Comparative Efficacy and Safety of Diacerein in Patients with Knee Osteoarthritis: A Pilot Study

Shakya Shrestha S,[1,2] Tamrakar S,[1] Shrestha R,[1,2] Shrestha R,[3] Basi A,[3] Malla M,[3] Khadka SK[3]

[1]Department of Pharmacology,
[2]Pharmacovigilance unit/ Research and Development Division,
[3]Department of Orthopedics,
Dhulikhel Hospital, Kathmandu University Hospital,
Kathmandu University School of Medical Sciences
Dhulikhel, Kavre, Nepal.

Corresponding Author
Sony Shakya Shrestha
Department of Pharmacology,
Pharmacovigilance Unit/Research and Development Division,
Dhulikhel Hospital, Kathmandu University Hospital,
Kathmandu University School of Medical Sciences
Dhulikhel, Kavre, Nepal.
E-mail: sonyshakya@hotmail.com

Citation

Shakya Shrestha S, Tamrakar S, Shrestha R, Shrestha R, Basi A, Malla M, et al. Comparative Efficacy and Safety of Diacerein in Patients with Knee Osteoarthritis: A Pilot Study. *Kathmandu Univ Med J.* 2021;74(2):260-4.

ABSTRACT

Background

Osteoarthritis (OA) is the most common chronic rheumatic disease. The prevalence of OA is skyrocketing with time. Providing a proper treatment regimen for OA is also growing as a major public health challenge. Conventional pharmacological treatments are mainly for alleviating pain and have some severe adverse effects. Diacerein is a new oral anti-inflammatory drug especially developed for the management of OA having only mild to moderate adverse effects. However, the evidence of efficacy and safety of Diacerein in OA is not well documented and yet to be explored.

Objective

To compare the efficacy and safety of Diacerein in knee OA with conventional non-steroidal anti-inflammatory drugs (NSAIDs).

Method

A comparative study was conducted among knee OA patients attending Out-Patient Orthopedic department in Dhulikhel Hospital, Nepal from December 2019 to September 2020, using self-structured and standard questionnaire. The patients were randomized to receive either a conventional standard treatment (Treatment Group I: NSAIDs) or alternative treatment regimen (Treatment Group II: NSAIDS+ Diacerein). Patients were followed-up after two months and data were analyzed using SPSS 21.0.

Result

Among 72 patients enrolled in this study, majority (44.44%) were between 51-60 years of age in which 81.94% of the patients were female. Post treatment data was collected from 15 participants. The mean KOOS-PS score of the participants in Treatment Group I decreased from 35.56 ± 14.33 to 35.14 ± 12.65 while that of the Treatment Group II participants reduced from 63.31 ± 12.08 to 49.99 ± 13.10 in two months. Similarly, the mean WOMAC score decreased from 46.87 ± 17.80 to 34.37 ± 16.83 in Treatment Group I and from 54.23 ± 14.66 to 46.22 ± 12.16 in Treatment Group II. The mean Lysholm score in Treatment Group I increased from 55.57 ± 8.16 to 60.86 ± 15.01 and in Treatment Group II, it increased from 46.62 ± 13.01 to 60.25 ± 17.598.

Conclusion

Diacerein treatment group had better functional outcome compared to the patients in the treatment group with conventionally used drugs. Also, the adverse effects faced by the patients were minor. The current study are suggestive of better efficacy and safety of Diacerein compared to other drugs.

KEY WORDS

Adverse effects, Diacerein, Efficacy, Osteoarthritis, Safety

INTRODUCTION

Osteoarthritis (OA) is the most common chronic rheumatic disease affecting a large portion of elderly population.[1-3] The incidence of prevalence of OA is expected to skyrocket in the coming years considering the increase in aging population, obesity rates and even the rate of traumatic knee injuries.[4] Both developed and developing countries are facing OA as an increasing important medical challenge thus, designated as a "priority disease" by WHO.[5-7] There are reports suggesting that factors such as age, sex, occupation, diet, weight status and recreational activity are responsible for development and progression of OA.[1,8] Providing a proper treatment for OA is still a major public health challenge.[4] As there are no proper curative measures, the management measures are mainly focused on alleviating pain, reducing functional disability and limiting structural changes through a combination of pharmacological and non-pharmacological methods.[9-11] Pharmacological measures include use of systemic and topical non-steroidal anti-inflammatory drugs (NSAIDs), opioids and intra-articular steroids.[12,13] NSAIDs are usually discontinued due to its side effects and no more than three -four knee joint injections are suggested per year.[5,14] Diacerein is a new oral anti-inflammatory, slow acting, symptom or even disease modifying drug especially developed for the management of OA, recommended by European League against Rheumatism guidelines 2003.[3,10,15] Pain relieving effect is seen immediately after starting the treatment while the disease modifying effect becomes apparent two-four weeks after administration.[9] Mild to moderate diarrhea are frequently reported with Diacerein use which usually decreases with the continuous treatment.[16]

Nowadays, the rampant use of the conventional drugs is increasing alarmingly and so are their adverse effects. The risk-benefit ratio of Diacerein in OA patients has been documented to be far better than NSAIDs or any other conventionally used drugs. However, the evidence of efficacy and safety of use of Diacerein in OA is not well documented and yet to be explored. Therefore, our study attempted to compare the efficacy and safety of Diacerein in knee OA with conventional NSAIDs.

METHODS

A comparative study was conducted in the Dhulikhel Hospital, Kathmandu University Hospital after an ethical approval from Institutional Review Committee, Kathmandu University School of Medical Sciences (IRC-KUSMS) from December 2019 to September 2020. This study was carried out among seventy-two patients visiting the Out-Patient Orthopedic department fulfilling the inclusion criteria. The patients who met the inclusion criteria and gave written consent to the study were interviewed using self-structured questionnaire. A baseline survey was conducted using self-structured questionnaire (personal history, socio-demographics and adverse effects) and clinical/ functional outcomes were measured using standard questionnaire containing various scores (Knee Injury and Osteoarthritis Outcome Score (KOOS-PS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Lysholm). The scale range of all the standard scores was 0-100. For KOOS-PS and WOMAC, higher scores indicate worse condition of OA while for Lysholm, lower scores indicate worse condition of OA. The patients were randomized to receive either a conventional standard treatment i.e, - Treatment group I (NSAIDs+ Physiotherapy) or alternative treatment regimen, i.e - Treatment group II (NSAIDS+ Physiotherapy+ Diacerein). Patients were asked to visit again after two months as per a part of their usual treatment protocol and during that visit, the patients were asked to fill the standard questionnaire containing scores (KOOS-PS, WOMAC and Lysholm) again to carry out the after-treatment survey.

Collected data was entered and analyzed in Statistical Package for Social Sciences (SPSS) software version 21.0. The quantitative data was expressed in percentages and mean ± standard deviation (SD) and presented with the help of relevant tables, charts, and bar-graphs. The flow-chart displaying the step-wise procedure of the data collection and analysis is shown in figure 1.

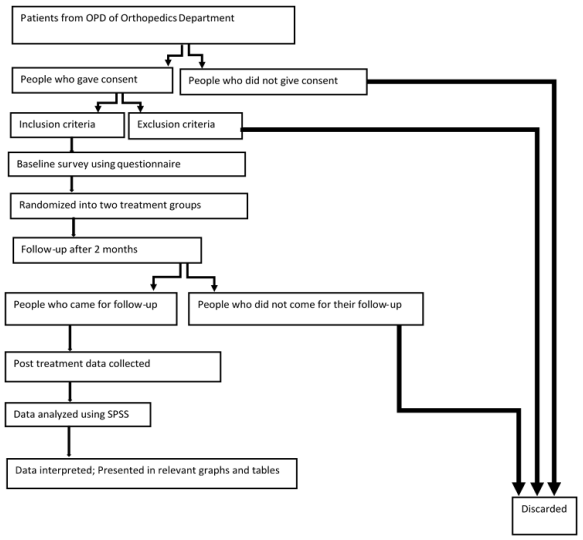

Figure 1. Flowchart showing stepwise procedure of data collection and analysis.

RESULTS

A total of 72 patients who agreed to sign the informed consent and participate in the study were approached. The mean age was 57.24 ± 7.26 years and the majority of the patients 32 (44.44%) were between 51-60 years of age. Figure 2 shows the age group of the 72 participants. Among the 63 patients, 53 (84.13%) were female. The follow-up data was collected from 15 of the participants and all of the participants were female.

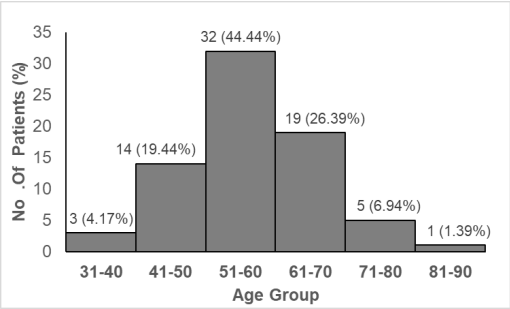

Figure 2. **Bar Diagram showing the age group of 72 participants.**

Majority of the participants, 27 (37.50%) were found to have grade I osteoarthritis based on the K-L (Kellgren and Lawrence) Grade. Table 1 shows the K-L Grade of the 72 participants. Six out of the 15 participants had K-L Grade I Table 2 shows the K-L Grade of the 15 participants.

Table 1. **K-L Grade of 72 participants**

K-L Grade	No. of Participants (%)
0	0(0.00%)
I	27 (37.50%)
II	19 (26.39%)
III	26 (36.11%)
IV	0(0.00%)

Table 2. **K-L Grade of the 15 participants**

K-L Grade	No. of Participants (%)
I	6(40.00%)
II	4(26.67%)
III	5(33.33%)
IV	0(0.00%)

Among 15 participants who came for the follow-up visits, 7(46.67%) were given NSAIDs and 8(53.33%) were prescribed with Diacerein and NSAIDs as shown in figure 3.

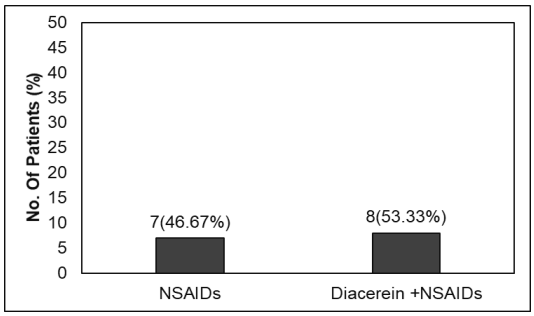

Figure 3. **Treatment Group of 15 Participants**

The mean KOOS-PS score of the participants in Treatment Group I (NSAIDs) before starting the treatment was 35.56 ± 14.33 which decreased slightly after the treatment (35.14 ± 12.65). Similarly, the mean WOMAC score before treatment was 46.87 ± 17.80 and it decreased to 34.37 ± 16.83 after treatment. The mean Lysholm score before the treatment was 55.57 ± 8.16 and it increased to 60.86 ± 15.01 after treatment. The before treatment and after treatment mean scores for Group I is shown in figure 4.

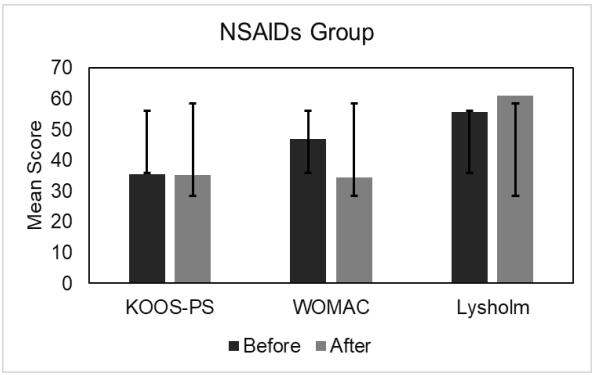

Figure 4. **Mean scores (before and after treatment) for NSAIDs group.**

The mean KOOS-PS score of the participants in Treatment Group II (Diacerein + NSAIDs) before starting the treatment was 63.31 ± 12.08 which decreased to 49.99 ± 13.10 after the treatment. Similarly, the mean WOMAC score before starting the treatment was 54.23 ± 14.66 and at the end of the treatment it decreased to 46.22 ± 12.16. The mean Lysholm score before treatment was 46.62 ± 13.01 and after treatment it increased to 60.25 ± 17.60. The before treatment and after treatment mean scores for Group II is shown in figure 5.

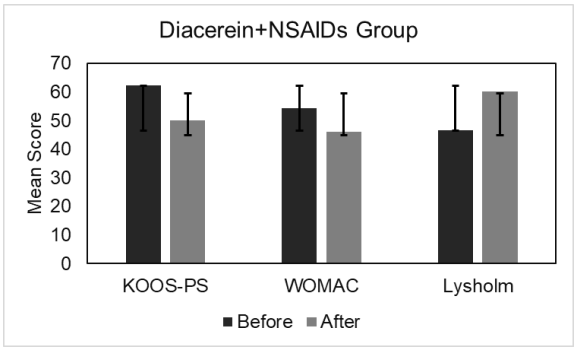

Figure 5. **Mean scores (before and after treatment) for NSAIDs+Diacerein group.**

Out of the 15 participants, 8 (53.33%) experienced discoloration of urine and 7 (46.67%) experienced gastritis during the treatment period as an adverse effect. All the 8 participants having discoloration of urine were in Diacerein treatment group and the rest 7 were in the other group. Figure 6 shows the adverse effects among the 15 participants.

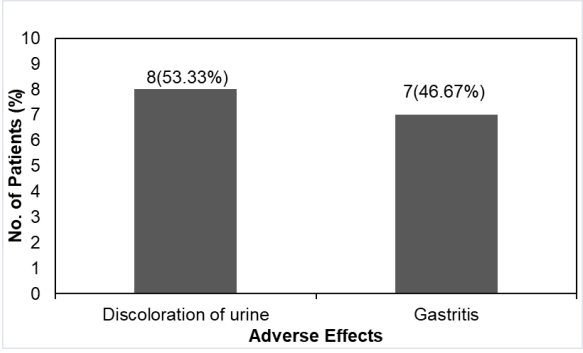

Figure 6. **Adverse effects among 15 participants.**

DISCUSSION

In both developed and developing countries, OA is the most common chronic rheumatic disease.[1,2] It has been designated as a "priority disease" by WHO.[9] The number of OA patients is increasing with the increase in aging population, obesity rates and even the rate of traumatic knee injuries.[4] In this study, the mean age was 59.5 ± 34.65 years and the majority of them were between 51-60 years of age. Similar to this result, in the study conducted by Kawano et al. the mean age was 61.2 ± 11 years.[17] OA is a progressive disease and the symptoms develop gradually, this could be the reason why prevalence of OA is higher in the older adults.

After 50 years, OA is more common in females.[5,18] Majority (84.13%) of the patients in this study were females. In the study by Salve et al. high prevalence of OA in women more than 40 years of age was reported.[19] The high prevalence of OA in women specially after menopause may be because of the depletion of estrogens after menopause as estrogens have a prominent role in bone regrowth and remodeling.[2]

Our study revealed that Diacerein had better functional outcome compared to the conventionally used drug with reference to the KOOS-PS, WOMAC, Lysholm score. Our findings are consistent to the findings of previous study which showed improvement in the baseline WOMAC score in sixweeks with the Diacerein treatment.[9] Similar results have been observed in another study which used Lysholm Knee Scoring Scale to measure the efficacy of Diacerein therapy.[20] Also, in the study by Kongtharvonsku et al the mean functional and stiffness WOMAC scores were significantly lower in the Diacerein groups when compared to the NSAIDs.[15] These results also suggestive of better functional outcome for Diacerein treatment. However, one of the previous study showed no statistically significant differences in the beneficial effects of Diacerein over other NSAIDs.[12] These results show the need of further studies to document the better clinical outcomes of Diacerein.

In this study, the participants with NSAIDs treatment had faced the problem of gastritis and the participants with Diacerein had discoloration of urine. In line with our findings, another study also showed minor adverse effects in which the most common adverse effect was diarrhea followed by discoloration of urine.[12] Similarly, Pelletier et al. also reported mild to moderate diarrhea as the most common adverse effect among Diacerein treated patients.[21] Presence of these minor adverse effects in Diacerein treated patients indicate that Diacerein might be a safer treatment option than the conventionally used drugs.

The major limitation of our study was the Covid-19 pandemic due to which we were unable to reach all the participants for their follow-up. This limited sample size and mono-centered study might not reflect the real scenario of the patients suffering from knee OA in Nepal. Secondly, lack of "gold standard" method of measuring safety and efficacy might limit the interpretation of the study though it is unlikely. Despite these limitations, it is believed that the study has provided a brief preview of the condition of the patients with knee osteoarthritis. Furthermore, the findings might have provided an insight addressing the efficacy and safety of Diacerein. So, it can be believed that the outcomes of this study if measured might help health care professionals and patients to look for alternative measures for more efficient management of OA. Therefore, further detailed research is required.

CONCLUSION

The study intended to explore the efficacy of Diacerein in the management of OA. Management of OA is associated with better functioning of the joints and as a whole improved quality of life. The patients in the Diacerein treatment group had better functional outcome compared to the patients in the treatment group with conventionally used drugs. Also, the adverse effects faced by the patients in the Diacerein treatment group during the treatment period were far more minor compared to the conventional drugs.

REFERENCES

1. Plotnikoff R, Karunamuni N, Lytvyak E, Penfold C, Schopflocher D, Imayama I, et al. Osteoarthritis prevalence and modifiable factors: A population study Chronic Disease epidemiology. *BMC Public Health* [Internet]. 2015;15(1):1-10. Available from: http://dx.doi.org/10.1186/s12889-015-2529-0
2. Bortoluzzi A, Furini F, Scirè CA. Osteoarthritis and its management -Epidemiology, nutritional aspects and environmental factors. *Autoimmun Rev* [Internet]. 2018;17(11):1097-104. Available from: https://doi.org/10.1016/j.autrev.2018.06.002
3. Shin K, Kim JW, Moon K won, Yang JA, Lee EY, Song YW, et al. The Efficacy of Diacerein in Hand Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Study. *Clin Ther* [Internet]. 2013;35(4):431-9. Available from: http://dx.doi.org/10.1016/j.clinthera.2013.02.009
4. Mandl LA. Osteoarthritis year in review 2018: Clinical. *Osteoarthr Cartil* [Internet]. 2019;27(3):359-64. Available from: https://doi.org/10.1016/j.joca.2018.11.001
5. Haq I, Murphy E, Dacre J. http://pmj. bmjjournals. com/cgi/content/full/79/933/377. *Postgrad Med J.* 2003;79:377-83.
6. Tehrani-Banihashemi A, Davatchi F, Jamshidi AR, Faezi T, Paragomi P, Barghamdi M. Prevalence of osteoarthritis in rural areas of Iran: A WHO-ILAR COPCORD study. *Int J Rheum Dis*. 2014;17(4):384-8.
7. Zamri NA, Harith S, Yusoff NA, Hassan NM, Ong YQ. Prevalence, risk factors and primary prevention of osteoarthritis in Asia: a scoping review. *Elderly Health Journal*. 2019; 5(1): 19-31.
8. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *BMJ* [Internet]. 2012;345(July):e4934. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22846469
9. Bhat TJ, Bhat JA, Bhat F. Comparative analysis of analgesic efficacy, safety and compliance of fixed dose combination (Aceclofenac + Diacerein) versus free drug combination in 400 patients of early Osteoarthritis knee. *International Journal of Pharmacological Research.* 2017;07(05):107-19.

10. Akhter N, Khan AA, Ayaz S Bin, Akhter SMH, Afzal A. Diacerein: a treatment option in painful primary knee osteoarthritis. P*akistan Armed Forces Med J.* 2015;65(1):77-80.

11. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64(4):465-74.

12. Gupta N, Datta S. Effi cacy and safety of diacerein and diclofenac in knee osteoarthritis in Indian patients- a prospective randomized open label study. J Biomed Sci. 2012;1(1):1-14.

13. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JWJ, Dieppe P, et al. EULAR Recommendations 2003: An evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2003;62(12):1145-55.

14. Courtney P, Doherty M. Key questions concerning paracetamol and NSAIDs for osteoarthritis. *Annals of the rheumatic diseases.* 2002 Sep 1;61(9):767-73.

15. Kongtharvonskul J, Anothaisintawee T, McEvoy M, Attia J, Woratanarat P, Thakkinstian A. Efficacy and safety of glucosamine, diacerein, and NSAIDs in osteoarthritis knee: A systematic review and network meta-analysis. *Eur J Med Res*. 2015;20(1):1-11.

16. Pavelka K, Bruyère O, Cooper C, Kanis JA, Leeb BF, Maheu E, et al. Diacerein: Benefits, Risks and Place in the Management of Osteoarthritis. An Opinion-Based Report from the ESCEO. *Drugs and Aging.* 2016;33(2):75-85.

17. Kawano MM, Araújo ILA, Castro MC, Matos MA. Assessment of quality of life in patients with knee osteoarthritis. *Acta Ortopédica Bras*. 2015;23(6):307-10.

18. Cho HJ, Chang CB, Kim KW, Park JH, Yoo JH, Koh IJ, et al. Gender and Prevalence of Knee Osteoarthritis Types in Elderly Koreans. *J Arthroplasty* [Internet]. 2011;26(7):994-9. Available from: http://dx.doi.org/10.1016/j.arth.2011.01.007

19. Salve H, Gupta V, Palanivel C, Yadav K, Singh B. Prevalence of knee osteoarthritis amongst perimenopausal women in an urban resettlement colony in South Delhi. *Indian J Public Health*. 2011;54(3):155.

20. Gayathri CR, Vanitha S, Felix JW, Nirmala P. Comparative analysis of efficacy and safety of diacerein versus s-adenosyl methionine in the management of Osteoarthritis of knee joint. *Int J Curr Pharm Res*. 2017;9(6):46-51.

21. Pelletier J, Yaron M, Haraoui B, Cohen P, Nahir MA, Choquette D, et al. Efficacy and safety of diacerein in osteoarthritis of the knee. *Arthritis Rheum.* 2000;43(10):2339-48.