

A randomized comparative study of safety and efficacy of immediate release glucosamine HCL and glucosamine HCL sustained release formulation in the treatment of knee osteoarthritis: A proof of concept study

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ABSTRACT

Objectives: To compare the safety and efficacy of glucosamine HCl- sustained release (GLU-SR) with that of Glucosamine HCl- immediate release (GLU-IR) in patients with knee osteoarthritis (OA). **Materials and Methods:** This study involved 59 patients with knee OA, randomised to receive single oral dose of 1,500 mg, GLU-SR and GLU-IR for 60 days with 31 and 28 patients, respectively. The primary efficacy (pain and function) was assessed using visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. Intention-to-treat principle, repeated measure of ANOVA and mixed model analysis were used. **Results:** The patients baseline, demographic and clinical characteristics were comparable between groups with female preponderance (71.20%). There was a significant reduction in algofunctional indices as primary outcome measure in both the groups across time ($P < 0.001$) and 29% lesser adverse events (AEs) in GLU-SR group, with no difference in the use of rescue medications. **Conclusions:** The study showed equal efficacy of the glucosamine formulations on algofunctional indices in reducing pain in patients with knee OA with less number of AEs in GLU-SR.

Key words: Glucosamine, sustained release, immediate release, osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is the most prevalent form of arthritis and a leading cause of chronic disability between fourth and fifth

decade of life.^[1] Prevalence of OA in India is reported to be in the range of 17-60.6%.^[2] Factors like old age, female gender and obesity are known to play a major role in the development of OA.^[3,4]

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	DOI: 10.4103/0976-500X.92515

Glucosamine, used in the management of OA, has shown modest benefit in slowing of joint space narrowing.^[5] Based on the earlier bioavailability (BA) studies, it was hypothesized that sustained release formulation would provide optimal benefits in view of more uniform blood levels and proportionately higher uptake by joint cartilage.^[6,7] Therefore, the present study was designed to evaluate the clinical implication of this

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hypothesis and the objective was to compare the safety and efficacy of 1,500 mg single, oral dose of Glucosamine-HCl sustained release (GLU-SR) with that of immediate release (GLU-IR) preparation.

MATERIALS AND METHODS

This was a randomized, open-labeled, comparative study, carried out by the Division of Clinical Pharmacology over a period of one year at the outpatient department of Orthopedics of a tertiary care hospital in subjects diagnosed with knee OA. Based on computer generated random sequence patients were assigned to one of the two treatment arms i.e. GLU-IR and GLU-SR after obtaining informed consent.

Postmenopausal women and men aged 40 years and above seen in the orthopaedic clinic having primary symptomatic knee OA (in one or both knees), diagnosed according to the clinical examination and radiographic features by orthopaedician having a minimum visual analogue scale (VAS) score of four in the target joint for at least 15 days in a month, belonging to any one category of American Rheumatism Association, functional class - I, II or III and willing to provide informed and written consent were enrolled for the study.^[8] The patients with uncontrolled diabetes ($\text{GRBS} \geq 200\text{mg/dl}$), infectious arthritis or gout, gastro-intestinal diseases, showing evidence of active peptic ulcer during the last six months and with a history of drug abuse or likelihood of orthopaedic surgery were excluded.

The approval was obtained from Institutional Review Board and ICH-GCP 2008 Seoul amendment and ICMR 2006 guidelines were followed during the study procedure. The study was registered in clinical trial registry of India (CTRI/2010/091/000416, 21-07-2010). The subjects with confirmed diagnosis of OA were examined by an orthopaedician to exclude other causes of knee joint pathology. The trial patients were subjected to biochemical investigations [Random Blood Sugar (RBS), Liver Function Tests (LFT) and Renal Function Tests (RFT), Uric acid] prior to and after administration of study medications to assess the safety profile of study medications.

The aim of the study was to establish the proof of concept pertaining to the sustained release formulation. A total of 59 patients fulfilling selection criteria were randomized into GLU-IR ($n = 28$) and GLU-SR ($n = 31$) groups.

The study products GLU-IR and GLU-SR (Medreich Private Ltd) were used as 1,500 mg, oral tablets. The trial subjects in both the groups were advised to take a single tablet, once-daily, half an hour before food at night with water for a period of 60 days. There were total of five clinic visits including screening visit and four follow-up visits once in 15 days after

starting the treatment. Data of each subject were collected on a specially designed Case Record Form at baseline and at every clinic visit.

The study subjects were instructed to avoid other medications during the trial period. Treatment compliance was checked at each clinic visit by patient interview, entry of information regarding consumption of medication on calendars provided and counting the number of un-used doses of study medications. The use of rescue medications was restricted to administration of acetaminophen (paracetamol) to avoid confounding in the efficacy assessment.

The clinical assessment was done at the beginning of the study and was repeated at each clinic visit during the treatment period. The parameters assessed were tenderness of the joint, synovial thickening, terminal limitation of joint movement graded as improved and not improved.

The parameters of primary outcome measure were assessed based on subjective and clinical improvement. The subjective assessment of joint pain was carried out using - VAS by grading pain as 0 to 10 (0 = no pain and 10 = severe pain). The functional pain level was assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale score and was graded as - No pain = 0, Mild = 1, Moderate = 2, Severe = 3 and Extreme = 4 with 108 as a maximum score.

The assessment of secondary efficacy end point was by counting the number of acetaminophen tablets consumed during study period as rescue medication. This was recorded and analyzed.

Reporting of adverse events was carried out by eliciting information through non-leading questions during clinic visits and was recorded based on the system affected. Also, record of untoward reactions to study medication was considered from a calendar provided to them. The study specific biochemical investigations performed at enrollment and after two months of treatment at the final follow-up visit like measurement of RBS, LFT and RFT were considered after matching them with standard lab values.

The comparison of data between GLU-IR vs GLU-SR groups for the baseline characteristics of study patients are presented as numbers, percentages and Mean $\pm$ SD depending on the nature of variable. Normality of the data was checked using Kolmogorov Smirnov test and Q-Q plot. Independent t test and chi square tests were used to find the difference between the study groups at baseline.

All patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment according to intention to treat analysis

(ITT). Repeated measure of ANOVA was used for assessing the effectiveness of intervention in reducing pain scores (VAS and WOMAC) between the study groups considering the baseline as covariate. A mixed model analysis was used to assess the effect of intervention on VAS and WOMAC scores across time between the study groups. Probability value less than 5% was considered as statistically significant. All analyses were carried out using SPSS version 17 (SPSS Inc, Chicago, USA).

RESULTS

The study profile of patients enrolled is shown in Figure 1. A total of 63 patients were screened and 59 were enrolled and randomized into two treatment groups. Out of these, there were 9 dropouts, 2 withdrawals due to non-compliance and protocol deviation with total of 48 patients completing the study.

The patient demographic data and clinical characteristics such as - body mass index (BMI), grading of OA based on American Rheumatism Association, functional class - I, II, III, of the

randomized patients were comparable between the two groups at baseline. The gender wise distribution as expected showed more number of females (71.20%) as compared to males.^[9] However, the gender wise randomization was equal in both the treatment groups. [Table 1]

On an average, 41.37% patients were overweight and 32.2% (BMI >30) were obese. The number of both overweight and obese patients were more in GLU-SR group (41.9% and 35.5%, respectively) as compared to those in GLU-IR (39.3% and 28.6%, respectively), but this difference was not statistically significant (χ^2 1.55, df = 3, P = 0.66). Further, all the patients belonged to OA functional grade – II and III.

Clinical examination for assessment of parameters such as joint tenderness, effusion, terminal limitation and crepitus showed improvement in both the treatment arms over the follow-up period of 60 days, with no significant difference between the groups treated with GLU-IR and GLU-SR for any of the parameters.

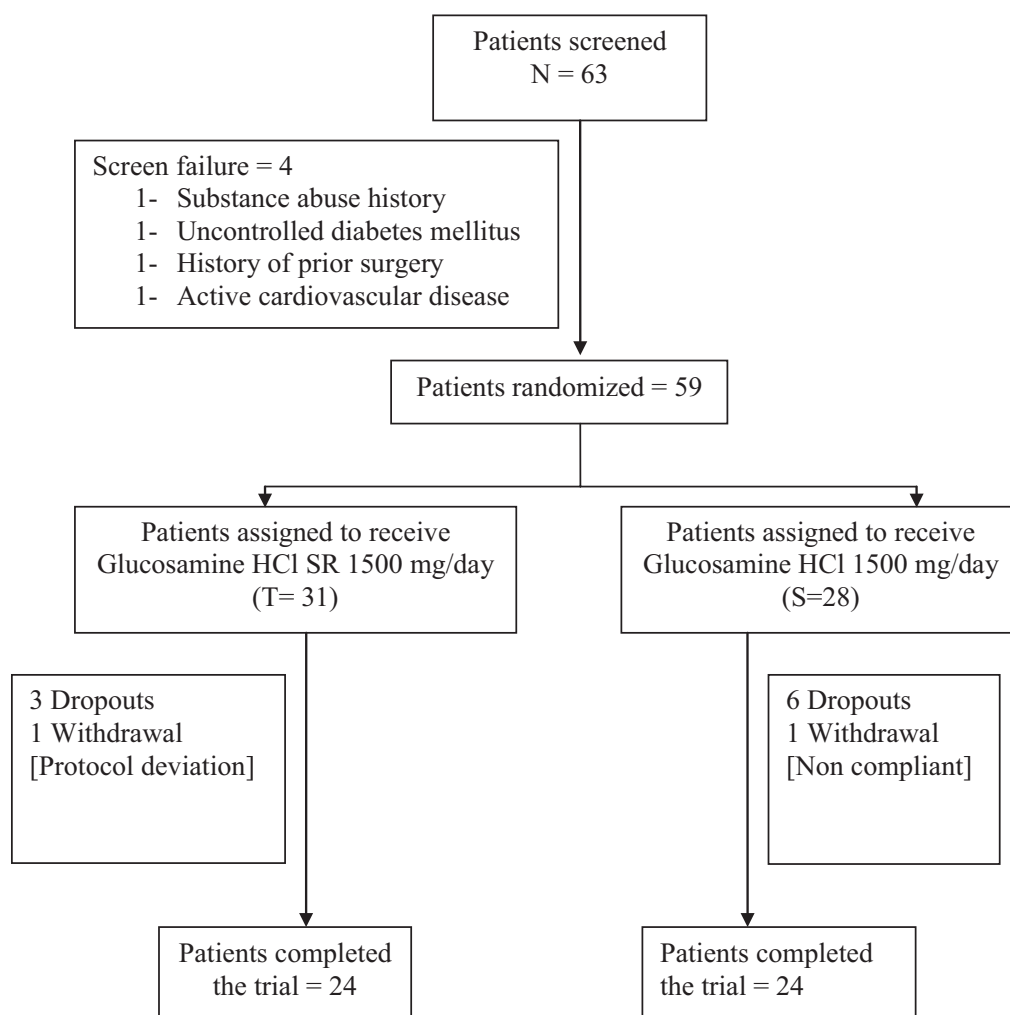


Figure 1: Trial profile of patients randomised to receive glucosamine-HCl sustained release (GLU-SR) and immediate release (GLU-IR)

The VAS and WOMAC scores as primary efficacy outcome measures was expressed as the change in total index scores at the end of two months. The values for VAS scores, showed a significant reduction across time ($P < 0.001$) when analyzed using the repeated measure ANOVA in both the treatment groups. [Figure 2] Further, the degree of OA symptoms relief was more in GLU-SR compared to GLU-IR, but this difference was not significant ($P = 0.21$) when analyzed using the repeated measure ANOVA and mixed model regression analysis.

The functional improvement of the affected joint/joints using WOMAC showed a similar trend with a significant reduction in the scores from baseline across time in both the study groups when analyzed using repeated measure ANOVA ($P < 0.001$), Figure 3. While, the group treated with GLU-SR showed greater reduction of scores across time, the difference was not

significant ($P = 0.48$), when determined using mixed model regression analysis. The extent of use of rescue medication (acetaminophen) did not differ significantly between two treatment groups.

Table 2 summarizes the adverse events reported as a primary safety outcome measured during two month treatment period. A total of 31 AEs were reported in 25 patients. The most frequent AEs were of minor clinical significance in both the groups and the number was less in GLU-SR 35.5% as compared to 64.52% in GLU-IR treated group. There were no significant differences between groups in the proportion or pattern of AEs according to body systems involved. Further, the study specific laboratory biochemical examinations of glucose levels and liver function test showed values within the normal range with no abnormalities or significant difference when compared between GLU-SR vs GLU-IR groups, including other lab parameters. Compliance with the study medication among trial completers was good, 92.00% in GLU-IR and 93.5% in GLU-SR.

Table 1: Baseline demographic and clinical characteristics of study participants

Baseline characteristics	GLU-IR* (n = 28) (Male - 8, Female - 20)	GLU-SR† (n = 31) (Male - 9, Female - 22)
Age(yrs)	54.14 ± 7.35	57.06 ± 11.22
Male (%)	28.57	29.03
n = 17/59 (28.81%)		
Female (%)	71.42	70.96
n = 42/59 (71.18%)		
BMI	28.86 ± 10.34	28.75 ± 5.34
Systolic BP	130.20 ± 15.90	127.90 ± 19.20
Diastolic BP	84.40 ± 10.90	84.30 ± 9.10
OA - Functional grade		
II -	23	23
III -	5	8
VAS score	6.00 ± 1.50	5.50 ± 1.10
WOMAC score	48.80 ± 16.20	46.40 ± 10.40

Values are mean ± SD. *GLU-IR- glucosamine- immediate release, †GLU-SR- glucosamine – sustained release, BMI – Body mass index, BP – blood pressure, VAS – Visual analog scale, WOMAC - Western Ontario and McMaster Universities Arthritis Index

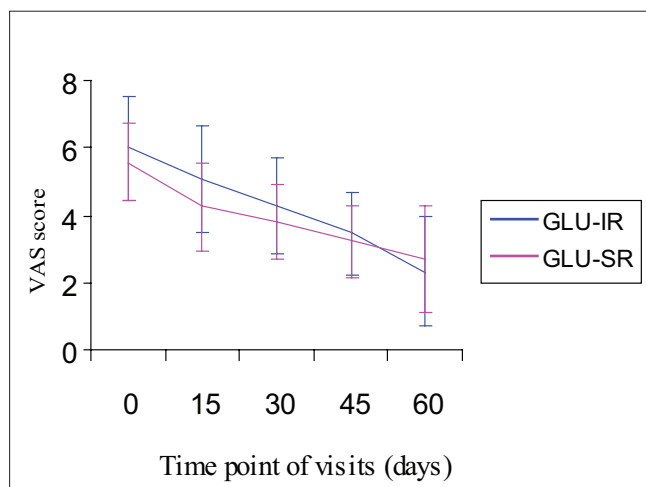


Figure 2: The mean ± SD VAS scores across time in GLU-IR and GLU-SR treated groups

Table 2: Summary of adverse events occurring in study patients(n)

Organ system involved	Type of AE	No. AEs GLU-IR* (n=15)	No. AEs GLU-SR† (n=10)	Total AEs
Gastrointestinal	Gastritis	5	3	8
	Diarrhea	2	3	5
	Constipation	-	1	1
Central nervous system	Fatigue	2	2	4
	Increased sleep	1	-	1
	Burning sensation feet	1	-	1
	Occipital pain	1	-	1
	Nausea, giddiness	1	-	1
Cutaneous	Generalized rash	1	1	2
	Itching	2	-	1
Respiratory	Upper respiratory tract infection	1	1	2
Genito-urinary system	Urinary tract infection	1	-	1
Hospitalizations	Flexion deformity - 1	-	2	2
	Coronary artery diseases - 1	-	-	-
Total AEs		20	11	31

AE- Adverse events

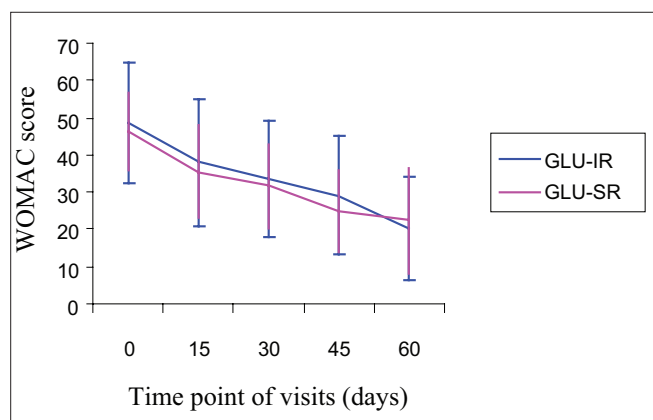


Figure 3: The mean $\pm$ SD WOMAC scores across time in GLU-IR and GLU-SR treated groups

DISCUSSION

Patients with OA are often reported to deteriorate because of pain, loss of mobility, bone deformity, frustration and depression. A variety of treatment options are reported to significantly relieve these symptoms and improve the quality of life in patients with OA, but none are known to offer cure or alter its progression with certainty.^[10] The existing pharmacotherapy includes acetaminophen, NSAIDS, mild narcotics, corticosteroids, hyaluronic acid substitutes, and nutritional supplements such as glucosamine and chondroitin.^[11]

In the present proof of concept study, the patients' baseline, demographic and clinical characteristics were comparable between two groups (GLU-IR and GLU-SR). There was a significant reduction in algofunctional indices (VAS and WOMAC) as primary outcome measure in both the groups across time ($p < 0.001$) and 29% lesser adverse events (AEs) in GLU-SR group, with no difference in the use of rescue medications. Acetaminophen is reported as first line choice for relieving pain, due to its safety profile compared to other agents, and hence, was used as a rescue medication in the present study.^[12-14]

The GLU-IR and equivalent dose of GLU-SR produced significant pain relief. The degree of relief of OA symptoms was more in GLU-SR group despite a higher percentage of overweight and obese patients. This appears to be related to its PK profile demonstrated in preliminary BA study.^[6] Also, interestingly the onset of beneficial effects in the present study with once-daily 1,500 mg of glucosamine is similar to those reported in the GUIDE trial which may be attributed to the steady-state with similar plasma and synovial fluid (10 μ M range) glucosamine concentrations.^[7,15] While, it has been argued out that these levels may be insufficient to stimulate the synthesis of cartilage glycosaminoglycans, their effect may be due to inhibition of interleukin-1-induced gene expression

a hypothetical mechanism of action of GLU-sulfate in OA.^[7]

In contrast, the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), using glucosamine and/or chondroitin sulphate, did not show statistically significant or clinically meaningful structural modification in patients with OA. But, a small subgroup of subjects with moderate-to-severe OA exhibited a significant pain relief with this combination. Hence, GAIT concluded that failure to demonstrate significant improvement in pain relief may have been due to decreased absorption leading to inadequate levels of glucosamine when administered concurrently with chondroitin sulfate.^[16,17] In addition, enrollment of higher proportion of patients with K/L grade III knee OA, were thought to be responsible for such outcome. However, in our study although the duration of treatment was only two months and both K/L grade II and III knee OA patients were included there was a significant reduction in symptoms when measured using the algofunctional scales (VAS and WOMAC). Also it is to be noted that the observed beneficial effects in the present study were statistically insignificant which may be attributable to a small sample size and to more number of overweight and obese patients enrolled in GLU-SR group.

A multi-dose comparative BA study by Basak M, 2004 using timed release and powder-filled glucosamine sulfate formulation showed that although the time to attain C max was delayed (4.13h) with time release glucosamine the excretion was less compared to powder-filled glucosamine.^[18] In addition the AUC₀₋₂₄ was more with timed release preparation compared to powder-filled glucosamine. A similar cross over, proof of concept BA study, carried out in eighteen healthy human volunteers showed that a single dose of 1,500 mg, immediate release formulation, got absorbed and eliminated faster during the first two hours itself, while sustained release formulation, showed elimination after 5 hrs with increase in residence time of glucosamine in blood.^[6] Further, immediate release formulation showed a higher peak concentration for a short time and faster elimination. This observation may support the inconsistent and delayed efficacy outcome of glucosamine-IR in clinical practice as reported in earlier multi-centric studies as well as in the present study.^[19]

Based on these observations, we used one glucosamine 1,500 mg SR tablet equivalent to 500 mg GLU-IR tablets three times a day, to achieve consistent bio-availability and to improve efficacy.

In view of the reported short plasma half-life of GLU-IR and variable plasma levels (10.4 to 204 ng/ml) leading to unpredictable efficacy,^[20] it was hypothesized that SR formulation of glucosamine would provide clinically optimal benefits.^[21] Further, it is reported that supplements of glucosamine are rapidly broken down leaving a miniscule of glucosamine to enter the cartilage. Therefore, to provide

sustained blood levels through SR formulation was proposed to ensure higher uptake of glucosamine by the cartilage.^[20] Also, glucosamine as SR was considered justifiable due to its small size (molecular weight: 179) with a pKa of 6.91 that would favor crossing of biological barriers.^[22] The proportions of collagen and proteoglycans are reported to increase proportionately with increase in glucosamine which in turn improves water content resulting in healthier cartilage. Presently the search is on to identify influence of glucosamine on involvement of specific type-II collagen in patients with knee OA using biomarkers.^[23]

Therefore, considering the findings of the present study as well as preliminary BA studies, the efficacy of GLU-SR vs GLU-IR in patients with knee OA showed promising results. In this respect, ours is the first proof of concept Indian study which evaluated relationship between the findings of BA study and clinical outcome measures of administering GLU-SR with GLU-IR.^[6,7]

The AE profile observed in the present study followed a similar trend in both the treatment groups and were minor, self limiting and have been well-documented.^[19] However, the numbers of events were more compared to previous reports of multi-centric study. This difference may be due to relatively small sample size in our study. The serious AEs reported did not reveal any causality relation to study medications.

The limitations of this proof of concept study include small sample size, shorter treatment duration and lack of simultaneous PK-PD study design. However, the study demonstrated significant and comparable symptomatic relief of pain following administration of identical doses of GLU-IR and GLU-SR. Yet another possible limitation of the present study is that there was more number of obese subjects in GLU-SR which may have contributed to failure to recognize significant difference in the primary efficacy outcome measure. Further, interestingly the GLU-SR, formulation exhibited greater degree of symptom relief as early as one month after administration and also a sustained reduction in OA symptoms with lesser adverse effects compared to GLU-IR. This latter finding appears to lend support and add evidence to the hypothesis of findings of earlier BA studies that patients treated with GLU-SR may offer sustained and long lasting relief from OA symptoms.^[6,7]

Studies in larger number of patients for longer duration may be necessary to confirm the above findings to help in guiding future therapeutic practices.

ACKNOWLEDGMENT

Authors wish to gratefully acknowledge clinical consultation offered by Dr. K.T.Thomas, Professor, Department of Orthopedics,

in recruiting the patients for this study and MEDREICH Limited, Bengaluru for financial assistance.

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How to cite this article: Kulkarni C, Leena A, Lohit K, Mishra D, Saji MJ. A randomized comparative study of safety and efficacy of immediate release glucosamine HCL and glucosamine HCL sustained release formulation in the treatment of knee osteoarthritis: A proof of concept study. J Pharmacol Pharmacother 2012;3:48-54.

Source of Support: Nil, **Conflict of Interest:** None declared.

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