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Original Research Article

Randomized double blind comparative study on efficacy and safety of oral oxaceprol 200 mg versus oral diclofenac 50 mg in patients with moderate osteoarthritis

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ABSTRACT

Background: Osteoarthritis of knee is the most common form of arthritis globally, approximately 250 million people are suffering from osteoarthritis of the knee alone throughout the world. It is a chronic joint disease leading to cause cartilage degradation that involves synovial Inflammation, Subchondral bone remodelling, and Formation of osteophyte pathologically, which leads to cause pain, joint destruction and difficulty in walking. Aim of the current study was to compare the safety and efficacy of oxaceprol 200 mg versus diclofenac 50 mg in patients with moderate osteoarthritis and to determine cost-effectiveness between these two drugs

Methods: this is a randomized controlled study, in our study total of 94 patients were screened, of which 85 patients met inclusion and exclusion criteria. In this, 78 members gave written informed consent, they were randomly assigned by double-blind fashion into two treatment groups (oxaceprol and diclofenac). Results were analyzed by applying paired and unpaired student t-test by using SPSS software

Results: In our study, both oxaceprol and diclofenac were extremely significant in reducing joint pain and joint stiffness and improving physical activity, but when comparing with one another oxaceprol group showed better results in improving physical activity

Conclusions: From our study, it is concluded that oxaceprol is equally efficacious as diclofenac in reducing knee pain, joint stiffness but more efficacious than diclofenac in improving physical activity of patients by enhancing bone remodelling.

Keywords: Oxaceprol, Diclofenac, Osteo Arthritis, Randomized controlled trial

INTRODUCTION

Osteoarthritis (OA) is a common musculoskeletal disorder characterized by joint pain and reduces joint performance and weight-bearing efficiency in patients.[1] It is the leading cause of pain and the fastest Increasing cause for morbidity and disability globally. It is a chronic joint disease leading to cartilage degradation that involves synovial Inflammation, Subchondral bone remodelling, and the Formation of osteophyte.[2,3] Previously osteoarthritis was thought to be a normal consequence of aging but now proved that osteoarthritis results from a group of multiple factors such as genetic predisposition, mechanical forces, local inflammation by cellular and biochemical processes.[4] Osteoarthritis of knee is the most common form of arthritis. Approximately 250 million people are suffering from osteoarthritis of the knee alone throughout the world.[5]

According to the WHO report (2017), 18% of women and 6.9% of men aged over 60 suffer from osteoarthritis.[6] In Asia, it is estimated the fourth leading cause of disability, the prevalence of osteoarthritis in the Indian population is about 4% in urban and 6% in rural areas.[7,8] Osteoarthritis is a progressive degenerative disease, so in chronic patients, joint replacement surgery is the best and last treatment option. But the joint replacement procedure is available at only a few specialized centers and expensive. Hence, the invention of new drugs will be a good option for preventing the disease's progression. Here in our study, we observe such newly developed and launched molecule oxaceprol after approval by CDSCO India. The number of studies on oxaceprol is less, and studies comparing oxaceprol and diclofenac are not done yet in India, so we choose these two drugs for our study.

METHODS

Written informed consent explained and obtained acceptance from the patient and their guardians before enrolment. The present study is conducted in the orthopedics department, Government general hospital, Rangaraya medical college, Kakinada, East Godavari district, Andhra Pradesh, India. The study duration was from July 2019 to September 2020. The study conducted for a period of 3 weeks and each patient was assessed at 0, 10th, and 21st days after initiation of therapy.

Inclusion criteria

Newly diagnosed patients of moderate osteoarthritis based on the "Kellgren and Lawrence system for classification of osteoarthritis of knee" in both genders, between the age group of 40 to 80 years were included in the study.

Exclusion criteria

Patients with rheumatoid arthritis and gout, patients who were suffering from abnormal liver or kidney function and patients with a history of gastrointestinal surgeries and patients who were hypersensitive to test medication and who were receiving anticoagulant therapy and who were taking intra articular corticosteroids for the last two months were excluded from study.

Study procedure

After meeting the study criteria, the study protocol is provided to them in their preferred language. Necessary time was given to them to decide whether to participate or not. If they were willing to participate, written informed consent is obtained from them, and a patient identification number (PID) was allotted to them. The enrolled patients are randomly allocated into two groups (A & B), which was predetermined by computer-based randomization. According to the group to which they were assigned, the treatment was provided in a double-blinded manner. The randomization code and blinding will be unmasked at the end of the study or if any serious ADR occurs. At the start of the study, general demographic information, proper medical history is obtained, and baseline investigations are performed and recorded in patient CRF. After obtaining baseline scores using specified assessment parameters patients are given respective study medication based on the group they are being allotted. Group A: will receive tablet oxaceprol 200 mg thrice daily. Group B: will receive tablet diclofenac 50 mg thrice daily.

The study medications were given at 0 day then at 10thday and advised them to come on follow-up visit at 10th & 21st day for assessment, during each follow-up interim history was taken, necessary assessment parameters were collected and enquired about the compliance and adverse effects. During each visit, tablets were provided for treatment days until the next schedule of follow up. Extra tablets were provided to the patient on day 0, and each follow up visit. They are advised to bring the remaining tablets during each follow-up visit. patients were instructed to note down if any missed doses or broken tablets, or spilled tablets from the strip on the patient's diary, which is provided at the beginning of the study. If the patient is illiterate, he or she is advised to help any literate in their house or nearby. The patients who were non-compliant with the use of study medication and followed up as per the study procedure and the patients who did not complete the total study period (i.e. 3 weeks) were not considered for the final analysis of the study.

Assessment parameters

The efficacy will be analyzed by assessing the WOMAC index (Western Ontario and McMaster universities), quality of life can be assessed by WOMAC questionnaire (the osteoarthritis knee and hip quality of life), safety will be analyzed by reporting adverse events, with their assessment as mild, moderate, and severe, and the investigator's opinion of their relationship to treatment with each drug (none, likely, possible or probable).

Statistical analysis

At the end of the study blinding is disclosed. The data are expressed as Mean±SD. The data of the patients who completed three weeks of follow up are only considered for analysis, $p<0.05$ was considered as statistically significant. Results were analyzed by applying paired and unpaired student t test by using SPSS software (version: 20). The analysis was started when the last patient completed the total study period.

RESULTS

In the present study, a total of 94 patients were screened, of which 85 patients met inclusion and exclusion criteria. In this, 78 members gave written informed consent, and 7 members refused to give written informed consent. These

78 patients were randomly assigned in a double-blind fashion to two treatment groups (38 in group A and 40 in group B). At the time of analysis, the blinding was revealed, and it is tablet oxaceprol 200 mg for group A and tablet diclofenac 50 mg for group B (Figure 1). During the study period, 2 patients from group A and 3 patients from group B lost to 1st follow up during 10th day due to personal reasons, and 2 patients from group A and 1 patient from group B lost to 2nd follow up during 21st day. A total of 70 (34 with group A intervention and 36 with group B intervention) patients had completed the 3 weeks follow up. The final results were collected and presented as mean±SD for each parameter. Out of 34 patients in group A, 22 were males, and 12 were females. Out of 36 patients in group B, 20 were males, and 16 were females. In the present study majority of the patients were males (60%). Out of 34 patients in group A, 10 patients were between 40-55 years age group, 18 patients were between 55-70 years age group, 6 patients were >70 years. The mean age of the patients in this group was 58.4±19.6 years. Out of 36 patients in group B, 07 patients were between 40-55 years age group, 23 patients were between 55-70 years age group,08 patients were >70 years. The mean age of the patients in this group was 60.9±18.9 years.

Table 1: Western Ontario and McMaster universities osteoarthritis index score changes in the oxaceprol (N=34) study group by paired test.

Parameter WOMAC	Group: Oxaceprol	Baseline, 0 day	1st follow up, 10th day	2nd follow-up/end of the study, 21st day
Pain	Mean±SD	9.91±3.32	7.32±2.81	5.02±2.59
	P value	<0.0001	<0.001	<0.001
Stiffness	Mean±SD	4.75±1.75	3.91±1.66	2.91±1.58
	P value	<0.0001	<0.0001	<0.0001
Physical activity	Mean±SD	35.35±8.22	31.32±8.61	27.44±9.01
	P value	<0.0001	<0.0001	<0.0001

Table 2: Western Ontario and McMaster universities osteoarthritis index score changes in the diclofenac (N=36) study group by paired test.

Parameter WOMAC	Group: Diclofenac	Baseline, 0 day	1st follow up, 10th day	2nd follow-up/end of the study, 21st day
Pain	Mean±SD	8.33±3.68	7.22±4.06	5.50±3.40
	P value	<0.0001	<0.0001	<0.0001
Stiffness	Mean±SD	4.47±2.09	3.75±2.29	3.17±2.21
	P value	<0.0001	<0.0001	<0.0001
Physical activity	Mean±SD	17.75±7.99	15.86±7.75	14.25±7.62
	P value	<0.0001	<0.0001	<0.0001

Efficacy assessment

Drug A, oxaceprol: in drug A (oxaceprol n=34) group, the baseline WOMAC index scores for pain is 9.9+3.32, joint stiffness is 4.75+1.75, and physical function is 35.35+8.22 and these parameters observed on the 10th and 21st day and recorded values and assessed through paired t test. It was observed that there is a significant difference (p value <0.0001) in the reduction of pain, joint stiffness, and improved physical activity from baseline to 10th day and 21st day within the groups (Table 1).

Drug B, diclofenac, in drug B (diclofenac n=36) group, the baseline WOMAC scores for pain is 8.33+3.68, joint stiffness is 4.47+2.09, and physical function is 17.75+7.99 and these parameters observed on the 10th and 21st day and recorded values and assessed through paired t test. It was observed that there is a significant difference (p value <0.0001) in the reduction of pain, joint stiffness, and improved physical activity from baseline to 10th day and 21st day within the groups (Table 2).

Safety assessment

Patients who were prescribed with respective intervention drugs tolerated well, but few were presented with side effects during the treatment phase. The adverse events did not cause discontinuation of treatment in any of the cases.

In group A (14.7%), 5 out of 34 patients were presented with adverse events, and in group B (19.4%), 7 out of 36 patients were presented with adverse events. The adverse events were not completely similar in both the groups (Table 4).

Table 3: Western Ontario and McMaster universities osteoarthritis index score changes in the oxaceprol (n=34), diclofenac (n=36) study groups by the unpaired test (efficacy analysis).

Parameter WOMAC	Groups	1st follow up, 10th day	2nd follow up/end of the study, 21st day
Pain	Oxaceprol (N=34)	7.32±2.81	5.02±2.59
	Diclofenac (N=36)	6.94±3.62	5.50±3.40
	Intergroup p value	0.6276	0.4935
Stiffness	Oxaceprol (N=34)	3.91±1.66	2.91±1.58
	Diclofenac (N=36)	3.75±2.29	3.17±2.21
	Intergroup p value	0.7369	0.5829
Physical activity	Oxaceprol (N=34)	31.32±8.61	27.44±9.01
	Diclofenac (N=36)	15.86±7.75	14.25±7.62
	Intergroup p value	<0.0001	<0.0001

Table 4: Safety profile assesment.

Adverse event	Group A (N=5)		Group B (N=7)	
	Frequency	%	Frequency	%
Nausea	02	40	03	42.8
Vomiting	00	00	01	14.2
Gastric irritation	01	20	03	42.8
Gastric pain	00	00	00	00
Drowsiness	00	00	00	00
Dizziness	00	00	00	00
Diarrhoea	01	20	00	00
Headache	01	20	00	00

Table 5: Cost-effective analysis between oxaceprol and diclofenac groups.

Parameters (WOMAC score)	Oxaceprol group	Diclofenac group	P value
Reduction in pain	5.00±1.28	2.86±0.80	<0.0001
Reduction in joint stiffness	1.82±0.58	1.19±0.40	<0.0001
Improved physical activity	7.91±2.39	3.50±1.03	<0.0001

Cost- effectiveness analysis

In our study, both oxaceprol and diclofenac were extremely significant in reducing joint pain and joint stiffness and improving physical activity, but when comparing with one another oxaceprol group has more in the reduction of joint pain and joint stiffness score and improving physical activity, but now we can't comment on cost-effectiveness here due to short period observation of our study, it needs longterm studies for proper analysis (Table 5).

DISCUSSION

The present study was conducted to evaluate the efficacy and safety of oxaceprol versus diclofenac in moderate osteoarthritis of the knee. In this study, by the end of the study period (3 weeks), oxaceprol and diclofenac showed statistical significance in the reduction of WOMAC index features (joint pain, joint stiffness, physical function) (Table 3), it is indicating that both the treatments were effective in reducing bone pain and joint stiffness in both study groups (Figure 2-3), but the group which is receiving Oxaceprol showed improved quality of life by improving physical activities too when comparing with diclofenac group (Figure 4).

Figure 1: Study participants.

When comparing current study with Mukhopadhyay et al study (Table 6), the study drug, study design and the primary and secondary objectives were similar and differences were like the sample size, recruitment of age group, drug dosage form and the study duration. While considering about results both studies showed oxaceprol is an alternative therapy for both opioids and diclofenac in osteoarthritis patients.[9]

Table 6: Comparison of Mukhopadhyay et al with the current study.

Criteria	Mukhopadhyay et al	Current study		
Problem understudy	Osteoarthritis of knee	Moderate osteoarthritis of knee		
Objective	To assess efficacy and safety of Oxaceprol	To assess efficacy and safety of Oxaceprol		
Study design	Parallel group, double-blind, randomized controlled trial	Randomized, double-blind, Comparative study		
Sample size	91	78		
Age group (years)	>50	>45		
Drug dosage	Cap. Oxaceprol 200mg p/o t.i.d Cap. Tramadol 50mg p/o t.i.d	Tab. Oxaceprol 200mg p/o t.i.d Tab. Diclofenac 50mg p/o t.i.d		
Study duration (weeks)	12	3		
Efficacy parameters	WOMAC INDEX VAS scale	WOMAC INDEX VAS scale		
Side effects	Incidence of side effects was similar in both groups but less with oxaceprol group		Oxaceprol	Diclofenac
		Nausea	02	03
		Vomiting	00	01
		Gastric irritation	01	03
		Diarrhoea	01	00
		Headache	01	00
Conclusion	Oxaceprol can be considered as an alternative to low potency opioids in the management of knee osteoarthritis.	Oxaceprol can be considered as a better alternative to Diclofenac in Osteoarthritis with minimal side effects, and it is cost-effective also.		

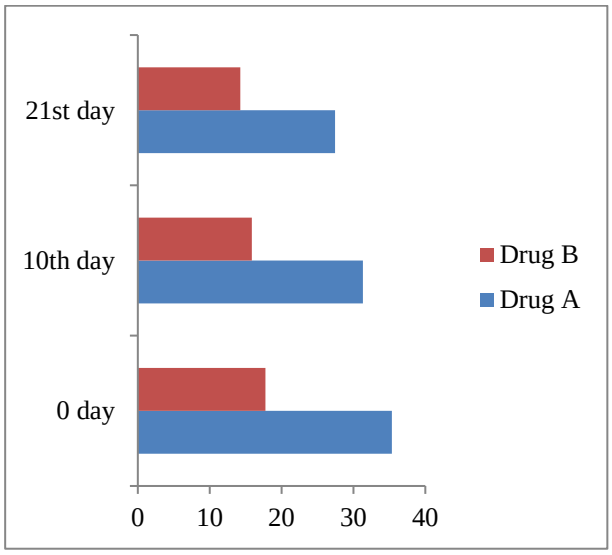

Figure 2: WOMAC score (joint pain) difference between two groups.

When comparing current study with Herrmann et al study (Table 7), the study drug, study design, drug dosage form and the primary and secondary objectives were similar and differences were like the sample size, recruitment of age group, drug dose and the study duration. While considering about results both studies showed similar results like oxaceprol is a better alternative in osteoarthritis patients.[10] When comparing current study with Bauer et al study (Table 8), the study drug, drug dosage form and the primary and secondary objectives were similar and differences were like sample size, recruitment of age group and the study design and duration. While considering about results both studies showed similar results like oxaceprol is a better alternative in osteoarthritis patients with minimal side effects.[11]

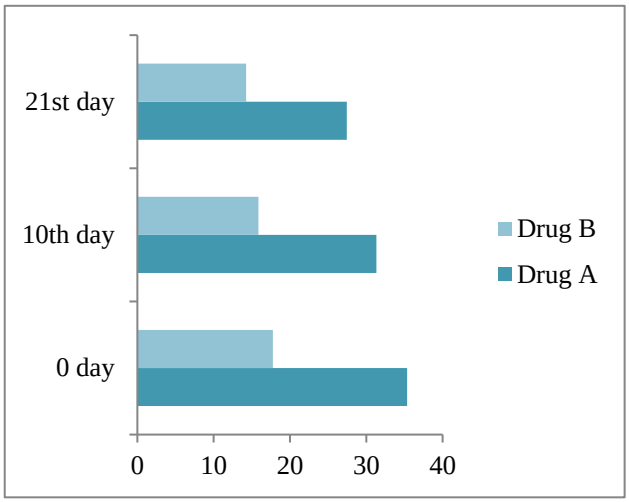

Figure 3: WOMAC score (joint stiffness) difference between two groups.

Table 7: Comparison of Herrmann et al with the current study.

Criteria	Herrmann et al			Current study		
Problem understudy	Osteoarthritis of the knee or hip			Moderate osteoarthritis of knee		
Objectives	To assess safety and efficacy equivalent of oxaceprol with diclofenac in osteoarthritis patients			To assess efficacy and safety of oxaceprol		
Study design	Double-blind, randomized, multi-centric study			Randomized, double-blind, comparative study		
Sample size	219			78		
Age group (years)	>50			>45		
Drug dosage	Tab.Oxaceprol 400mg p/o t.i.d Tab.Diclofenac 50mg p/o t.i.d			Tab. Oxaceprol 200 mg p/o t.i.d Tab. Diclofenac 50 mg p/o t.i.d		
Study duration	21 days			3 weeks		
Efficacy parameter	Lequesne joint index VAS scale			WOMAC INDEX VAS scale		
Side effects		Oxaceprol	Diclofenac		Oxaceprol	Diclofenac
	Nausea	03	03	Nausea	02	03
	G.I. pain	03	04	Vomiting	00	01
	G.I. disturbance	00	05	Gastric irritation	01	03
	Palpitation	01	00	Diarrhoea	01	00
	Dizziness	01	01	Headache	01	00
	Constipation	02	00			
Conclusion	This study confirms that Oxaceprol provides similar efficacy to Diclofenac in the short-term therapy of osteoarthritis of the knee or hip			Oxaceprol can be considered as a better alternative to diclofenac in osteoarthritis with minimal side effects and its cost-effective also.		

Table 8: Comparison of Bauer et al with the current study.

Criteria	Bauer et al			Current study		
Problem understudy	Osteoarthritis of knee and hip			Moderate osteoarthritis of knee		
Objectives	To assess efficacy of oxaceprol in treatment of osteoarthritis of knee and hip			To assess efficacy and safety of oxaceprol		
Study design	Prospective, randomised, double-blind, controlled, multicenter phase iv trial in Germany			Randomized, double-blind, comparative study		
Sample size	124			78		
Age group (years)	>50			>45		
Drug dosage	Tab Oxaceprol 200mg p/o t.i.d Tab Diclofenac 25mg p/o t.i.d			Tab. Oxaceprol 200mg p/o t.i.d Tab. Diclofenac 50mg p/o t.i.d		
Study duration	7 months			3 weeks		
Efficacy parameter	Lequesne index VAS scale			WOMAC INDEX VAS scale		
Side effects		Oxaceprol	Diclofenac		Oxaceprol	Diclofenac
	Nausea	03	03	Nausea	02	03
	G.I. pain	03	04	Vomiting	00	01
	G.I. disturbance	00	05	Gastric irritation	01	03
	Palpitation	01	00	Diarrhoea	01	00
	Dizziness	01	01	Headache	01	00
	Constipation	02	00			
Conclusion	Oxaceprol is a good alternative to standard NSAIDs (diclofenac) in the treatment of osteoarthritis.			Oxaceprol can be considered as a better alternative to diclofenac in osteoarthritis with minimal side effects and its cost-effective also.		

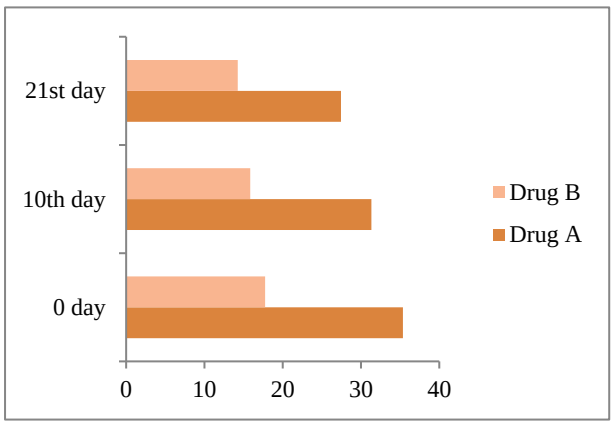

Figure 4: WOMAC score (physical function) difference between two groups.

Strengths of the study

Since all patients were enrolled from the same city, the people will have more similar baseline characteristics, and there is less chance of inter-individual changes.

Commonly used analgesics for knee pain were associated with renal impairment and gastrointestinal toxicity, whereas the current study drug oxaceprol showed less severity on the gastrointestinal system and the current study is a randomized double-blind study, Hence the chance of bias is less, leading to reliable results.

Limitations of the study

Limitations of the current study was that the was conducted only for 3 weeks. The sample size of the present study was 78, which is less and it may affect the power of the study which interferes with translation of the results of this study into general population. The current study was a single-center study, conducting a study at multi centric level might be good to make the results more generalizable. The current study was done in a per-protocol fashion by omitting the missing data, and intention to treat analysis was not done.

CONCLUSION

From current study, it is concluded that oxaceprol is equally efficacious as diclofenac in reducing knee pain, joint stiffness but more efficacious than diclofenac in improving physical activity of patients by enhancing bone remodelling so oxaceprol is a cost-effective treatment option for those patients who were not willing and not fit for total knee replacement surgeries.

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