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Original Article

Comparison of Efficacy and Tolerability of Immediate Release Glucosamine HCL And Glucosamine HCL Sustained Release Formulation in the Treatment of Knee Osteoarthritis; A Randomised Clinical Trial

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ABSTRACT

Background: *Osteoarthritis (OA) is the most common form of and a leading cause of chronic disability between fourth and fifth decade of life, with a prevalence ranging between 17-60.6% in India.* ***Objective:*** *To compare the efficacy and safety profile of glucosamine HCl- sustained release (GLU-SR) with that of Glucosamine HCl- immediate release (GLU-IR) in patients with knee osteoarthritis (OA).* ***Methods:*** *This was an open labelled, randomised, controlled trial conducted in a tertiary care hospital at Kanpur. The study involved 60 patients with knee OA, randomised to receive single oral dose of 1,500 mg GLU-SR and GLU-IR for 60 days with 30 patients in each group. The primary efficacy being reduction in pain and improvement in 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 for statistical analysis. The history of adverse reactions experienced was collected throughout the study period.* ***Results:*** *There was a significant reduction in algo functional indices as primary outcome measure in both the groups ($P < 0.001$). A significant difference ($P < 0.05$) in the number of patients reporting ADR in the GLU-SR arm (38% lesser) was noted as compared to GLU-IR arm, with no difference in the use of rescue medications in both arms.* ***Conclusions:*** *From the observations made in this study it is concluded that GLU-SR is as effective as GLU-IR in the management of knee OA; with an advantage of having a better safety profile.*

Keywords: *Glucosamine, sustained release, immediate release, osteoarthritis, visual analogue scale, Western Ontario and McMaster Universities Osteoarthritis Index*

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INTRODUCTION

Osteoarthritis (OA) is the most common form of degenerative joint disease and a leading cause of chronic disability in 40-50 years of age group with knee being the most commonly affected areas.[1] Its prevalence in India ranges between 17-60.6%.[2] The major risk factors in the development of OA are old age, female gender and obesity.[3,4] There are various pharmacologic and non-pharmacologic treatment options available for the relief of symptoms and improving the quality of life in knee OA patients.[5] However, no intervention is known to offer therapeutic cure or alter the disease progression.[6] The recommended treatment options for knee OA include oral glucosamine sulfate with the highest level of scientific evidence. Only 6 of the 34 therapeutic interventions considered were ascribed the same degree of evidence and recommendation as glucosamine sulphate.[7] Glucosamine has exhibited modest benefit in slowing the process of joint space narrowing.[8] Various bioavailability (BA) studies have reflected that the sustained release formulations result in uniform blood levels which in turn is responsible for a higher uptake by the joint cartilage.[9,10] However, very few studies have been conducted globally comparing the efficacy and safety profile of glucosamine sustained release and immediate release formulations. Hence, this study was planned to compare the efficacy and safety of glucosamine HCl sustained release (GLU-SR) and Glucosamine HCl

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immediate release (GLU-IR) in Indian patients with knee osteoarthritis.

METHODS

This was an open labelled, randomized, controlled, comparative study, carried out under the joint auspices of department of pharmacology and department of orthopaedics at a tertiary care hospital, Kanpur. A total of 60 patients diagnosed with knee OA were included in the study after due approval from the Institutional Ethics Committee. The study was conducted in accordance with the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines.

The inclusion criteria comprised of postmenopausal women and men aged 40 years and above having primary symptomatic knee OA (in one or both knees), diagnosed according to the clinical examination and radiographic features by orthopaedican, having a minimum visual analogue scale (VAS) score of 4 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 for participating in the study.[11] The patients with infectious arthritis, knee joint pathology, gout, uncontrolled diabetes (GRBS ≥200mg/dl), 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 from the study.

Based on computer generated random sequence, the patients were assigned to one of the two treatment arms i.e. GLU-IR and GLU-SR, with 30 patients in each arm. The study drugs 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 8 weeks. Standard marketed brands of both the drugs were supplied free of cost and administered in a single blind manner, with medication identity not being revealed to the patients. Allocation concealment was achieved using the serially numbered, opaque, sealed envelope technique. The randomization process and the code breaking authority was given to a senior pharmacologist not interacting with the subjects. The subjects were instructed to avoid other medications during the trial period. The use of rescue medications was restricted to administration of acetaminophen (paracetamol) to avoid confounding in the efficacy assessment. There were total of five clinic visits including the screening visit and four follow-up visits quarterly. The patients received the total medication in four instalments at 0, 2, 4, and 6 weeks; and were followed up at 2, 4, 6 and 8 weeks from the start of the treatment. The data of each subject was collected on a specially designed case record form at the baseline and at every follow up visit. Each subject enrolled was given a personal calendar to document the daily dose intake and any adverse event experienced during the study period. The basic biochemical investigations (random blood sugar RBS, liver function tests LFT, renal function tests RFT and uric acid) were performed at the baseline and after completion of the study at the end of treatment follow-up visit.

The primary outcome of drug efficacy was assessed by subjective and clinical improvement. The subjective assessment of joint pain was carried out using visual analogue scale (VAS) by grading pain from 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) and was graded as; No pain = 0, Mild = 1, Moderate = 2, Severe = 3 and Extreme = 4; with 108 as a maximum score.[12] The number of rescue medication (acetaminophen tablets) consumed during study period was used as a secondary outcome parameter reflecting the drug efficacy. The clinical assessment was done at the baseline and was repeated at each follow up visit during the study period. The parameters assessed were joint tenderness, effusion, terminal limitation and crepitus; graded as improved and not improved.

The assessment of safety profile of the study drugs was based on the history of adverse events experienced, which was collected from the calendars provided and through non-leading questions during the follow up visits.

Treatment compliance was checked at each clinic visit by patient interview, entry of information on calendars provided and counting the number of un-used doses of study medications.

Statistical analysis

Independent t-test and chi square tests were used to find the difference between the study groups at baseline. Repeated measure of ANOVA was used for assessing the effectiveness of intervention in reducing pain scores (VAS and WOMAC) between the study groups. A mixed model analysis was used to assess the effect of intervention on VAS and WOMAC scores across time between the two study arms. All statistical analysis was done using SPSS version 17 with $p < 0.05$ as significant

RESULTS

The baseline demographic and clinical characteristics of the subjects in both GLU-IR and GLU-SR groups is summarised in Table 1.

The patient demographic data, body mass index (BMI) and grading of OA based on American Rheumatism Association of the patients was comparable between the two groups at the baseline. The gender wise distribution in accordance with the global prevalence showed more number of females (76.66%) as compared to males (24.14%).[13] However, the gender wise randomization was equal in both the treatment arms. On an average, 40% were obese with BMI >30; whereas, all the patients belonged to either OA functional grade II and III.

The VAS and WOMAC scores were expressed as the change in total index scores at the end of the study reflecting the primary efficacy outcome measure.

The values for VAS scores, showed a significant reduction throughout the study period ($P < 0.001$) using the repeated measure ANOVA in both the treatment arms as seen in Figure 2. However, the degree of OA symptoms relief was more in GLU-SR arm compared to GLU-IR arm, but with no statistical significance ($P > 0.05$) using mixed model regression analysis.

The Figure 3 reflects that the functional improvement of the affected joint/joints showed the similar significant reduction pattern in the WOMAC scores across time in both the study arms using repeated measure ANOVA ($P < 0.001$). Once again, the GLU-SR arm showed greater reduction of scores with no statistical significance ($P > 0.05$).

The secondary efficacy outcome, measuring the extent of use of rescue medication (acetaminophen) did not differ significantly between two study arms. Clinical assessment of parameters such as joint tenderness, effusion, terminal limitation and crepitus showed improvement in both the treatment arms on the end of the treatment follow-up at 8 weeks, with no significant difference between the two arms treated with GLU-IR and GLU-SR

Table 2, summarizes the adverse events reported as a secondary study outcome measured during two month study period.

A total of 26 AEs were reported in 20 patients. The number of ADRs reported was less in GLU-SR arm (30.76%) as compared to GLU-IR arm (69.23%), which was a statistically significant difference (38% lesser; $P < 0.05$). The maximum number of reported AEs was in the system organ class of "Gastrointestinal system" (57.69%).

The basic laboratory biochemical investigations (RBS, LFT, RFT and uric acid) showed values within the normal range with no significant difference in both GLU-SR and GLU-IR groups. Compliance with the study medication among trial subjects was good with no dropouts.

Table 1: Baseline demographic and clinical characteristics of study subjects (mean + SEM)

Characteristic parameters (units)	GLU-IR (1500mg) (n = 30)	GLU-SR (1500mg) (n = 30)
Age(yrs)	59.63 ± 4.42	58.98 ± 4.69
Male (%)	20 (6)	26.66 (8)
Female (%)	80 (24)	73.33 (22)
BMI	26.32 ± 7.05	25.44 ± 6.51
Duration of knee OA (yrs)	4.2 ± 3.16	4.5 ± 4.02
Systolic BP (mmHg)	128.66 ± 7.38	129.15 ± 8.29
Diastolic BP (mmHg)	84.40 ± 10.90	84.30 ± 9.10
OA - Functional grade		
II	24	26
III	5	4
VAS score	5.89 ± 1.38	5.32 ± 1.56
WOMAC score	49.12 ± 10.98	45.79 ± 9.44

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

Table 1: Summary of distribution of adverse events occurring in study subjects

Organ system involved	Type of AE	GLU-IR (n=13)	GLU-SR (n=7)	Total AEs
Gastrointestinal system	Gastritis	6	3	9
	Diarrhoea	2	2	4
	Constipation	1	1	2
Central nervous system	Fatigue	3	2	5
	Increased sleep	1	0	1
	Burning sensation feet	1	0	1
	Occipital pain	1	0	1
	Nausea, giddiness	1	0	1
Cutaneous	Generalized rash	1	0	1
	Itching	1	0	1
Respiratory	Upper respiratory tract infection	0	0	0
Genito-urinary system	Urinary tract infection	0	0	0
Total AEs		18	8	26

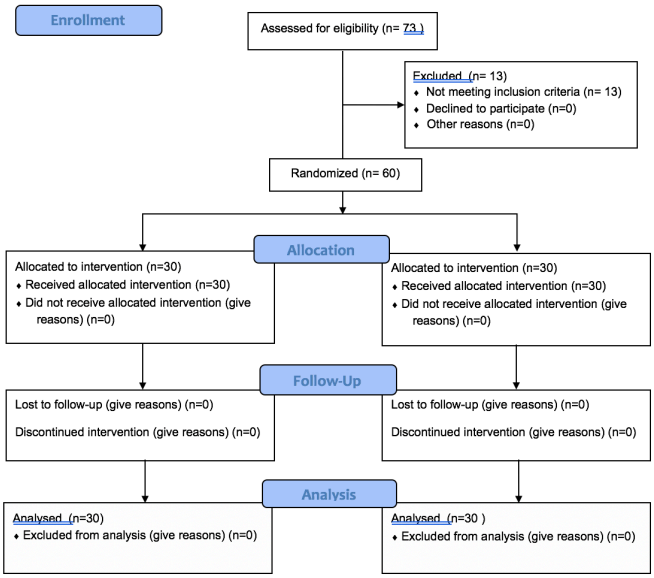

Fig 1: Consort Flow Chart Diagram

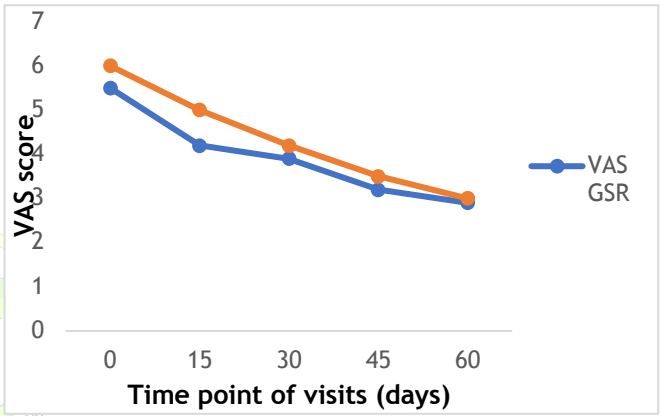

Fig 2: The mean VAS scores across time in GLU-IR and GLU-SR treated groups.

VAS GSR – VAS score in GLU-SR arm, VAS GIR – VAS score in GLU-IR arm.

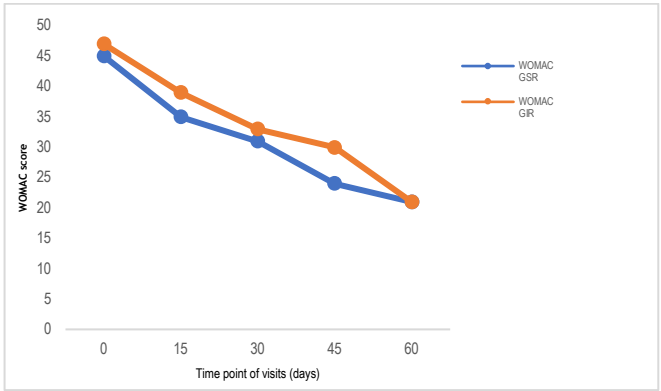

Fig 3: The mean WOMAC scores across time in GLU-IR and GLU-SR treated groups.

WOMAC GSR – WOMAC score in GLU-SR arm, WOMAC GIR – WOMAC score in GLU-IR arm.

DISCUSSION

Knee OA is the most common and depressing presentation of OA, leading to chronic disability due to pain, loss of mobility and bone deformity. The current pharmacotherapy for knee OA includes a cafeteria of drugs comprising of acetaminophen, NSAIDS, mild narcotics, corticosteroids,

hyaluronic acid substitutes, and nutritional supplements such as glucosamine and chondroitin.[14]

In the present study, the baseline demographic and clinical characteristics of the subjects were comparable between two study arms (GLU-IR and GLU-SR). There was a significant reduction in algo functional indices (VAS and WOMAC) as primary outcome measure in both the groups across time ($p < 0.001$) with 38% lesser adverse events (AEs) in GLU-SR group. Acetaminophen is reported as drug of choice for relieving pain in patients of OA, owing to its safe adverse effect profile and hence it was used as a rescue medication in the present study.[15-17] However, no difference in the use of rescue medications in both the study arms was observed. It was observed in our study that the GLU-IR and equivalent dose of GLU-SR were comparable in efficacy, producing a significant relief in pain. It was also observed from our data that the onset of pharmacological effects with once daily 1,500 mg of GLU-SR is similar to that reported in the glucosamine unum in die efficacy (GUIDE) trial[18,19] as well as a similar proof of concept Indian study;[20] which may be attributed to the steady-state achieved in the plasma and synovial fluid (10 μM range).[10,21] It has been argued by many researchers that the GLU-SR steady-state levels are insufficient to stimulate the synthesis of cartilage glycosaminoglycans. It has further been suggested that the effect manifested may be due to inhibition of interleukin-1-induced gene expression; one of the supposed mechanism of action of GLU-sulfate in knee OA.[10]

In a multi-dose comparative bioavailability study by Basak M in 2004, using 'timed release glucosamine sulphate' and 'powder-filled glucosamine sulphate', it was reflected that with 'time release glucosamine', the time to attain C max was delayed (4.13 hours); whereas, the renal elimination was less as compared to the 'powder-filled glucosamine'. It was also observed in the study that the AUC0-24 was more with 'timed release preparation'.[22] In a similar study, conducted by Synchron Research Services Pvt. Ltd. Ahmedabad, 2008; it was observed that a single dose of 1,500 mg GLU-IR got absorbed and eliminated faster within the first two hours. On the contrary, the sustained release formulation showed elimination after 5 hours; resulting in the increase of residence time of glucosamine in blood.[9] The data from various multi centric studies confirm the short plasma half-life and variable plasma levels (10.4 to 204 ng/ml) of GLU-IR leading to its unpredictable efficacy [23,24] As such it was hypothesized in a study by Kelly GS that SR formulation of glucosamine would provide clinically optimal benefits.[25] In our study the GLU-SR, formulation exhibited its pharmacological effect at one month after the administration and a sustained reduction in knee OA symptoms which once again confirm the findings of earlier studies.[9,10]

On the other hand glucosamine/chondroitin arthritis intervention trial (GAIT),[26] using glucosamine and/or chondroitin sulphate, did not show any statistically significant structural modification in patients with knee OA. However, a small subgroup of patients with moderate-to-severe knee OA reported a significant pain relief in this trial. From the data generated by the GAIT, it was concluded that the failure to demonstrate significant relief in pain may be due to the low dose preparation used whereas, the significant pain relief in the sub group was attributed to the increased absorption of glucosamine when administered concurrently with chondroitin sulfate.[27,28] The failure to demonstrate significant pain relief was also attributed to the enrolment of higher proportion of patients with K/L grade III knee OA. In our study, with a comparable number of both K/L grade II and III knee OA patients, there was a significant reduction in OA symptoms in both the study arms. It is noteworthy that in our study, the improvement in knee OA symptoms was more pronounced in GLU-SR group which however was not statistically significant. This statistically insignificant result may be attributable to the small sample size and short duration of treatment.

Interestingly, it is also reported by Persiani S. et,al, 2005 that glucosamine being rapidly broken down in the body, the sustained release formulations would be highly desired to provide the therapeutic levels of glucosamine for entry into the cartilage.[20] GLU-SR has an additional advantage of its small size (molecular weight: 179) with a pKa of 6.91 which is supposed to facilitate its transport across the biological membranes.[29]

The AE profile observed in the present study followed a similar pattern in both the treatment groups. [20,23] Both the drugs were well tolerated and no serious adverse events were encountered. All the adverse effects (AEs) noted were mild and classified as treatment emergent adverse events (TEAEs) across both study arms. There was a statistically significant difference ($P < 0.05$) in the number of patients reporting ADR in the GLU-SR arm (30.76%) as compared to GLU-IR arm (69.23%). The maximum number of reported AEs was in the system organ class of "Gastrointestinal system" (57.69%).

Limitations

The limitations of the present study include small sample size, short treatment duration and lack of simultaneous pharmacokinetic as well as pharmacodynamic studies. However, the study demonstrated significant and comparable symptomatic relief in patients of knee OA following administration of similar doses of GLU-IR and GLU-SR.

CONCLUSION

From the observations of the present study it can be concluded that GLU-SR is comparable in terms of efficacy and to GLU-IR in patients with knee OA with a better safety profile. However, studies in larger number of patients for longer duration are recommended to confirm our findings and help in formulating therapeutic guidelines for patients of knee OA.

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Ethical Committee Approval: Approved

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