

Efficacy and Safety of Diacerein versus Glucosamine in Patients with Osteoarthritis of the Knee: A Prospective Comparative StudySruthi N.¹, Anuradha M.², Divya Anirudhan³, Hemalata⁴¹Junior Resident, Department of Pharmacology, Government Medical College, Kozhikode, Kerala, India.²Professor and HOD, Department of Pharmacology, Malabar Medical College, Modakkallur, Kerala, India.³Associate Professor (CAP), Department of PMR, Government Medical College, Thrissur, Kerala, India.⁴Associate Professor (CAP), Department of Physical Medicine and Rehabilitation, Government Medical College, Kannur, Kerala, India.

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Conflict of interest: Nil

Abstract**Background:** In this study, we wanted to compare the efficacy and safety of Diacerein with Glucosamine in osteoarthritis of the knee.**Methods:** This was a hospital-based prospective cohort study conducted among 50 patients with grade 2 or 3 osteoarthritis of the knee, at the Department of Physical Medicine and Rehabilitation, and Department of Pharmacology, Government Medical College, Kozhikode, for one year after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.**Results:** All the parameters were comparable between Diacerein and the Glucosamine group (P value>0.05). No adverse reactions were reported in both groups during the study period.**Conclusion:** According to the study, the efficacy of Glucosamine and Diacerein in management of osteoarthritis was comparable on follow-up and no adverse effects related to the drugs were reported in both groups during the study period.**Keywords:** Osteoarthritis, Knee, Diacerein, Glucosamine, WOMAC, VAS.

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Introduction

Osteoarthritis (OA) is one of the most common rheumatologic problems affecting about 10%–15% of all adults aged over 60. [1] In the Indian population, osteoarthritis is the most prevalent joint disease with an incidence of 22 to 39%. [2] The prevalence of osteoarthritis is found to be more in urban areas than in rural areas. [3] India has got a high proliferative rate for osteoarthritis and by the end of 2020, India will be leading the chart worldwide. [4] According to American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, “Osteoarthritis is defined as a group of conditions that produce joint symptoms and signs which are associated with defects in the integrity of articular cartilage and changes in the underlying bone at the joint margins” [5] Osteoarthritis can be classified as primary and secondary. Primary osteoarthritis is in patients with no pre-existing lesions, while secondary osteoarthritis occurs in people with pre-existing joint abnormalities. [6] It mainly affects larger weight-bearing joints like knee and hip, but it can also affect joints of hands, spine and feet. Knee osteoarthritis accounts for the

majority of knee joint pain in old age. The prevalence of symptomatic knee osteoarthritis is 13% in women and 10% in men aged 60 years and above. [7] Currently, no curative treatment options are available for treating osteoarthritis. The management options of osteoarthritis are mainly focused on controlling symptoms and preventing disease progression. We have pharmacological measures, non-pharmacological measures and surgical options available for treating osteoarthritis. Non-pharmacological options like exercise, weight reduction, assistive devices and physical therapies have shown benefits in reducing symptoms of osteoarthritis. [8] Surgical treatments including total knee replacement are usually reserved for advanced cases of osteoarthritis with severe disability. [9] Pharmacological treatment comprises of the NSAIDs, being the most commonly prescribed drugs for osteoarthritis. [10] NSAIDs have no disease-modifying effect; they act by just reducing the symptoms of osteoarthritis and on long term use, are known to produce several adverse effects. [11] Diacerein and Glucosamine

can be considered as disease-modifying agents that can delay the progression of the disease as well as alleviate the symptoms. [12] Diacerein is an anthraquinone derivative which is converted to an active metabolite Rhein which acts by inhibiting the Interleukin-1 β . Interleukin-1 β is a pro-inflammatory cytokine that stimulates the degradation process of cartilage and suppresses synthesis of the cartilage matrix. Glucosamine is an endogenous aminomonosaccharide synthesized by chondrocytes. It is the basic precursor of glycosaminoglycans and other proteoglycans present in cartilage. [13] The safety and efficacy of these agents in the treatment of osteoarthritis are not much studied in our population. Knee osteoarthritis is one of the most prevalent and disabling diseases which significantly affects the quality of life of patients. [14] The pharmacological agents available mainly focus on the alleviation of symptoms. [15] Hence, it is important to study the efficacy and safety of available drugs that are claimed to have disease-modifying effects. The efficacy of treatment options in osteoarthritis is assessed based on various endpoints like their effect on pain and function of joints and joint space narrowing in plain x-ray. [16] The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the visual analogue scale (VAS) are the two widely used scales to assess pain, stiffness and physical function of the joints. [17,18] Osteoarthritis is mainly a disease of old age where the person may already be on multiple medications for various comorbidities, so considering all these factors, the adverse effect profile of the drugs needs to be evaluated. This can be done effectively using WHO-UMC scale for adverse drug reaction monitoring. [19,20] Diacerein and Glucosamine are two popular disease modifying drugs used in the treatment of osteoarthritis. There are many studies available which are analysing their individual efficacy in the management of osteoarthritis but there are only a limited number of studies available to compare their efficacy and adverse effects especially in the Indian population.

Aims and Objectives

To compare the efficacy and safety of Diacerein with Glucosamine in osteoarthritis of the knee.

Materials & Methods

This was a hospital-based prospective cohort study conducted among 50 patients with grade 2 or 3 osteoarthritis of the knee, at the Department of Physical Medicine and Rehabilitation, and Department of Pharmacology, Government Medical College, Kozhikode, for one year after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Patients between 50 and 65 years with knee osteoarthritis (satisfying American college of rheumatology clinical criteria and Kellgren - Lawrence grade 2 or 3).
- Patients who were willing to participate after signing the written informed consent.

Exclusion Criteria

- Pregnancy and lactation.
- Patients with gastrointestinal, renal and liver diseases and diabetes.
- Patients with acute exacerbation of OA at the time of enrolment.
- Secondary OA and other rheumatologic diseases.
- Patients who had undergone knee surgeries.
- Patients who were on physical modalities.
- Patients with a history of intraarticular injections.

Statistical Methods

Statistical analysis was done using the statistical package for social sciences (SPSS) software. The efficacy based on the WOMAC score was assessed at the baseline, end of the first month, second month and the third month using the Mann-Whitney U test and VAS score changes were analysed by the Independent T-test. Secondary outcomes were assessed using the Chi-square test. Analysis at the end of fourth month to assess the carry-over effect could not be conducted as the number of patients who completed the fourth month of the study period was inadequate. A p-value <0.05 was considered as statistically significant.

Results

Table 1

WOMAC	Diacerein Mean (SD) (n=25)	Glucosamine Mean(SD) (n=25)	P-value
WOMAC A	12.28(3.19)	12.84(3.13)	0.418
WOMAC B	5.28(1.31)	5.60(1.32)	0.440
WOMAC C	44.00(7.86)	46.92(7.57)	0.123
Total WOMAC	61.56(11.64)	65.36(11.33)	0.200
Comparison of baseline WOMAC* A, WOMAC B, WOMAC C and TOTAL WOMAC scores			
*Western Ontario and McMaster Universities Arthritis Index			
WOMAC	Diacerein Mean(SD)	Glucosamine Mean(SD)	P-value

	(n=25)	(n=25)	
WOMAC A	11.84(2.99)	11.84(3.30)	0.992
WOMAC B	5.00(1.29)	5.44(1.27)	0.283
WOMAC C	41.88(7.39)	44.28(7.26)	0.251
Total WOMAC	58.72(11.09)	61.56(11.17)	0.346
Comparison of WOMAC* A, WOMAC B, WOMAC C and TOTAL WOMAC scores at first month			
*Western Ontario and McMaster Universities Arthritis Index			

Comparison of the grade of osteoarthritis in both groups

Grade of Osteoarthritis in both groups was compared using the chi-square test and was found to be comparable (p value>0.05). In Diacerein group, 52% were grade 2 and 48% were grade 3. In the Glucosamine group, 32% were grade 2 and 68% were grade 3.

Baseline WOMAC scores of both groups were compared using the Mann-Whitney U test and found to be comparable (p value>0.05).

WOMAC scores of both groups in the first month were compared using the Mann-Whitney U test and found to be comparable (p value>0.05).

Table 2

WOMAC	Diacerein Mean(SD) (n=25)	Glucosamine Mean(SD) (n=25)	P-value
WOMAC A	10.28(3.21)	10.16(3.15)	0.922
WOMAC B	4.56(1.45)	4.80(1.39)	0.619
WOMAC C	38.28(8.01)	40.72(7.47)	0.221
TOTAL WOMAC	53.12(12.18)	55.40(11.24)	0.382
Comparison of WOMAC* A, WOMAC B, WOMAC C and TOTAL WOMAC scores at second month			
*Western Ontario and McMaster Universities Arthritis Index			
WOMAC	Diacerein Mean(SD) (n=24)	Glucosamine Mean(SD) (n=25)	P-value
WOMAC A	8.58(3.48)	9.08(3.72)	0.546
WOMAC B	3.88(1.36)	4.44(1.47)	0.241
WOMAC C	35.17(8.98)	38.32(8.21)	0.113
TOTAL WOMAC	47.83(13.02)	51.84(12.74)	0.183
Comparison of WOMAC* A, WOMAC B, WOMAC C and TOTAL WOMAC scores at third month			
*Western Ontario and McMaster Universities Arthritis Index			

WOMAC scores of both groups in the second month were compared using the Mann-Whitney U test and found to be comparable (p value>0.05).

WOMAC scores of both groups at the third month were compared using Mann-Whitney U test and found to be comparable (p value>0.05).

Table 3: Comparison of VAS* scores at baseline, first month, second month and third month

Month	Group	Mean VAS	SD	P-value
Baseline	Diacerein (n=25)	6.29	1.01	0.445
	Glucosamine (n=25)	6.52	1.11	
First month	Diacerein (n=25)	6.2	1.02	0.806
	Glucosamine (n=25)	6.28	1.15	
Second month	Diacerein (n=25)	5.54	1.13	0.540
	Glucosamine (n=25)	5.72	1.03	
Third month	Diacerein (n=24)	5.11	1.12	0.420
	Glucosamine (n=25)	5.39	1.27	
*Visual analogue scale				

VAS scores of both groups were compared at baseline, one month, second month and third month using Independent Sample T test and found to be comparable (p value>0.05).

Table 4: Comparison of presence of joint line tenderness in both groups at baseline, first month, second month and third month

Month	Group	Joint line tenderness n (%)	No joint line tenderness n (%)	P-value
Baseline	Diacerein (n=25)	18(72%)	7(28%)	0.758
	Glucosamine (n=25)	17(68%)	8(32%)	
One month	Diacerein (n=25)	14(56%)	11(44%)	0.571
	Glucosamine (n=25)	12(48%)	13(52%)	
Second month	Diacerein (n=25)	8(32%)	17(68%)	0.556
	Glucosamine (n=25)	10(40%)	15(60%)	
Third month	Diacerein (n=24)	6(25%)	18(75%)	0.263
	Glucosamine (n=25)	10(40%)	15(60%)	

The presence of joint line tenderness in both groups at baseline, first month, second month and third month was compared using Chi-square test and found to be comparable (p value>0.05).

Table 5: Comparison of fasting Total cholesterol values at baseline and at the end of third month

Group	Baseline Total cholesterol(Fasting) % (n)		P-value	Group	Third month Total cholesterol(Fasting) % (n)		P-value
	Within normal limit	Above normal limit			Within normal limit	Above normal limit	
Diacerein (n=25)	80%(20)	20%(5)	1.000	Diacerein (n=24)	87.5%(21)	12.5%(3)	0.667
Glucosamine (n=25)	80%(20)	20%(5)		Glucosamine (n=25)	92%(23)	8%(2)	

All the baseline investigations except total cholesterol (fasting) value were within the normal limits. So total cholesterol at baseline and at the end of third month was compared using Chi-square test between two groups and was found to be comparable (p value>0.05). No adverse drug reactions were noted in both groups during the study period.

Discussion

Osteoarthritis is a chronic musculoskeletal disorder, and it accounts for the majority of knee pain especially in the elderly. Osteoarthritis is a disease that significantly impairs the quality of life and the prevalence of this disease is expected to increase in the coming years. Osteoarthritis is mainly characterized with a defective integrity of articular cartilage with associated changes in underlying bone.

Knee joint is the largest weight bearing synovial joint and one of the most common joints to get affected with osteoarthritis. Pain and stiffness of the affected joint are the main symptoms which significantly affect the movement. Diagnosis of osteoarthritis is made based on the criteria put forward by American college of Rheumatology and grading is done using Kellgren and Lawrence system based on the X-ray.

Osteoarthritis is a progressive disease and no curative treatment options are available till date. Treatment is mainly based on pharmacological and

non-pharmacological methods. NSAIDs are the widely used drugs which give symptomatic relief only and the side effect profile is a major drawback for its use. Corticosteroids are widely used for the management of progressive osteoarthritis. Based on the latest information on the pathogenesis of osteoarthritis many other drugs are also in pipeline. Surgical option like total knee replacement is reserved for end-stage of disease.

Diacerein and Glucosamine are symptomatic slow acting drugs which are widely used in the treatment of osteoarthritis and said to have a disease modifying effect with lesser adverse effects. This study was conducted to compare the efficacy and safety of Diacerein versus Glucosamine in patients with osteoarthritis of the knee. No studies have been conducted in the country previously to compare the efficacy of these two drugs in osteoarthritis.

A total of 50 participants satisfying the inclusion criteria were enrolled into the study of which 25 participants received Diacerein and the rest 25 received Glucosamine. Follow-up was done at first, second, third and fourth month. The fourth month follow-up was to look for carry over effect without giving drug for a month. During the third month one patient in Diacerein group was changed to intra-articular steroids due to persisting pain, so was not included in further follow-up. At the end of fourth month only 3 participants from Diacerein group and 4 participants from Glucosamine group

could complete the study. So carry over effect could not be analysed owing to the limited number of participants. On follow-up, WOMAC score for pain, stiffness, function, total WOMAC score, VAS score, presence of joint line tenderness and effusion and consumption of paracetamol were compared between the groups. Both groups were also closely monitored for presence of any adverse events.

In the present study, age, sex, BMI and grade of osteoarthritis were comparable between the two study groups. In both groups, the majority of participants were females (84% in Diacerein group and 72% in Glucosamine group). Various studies like that conducted by Pal et al in Indian population have shown similar results. The mean age of participants in Glucosamine group was 56.68±6.6 and Diacerein group was 58.60±6.4. According to studies the estimated mean age for diagnosing symptomatic knee osteoarthritis is 55. [21] The mean BMI of patients in the Diacerein group was 23.58±2.6 while that of the Glucosamine group was 24.12±3.2. As per Asian standards BMI above 23 is overweight and is a risk factor for osteoarthritis as well. [22] Grade of osteoarthritis at the time of diagnosis is also an important factor in the prognosis of osteoarthritis. [23]

The number of participants with grade 3 was slightly higher in Glucosamine group and that with grade 2 was slightly higher in Diacerein group. But statistical test showed no significant difference in grade of osteoarthritis between the two groups.

In the present study, the baseline total WOMAC, Sub WOMAC groups, VAS, presence of joint line tenderness and effusion were comparable in both groups. Though the mean WOMAC scores were higher in the Glucosamine group, no statistical significance was noted. The follow-up at first and second month showed similar results. In the third month follow-up, a patient from Diacerein group with grade 3 osteoarthritis had opted for intra-articular steroids and was excluded from the study and analysis was done with rest of participants which showed comparable results (WOMAC A; p value=0.546, WOMAC B; p value=0.241, WOMAC C; p value=0.113 and Total WOMAC; p value =0.183). There are no studies available which directly compare the efficacy of Diacerein and Glucosamine, but for a meta-analysis on efficacy and safety of Glucosamine, Diacerein and NSAIDs in osteoarthritis of the knee conducted by Kongtharvonskul et al endorsed similar results. [24]

The VAS score was also comparable ($p > 0.05$) and showed a significant reduction in both groups at the end of the third month. (Mean VAS score Diacerein=5.11 and mean VAS score Glucosamine=5.39). The meta-analysis from eight different studies showed a similar effect in VAS score (p value =0.964) with lowest VAS score in the Diacerein group.

Joint line tenderness and effusion were reduced in both groups and no statistically significant difference was noted between the groups.

The number of paracetamol tablets consumed per week at the end of third month was also comparable between both groups. The meta-analysis comparing Diacerein and Glucosamine did not compare the above parameters, but the individual drugs had shown statistically significant reduction in the scores. [25,26]

No adverse drug reactions were reported in both groups in this study though the meta-analysis with Diacerein and individual studies with Diacerein had showed a higher incidence of diarrhoea in subjects. [27] All the laboratory investigations were normal at baseline and third month of the study in all participants except for the fasting cholesterol value, hence fasting total cholesterol values were compared between two groups and found to be comparable.

Conclusion

This study was conducted to compare the efficacy and safety of Diacerein versus Glucosamine in knee osteoarthritis. According to the study the efficacy of Glucosamine and Diacerein was comparable on follow-up and no adverse effects related to the drugs were reported in both groups during the study period.

The major limitation of the study is that it couldn't compare the carry over effect and some confounding factors were not taken into account. Hence, a randomized blinded study, for a longer duration and on more number of patients, has to be conducted to find out the superior drug.

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