



Original Work

A Randomized, Controlled Clinical Trial Comparing Efficacy, Safety and Cost Effectiveness of Lornoxicam with Diclofenac Sodium in Patients of Osteoarthritis Knee

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ABSTRACT: Osteoarthritis is a chronic painful condition affecting larger joints; most commonly knee joint. Pharmacological control of pain is the mainstay of management of osteoarthritis. Many patients fail to achieve satisfactory reduction in pain with one of the most commonly prescribed drugs, diclofenac sodium, even after maximum daily allowed doses. Lornoxicam is a newer molecule in the Indian market promising better pain relief in context of low back pain and post knee replacement surgery pain as compared to standard therapies. As per profile of lornoxicam, if it is better than diclofenac sodium then it will be helpful in managing the patients of osteoarthritis more effectively. Till date no comparative clinical trial has been done to compare these two drugs for the management of osteoarthritis knee. So, to evaluate the same we carried out this study to compare safety, efficacy and cost effectiveness of lornoxicam and diclofenac sodium in relieving pain in patients of osteoarthritis knee. This study is a randomized, open labeled, controlled clinical trial having 40 newly diagnosed patients with osteoarthritis knee. After random allocation into two groups i.e. group D and group L (each having 20 patients); group D received diclofenac sodium 50 mg 12 hourly and group L received lornoxicam 4 mg 8 hourly for a period of 3 months. All patients were assessed with visual analogue scale and 100 meter walking test before starting of therapy, at 15 days and at 1, 2 and 3 months of therapy. Adverse drug reactions and cost of therapy was monitored during the study period. Mean decrease in visual analogue scale and time of 100 meter walking test was statistically significant in lornoxicam group as compared to diclofenac sodium. Gastric irritation was reported in one patient from group L and two patients from group D. Lornoxicam significantly relieves pain of osteoarthritis knee than diclofenac sodium without adversely affecting the tolerability to the patients.

KEY WORDS: *Osteoarthritis knee; Lornoxicam; Diclofenac sodium; Open label RCT*

INTRODUCTION

Osteoarthritis is a chronic degenerative condition affecting joints including articular cartilage and subchondral bone. Symptoms may include joint

pain, tenderness, stiffness and locking of affected joint and sometimes joint cavity effusion. In majority, large joints of human body are affected more than smaller joints¹. Among these larger joints, knee joint is most commonly affected. Osteoarthritis affects women more than men and prevalence increases with age². Osteoarthritis of knee is one of five leading causes of disability among non-institutionalized adults and also is a leading cause of impaired mobility in elderly³.

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Approximately 25% of persons of 55 years of age or older have had knee pain on most days in a month in the year 2000⁴.

Apart from permanent cure in the form of costly joint replacement surgery; management of osteoarthritis knee generally involves a combination of exercise, lifestyle modification and analgesics. Diclofenac sodium and lornoxicam⁵ both are acid derivative analgesics which gets accumulated in the inflamed tissue like joints affected by osteoarthritis⁶. Diclofenac sodium is one of the most commonly prescribed drugs for the osteoarthritis knee. But, observational studies have raised the possibility of a cardiovascular risk from chronic therapy with diclofenac sodium⁷. Lornoxicam has come in Indian market since last few years. It is found to be a better alternative for management of conditions like post lumbar puncture pain⁸, post tooth extraction pain⁹ but less information is available regarding its safety, efficacy and cost effectiveness in osteoarthritis knee. As per the profile, if lornoxicam is really more beneficial than diclofenac sodium then it will be helpful in managing the patients of osteoarthritis more effectively. To confirm the same we planned this study.

METHODOLOGY

With prior approval of institutional review board of Government Medical College, Bhavnagar, Gujarat (India); the study was carried out at Department of Orthopedics, Sir Takhtasinhji General Hospital and Government Medical College, Bhavnagar. Study was registered on www.clinicaltrials.gov (NCT01055470). Study was conducted as per Declaration of Helsinki and ICH-GCP. Study was randomized, open labeled, parallel group comparative clinical trial with 3 months duration in addition of one week run-in period. The aim of the run-in period was to make the groups comparable with regard to the treatment strategy at the point of randomization. Tablet diclofenac sodium (50 mg), Tablet lornoxicam (4 mg), visual analogue scale, patient information sheet, consent form (in vernacular language) were used for study. As this was a pilot study to compare the effectiveness of two medications in the management of osteoarthritis knee, no formal sample size calculation was performed.

Patients aged between 25 to 65 yrs of either gender suffering from osteoarthritis of knee diagnosed according to criteria given by American College of Rheumatology¹⁰ were explained about the study. 40 patients who gave written informed consent were assigned randomly (using Random Number Table) into two groups i.e. group D (diclofenac sodium

group) and group L (lornoxicam group) of 20 patients each with allocation ratio of one.

Patients having any other systemic illness, pregnant and lactating women, patients taking other drugs like lithium¹¹, digoxin, methotrexate, anticoagulants, antidiabetic drugs namely sulfonylureas and biguanides, diuretics, cyclosporine, quinolone antibiotics, having history of hypersensitivity to non steroidal anti-inflammatory drugs and patient who consumed any analgesic in last 1 month were excluded from the study.

For 3 months, patients of group D received diclofenac sodium 50 mg (Generic Supply) every 12 hourly and group L received lornoxicam 4 mg (Tab. Fulactive, Ranbaxy Pharmaceuticals, India) every 8 hourly. Medicines were given orally and the patients were advised to take them after meals. Patients were assessed with the help of visual analogue scale¹² and 100 meters walking test. Visual analogue scale is a pain scale in which pain of osteoarthritis of knee is recorded in gradations from 0 to 4. Zero means no pain and 4 means severe pain. In 100 meters walking test, time taken by the patient to walk distance of 100 meters is recorded in seconds. Visual analogue scale was recorded immediately after completing 100 meters walking test. The outcome was difference in reduction in the visual analogue scale reading as well as in time of 100 meters walking test in both groups. Visual analogue scale and 100 meters walking test were checked by same person at every time to eliminate observer bias.

Observations of visual analogue scale and 100 meters walking test were compared at the end of 15 days, and at the end of 1, 2 and 3 months of therapy. For visual analogue scale, groups were compared to each other by Mann Whitney Rank sum test and for 100 meters walking test by unpaired "t" test. Intra-group results of visual analogue scale test were analyzed by Friedman's test followed by Dunn's multiple comparison test. Intra-group results of 100 meters walking test were analyzed by repeated measure ANOVA followed by Tuckey Cramer multiple comparison test. $P < 0.05$ was considered as statistically significant. During study period, side effects and cost of drugs were monitored in both groups. Statistical analysis was carried out using Graphpad InStat 3 (Demo version).

Direct medical costs (cost of interventional drug) and clinical outcome of patients managed with the two study groups were estimated in order to identify the differences among them and to obtain an incremental cost-effectiveness ratio (ICER), integrating the values obtained from the study to the following formula:

$$\text{ICER} = \frac{\text{Total Cost (Lornoxicam)} - \text{Total Cost (Diclofenac Sodium)}}{\text{Effectiveness (Lornoxicam)} - \text{Effectiveness (Diclofenac Sodium)}}$$

Thus, in this study, ICER was obtained by dividing net cost difference with the difference in net effectiveness for two alternative treatments (Lornoxicam vs. Diclofenac Sodium). Effectiveness measure used for this evaluation was the number of patients with effective pain control (visual analogue scale score = 0 at 3 month therapy) without any adverse event per each study group.

RESULTS

Demographic characteristics of both groups were comparable to each other; with preponderance of female patients in both, and mean age of patient was 49.6 years. No patient dropped out from the study. Overall pain reduction, assessed by the visual analogue scale, achieved in both groups continued to be same till 1 month treatment. But thereafter there was statistically significant difference between reduction of pain assessed by visual analogue scale (68.09 % reduction in group

L as compared to 45.45 % reduction in group D at 2 months; $P < 0.05$ and 80.89% reduction in group L as compared to 45.45 % reduction in group D at 3 months; $P < 0.001$). Mean pain score of group L was less than results of group D after 2 and 3 months of treatment (**Table 1**).

In both groups, pain reduction assessed by the 100 meters walking test continued to be same till 2 months treatment. But at the end of 3 months there was statistically significant difference between both groups (20.11% reduction in time for group L as compared to 13.11 % reduction in time for group D at 3 months; $P < 0.05$). Mean time of 100 meters walking test for group L was less than that of group D. Also at 3 months, group L shows significant difference compared to baseline as well as at 15 days, 1 month and 2 month duration of treatment ($P < 0.001$). (**Table 2**)

ICER was found to be 0.949 which was obtained by dividing net cost difference with the difference in net effectiveness for two alternative treatments drugs (lornoxicam vs. diclofenac sodium).

Table 1: Showing comparison of group D and group L by visual analogue scale (From 0 to 4) (n=20 in each group).

Timeline	Group D (diclofenac sodium) (Percent reduction as compared to base line)	Group L (lornoxicam) (Percent reduction as compared to base line)
Baseline	2.2±0.15	2.35±0.13
15 days	1.5±0.17* (31.82 %)	1.4±0.18 (40.43 %)
1 st month	1.3±0.12@ (40.90 %)	0.9±0.16# (61.70 %)
2 nd month	1.2±0.11# (45.45 %)	0.75±0.14#§ (68.09 %)
3 rd month	1.2±0.11# (45.45 %)	0.45±0.11^# (80.85 %)

Values expressed as mean ± SEM. * $P < 0.05$, @ $P < 0.01$, # $P < 0.001$ compared to baseline, !

$P < 0.01$ compared to 15 days (Friedman's test followed by Dunn's multiple comparison test),

§ $P < 0.05$, ^ $P < 0.001$ compared to Group D (Mann Whitney Rank sum test)

Table 2: Showing comparison of group D and group L by 100 m. walking test (n=20 in each group)

Timeline	Group D (diclofenac sodium) (Percent reduction as compared to base line)	Group L (lornoxicam) (Percent reduction as compared to base line)
Baseline	141.1 ± 4.0	144.7 ± 3.6
15 days	131.8±3.1* (7.09 %)	132.5±2.9* (8.43 %)
1 st month	126.0±2.8* [@] (10.70 %)	124.9±2.7* [!] (13.68 %)
2 nd month	123.8±2.7* [!] (12.26 %)	121.6±2.2* [!] (16.00 %)
3 rd month	122.6 ± 2.5* [!] (13.11 %)	115.6 ± 1.8* ^{!€§} (20.11 %)

Values expressed as mean ± SEM. * $P < 0.001$ compared to baseline, @ $P < 0.01$ compared to 15 days, [!] $P < 0.001$ compared to 15 days, [^] $P < 0.001$ compared to 1 month, [€] $P < 0.01$ compared to 2 month (Repeated measure ANOVA followed by Tukey Kramer multiple comparison test), [§] $P < 0.05$ compared to Group D (Unpaired t test)

DISCUSSION

The main aim of this study was to compare analgesic effectiveness of lornoxicam and diclofenac sodium in patients of osteoarthritis of knee. Our study showed that lornoxicam was more effective than diclofenac. These results are in accordance with previous clinical trials like a randomized, double-blind, placebo controlled trial involving 46 patients in each group which concluded that lornoxicam administration in total knee replacement was associated with decreased morphine consumption for postoperative analgesia and fewer side effects¹³. Lorenz *et al* reported that intravenously administered lornoxicam typically suppressed pain-induced brain activation in all regions except the hippocampus in a Functional Magnetic Resonance Imaging (fMRI) compatible pain model mimicking surgical pain at anterior margin of the right tibia¹⁴. Yakhno *et al* found that lornoxicam administered as a quick-release formulation was non-inferior to the equivalent formulation of diclofenac potassium in terms of onset of pain relief and more effective on most of the major standard efficacy outcomes in 220 patients having low back pain¹⁵.

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 inflammation¹⁶. Accumulation of polymorphonuclear cells also leads to release of

mediators which further enhance the inflammatory cascade¹⁶.

Effect of the lornoxicam increased over duration of therapy (i.e. reduction in pain- 40.43 % at 15 days, 61.70 % at 1 month, 68.09 % at 2 months and 80.85 % at 3 months, Table 1). Probable reason of this incremental effect is that lornoxicam inhibits human polymorphonuclear cell migration induced by f -myeloperoxidase, IL-8 and substance P¹⁷ which are some of the important chemotactic mediators of inflammation. As it is clinically difficult to study the effect of a drug on articular cartilage, it should be confirmed with advanced procedures like arthroscopy.

During the study, no other adverse drug reaction except gastric irritation was reported in one patient from group L and two patients from group D. This was managed by Cap. Omeprazole 20 mg 12 hourly for 5 days and these patients showed their willingness to continue in study and successfully completed full duration of study. None of the patients developed cardiovascular adverse reactions like edema or increase in blood pressure.

Drug with the highest per day therapy cost was lornoxicam (Rs. 11.17) and difference in cost was significant with the use of diclofenac sodium (Rs. 1.68). But, as far as effectiveness is concerned, the drug with the largest number of patients with effective pain control without developing adverse events is again lornoxicam. In addition, per 3 months therapy, treatment of adverse drug reactions reported in both groups increased average one day therapy cost by Rs. 0.45 in group D and Rs. 0.22 in group L in respective patients. When integrating both measures (costs and effectiveness),

it is observed that lornoxicam is more effective than diclofenac sodium with a higher cost. As lornoxicam is newer molecule in the market, there is scope for its price reduction in future.

CONCLUSION

From above results we can conclude that lornoxicam significantly relieves pain of osteoarthritis knee more than diclofenac sodium without adversely affecting the tolerability to the patients. However, as this was a pilot study with limited sample size, relative short study duration and open-label design, more studies with larger sample size, longer duration, and blinding techniques are necessary to substantiate our observations.

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