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Research Article

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A comparative study to assess the efficacy and tolerability of lornoxicam and diclofenac in patients with osteoarthritis of knee in a tertiary care hospital

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ABSTRACT

*Cardiovascular adverse effects of COX-2 inhibitors and gastro-intestinal intolerability of NSAIDs for the treatment of osteoarthritis has prompted for better tolerated and efficacious NSAID but as there is paucity of data in Indian population, the present study was taken up. To evaluate the efficacy and tolerability of lornoxicam and diclofenac in patients with osteoarthritis of knee. A 4week, randomized open label comparative study was conducted in Department of Orthopedics, Victoria Hospital, Bangalore, on outpatients with osteoarthritis of knee who met the inclusion and exclusion criteria. About 100 patients were involved and randomized into two groups of 50 each receiving lornoxicam 8mg BD (group L) and Diclofenac 50mg TID in other (group D). Efficacy was assessed by VAS scores (visual analog scale), WOMAC scale (Western Ontario and McMasters Individual Osteoarthritis Index) for pain and Likert scale for patients assessment to response for therapy and tolerability monitored by incidence of adverse events and any changes in laboratory parameters done on follow up visits. Both drugs were associated with sustained reduction in the scores of osteoarthritis symptoms and improved response to therapy compared with baseline with P<0.001**. However there was significantly greater reduction in symptoms score and better response to therapy with lornoxicam compared to diclofenac as measured by VAS, WOMAC index of osteoarthritis knee and Likert scale with P<0.001**. Most of the patients reported gastro-intestinal intolerability with no cardiovascular and renal adverse effects but there was significantly less adverse events with lornoxicam compared to diclofenac with P<0.001**. In the present study lornoxicam significantly relieves pain of osteoarthritis knee more than diclofenac with better patient's response to therapy and tolerability.*

Keywords: osteoarthritis, lornoxicam, diclofenac, NSAIDs.

INTRODUCTION

Worldwide, osteoarthritis is estimated to be the fourth leading cause of disability [1] burden which is attributable to the involvement of the hips or the knees. OA is strongly associated with ageing and the Asian region is ageing rapidly [2].

OA is the second most common rheumatological problem causing locomotor disability and morbidity leading to loss of quality of life in the elderly [3] with OA of knee as one of the five leading causes of disability among non-institutionalized adults and impaired mobility in elderly, affecting all age groups but prevalence increases dramatically with age[4], though age trends are clearer in women than men, with a greater incidence in subjects between 40 and 50years of age[5] with prevalence of 22% to 39% in India[3].

Its most prominent feature is the progressive destruction of articular cartilage which results in impaired joint motion, stiffness, severe pain, and ultimately, disability[6].As it is an active disease process involving cartilage destruction, subchondral bone thickening, and new bone formation[3] it has high prevalence and its moderate-to-severe impact on daily life pose a significant public health problem[6].

Treatment is multidisciplinary and involves physical therapy, medication, and surgery but today a cure for OA remains elusive and makes the management largely palliative, focusing on the alleviation of symptoms. Current recommendations for the management include combination of non-pharmacological interventions (weight loss, education programs, exercise etc) and pharmacological treatments (paracetamol, non-steroidal anti-inflammatory drugs etc) [6].

Among these pharmacological treatments, NSAIDs, despite serious adverse effects associated with their long-term use, remain among the most widely prescribed drugs for OA worldwide [6], to achieve rapid and efficient analgesia and stability. Selective COX-2 inhibitors developed to circumvent gastrointestinal toxicity associated with NSAIDs. The response to any given agent and the unwanted effects encountered vary between subjects and this has resulted in the development of wide range of NSAIDs [7, 8].

The current study is aimed at assessing efficacy and tolerability of Lornoxicam with Diclofenac, a modern NSAID belonging to oxicam group having pronounced analgesia and anti-inflammatory properties with short half-life of 3-4hrs and 100 times more potent than tenoxicam with balanced COX inhibition and excellent tolerability [9] as only few studies have compared and concluded that they have equal efficacy and tolerability.

EXPERIMENTAL SECTION

After approval from Institutional Ethics Committee of Bangalore Medical College and Research Institute, Bangalore, Karnataka (India), study was carried out in department of Orthopedics, Victoria Hospital, Bangalore. Study was randomized, open labeled parallel group comparative clinical trial for duration of two years with 4weeks of study period after a wash out period of 2-4days in patients who received other analgesics.

Patients aged between 45-65years suffering from osteoarthritis of knee fulfilling criteria of osteoarthritis of knee given by American college of Rheumatology-1986 were explained about the study and those who gave informed consent were assigned randomly into two groups i.e. group D and group L of 50 patients in each group.

Patients having any other systemic illness, pregnant and lactating women, patients taking other drugs like lithium, digoxin, methotrexate, anticoagulants, Sulfonylureas, Furosemide, Thiazides and Spiranolactone, having history of hypersensitivity to non steroidal anti-inflammatory drugs and patient who consumed any analgesic in last 1 month, having clinically significant abnormal laboratory values of clotting time, bleeding time, liver and renal functions test etc and who were unable to comply with the study assessment were excluded from the study.

Group D patients were treated with diclofenac sodium 50mg TID and Group L with lornoxicam 8mg BD both given orally after food for 4weeks. Patients were assessed with help of Visual analogue scale of 1-10 score, WOMAC (Western Ontario and McMaster Universities) osteoarthritis index of knee and Likert scale for efficacy and tolerability by any adverse event, significant changes in vital signs and physical examination which was assessed every week, where as Likert scale was used from 2nd visit onwards and

clinically significant abnormal changes in the laboratory values of investigation which were done on 2nd and 4th week of the study period.

STATISTCAL ANALYSIS

Mean± SD (min-max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test both paired and unpaired test, chi-square test and Fischer Exact test were used for analysis.

RESULTS

Demographic characteristics of both groups were comparable to each other, with preponderance of female patients in both groups and mean age of patient was 59±5.77 in group L & 61.16±6.81 in group D. Initially, before administration of drug the parameters were tested and the groups did not differ much with each other.

There was statistically significant reduction from first visit to the fourth visit (P<0.001**) in both the groups but Lornoxicam had significantly superior efficacy on visual analogue scale compared to the diclofenac with P<0.001** in 3rd visit and P=0.005** in 4th visit (Table 1)

Table 1: Comparison of Visual analogue scale in two groups of patients studied

VAS	Group L	Group D	P value	Difference & P value from baseline	
Baseline	8.82±0.92	8.82±0.83	1.000	Group L	Group D
Visit 2	5.44±1.05	6.02±0.94	0.004**	d=3.38;P<0.001**	d=2.80;P<0.001**
Visit 3	2.50±0.95	3.34±0.92	<0.001**	d=6.32;P<0.001**	d=5.48;P<0.001**
Visit 4	0.62±0.78	1.08±0.80	0.005**	d=8.20;P<0.001**	d=7.74;P<0.001**

There was significant response to treatment in both the groups with mean reduction in score with Likert's scale on 2nd, 3rd and 4th visits. But at the end of study there was statistically significant response to treatment with lornoxicam group compared to diclofenac in the 4th visit with P < 0.001** (TABLE 2)

Table 2: Comparison of Likert scale in two groups of patients studied.

LIKERT'S SCALE(score)	Group L	Group D	P value
Visit 2	2.64±0.83	2.66±0.85	0.905
Visit 3	1.68±0.62	1.82±0.72	0.300
Visit 4	1.08±0.27	1.42±0.57	<0.001**

There was statistically significant reduction in pain(P<0.001**), stiffness (P<0.001) & physical activity (P<0.001**) assessed by WOMAC index of OA knee from first visit to last visit in study subjects in both the groups but on comparison between the groups the pain reduction (with P=0.003** in 4th visit), stiffness reduction(with P<0.001** in 2nd visit) and physical activity score (with P<0.001** & P=0.003** in 3rd & 4th visit) was statistically significant with lornoxicam group compared to diclofenac group. (TABLE 3a, 3b & 3c)

Table 3a: Comparison of WOMAC INDEX (pain Score) in 2 groups of patients studied.

WOMAC score	Group L	Group D	P value	Difference & P value from visit 1	
Pain				**Group L**	Group D
Visit 1	16.10±2.23	17.10±2.00	0.020*	-	-
Visit 2	9.94±1.74	9.70±1.78	0.497	d=6.16;P<0.001**	d=7.40;P<0.001**
Visit 3	5.12±1.70	5.12±1.44	1.000	d=10.98;P<0.001**	d=11.98;P<0.001**
Visit 4	0.62±0.78	1.12±0.85	0.003**	d=15.48;P<0.001**	d=15.90;P<0.001**

Table 3b: Comparison of WOMAC INDEX (stiffness score) in two groups of patients studied

WOMAC score	Group L	Group D	P value	Difference & P value from visit 1	
Stiffness				**Group L**	Group D
Visit 1	6.42±1.11	5.78±1.40	0.013*	-	-
Visit 2	4.42±0.97	3.38±1.05	<0.001**	d=2.00;P<0.001**	d=2.40;P<0.001**
Visit 3	2.62±1.01	2.18±0.77	0.016*	d=3.80;P<0.001**	d=3.60;P<0.001**
Visit 4	0.88±0.77	1.18±0.69	0.043*	d=5.54;P<0.001**	d=4.60;P<0.001**

Table 3c: Comparison of WOMAC index (physical function score) scale in two groups of patients studied

WOMAC score	Group L	Group D	P value	Difference & P value from visit 1	
Physical function				**Group L**	Group D
Visit 1	53.94±4.95	55.68±6.61	0.139		
Visit 2	36.82±4.81	38.84±5.27	0.048*	d=17.12;P<0.001**	d=16.84;P<0.001**
Visit 3	22.26±4.53	25.80±4.81	<0.001**	d=31.68;P<0.001**	d=29.88;P<0.001**
Visit 4	10.68±4.05	13.60±5.33	0.003**	d=43.62;P<0.001**	d=42.08;P<0.001**

Other parameters like laboratory investigations (complete blood count, liver function test, renal function test, ESR, ECG, clotting time, bleeding time, a PTT, random blood sugar) were within normal limits throughout the study period.

Common adverse events noted in both the groups during the study were due to gastric intolerance i.e. nausea, vomiting, epigastric discomfort, dyspepsia and diarrhoea but only 20% of patients from Group D did not report any adverse event compared to 32% in Group L. There was statistically significant (P<0.001**) reduction which showed that lornoxicam was better tolerated compared to diclofenac.

DISCUSSION

The selection of NSAIDs for treatment of osteoarthritis is complex decision for which the clinicians must weigh individual factors and numerous drug factors including safety. Assessment of safety of NSAIDs is important to ensure patient safety and better therapeutic outcome.

The main aim of this study was to compare the effectiveness in the reduction of symptoms and tolerability of lornoxicam and diclofenac in patients with osteoarthritis of knee and the study was completed without any dropouts and serious adverse effects.

Polymorphonuclear cell invasion into the joint cavity is one of the important factors in acute inflammatory diseases like osteoarthritis of knee. This process depends on the augmentation of several biological factors with chemotactic activity and probably interleukin-8 (IL-8) at the site of inflammation. Accumulation of polymorphonuclear cells also leads to release of mediators which further enhance the inflammatory cascade. Lornoxicam inhibits human polymorphonuclear cell migration induced by f-myeloperoxidase, IL-8 and substance P which are some of the important chemotactic mediators of inflammation and as it is clinically difficult to study the effect of a drug on articular cartilage, it has to be confirmed with advanced procedures like arthroscopy. [10]

37% of the study patients were known cases of osteoarthritis knee on treatment with other NSAIDs and were given a washout period of 2-4 days and then taken up in this study and they did not have any major co-morbid diseases and hypersensitivity/allergy to NSAIDs and to any other drugs. Among these patients 46% were males and 52% were females showing that there is increased prevalence of OA in females compared to males [11]. A study done on osteoarthritis patients by Cannon GW et al., showed that the mean age was 63±10.2 in rofecoxib and diclofenac group with 67.5% of total study subjects being females [12].

There was significant (P<0.001**) reduction in the overall pain score assessed by VAS, in both the groups compared to baseline but there was statistically significant reduction with lornoxicam group compared to diclofenac group (table 1 and figure 1). Moller et al., showed better efficacy and pain relief with lornoxicam quick release, single dose compared to placebo for pain after third molar surgery [13] and lornoxicam showed statistically significant reduction in pain at night compared to rofecoxib in patients with

activated osteoarthritis in COLOR study by Peter R et al [14]. In other study done by Sener M et al., for acute postoperative pain relief after septoplasty assessed by VAS has shown that lornoxicam was not superior to other non-opioid drugs like diclofenac, Dipyrone and Ketoprofen used in that study [15] but in a study done by Daabiss M et al., has shown that lornoxicam 16 mg is comparable to fentanyl as intra-operative IV analgesia but more effective than fentanyl in preventing pain in patients undergoing minor to moderate day case ENT surgical procedures [16]. Lornoxicam had statistically significant lower VAS values than tramadol showing improved postoperative analgesia in a study done by Kirdemir et al [17].

Patient's assessment of response to treatment was assessed using Likert scale on subsequent visits which showed that there was significant response to treatment in patients with lornoxicam group compared to diclofenac group (table2). This was similar to a study done by Peter R et al., with lornoxicam showing that patient's assessment of response to therapy was superior to rofecoxib in osteoarthritis patients [14] and is also better than placebo in its efficacy in patients with osteoarthritis as shown in a study by Berry H et al [18].

Orthopedic evaluation of study subjects using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC in tistically significant reduction in the pain score, physical function score and stiffness score in both the treatment groups compared to baseline with more significant reduction in lornoxicam group than diclofenac with P<0.001** as shown in table 3a, 3b and 3c and figures 3-5. In earlier studies by Kidd B and Frenzel W et al., had shown that there was intergroup equivalent improvement in function index in both lornoxicam and diclofenac treated OA patients [19].

There were no significant changes in the laboratory parameters of study subjects during the period. Adverse drug effects were assessed throughout the study period and most commonly reported were gastrointestinal events in both the groups which was managed with Tab. Rantac 150 mg 12^{th} hourly and these patients showed willingness to continue study and successfully completed the study. None of the patients developed cardiovascular, renal or other adverse reactions during the study period. There were significantly less adverse events in lornoxicam group compared to diclofenac i.e. tolerability with lornoxicam is better than diclofenac with P<0.001**. In comparison to a study done by Yakhno et al., it was found that lornoxicam administered as a quick release formulation was non-inferior to the equivalent formulation of diclofenac potassium in terms of pain relief and more effective on most of the major standard efficacy outcomes in 220 patients having low back pain [20]. In Kidd B et al., multicenter, randomized double blind study in OA patients, showed that there was no significant difference in tolerability of lornoxicam and diclofenac group and lornoxicam appeared to be better alternative to diclofenac in terms of efficacy [19]. In Norholt SE et al., lornoxicam possesses a more favorable tolerability profile than morphine and thus represents an attractive alternative to morphine for the treatment of moderate to unendurable acute pain [21].

Lornoxicam is a highly potent NSAID exhibiting anti-inflammatory action and analgesic activity which is comparable to opioids in various acute and chronic painful inflammatory conditions. It has short half life of 3-5 hrs which probably explains the dex) of OA knee was used to assess the efficacy of drugs. In the present study there was sta improved gastrointestinal safety profile.

CONCLUSION

In terms of efficacy, lornoxicam is more efficacious in ameliorating symptoms of osteoarthritis of knee than diclofenac.

In terms of tolerability, although the nature of adverse effects is similar with symptoms of gastro-intestinal intolerance, between the individual groups there is significantly better tolerability with lornoxicam compared to diclofenac.

Limitations

As this was a study of short duration with limited sample size and open-label design, study with larger sample size, longer duration and blinding techniques with pharmacoeconomic analysis could have been done to substantiate our observations.

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REFERENCES

[1] Fransen M, Bridget L, March L, Hoy D, Penserga E and Brooks P. *International Journal of Rheumatic Diseases*. **2011**, 14, 113–121.
[2] Van Saase J.L.C.M, Vandenbroucke J.P, van Romunde L.K.J, Valkenburg H.A. *J Rheumatol*., **1988**, 15, 1152-1158.
[3] Mahajan A, Verma S, Tandon V. Osteoarthritis. Update article. *JAPI*.**2005**, 53, 634-641.
[4] Guccione AA, Felson DT, Anderson JJ et al. *Am J Public Health*., **1994** Mar, 84(3), 351-358.
[5] Loeser RF, Shakoor N. *Rheum Dis Clin North Am.,* **2003**, 29, 653-673.
[6] Ameye LG, Chee WS, *Arthritis Research & Therapy*., **2006**, 8(4), R127.
[7] Berry H, Hamilton EBD, Bird HA, Black C, Blake DR, Freeman AM et al. *Ann Rheum Dis*., **1992**, 51, 238-242.
[8] Fendrick AM, Greenberg BP. *Osteopath med prim care.,* **2009**, 3, 1-7.
[9] Hall PE, Derry S, Moore RA, McQuary HJ. Single dose lornoxicam for acute postoperative pain in adults. Review article. The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. The Cochrane library., **2011**, 11, 1-21.
[10] Sacerdote P, Bianchi M. *Int J Pharmacol*., **2005**, 1(2), 180-4.
[11] Mahajan A, Tandon V, Verma S. *J Indian Rheumatol Assoc*., **2005**, 13, 21-25.
[12] Cannon GW, Caldwell JR, Holt P, McLean B, Seidenberg B, Bolognese J et al. *Arthritis and Rheumatism.,* **2000**, 43(5), 978-987.
[13] Moller PL, Norholt SE. *Clinical drug investigation*., **2008**, 28(12), 757–766.
[14] Stenhauser C, Rose P. *Clin Drug Invest*., **2004**, 24(4), 1-6.
[15] Sener M, Yilmazer C, Yilaz I, Bozdogan N, Ozer C, Donmez A et al. *Journal of Clinical Anesthesia*., **2008**, 20(2), 103-108.
[16] Daabiss M, Al-Sherbiny M, Al-Otaibi and Al-Nimar R, *BJMP*., **2009**, 2(3), 46-50.
[17] Kirdemir P, Marsan A. *J Clin Exp Invest*., **2010**, 1(1), 1-6.
[18] Berry H, Hamilton EBD, Bird HA, Black C, Blake DR, Freeman AM et al. *Ann Rheum Dis*., **1992**, 51, 238-242.
[19] Kidd B, Frenzel W. *J Rheumatol*., **1996** sep, 23(9), 1605-1611.
[20] Yakhno N, Guekht A, Skoromets A, Spirin N, Strachunskaya E, Temavsky A et al. *Clin Drug Invest*., **2006**, 26(5), 267-77.
[21] Norholt SE, Pedersen SS, Larsen U, Bang U, Ingerslev J, Nielsen O. *Pain*., **1996**, 67, 335-343.