

Comparison Of Naproxen And Diacerein In The Treatment Of Knee Joint Osteoarthritis

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Abstract

Background: Knee osteoarthritis is a common disease in older age. Pain and limitation of movement are the main symptoms of knee osteoarthritis. Many pharmacological options are available for symptomatic relief but NSAIDs are mostly prescribed. Diacerein is also prescribed for osteoarthritis but data regarding its efficacy is still controversial. Moreover, studies regarding the comparison of diacerein with NSAIDs are deficient in Pakistan.

Objective: The objective of the study was to compare the clinical efficacy of naproxen (NSAID) with diacerein in treating knee osteoarthritis.

Methodology: Patients fulfilling inclusion criteria were included in the study. After written informed consent 60 patients of knee osteoarthritis were included in the study. They were divided randomly into two groups. Group A (n=30) was prescribed with tablet naproxen 500mg twice daily and group B (n=30) was given capsule diacerein 50mg twice daily for 12 weeks. Baseline VAS and WOMAC scores of the patients were noted. These scores were compared with scores achieved 12 weeks after intervention. Intra-group comparison of the scores was also carried out. SPSS version 23.0 was used for statistical analysis.

Results: WOMAC and VAS scores comparison of the two groups (A & B) before intervention showed an insignificant p-value that is 0.815 for the WOMAC score and 0.509 for the VAS score. After intervention mean WOMAC score i.e. 10.50 ± 2.46 of group A (treated with naproxen) was better than the mean 29.62 ± 7.03 of group B (treated with diacerein) showing significant p-value (< 0.001). Similarly mean VAS of group A 1.92 ± 0.58 improved more than the mean VAS of group B i.e. 3.38 ± 0.75 with significant p-value (< 0.001). Intra-group comparison of the groups also showed a significant p-value.

Conclusion: Clinical efficacy of naproxen is better than diacerein in treating knee osteoarthritis.

Keywords: Knee osteoarthritis, NSAIDs, naproxen, diacerein, WOMAC score, VAS

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1. Introduction

Osteoarthritis is a disease that affects joints and causes inflammation. It generally involves the knee, hip and spine causing a decrease in function because of joint space narrowing. This is the result of loss of hyaline cartilage and sclerotic bone changes in the joint.^[1]

Osteoarthritis is a degenerative joint disease and the most common form of arthritis. There is an intricate interaction of genetic, metabolic, biochemical and bio mechanical factors, resulting in damage to articular cartilage. There is the activation of inflammatory responses that involve anatomical structures of the joint that are cartilage, subchondral bone and synovium.^[2]

Worldwide 18% of females and 10% of males aged more than 60 years have symptomatic OA. Prevalence of OA increases with age and it is more common in women.^[3,4] As OA is associated to aging;

its prevalence is expected to increase so that it will be the greatest cause of disability in 2030. OA results in a decrease in the quality of an individual's life and increases the burden on health care system.^[5] Several factors contribute to the development of knee OA like age, weight, sex, type of activity, mal alignment of knee, genetic factors, etc.^[6]

Knee OA is a common disease and the most common type of presentation in patients suffering from OA. Clinically it is labelled through a plain radio graph using *Kallgren and Lawrence classification*.^[7] The diagnosis of OA is complex as there is a lack of specific physical and laboratory findings. The *American College of Rheumatology* has recommended criteria for knee OA diagnosis. Out of three criteria including clinical only, clinical plus radiologic and clinical plus laboratory, one can be used for diagnosis of knee OA.^[8]

Knee OA management includes non-pharmacological and pharmacological options. Knee replacement

surgery is also an option but is associated with serious risk and even severe pain and disability after surgery. Therefore pharmacological options are a mainstay for the treatment.^[9] Among these NSAIDs are the most commonly prescribed drugs for OA. Guidelines for management of OA recommend oral NSAIDs to the patients with persistent symptoms with or without topical NSAIDs. The underlying mechanism is inhibition of cyclo-oxygenase pathway, producing analgesic and anti-inflammatory effect.^[10] Naproxen is one of the non-selective NSAIDs that inhibits both isoforms of cyclo-oxygenase. It has better cardiovascular profile and milder gastrointestinal adverse effects as compared to other NSAIDs.^[11]

Chondroprotective agents that act on the underlying pathological agent in osteoarthritis providing symptomatic relief with less adverse effects are categorized as *Symptomatic slow acting drugs for osteoarthritis (SYSADOA)*. This group includes chondroitin sulfate, glucosamine, avocado-soybean unsaponifiable and diacerein. These are expected to limit the progression of osteoarthritis.^[12] Diacerein is an anthraquinone with an active metabolite called rhein. It is an oral Interleukin 1 β inhibitor and has moderate analgesic and anti-inflammatory effect. It acts on all tissues of the joint in OA including synovial membrane and articular cartilage.^[13] Diarrhoea is the most common adverse effect of diacerein that is mostly time limited. Cardiovascular adverse effects are not observed with diacerein.^[14]

To provide better management to the patients, our practitioners should know risks and benefits of the available drugs.^[16] Although Naproxen and diacerein are prescribed by the physicians to OA patient no research has been conducted to compare their efficacy in Pakistan. Hence the objective of this study is to compare the effects of naproxen and diacerein on knee osteoarthritis.

2. Materials & Methods

It is an open label, randomized clinical trial conducted in medical OPD from September 2018 to April 2019. The sample size was calculated by comparing two means on www.Openepi.com to be 23 members in each group. However 30 patients were registered in each group.

Males and females having age equal and above 50 years, having pain in one or both knees were included in the study. These patients had clinical and X-ray findings according to the clinical criteria of *American college of rheumatology*. Patients with known hypersensitivity to the study drugs and *Kallgren-Lawrence grade* of 0 or 4 were excluded from the study. Moreover overweight patients with body mass index above 30 and received corticosteroid therapy in 3 months preceding enrolment in the study were also excluded.

After written informed consent 60 knee OA patients were registered in the study. These were randomly divided into two groups using systematic sampling technique. Group A (n=30) was prescribed with tablet Naproxen 500mg twice daily and group B (n=30) was given capsule Diacerein 50mg twice daily. The required demographic profile and condition of the involved joint were noted on Performa designed for the study. Pain at movement on *Visual analogue scale (VAS)* and *WOMAC score (Western Ontario and McMaster Universities Osteoarthritis)* were assessed at the beginning before giving drugs. The same parameters were assessed at the 6th week and 12th week of prescribing drugs. VAS is marked from 0 (no pain) to 10 (severe pain). *WOMAC score* is a 24 item questionnaire graded on *Likert scale* from 0 to 4. Statistical analysis was done using SPSS version 23.0. The normality of the data was checked by constructing histogram. Scores of the two groups before and after intervention were compared by applying a t-test. P-value < 0.05 was considered significant.

3. Results

The study was conducted on 60 patients of knee OA which were randomly divided into two groups i.e. A (n=30) and B (n=30). During the study, 4 participants of group A and 6 patients of group B dropped out. Data of the patients for each parameter showed normal distribution on histogram demonstrating well defined bell shaped curve with no outliers. The demographic profile of the patient showed 68.33% females and 31.66% males having mean BMI of 27.9. Right sided knee OA was noted in 73.33% of the participant and 26.66% were suffering from left sided knee OA. (Table 1)

Table-1 Demographic profile of participants

Parameter	Group A	Group B
Total number of patients (n)	30	30
Males	8 (26.67%)	11 (36.67%)
Females	22 (73.33%)	19 (63.33%)
Dropout	4	6
Mean age	57.03 ± 4.86 [§]	57.69 ± 4.55 [§]
Mean BMI	27.71 ± 1.39 [§]	28.09 ± 1.53 [§]

Group A treated with Tab Naproxen 500mg twice daily

Group B treated with Cap Diacerein 50mg twice daily

[§] Mean ± standard deviation

WOMAC score of the two groups was compared before intervention that showed insignificant P-value. After 12 weeks of drugs WOMAC score of the two groups was compared again and showed significant P-value i.e. < 0.05. (Table 2)

Table-2 Comparison of WOMAC score of Group A and B before and after intervention

	Group A(n=26) (Naproxen) Mean ± standard deviation	Group B(n=24) (Diacerein) Mean ± standard deviation	P-value*
WOMAC score Before intervention	36.27 ± 8.57	36.83 ± 10.04	0.815**
WOMAC score After intervention	10.50 ± 2.46	29.62 ± 7.03	< 0.001***

WOMAC score = Western Ontario and McMaster Universities Osteoarthritis

*Student t-test

** P-value > 0.05 is insignificant

*** P-value <0.05 is significant

VAS score (pain at movement) of the two groups was also compared before and after intervention, that showed improvement in means of both groups but P-value was significant showing greater improvement in group A. (Table 3)

Table-3 Comparison of VAS score of group A and B before and after intervention

	Group A (Naproxen) Mean ± standard deviation	Group B (Diacerein) Mean ± standard deviation	P-value*
VAS score Before intervention	5.57 ± 0.78	5.40 ± 0.77	0.509**
VAS score After intervention	1.92 ± 0.58	3.38 ± 0.75	< 0.001***

VAS = Visual analogue score

*Student t-test

** P-value > 0.05 is insignificant

*** P-value <0.05 is significant

WOMAC and VAS scores were also compared within the groups. Comparison of the scores for group A showed significant P-value. (Table 4) Diacerein (group B) showed less improvement in WOMAC and VAS scores as compared to Naproxen (group A) but comparison of the scores within group B showed significant P-value. (Table 4)

5. Discussion

In our study 60 patients of knee OA were divided randomly into two groups. More females (68.33%) were suffering from osteoarthritis than males (31.67%). Mean BMI of the patients was higher than normal i.e. 27.9. In this study patients in group A (naproxen) showed significantly greater improvement in WOMAC and VAS scores as compared to group B (diacerein). Hence Naproxen (one of the NSAIDs) give better symptomatic improvement than diacerein. This is consistent with an open label, prospective comparative study conducted on 40 knee OA patients in Nepal. These patients were divided into two groups.

Group A were given diacerein 50 mg twice daily orally and group B was given aceclofenac 200mg sustained release tablets once daily orally for 4 weeks. VAS and WOMAC scores were compared before and after intervention. Group B showed better results than group A however diacerein showed a significant decrease in scores in intra-group analysis.[16] Another study was conducted in China on 223 patients of knee OA. The participants were randomized into two groups; one group was given diacerein 100mg/day and other was prescribed diclofenac 75mg/day. At the end of 17 weeks the study demonstrated diclofenac showed significantly greater improvement in VAS and WOMAC score than diacerein (P-value < 0.05). Hence the results are in harmony with our study. [17]

Table-4 Comparison of WOMAC and VAS scores within Group A (Naproxen) and Group B (Diacerein) before and after intervention

Study Group		Before intervention	After intervention	P-value*
Group A	WOMAC score	36.27 ± 8.57	10.50 ± 2.46	< 0.001**
	VAS score	5.27 ± 0.78	1.92 ± 0.58	< 0.001**
Group B	WOMAC score	36.83 ± 10.04	29.62 ± 7.03	0.002* *
	VAS score	5.40 ± 0.77	3.38 ± 0.75	< 0.001**

WOMAC score = Western Ontario and McMaster Universities Osteoarthritis

VAS = Visual analogue score

*Student t-test

** P-value <0.05 is significant

A study was conducted on patients of knee osteoarthritis randomly divided into two groups. One

group received diacerein 50mg twice daily and other group received celecoxib 200mg once daily for 6 months. Contrary to our study an insignificant difference was found in WOMAC scores of the two groups after intervention (P-value = 0.597). The inter-group difference was 0.7 (95% CI), meeting the non-inferiority margin. The contrast in results of the two studies is may be because of difference in duration of the studies and also celecoxib belongs to selective COX 2 inhibitor subgroup of NSAIDs as compared to naproxen.[18]

In this study when WOMAC and VAS scores of patients receiving naproxen (group A) were compared, before and after intervention, which showed highly significant results (P-value < 0.001). A double blinded, placebo controlled trial conducted with low dose naproxen showed similar results. 818 participated were recruited in the study for 7 days. The patients were assessed for stiffness after rest, day and night pain and 50 feet walking time. It was observed that pain and stiffness scores improved from baseline. Both investigators and participant rated naproxen as ‘good’ or ‘excellent’.[19] A double blinded, randomized study was conducted to observe analgesic effects of naproxen on brain response to painful stimulus, using fMRI pain sequence. Total 25 patients of knee OA were randomly given naproxen, placebo or no treatment in three different sessions. A significant reduction in subjective pain scores was observed with naproxen as compared to other groups (p-value = 0.037). It was concluded that naproxen causes significant reduction in brain response to pain. [20]

This study also demonstrated statistically significant improvement of the scores after 12 weeks of diacerein administration compared to the baseline scores of the participants. Concordant outcome was seen in a quasi experiment conducted in Rawalpindi on ninety patients of knee OA. The patients were in grade I to III according to *Kallgren-Lawrence radiological classification*. Diacerein 50mg /day was administered orally to patients for 4 months. A significant reduction in VAS was observed (p<0.001). The study recommended Diacerein for mild to moderate KOA.[21] A retrograde study was conducted in Lahore on 40 patients of OA. Baseline VAS and WOMAC scores were compared with scores after prescribing 100mg of diacerein for 6 months. The means of VAS (5.88+1.20)

and WOMAC (48.78+6.42) score decreased to 3.58+3.22 and 36.20+20 respectfully after diacerein administration ($p < 0.05$). Authors recommended it as alternative drug if symptoms do not ameliorate with conventional analgesics. [22]

5. Conclusion

It can be concluded that naproxen is better than diacerein in improving symptoms of knee OA. However diacerein can be used alone for controlling OA symptoms. Further studies are warranted to compare adverse effects and laboratory parameters for NSAIDs and Diacerein in Pakistan.

CONFLICTS OF INTEREST- None

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Contributions:

M.M, A.K, T.S, - Conception of study

M.M, A.K, - Experimentation/Study conduction

A.K, T.S, M.M, I.S, S.T.A -

Analysis/Interpretation/Discussion

M.M, M.M, I.S, S.T.A - Manuscript Writing

T.S, M.M, - Critical Review

M.M, A.K, T.S, I.S, S.T.A - Facilitation and Material analysis

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