Original Article

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Investigating the Efficacy and Safety of Diacerein in the Management of Knee Osteoarthritis with reference to its conventional management

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ABSTRACT

Background: Osteoarthritis has been designated as a "priority disease" but a proper treatment is still a major challenge. Although proposed as a drug having better risk-benefit ratio than conventionally used drugs for the treatment of osteoarthritis, the efficacy and safety of Diacerein is unexplored. Hence, this study attempted to investigate the efficacy and safety of Diacerein in the management of knee osteoarthritis.

Methods: This is a cohort study comparing Diacerein (Treatment Group I) with conventionally used drugs (Non-steroidal anti-inflammatory drugs- Treatment Group II) for two months in the management of knee osteoarthritis. Efficacy was assessed by scores of Lysholm Knee Scoring Scale, Knee injury and Osteoarthritis Outcome Score – Physical Function Short form and Western Ontario and McMaster Universities Osteoarthritis Index.

Results: After two months of treatment, in Treatment group I, the mean KOOS-PS decreased from 41.8 ±6.8 to 34.4 ±10.4 and mean WOMAC score decreased from 46.1 ±10.5 to 32.7±13.9. The mean Lysholm score increased from 46.7±15.1 to 57.8±18.1. Similarly, in Treatment Group II, the mean KOOS-PS score deceased from 43.3 ±8.3 to 32.6 ±7.9, mean WOMAC score decreased from 48.1 ±11.0 to 31.8±12.2 and the mean Lysholm score increased from 41.9±18.0 to 58.0±17.9. Gastritis and discoloration of urine were the frequent adverse effects in Treatment group I and Treatment group II respectively.

Conclusions: In the study, Diacerein was as effective as conventional drugs in treating knee osteoarthritis. Diacerein was well tolerated, with a good safety profile. These findings indicate the need for further studies with large scale experimental study.

Keywords: Diacerein; efficacy; knee osteoarthritis; non-steroidal anti-inflammatory drugs ; safety

INTRODUCTION

Osteoarthritis (OA) is a common chronic rheumatic disease affecting a large portion of the population both in developing and developed nations.[1,2] The number of people suffering from OA is augmenting and therefore has been designated as a "priority disease" by the World Health Organization (WHO).[3] Providing a proper medical treatment is still a major public health challenge.[4] Conventionally, Non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly used drugs for the treatment of OA.[5] However, the magnitude of adverse effects associated with these drugs is huge.[6]

Diacerein has been presented as one of the most promising drugs for the management of OA.[7,8] Its adverse effects are mild diarrhoea.[9] Study on efficacy and safety of Diacerein is necessary for the management of a proper treatment regimen for OA as these aspects are not well explored. The main focus of this study is to explore the efficacy and safety of Diacerein in the management of OA.

METHODS

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This is a cohort study conducted among the individuals visiting the Out- patient Department (OPD) of the Orthopaedic Department in Dhulikhel Hospital for six months duration (December 2021 to May 2022). Ethical approval was taken from Nepal Health Research Council (620/2021P) and Institutional Review Committee of Kathmandu University School of Medical Sciences-KUSMS-IRC (249/ 2021).

Newly diagnosed patients who met the American College of Rheumatology (ACR) Clinical Criteria for Osteoarthritis of the knee (Clinical features and Radiographic findings) and graded I /II /III according to the Kellgren Lawrence (KL) grading were included in the study. Patients with abnormal liver and kidney function tests, severe gastro-peptic diseases, other rheumatological disorders, advance stage of osteoarthritis (KL-criteria Grade IV) and patients involved in intra-articular/systemic corticosteroid treatment were not included in the study.

Non-probability sampling was used as the sampling method for this study and the sample size allocated was 210 (105 for Treatment group I (TAB ACECLOFENAC 100 mg OD for 2 weeks and then as needed+ Physiotherapy) and 105 for Treatment group II (TAB ACECLOFENAC 100 mg OD for 2 weeks and then as needed + Physiotherapy+ CAP DIACERIN 50 mg OD for 2 weeks followed by BD for 6 weeks)). Sample size was calculated by using Z1-α/2 as a standard normal variate (1.96 at 5% type I error (P <0.05) where absolute precision or error (d) was taken as 7% at type I error of 5%, previous prevalence of 34% and non- response error of 10%.

The information regarding age, occupation, height, weight and adverse effects were recorded using self-questionnaire. Questions related to the patient's condition were asked according to the standard questionnaire: Lysholm Knee Scoring Scale, Knee injury and Osteoarthritis Outcome Score (KOOS) – Physical Function Short form (KOOS-PS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The variables in this study are: age, gender, occupation, height, weight, BMI, K-L Grade, KOOS-PS Score, WOMAC score, Lysholm Score and adverse effects.

Data was entered in EpiData software v3.1 (EpiData Association, Odense, Denmark) and analysed in the IBM Statistical Package for Social Sciences (SPSS) (version 25.0). All the quantitative variables were expressed in terms of percentage, mean±standard deviation (SD). On the other hand, all the categorical variables were analysed using Pearson's chi square test. P-value < 0.05 was considered statistically significant.

RESULTS

Out of the 326 participants enrolled in the study from December 2021 to May 2022, post treatment data was collected from 118 (78.1%) participants from Treatment Group I and 128 (73.1%) from Treatment Group II (Figure 1).

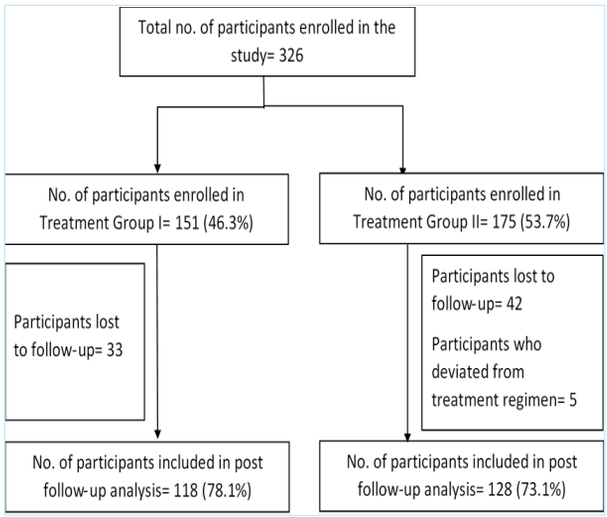

Figure 1. Participants in Treatment Group I and II.

The mean age and BMI of the participants in Treatment group I was 55.7±9.3 years and 24.1±3.7 kg/m^2 respectively. Majority of the participants were females (90, 76.3%). Similarly, the mean age and BMI of the participants in Treatment group II was 58.9±10.8 years and 25.4±3.9 kg/m^2 respectively. Majority of the participants (54, 45.8%) in Treatment Group I were homemakers while 59 (46.1%) of the participants in Treatment Group II were involved in farming (Table 1).

Table 1. Socio-demographic data of the participants in Treatment Group I and II.

	Treatment Regimen I n(%) N=118	Treatment Regimen II n (%) N=128	p value#
Age (years)			
≤50	35 (29.7)	32 (25.0)	0.030
51-60	49 (44.5)	38 (29.7)	
61-70	27 (22.9)	31 (24.2)	
>71	7 (5.9)	27 (21.1)	
Gender			
Male	28 (23.7)	38 (29.7)	0.292
Female	90 (76.3)	90 (70.3)	
BMI (kg/m2)			

Underweight (<18.5)	8 (6.8)	5 (3.9)	
Normal (18.5-24.9)	61 (51.7)	57 (44.5)	0.256
Pre-obese (25.0-29.9)	43 (36.4)	53 (41.4)	
Obese (>29.9)	6 (5.1)	13 (10.2)	
Occupation			
Farmer	49 (41.5)	59 (46.1)	
Housemaker	54 (45.8)	55 (43.0)	0.820
Others*	15 (12.7)	14 (10.9)	

**= Business, Receptionist, Teacher, Army, Security Guard, Driver, Iron material Maker. # Chi-square test*

Most of the participants in Treatment group I had K-L Grade I osteoarthritis (64, 54.2%) and in Treatment group II, most of the participants had K-L Grade II osteoarthritis (47, 36.7%) (Table 2).

Table 2. K-L Grade of the participants in Treatment Group I and II.

K-L Grade	Treatment Regimen I n (%) N= 118	Treatment Regimen II n (%) N= 128	p value#
I	64 (54.2)	36 (28.1)	
II	36 (30.5)	47 (36.7)	<0.001
III	18 (15.3)	45 (35.1)	

 # Chi-square test

The baseline scores KOOS-PS and WOMAC were similar in both the treatment groups (p>0.05). The baseline Lysholm score was slightly higher in Treatment Group I (p<0.05). Similarly, there is also no significant difference among two treatment groups after the treatment period (p>0.05) (Table 3).

Table 3. Baseline and Post- treatment scores in Treatment Group I and II.

	Treatment Group I (N=118)	Treatment Group II (N=128)	p value#
Baseline scores			
KOOS-PS (Mean ± SD)	41.8 ±6.8	43.3 ±8.3	0.123
WOMAC (Mean ± SD)	46.1 ±10.5	48.1 ±11.0	0.164
Lysholm (Mean ± SD)	46.7±15.1	41.9±18.0	0.026
Post treatment scores			
KOOS-PS (Mean ± SD)	34.4 ±10.4	32.6 ±7.9	0.024
WOMAC (Mean ± SD)	32.7±13.9	31.8±12.2	0.138
Lysholm (Mean ± SD)	57.8±18.1	58.0±17.9	0.958

 # Independent t-test

In Treatment group I, the baseline mean KOOS-PS score was 41.8 ±6.8, baseline mean WOMAC score was 46.1 ±10.5 and the baseline mean Lysholm score was 46.7±15.1. Similarly, in Treatment Group II, the baseline mean KOOS-PS score was 43.3 ±8.3, baseline mean WOMAC score was 48.1 ±11.0 and the baseline mean Lysholm score was 41.9±18.0. Two months post treatment, the mean KOOS-PS score decreased to 34.4 ±10.4, mean WOMAC score decreased to 32.7±13.9 and the mean Lysholm score increased to 57.8±18.1 among the participants in Treatment Group I (Figure 2). Among the participants in Treatment group II, the mean KOOS-PS score decreased to 32.6 ±7.9, mean WOMAC score decreased to 31.8±12.2 and the mean Lysholm score increased to 58.0±17.9 (Figure 3). In both the treatment groups, the mean KOOS-PS scores and the mean WOMAC scores have decreased and the mean Lysholm scores have increased significantly (Figure 2 and 3).

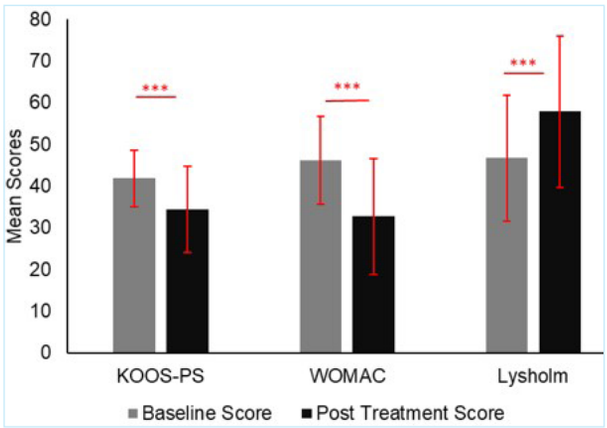

Figure 2. Baseline and Post-treatment scores in Treatment Group I. * -p<0.001.**

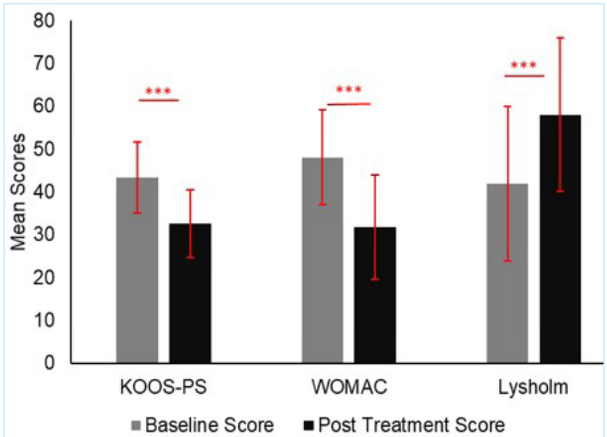

Figure 3. Baseline and Post-treatment scores in Treatment Group II. * -p< 0.001.**

Very few participants in Treatment group I had faced adverse effects such as gastritis (8, 6.8%) whereas more than 80% of the participants in Treatment group II had experienced discoloration of urine which was clinically not significant.

DISCUSSION

In this study, we observed significant improvements in the functional outcome when comparing the baseline scores to the post-treatment scores of both the treatment groups, treatment group I and II. Both the treatment groups were effective in management of osteoarthritis. However, there were no significant differences among the post-treatment scores in two different treatment groups due to which either treatment modality could not be established as superior to another. The participants had had urine discoloration and minor gastritis over the study period, but no serious side effects were reported.

Studies conducted in Pakistan and India observed significant reduction in pain after administration of Diacerein among the patients with osteoarthritis.[3,10] Similar to our findings, in a study conducted in India comparing fixed dose combination (Aceclofenac + Diacerein) and free dose combination for six weeks, there was significant decline in the scores on comparison with baseline score in both groups but inter group comparison revealed no significant difference between the two groups indicating equal efficacy.[11] Three NSAIDs- controlled randomized trials conducted in France in 1994, in China in 2006 and in Thailand in 2007 noted that there was no significant differences between the two interventions.[6,8,12,13] A prospective randomized interventional study comparing Diacerein with S-adenosyl methionine for twelve weeks in the management of OA of the knee found that although minute differences existed, both treatment groups were equally effective in reducing the pain levels.[14] The study by Zheng et al. reported significant improvement in Diacerein group at week 16 demonstrating the carry over effect of Diacerein.[13] Similar findings were observed in a study conducted in India in 2009.[7] These findings could be attributed to the longer duration of their study in comparison to our study findings.

Concurrent to the finding of our study, several studies have stated that no severe adverse effects were recorded during their study.[4,15,16] Discoloration of urine and diarrhoea were the main reported adverse effects with Diacerein.[13] Discoloration of urine is due to elimination of Diacerein metabolite from urine which has no clinical consequences.[17]

This study was an observational study where there was no control on the patient selection. Data was collected from the patients treated by the clinician on his / her clinical judgment. In present study, most of the patients who received Treatment regimen I appear to have lower grade of severity of osteoarthritis, irrespective of age or gender or BMI of the patient. It seems that the clinician was "biased" toward using Diacerein in addition to NSAIDs among the patients with severe grade of OA. Use of Diacerein along with NSAIDs in such population still showed improved outcome in post treatment score as compared to the baseline scores. This indicated that Diacerein can be another promising pharmacological agent in the treatment of knee osteoarthritis along with conventional therapy. Also, this study was mono-centred, and therefore the results cannot be generalized to Nepal.

CONCLUSIONS

In this study, both the treatment regimens were shown to be as effective in treating knee OA patients. We could not establish one treatment regime as superior to another over the two months study period. Urine discoloration and gastritis were the most commonly reported side effects in the Diacerein and NSAID therapy groups, respectively. These findings indicate the need for further studies with experimental study design where the study variables are better controlled for a longer duration such that firm conclusion could be drawn.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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