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COMPARATIVE SAFETY AND COST EFFECTIVE ANALYSIS BETWEEN ACECLOFENAC, LORNOXICAM AND DICLOFENAC IN PATIENTS OF MUSCULO SKELETAL DISORDER

K.P. Patnaik*[1], P. Das, S. Hota [1], B. N. Mohapatra [2], S. Mohapatra [1], S. Nayak [2], S. Panigrahi [3]

Department of Pharmacology [1], Department of Orthopedics [2], Department of PSM [3], S.C.B. Medical College, Cuttack-753007, Odisha, India

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Correspondence to Author:

Dr. K.P. Patnaik

Department of Pharmacology, S.C.B. Medical College, Cuttack-753007, Odisha, India

E- mail: drkaliprasad@yahoo.co.in

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ABSTRACT

Newer NSAIDs like Aceclofenac and Lornoxicam are being marketed by pharmaceutical industries with claims of better efficacy and safety than conventional NSAIDs like Diclofenac. So this study aims to comparatively assess the safety, efficacy and cost of Aceclofenac, Lornoxicam and Diclofenac in patients of musculoskeletal disorders. Patients presenting with musculoskeletal disorders were randomized into three treatment groups (50 in each). Comparative analgesic efficacy assessment between the three drugs were done by using visual analog scale (VAS) reading on Day-0 and then weekly till 3 weeks; adverse drug reaction (ADR) information were collected by spontaneous reporting from patients and by active surveillance and were recorded in a predesigned proforma. Relative cost was assessed by comparative unit cost price of individual drugs (of different pharmaceutical companies). It was observed that Lornoxicam, Aceclofenac and Diclofenac are equally effective as analgesic. Both Aceclofenac and Lornoxicam have similar ADR profile which is significantly less than that of Diclofenac. Though analgesic activity and safety profile of Aceclofenac is comparable to Lornoxicam, but Aceclofenac is cheaper than Lornoxicam , hence comparatively cost effective.

INTRODUCTION: Non steroidal anti-inflammatory drugs (NSAIDs) are widely used in patients suffering from musculoskeletal disorders. The conventional NSAIDs which inhibit both COX-1 and COX-2 have high incidence of gastrointestinal adverse effects.

Selective COX-2 inhibitors like Rofecoxib, Valdecoxib, etc were introduced with claims of better GI safety. But Rofecoxib was withdrawn from market due to higher incidence of serious thromboembolic events (Bersa Lier *et al.,* 2005) [1] & Valdecoxib has higher incidence of toxic epidermal necrolysis. Recently newer NSAIDs like Aceclofenac and Lornoxicam are being marketed by various Pharmaceutical industries with claims of better efficacy and safety than conventional NSAIDs like Diclofenac and Piroxicam , on the basis of cox -1 sparing & preferential COX - 2 inhibition potential with Aceclofenac (Hinz B. *et al*) [2] and better synovial fluid penetrability of lornoxicam (Skjodt. N *et al*) [3]. Though there is some data regarding comparison of Aceclofenac with Diclofenac & lornoxicam with Diclofenac, but there is no comparative data between Aceclofenac & Lornoxicam or regarding the cost effectiveness among these three drugs.

So the aim of our study was to make a comparative assessment regarding the safety, efficacy and cost between Aceclofenac, Lornoxicam and Diclofenac.

This study may also expose any unreported ADR of newer NSAIDs like Lornoxicam and Aceclofenac.

MATERIALS AND METHOD: It was a prospective open labeled randomized interventional study conducted at S.C.B. Medical College & Hospital, Cuttack, Odisha, India, in the Department of Pharmacology, in collaboration with Deptt. of Orthopedics, in the year 2010 & 2011 with due approval of the Institutional Ethics Committee.

Inclusion criteria-Patients of either sex, between 15-50 years of age, attending Orthopedics O.P.D in S.C.B. Medical College and Hospital, Cuttack, with complaints of musculoskeletal disorders like arthritis, low backache (LBA) and traumatic injury, etc , requiring NSAIDs and willing to participate in this study were included .

Exclusion criteria: Patients with documented peptic ulcer, chronic kidney disease or established liver disorders were excluded.

Written informed consent was obtained from the patients participating in the study .

Study Procedure:

Enrollment into the study: Patients of musculoskeletal disorders fulfilling the inclusion criteria were enrolled into the study. Their detail clinical history was obtained regarding the site and severity of musculoskeletal pain. General examination (i.e. measurement of blood pressure, pulse, pallor, icterus, temperature, pedal edema etc.) along with examination of musculoskeletal system like straight leg raising (SLR) test, number of joints involved, limitations of range of movement (ROM) etc. were undertaken.

Relevant laboratory tests like Haemoglobin, DC, TLC and Stool Occult Blood Tests were also done routinely in each patient before administration of the test drugs.

Randomization & Administration of Test drugs (NSAIDs): After enrollment, each patient was randomly allocated into one of the three NSAIDs treatment group of 50 each. Randomization was done using table of random number method [4].

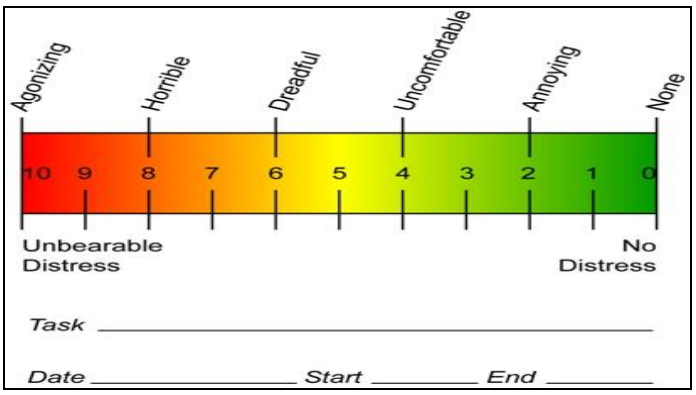
- Group-1 received - Lornoxicam **4 mg twice daily after food.**
- Group-2 received - Aceclofenac **100 mg twice daily after food.**
- Group-3 received - Diclofenac **50 mg twice daily after food.**

The duration of treatment varied from **2-3 weeks** depending on requirement of NSAIDs.

Co prescription of PPI(Proton Pump Inhibitors) along with NSAIDs: In view of claims of better G.I. safety of Lornoxicam & Aceclofenac, Proton Pump Inhibitor (Pantoprazole) was co prescribed in Lornoxicam and Aceclofenac treatment groups only in patients who have complaint of Acid Peptic disease (i.e. flatulence , hyperacidity or abdominal discomfort, etc) but the patients who denied any history of acid peptic disease were given only Lornoxicam or Aceclofenac without PPI to evaluate their GI safety. Patients with documented peptic ulcer were totally excluded from the study. In Diclofenac treatment group all the patients were co prescribed with PPI considering our previous experience of complaint of epigastric discomfort by majority of our patients when taken Diclofenac without PPI. Hence, while comparing the GI safety between the three treatment groups, the GI adverse events in patients co prescribed with PPI were only compared.

Evaluation of Study End Points:

The Primary Endpoint of the study was: Assessment of Analgesic Efficacy: Efficacy assessment for pain relief was done by using visual analog scale (Edgar E *et al*) [5]. The visual analog scale designed by Chris Adams [6] was used for recording level of pain.



A visual analog scale ranging from 0-10 on rating was used for the study. The patients were asked to mark the level of the pain on the scale in the zero day of treatment. Then, the scale was given to each individual patient and he was asked to come again at weekly intervals and mark the level of the pain on that visual analog scale, till completion of treatment. The VAS readings were recorded in the case record forms and were analysed statistically to evaluate the comparative analgesic activity.

The secondary end points were: Assessment of Adverse events (AE) & Assessment of Cost:

1. **Assessment of AE:** The AE (Adverse Events) data was collected under two broad categories i.e. GI AE (Gastro intestinal Adverse Events) as it is very common and other AE. AE reports were collected by two methods: (1) Voluntary AE reporting by the patient and (2) by Active Surveillance.

2. **GI AE (Gastro intestinal Adverse Events):** The patients were asked to inform the investigators if any symptoms like pain abdomen, nausea, vomiting, epigastric discomfort, haematemesis or malena, diarrhoea or constipation, etc. developed during treatment. They were also personally examined by direct home visit or asked telephonically regarding any of the above AE. The complaints of patients were recorded in the case record form and those developing GI symptoms were thoroughly examined. Stool occult blood examination was done for these patients. Upper GI endoscopy was planned to be done if any patient developed haematemesis, malena or had severe abdominal pain or if stool occult blood became positive.

3. **Other Adverse Events:** Patients were evaluated at weekly intervals to assess any other adverse events like rash, pedal edema, or any previously unreported adverse events and were recorded in the case record form. General physical examination i.e. blood pressure (B.P.), temperature, pallor, icterus etc. were recorded in all the visits to evaluate any other Adverse Events. LFT (Liver function Test) was planned to be done in patients who develop jaundice or nausea vomiting and pain abdomen. Serum urea, creatinine were planned to be studied if any patient developed pedal edema and / or oliguria.

4. **Assessment of cost:** The cost of per day therapy with Lornoxicam / Aceclofenac & Diclofenac was calculated by finding the mean cost of per day therapy of individual drugs from three different well known available brands. This mean per day cost of therapy was analysed statistically to find the comparative cost between the three drugs.

The data obtained were summarized and statistically analyzed using ANOVA, chi square tests or paired t test depending on the requirements.

RESULTS & DISCUSSION: The present study was undertaken to evaluate the Efficacy, Safety and Cost between Lornoxicam, Aceclofenac and Diclofenac in patients with musculoskeletal disorders. Majority of the patients in our study were patients of low backache, osteoarthritis or trauma.

The comparative efficacy assessment: Evaluation of analgesic activity between the three drugs was done by using Visual Analogue Scale (VAS) and is depicted in **table 1**.

TABLE 1 : COMPARATIVE ANALGESIC EFFICACY BETWEEN LORNOXICAM, ACECLOFENAC & DICLOFENAC .

TREATMENT	MEAN VISUAL ANALOGUE SCORE (VAS) ± SD						Percentage Reduction in VAS(%)
	N	Basal	N	1st Week	N	2nd Week	
Lornoxicam	50	4.16 ± 1.63	50	2.15 ± 1.46*	41	1.42 ±1.25*	48
Aceclofenac	50	4.34 ± 1.67	50	1.91 ± 1.24 *	39	1.03 ± 0.94*	56
Diclofenac	50	4.48 ± 1.35	50	2.07 ± 1.14 *	38	1.03 ± 0.97*	62
F value		0.528		0.448		1.745	
P value		0.591		0.640		0.179	

N= Number of patients. (Within Group comparison for assessment of analgesic activity of each individual drugs were done by by Paired t test & showed highly significant analgesic activity* = p< 0.001 in each of the three treatment group. Between Group comparison for analgesic activity (between Aceclofenac,Lornoxicam & Diclofenac) was done by using One way ANOVA followed by LSD Post Hoc Test.)

It revealed that the mean basal VAS in Lornoxicam, Aceclofenac and Diclofenac treatment group were 4.16±1.63, 4.34±1.6 and 4.80±1.5 respectively without significant difference between them. There was significant analgesic activity (p< 0.001) with each of the three drugs , as evidenced by decrease in VAS to 2.13±1.4, 1.9±1.2 and 1.8±1.2 after 1 wk and to 1.36±1.2, 1.06±0.97 and 0.9±0.83 after 2 weeks with Lornoxican, Aceclofenac and Diclofenac respectively from the Basal value.

However when the analgesic activity of each of the three drugs were compared by One way ANOVA (between group comparison) followed by LSD Post Hoc Test, the F & P value did not show any significant difference among their analgesic activity. Though the percentage reduction in VAS was highest i.e., 62% with Diclofenac followed by 56% with Aceclofenac & 48% with Lornaxicam, but this difference in the three treatment groups also did not demonstrate any statistically significant difference.

Hence, our study indicates equal analgesic potential of all the three drugs i.e. Lornoxicam, Aceclofenac and Diclofenac. This finding somehow corroborates with the study of Herrmann WA et al [7] who found Lornoxicam & Diclofenac had similar analgesic effect; but the finding of Ward DE *et al* [8] regarding statistically superior analgesic activity of Aceclofenac in comparison to Diclofenac and Pasero *et al* [9] i.e. higher - 22% improvement in handgrip with Aceclofenac vs. 17% with Diclofenac does not match with our study.

Comparative AE (Adverse Events) evaluation: Comparative AE (Adverse Events) observed among the patients in the three treatment groups are depicted in **table 2 & fig. 2**.

TABLE 2: COMPARATIVE ADVERSE EVENTS (AE) IN LORNOXICAM, ACECLOFENAC & DICLOFENAC

Treatment Groups	Incidence of adverse events (%)									
	GI AE						other AE		total AE	
	With PPI		Without PPI		Total	GI ADR	n/N	(%)	n/N	(%)
	n/N	(%)	n/N	(%)	n/N	(%)				
Lornoxicam	4/44	9%	1/6	16.6%	5/50	10%	2/50	4%	7/50	14%
Aceclofenac	2/44	4.5%	2/6	33.3%	4/50	8%	2/50	4%	6/50	12%
Diclofenac	10/50	20%			10/50	20%	2/50	4%	12/50	24%

% = n/N ; n = number of patients with AE , N = total number of patients .

Comparison for GI AE with PPI in different treatment groups (by Chi – square test):

Drugs	Chi –Square value	df	P
Diclofenac vs. Aceclofenac	5.02	1	<0.05
Diclofenac vs. Lornoxicam	2.18	1	>0.05
Aceclofenac vs. Lornoxicam	0.7	1	>0.05

Chi–Square value >3.84 is significant. (If no. of samples doubled, then chi value-4.39, df-1, p< 0.05)

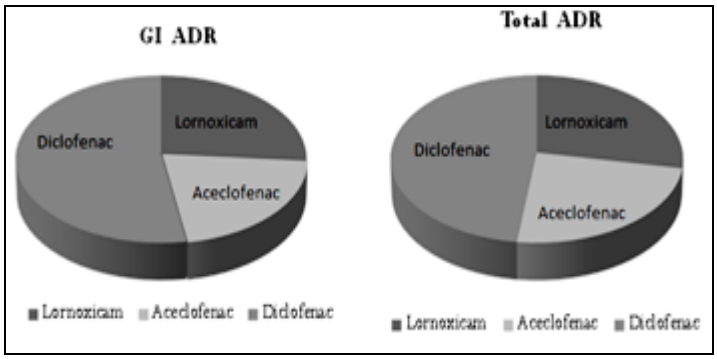


FIG. 2: COMPARATIVE INCIDENCE OF ADR BETWEEN LORNOXICAM, ACECLOFENAC & DICLOFENAC

This study showed that the GI AE (Gastro Intestinal Adverse events) i.e. dyspepsia, abdominal pain, vomiting etc. were maximum i.e. 20% with Diclofenac which was significantly higher than GI AE with Lornoxicam-10% (Chi 2.18 to 4.39) and Aceclofenac-8%(Chi 5.02), But there was no significant difference between incidence of AE with lornoxicam & Aceclofenac(Chi 0.7).

Our findings of better GI safety profile of Aceclofenac in comparison to diclofenac corroborates with that of pareek *et al* [10] & Ward DE *et al* [8] (where in 397 patients it was found that tolerability of Aceclofenac was better than with Diclofenac). Aceclofenac has COX-1 sparing & COX-2 inhibitory actions (Hinz B *et al*) [2] which may suggest its equal efficacy but better gastrointestinal tolerability than Diclofenac. In the Study conducted by Herrmann WA *et al* [7] on 164 patients showed that the incidence and severity of adverse events with Lornoxicam and Diclofenac were

comparable and overall tolerability was rated as 'very good/good' however in our study we found better GI safety with lornoxicam in comparison to Diclofenac. The GI Adverse events of 20% and total Adverse events of 24% with diclofenac in our study was nearly similar to report of other studies. i.e. 20% Adverse events with Diclofenac (P. Emery *et al*) [11]. All the patients in our study in diclofenac treatment group have received PPI.

The GI Adverse events in our study are comparatively less than other studies. According to Rawal N *et al* [7], an adverse events of 24.5% was found with Lornoxicam; but in our study, 9% GI and 14% total adverse events was found with Lornoxicam, similarly 8% GI adverse events with Aceclofenac in our study was less than 13% GI adverse events found by Pasero G *et al* [9] The less incidence of ADR in our study was again possibly due to concomitant use of PPI.

Comparative Cost Analysis:

TABLE 3: COMPARATIVE COST BETWEEN LORNOXICAM, ACECLOFENAC & DICLOFENAC

Name of Drugs	Dose	Cost per day In INR	Mean Cost	P value
Lornoxicam	4 mg BD			
Brand A Brand B Brand C		7.26 7.60 7.50	*7.43	
Aceclofenac	100 mg BD			
Brand A Brand B Brand C		4.60 4.00 5.40	4.66	<0.002 1 vs. 2
Diclofenac	50 mg BD			
Brand A Brand B Brand C		4.00 3.35 4.59	3.98	<0.001 1 vs. 3

1 vs. 2 = P<0.002 ; 1 vs. 3 = P<0.001; 2 vs. 3 = P<0.344. Anova with Multiple Comparison by Tukey HSD Test. Cost of Lornoxicam is significantly higher than Aceclofenac & Diclofenac.

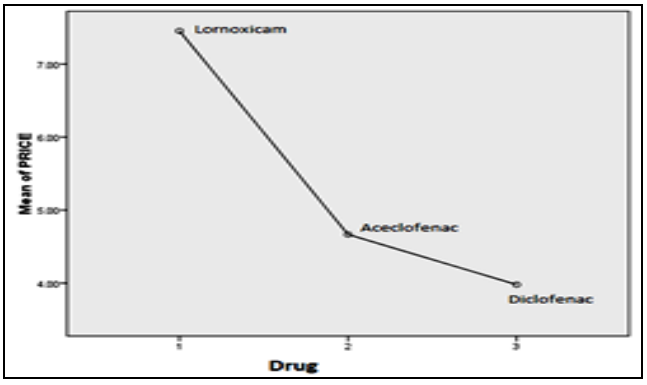


Table 3 showed that the mean per day treatment cost with Lornoxicam was INR 7.43 which was significantly higher than per day cost therapy with Aceclofenac (i.e. INR 4.7) and Diclofenac (INR 4.0). But there was no significant difference between cost of Diclofenac and Aceclofenac. Ultimately from the above study we conclude that – Diclofenac, Aceclofenac & Lornoxicam have equal analgesic activity. Aceclofenac and Lornoxicam have similar incidence of adverse events which is significantly less than Diclofenac. Though Aceclofenac and Lornoxicam have similar safety and efficacy profile but Aceclofenac is significantly cheaper than Lornoxicam, hence Aceclofenac may be considered as the most cost effective among the three.

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