 | 2.28 | 2.74 | 2.96 | 3.09 | 3.43 |
| C.I (95%) | | -0.2625 to -4.808 | -1.352 to -5.162 | -4.109 to -4.581 | | 3.426 to 13.96 | 8.541 to 23.22 | 19.00 to 34.53 |
| **Swelling Index** | | | | | | | | |
| Mean | 1.08 | 1.09 | 1 | 1.05 | 1.24 | 1.15 | 0.88 | 0.59*** $$ |
| S.D. | 0.5 | 0.5 | 0.43 | 0.038 | 0.6 | 0.58 | 0.47 | 0.49 |
| S.E. | 0.1 | 0.1 | 0.09 | 0.08 | 0.13 | 0.13 | 0.11 | 0.12 |
| C.I. (95%) | | -0.00 to -0.00 | -0.0616 to 0.1728 | -0.1616 to 0.2793 | | 0.0467 to 0.2572 | -0.7297 to 0.0938 | 0.3353 to 0.9588 |

P<0.5* P<0.01** P<0.001*** as compared to baseline; P<0.5 $ P<0.01 $$ P<0.001 $$$ as compared to placebo

The 15 meter walking time was decreased from 24.85 ± 9.5 to 19.7 ± 6.5 seconds at the end of 6 weeks with glucosamine sulfate, on the other hand the main walking time increase from 27.95 ± 9.37 to 33 ± 8.3 seconds at the end of 6 weeks in placebo group(Table 3).The degree of flections increases from 108.33 ± 7.76 to 118.82 ± 6.53 mm at the end of 6 weeks with glucosamine sulfate while it is decrease by placebo 108.9 ± 8.84 to105.47 ± 6.52 ( Table 3).There is no significant change in circumference of the knee(Table 3). Lequesne's index was significantly decrease compare to the basal value of 11.6 ± 2.38 to 8.47 ± 1.81 at the end of 6 weeks. In the patients who received placebo, there was no change in Lequesne's index.(Table 4).It was observed that the patient who received glucosamine sulfate the consumption of rescue medicine (paracetamol tablets) is significantly less compared with placebo group(Table 4).During the 6 weeks trial both glucosamine sulfate and placebo were very well tolerated by the patients. Except mild gastro-intestinal discomfort, there were no serious side effects noted. Good treatment

compliance was observed in more than 90% of the patients.

**Table 3**
Effect of Glucosamine Sulphate on 15 meter walking time (Sec) and Degree of Flexion and Knee Circumference (mm)

| | **Placebo** | | | | **Glucosamine sulfate** | | | |
|---|---|---|---|---|---|---|---|---|
| Parameters | 0 weeks n=23 | 2 weeks n=22 | 4 weeks n=21 | 6 weeks n=21 | 0 weeks n=21 | 2 weeks n=19 | 4 weeks n=17 | 6 weeks n=17 |
| **15 meter walking time(Sec)** | | | | | | | | |
| Mean | 27.95 | 29.04 | 30.28 | 33** | 24.85 | 24.85 | 22.35 | 19.7$$$ |
| S.D. | 9.37 | 8.81 | 7.82 | 8.30 | 9.52 | 9.58 | 7.88 | 6.05 |
| S.E. | 1.99 | 1.92 | 1.70 | 1.81 | 2.07 | 2.19 | 1.9 | 1.45 |
| C.I. (95%) | | -4890 to -0.6096 | -6.39 to 0.105 | -97 to 1.98 | | -1.174 to 1.911 | 0.691 to 3.753 | 0.8026 to 4.091 |
| **Degree of Flexion** | | | | | | | | |
| Mean | 108.9 | 108.18 | 105.7* | 105.47* | 108.33 | 109.47 | 113.82 | 118.82**$$ |
| S.D. | 8.84 | 9.35 | 7.28 | 6.52 | 7.76 | 8.25 | 7.77 | 6.53 |
| S.E. | 1.84 | 1.99 | 1.55 | 1.39 | 1.69 | 1.8 | 1.69 | 1.42 |
| C.I. (95%) | | -0.354 to 1.719 | 0.80 to 6.2 | 0.86 to 6.2 | | -2.89 to 0.2589 | -9.751 to 2.1 | -14.01 to 3.639 |
| **Knee Circumference (mm)** | | | | | | | | |
| Mean | 364.56 | 362.5 | 360.47 | 360.17 | 381.19 | 381.15 | 367.94 | 340.64 |
| S.D. | 39.2 | 38.25 | 36.41 | 36.9 | 43.91 | 46.39 | 30.92 | 79.86 |
| S.E. | 8.17 | 8.15 | 7.94 | 8.00 | 8.58 | 10.64 | 6.75 | 12.43 |
| C.I. (95%) | | -2.927 to 0.194 | -15.67 to -18.71 | -21.24 to 26 | | -2.89 to 0.2598 | -20.13 to 29.54 | -14.61 to 35.19 |

P<0.5*, P<0.01**, P<0.001*** as compared to baseline; P<0.5 $, P<0.01 $$, P<0.001 $$$ as compared to placebo

**Table 4**
Effect of Glucosamine Sulphate on Lequesne's Index and Rescue Medicine (Paracetamol)

| | **Placebo** | | | | **Glucosamine sulphate** | | | |
|---|---|---|---|---|---|---|---|---|
| Parameters | 0 weeks n=23 | 2 weeks n=22 | 4 weeks n=21 | 6 weeks n=21 | 0 weeks n=21 | 2 weeks n=19 | 4 weeks n=17 | 6 weeks n=17 |
| **Lequesne's Index** | | | | | | | | |
| Mean | 12.58 | 13.13 | 12.90 | 13.21 | 11.16 | 10.65 | 9.55 | $8.47^{**}_{\$\$}$ |
| S.D. | 2.7 | 2.97 | 2.02 | 1.86 | 2.38 | 2.23 | 1.72 | 1.81 |
| S.E | 0.56 | 0.63 | 0.43 | 0.39 | 0.52 | 0.51 | 0.42 | 0.44 |
| C.I (95%) | | - 0.843 to - 0.248 | -0.9831 to - 0.3502 | -1.423 to - 0.5297 | | 0.2806 to 1.035 | 1.028 to 2.325 | 2.072 to 3.458 |
| **Rescue Medicine** | | | | | | | | |
| No. of Paracetamol tablets per week | | | | | | | | |
| Mean | | 19.72 | $22.9^{***}$ | $24.23^{**}_{*}$ | | 18.78 | $15.94^{*}$ | $13.41^{**}_{\$\$\$}$ |
| S.D. | | 2.57 | 2.54 | 2.58 | | 2.76 | 3.68 | 4.14 |
| S.E. | | 0.54 | 0.54 | 0.55 | | 0.63 | 0.89 | 1 |
| C.I. (95%) | | | -4.064 to - 2.412 | -5.847 to - 3.295 | | | 1.022 to 4.272 | 3.648 to 7.411 |

P<0.5*, P<0.01** , P<0.001*** as compared to baseline; P<0.5 $^{\$}$, P<0.01 $^{\$\$}$, P<0.001 $^{\$\$\$}$ as compared to placebo

## Discussion

The result of this randomized double blind, placebo control parallel study showed that glucosamine sulfate (500mg) thrice daily over 6 weeks produced a significant improvement in the symptoms of osteoarthritis of knee.The current treatment modalities of OA are targeted at primary and secondary prevention.The primary prevention strategies include patient's education, protecting the joint from injuries, exercise, weight reduction and avoidance of repetitive motion occupations[10], Secondary prevention includes both pharmacological and non pharmacological therapy. NSAID$^{s}$ are one of the widely used drugs in OA, they decrease the pain, increase mobility and temporarily improve the quality of life but does not decrease the progress of disease and their use is limited by serious long term toxicities [11,12]. A number of pharmacological agents have been shown to reduce proteolytic cartilage breakdown and/or stimulate matrix repair in animal models of OA, such agents were called chondroprotective agents in the past. The International league against rheumatism (ILAR) labeled those drugs as slow acting drugs in osteoarthritis

(SADOA) [13]. The best example is glucosamine sulfate which shown to stimulate glycosaminoglycan and proteoglycan synthesis[14],in experimental models of OA. The dose 500mg/day of glucosamine sulfate was taken based on other clinical trials[15].Lequesne's index was taken as the main evaluation criteria for the efficacy of the treatment which is a balanced score that takes into account pain, maximum walking distance and movement limitations in common activities of daily living [16]. This index has been validated, inter observer reproducibility is good. The intake of paracetamol tablet depends on the pain status of the patient. In my study there was significant increase of paracetamol tablet consumption in placebo group while decrease in glucosamine group, indirectly indicating the beneficial anti arthritic effect of glucosamine sulfate. During 6 weeks of glucosamine sulfate administration none of patients reported any serious side-effects except mild gastrointestinal upset, all patients very well tolerated the treatment which was confirmed by other short term clinical trials [17], however long term studies are indicated for prolong therapy.
*Conclusion:* Oral administration of glucosamine sulfate was found to be significantly effective in controlling pain, swelling and improving the mobility in knee osteoarthritis without any serious side-effects.

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