Section: Pharmacology

Original Research Article

A RANDOMIZED SINGLE BLIND CONTROLLED STUDY OF THE EFFECTIVENESS AND SAFETY OF LORNOXICAM VERSUS SUSTAINED RELEASE DICLOFENAC IN ANKYLOSING SPONDYLITIS

Kali Charan Rajak[1], Rahul Ranjan[2], Awadhesh Kumar Jha[3], Shambhu Kumar[4]

[1]Tutor, Department of Pharmacology, Government Medical College Bettiah, India.
[2]Tutor, Department of Pharmacology, Government Medical College Bettiah, India.
[4]Associate Professor, Department of Pharmacology, Government Medical College Bettiah, India.
[5]Assistance Professor, Department of Pharmacology, Government Medical College Bettiah, India.

Received : 03/03/2024
Received in revised form : 25/04/2024
Accepted : 10/05/2024

Keywords:
Lornoxicam Versus Sustained Release Diclofenac, Ankylosing Spondylitis.

Corresponding Author:
Dr. Rahul Ranjan,
Email: rahul.dr.ranjan@outlook.com.

DOI: 10.47009/jamp.2024.6.4.217

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (4); 1093-1096

Abstract

Background: Ankylosing spondylitis, also known as axial spondyloarthritis, is an inflammatory disease that, over time, can cause some of the bones in the spine, called vertebrae, to fuse. This fusing makes the spine less flexible and can result in a hunched posture. If ribs are affected, it can be difficult to breathe deeply. As ankylosing spondylitis worsens, new bone forms as part of the body's attempt to heal. The new bone gradually. **Materials and Methods y:** With prior approval of institutional review board of Government Medical College Bettiah, Bihar. The study was carried out at Department of Orthopedics and Pharmacology. 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. bridges the gaps between vertebrae and eventually fuses sections of vertebrae together. Fused vertebrae can flatten the natural curves of the spine, which causes an inflexible, hunched posture. **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. **Conclusion:** From above results we can conclude that lornoxicam significantly relieves pain of ankylosing spondylitis more than diclofenac sodium without adversely affecting the tolerability to the patients.

INTRODUCTION

Ankylosing spondylitis, also known as axial spondyloarthritis, is an inflammatory disease that, over time, can cause some of the bones in the spine, called vertebrae, to fuse. This fusing makes the spine less flexible and can result in a hunched posture. If ribs are affected, it can be difficult to breathe deeply. As ankylosing spondylitis worsens, new bone forms as part of the body's attempt to heal. The new bone gradually bridges the gaps between vertebrae and eventually fuses sections of vertebrae together. Fused vertebrae can flatten the natural curves of the spine, which causes an inflexible, hunched posture.

Axial spondyloarthritis has two types. When the condition is found on X-ray, it is called ankylosing spondylitis, also known as axial spondyloarthritis. When the condition can't be seen on X-ray but is found based on symptoms, blood tests and other imaging tests, it is called nonradiographic axial spondyloarthritis. Symptoms typically begin in early adulthood. Inflammation also can occur in other parts of the body — most commonly, the eyes. There is no cure for ankylosing spondylitis, but treatments can lessen symptoms and possibly slow progression of the disease. Early symptoms of ankylosing spondylitis might include back pain and stiffness in the lower back and hips, especially in the morning and after periods of inactivity. Neck pain and fatigue also are common. Over time, symptoms might worsen, improve or stop at irregular intervals. Ankylosing spondylitis has no known specific cause, though genetic factors seem to be involved.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

In particular, people who have a gene called HLA-B27 are at a greatly increased risk of developing ankylosing spondylitis. However, only some people with the gene develop the condition. Onset generally occurs in late adolescence or early adulthood. Most people who have ankylosing spondylitis have the HLA-B27 gene. But many people who have this gene never develop ankylosing spondylitis. In severe ankylosing spondylitis, new bone forms as part of the body's attempt to heal. This new bone gradually bridges the gap between vertebrae and eventually fuses sections of vertebrae. Those parts of the spine become stiff and inflexible. Fusion also can stiffen the rib cage, restricting lung capacity and function. Diclofenac sodium is one of the most commonly prescribed drugs for the ankylosing spondylitis. But, observational studies have raised the possibility of a cardiovascular risk from chronic therapy with diclofenac sodium,[7] 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 pain,[8] post tooth extraction pain,[9] but less information is available regarding its safety, efficacy and cost effectiveness in ankylosing spondylitis. 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.

MATERIALS AND METHODS

With prior approval of institutional review board of Government Medical College Bettiah, Bihar.The study was carried out at Department of Orthopedics and Pharmacology. 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 ankylosing spondylitis no formal sample size calculation was performed. Patients aged between 25 to 65 yrs of either gender suffering from ankylosing spondylitis diagnosed according to criteria given by American College of Rheumatology10 were explained about the study. 30 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 15 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 ankylosing spondylitis 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 Crammer 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: 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

ISSN (O): 2687-5365; ISSN (P): 2753-6556

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 (69.08 % reduction in group 2 months; P<0.05 and 88.89% reduction in group L as compared to 44.55 % 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 (21.11% reduction in time for group L as compared to 15.11 % 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

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 %)
1st month	1.3±0.12@ (40.90 %)	0.9±0.16# (61.70 %)
2nd month	1.2±0.11# (45.45 %)	0.75±0.14#$ (68.09 %)
3rd month	1.2±0.11# (45.45 %)	0.45±0.11*#| (80.85 %)

Table 2

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 %)
1st month	126.0±2.8*@ (10.70 %)	124.9±2.7*| (13.68 %)
2nd month	123.8±2.7*| (12.26 %)	121.6±2.2*| (16.00 %)
3rd month	122.6 ± 2.5*| (13.11 %)	115.6 ± 1.8*|€$ (20.11 %)

DISCUSSION

The main aim of this study was to compare analgesic effectiveness of lornoxicam and diclofenac sodium in patients of ankylosing spondylitis. 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 effects.[13] 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 tibia.[14] 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

ISSN (O): 2687-5365; ISSN (P): 2753-6556

onset of pain relief and more effective on most of the major standard efficacy outcomes in 220 patients having low back pain.[15] Polymorphonuclear cell invasion into the joint cavity is one of the important factors in acute inflammatory diseases like ankylosing spondylitis. This process depends on the augmentation of several biological factors with chemotactic activity and probably interleukin-8 (IL-8) at the site of inflammation.[16] Accumulation of polymorphonuclear cells also leads to release o 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 polymorphoneuclear 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 patientmfrom 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 3m 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), f 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 ankylosing spondylitis 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.

REFERENCES

1. Osteoarthritis. Arthritis Foundation of Victoria. Arthritis Australia. 2006 Aug; Retrieved from:http://www.nevdgp.org.au/info/ArthritisF/arthritis/osteoart.htm
2. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications of research. Clin Orthop Relat Res. 2004 Oct:(427 Suppl): S6-15.
3. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health. 1994 Mar;84(3):351-8.
4. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis. 2001 Feb;60(2):91-7.
5. Balfour JA, Fitton A, Barradel LB. Lornoxicam: A review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. Drugs. 1996 Apr;51(4):639-57.
6. Burke A, Smyth E, FitzGerald GA. Analgesicantipyretic and antiinflamatory agents; Pharmacotherapy of gout. Brunton LL, Lazo JS, Parker KL, editors. In: Goodman & Gillman's the Pharmacological basis of Therapeutics, 11th edition. New Delhi: The McGraw Hill Companies. 2006;671-715.
7. M Cgettigan P & Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA. 2006 Oct;296(13):1633-44.
8. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesth Analg. 1998 May;86(5):1045-50.
9. Nørholt SE, Sindet-Pedersen S, Larsen U, et al. Pain control after dental surgery: a doubleblind, randomised trial of lornoxicam versus morphine. Pain. 1996 Oct;67(2-3):335-43.
10. Wu CW, Morrell MR, Heinze E, el al. Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. Semin Arthritis Rheum. 2005 Dec;35(3):197-201.
11. Baldessarini RJ, Tarazi FI. Pharmacotherapy of psychosis and mania editors In: Goodman & Gillman's the Pharmacological basis of Therapeutics, 11th edition. New Delhi: The McGraw Hill Companies; 2006;671-715.
12. Wong DL, Hockenberry-Eaton M, Wilson D, et al. Wong's Essentials of Pediatric Nursing, 6th Edition, Publisher: Mosby, St. Louis. 2001;130.
13. Inan N, Ozcan N, Takmaz SA, et al. Efficacy of lornoxicam in postoperative analgesia after total knee replacement surgery. Agri. 2007 Apr;19(2):38-45.
14. Lorenz IH, Egger K, Schubert H, et al. Lornoxicam characteristically modulates cerebral pain-processing in human volunteers: a functional magnetic resonance imaging study. Br J Anaesth. 2008 Jun;100(6):827-33
15. Yakhno N, Guekht A, Skoromets A, et al. Analgesic efficacy and safety of lornoxicam quick-release formulation compared with diclofenac potassium: randomised, doubleblind trial in acute low back pain. Clin Drug Investig. 2006;26(5):267-77
16. Partsch G, Matucci-Cerinic M. Effect of substance P and Somatostatin on migration of Polymorphonuclear (PMN) cells in vitro. Inflammation. 1992 Oct;16(5):539-47.
17. Sacerdote P, Bianchi M. Lornoxicam Inhibits Human Polymorphonuclear Cell Migration Induced by fMLP, Interleukin-8 and Substance P. Int J Pharmacol. 2005;1(2)180-4.

ISSN (O): 2687-5365; ISSN (P): 2753-6556