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Research Article

A comparative study of efficacy and safety of flupirtine versus piroxicamin patients with low back pain

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ABSTRACT

Background: Low back pain is a common musculoskeletal symptom caused by a variety of disorders that affect the lumbar spine. The most frustrating aspect in the treatment of low back pain is that there is "no magic bullets". The objective of the study was to compare the efficacy and safety of flupirtine versus piroxicam in patients with back pain.
Methods: This was prospective, open labeled, randomized, comparative clinical study conducted by the Departments Orthopedics and Pharmacology, BMC&H, Chitradurga. Study was conducted on 60 patients of either sex, aged above 18 years with low back pain. Assessments were done for Finger-to-Floor Distance (FFD), lumbar pain, Lasegue's sign, tenderness of vertebral muscles, pain & sensory disturbance in lower limbs and response to therapy for efficacy. Parametric data was analyzed by t-test and proportions were compared using Chi-square test.
Results: 74 patients were randomized to 2 groups of 37 each. Group I patients received flupirtine maleate 100 mg twice daily and Group II patients received piroxicam 20 mg twice daily for 14 days. 30 patients in each group completed the study and were analysed. On intergroup comparison, there was no statistical difference ($p>0.05$) in the efficacy parameters of finger-to-floor distance (FFD), lumbar pain, Lasegue's sign, tenderness of vertebral muscles, sensory disturbance in lower limbs, VAS scores & global assessment of response to therapy. 13.3% in flupirtine group and 16.6% in piroxicam group reported adverse events.
Conclusions: Both flupiritine and piroxicam were equally effective but flupirtine was better tolerated than piroxicam.

Keywords: Flupirtine, Piroxicam, Low back pain

INTRODUCTION

Low Back Pain (LBP) is a common human condition with 60-80% of the world population experiencing pain at some point of time in their life.[1] Low back pain is second only to the common cold as the most frequent reason for visiting a physician and is most common chronic pain syndrome in individual countries.[2]

Low back pain is a common musculoskeletal symptom that may be either acute or chronic. It may be caused by a variety of diseases & disorders that affect the lumbar spine. The most frustrating aspect in the treatment of low back pain is that there is "no magic bullets".[3] Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications worldwide and are widely used for patients with low back pain.[4]

Flupirtine maleate is a non-opioid drug without antipyretic and anti-inflammatory properties which is approved by European Medical Agency for acute & chronic pain especially of musculoskeletal origin.[5] It has

distinctive mechanism of action exerting a dual therapeutic effect with both analgesic and musculoskeletal properties that has utility in the treatment of pain including that associated with muscle tension.[6]

Piroxicam is an NSAID and a non-selective COX inhibitor possessing both analgesic and antipyretic properties. Some of the studies had shown the beneficial role of piroxicam in low back pain. However, sufficient studies with respect to safety and efficacy are lacking. Since both piroxicam and flupirtine are analgesics, it is difficult to recommend and ascertain the superiority of one drug over the other.

There is paucity of studies comparing flupiritine with piroxicam in low back pain and hence this study was undertaken by the Department of Orthopedics & Pharmacology at Basaveshwara Medical College Hospital & Research Centre, Chitradurga.

METHODS

Study design

This was a prospective, open labeled, randomized, comparative clinical study conducted by the Departments Orthopedics and Pharmacology, Basaveshwara Medical College Hospital & Research Centre, Chitradurga. Study was conducted in accordance with the principles of good clinical practice and declaration of Helsinki. A written informed consent was obtained from all the patients enrolled for the study.

Study protocol

Patients of either sex above 18 years of age attending the outpatient of the Orthopedics department were screened for lumbar pain and spasm by clinical and radiological examination, for inclusion in the study. It was planned to enroll patients with low back pain due to spondylosis deformans, prolapsed disc or muscle sprain. Those willing to comply with study procedures were included after obtaining the written informed consent. Laboratory evaluations were done at baseline to rule out any laboratory abnormalities for hemogram, complete blood count, renal function test (serum creatinine and blood urea nitrogen), hepatic function tests (total serum bilirubin, alkaline phosphatase, aspartate transaminase and alanine transaminase) and random blood sugar.

Inclusion criteria

- >18 years of age of either sex
- Complaints of low back pain of acute onset due to muscle sprains, prolapsed disc, spondylosis deformans

Exclusion criteria

- Pregnant/lactating women
- Pain associated with fractures
- Head injury patients with back pain
- Patients on opioid analgesics
- History of hypersensitivity to any of the ingredients of both the drugs
- Patients unwilling or unable to comply with study procedures

Figure 1 is the flow chart of study. Totally 99 patients were screened for the eligibility to be included in the study. Out of 99 patients, 25 patients were excluded from the study (not meeting inclusion criteria & unwilling to participate). 74 of the eligible study subjects, were then randomized into two groups of 37 each by computer based randomization. Group I patients received flupirtine maleate 100 mg twice daily and group ii patients received piroxicam 20 mg twice daily for 2 weeks. In Group I patients receiving flupirtine, 7 patients were lost to follow-up. In Group II patients receiving piroxicam, 6 patients were lost to follow-up and 1 patient discontinued treatment due to excess heartburn (patient was treated appropriately for heartburn using antacids). Ultimately, 30 patients in each group completed the study and were analysed for the results.

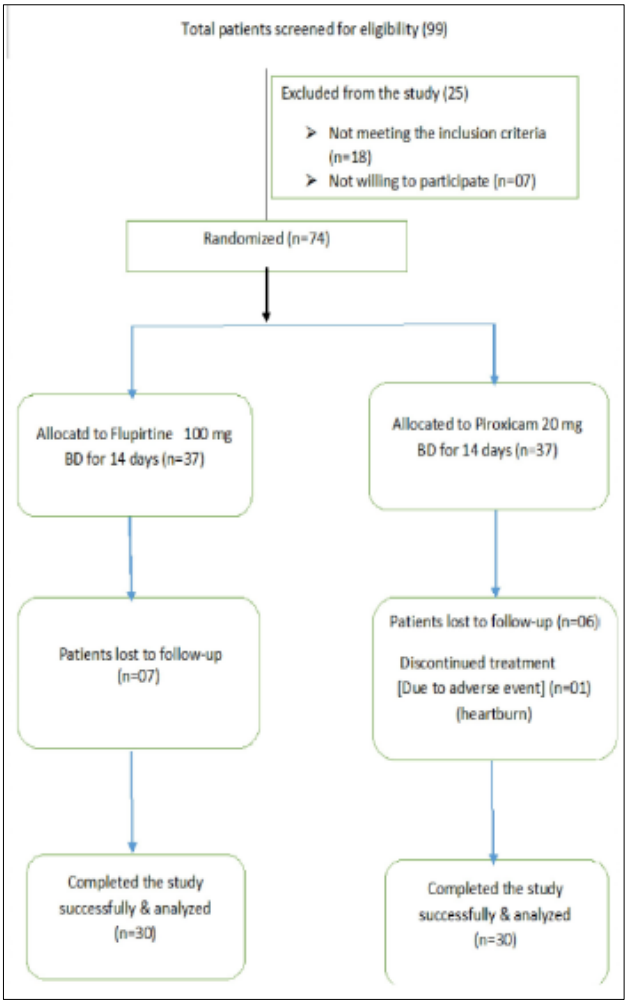

Figure 1: Flow chart of study.

Efficacy assessment

The patients were assessed on day 1 (1st visit), day 7 & day 14 for the following parameters - Finger to floor distance in cm, Lasegue's sign (lumbar pain or exacerbation of existing pain on passive movement of the legs during flexion of hip joint), tenderness of paravertebral muscle, sensory disturbance of lower limbs, Pain in lower limbs, Visual Analogue Scale (VAS) for rating of back pain, Global Assessment of Response to Therapy (GART).[3]

The efficacy parameters assessed included finger-to-floor-surface distance (FFD) measured as distance in cm when standing with the spinal cord flexed with complete extension of knee joint,[3] Lasegue's sign - lumbar pain or exacerbation of existing pain on passive movement of the legs during flexion of hip joint. Patients were assessed if Lasegue's sign was present or absent. Tenderness of paravertebral muscles and Sensory disturbance of lower limbs were evaluated as present or absent. Pain in lower limb was evaluated on a four-point rating scale of 0=No Pain, 1=Mild pain, 2=Moderate pain and 3=Severe pain.

The subjective efficacy parameters assessed were lumbar cinesalgia (assessed on a 0-100 mm VAS) with '0' representing 'No pain' and '100' representing (Severe intolerable pain) and GART was assessed on a four-point rating scale of 0=Poor, 1=Average, 2=Good and 3=Excellent.[3]

Safety assessment

The patients were assessed at day 1, day 7 and day 14 to record any adverse events during course of therapy of two weeks. In addition to the follow up, the patients were instructed to report immediately in case of any adverse event, as and when required.

Statistical analysis

Parametric data is expressed as means with standard deviation and discrete data is expressed as numbers with proportions. Two groups were compared for differences in mean values for finger to floor distance, lumbar pain (0-100 VAS), pain in lower limbs and global assessment of response to therapy by t-test. Between-groups comparisons for Lasegue's sign, sensory disturbance of lower limbs, tenderness of paravertebral muscles was assessed by Chi square test. All statistical calculations were performed with SPSS software package version 20. p value <0.05 was considered as statistically significant.

RESULTS

Table 1 shows the demography data. The two groups were comparable with respect to the age and gender (p>0.05).

Table 1: Demographic data.

	Group I (Flupirtine)	Group II (Piroxicam)	p value
Age	40.50 ± 16.47	42.93 ± 14.10	0.542
Gender (n)			
Male	13	15	
Female	17	15	

Table 2 shows the results of efficacy parameters assessment. On intergroup comparison of flupirtine and piroxicam, it was found that there was no significant differences in the objective efficacy parameters like FFD, Lasegue's sign, tenderness of paravertebral muscles & sensory disturbance of lower limbs (p>0.05). Similarly, assessment of objective efficacy parameters like Lumbar pain on VAS and GART showed no significant difference between two groups (p>0.05).

Table 2: Efficacy assessment parameters.

Parameter	Group I (Flupirtine)	Group II (Piroxicam)	p value
FFD in cm			**'t' test**
Day 1	16.66 ± 2.42	17.50 ± 2.64	0.209, NS
Day 7	12.76 ± 2.44	13.23 ± 2.38	0.458, NS
Day 14	10.53 ± 2.25	10.16 ± 2.13	0.520, NS
Lasegue's sign			**$\chi 2$**
Day 1	15 (50.0)	17 (56.6)	0.605, NS
Day 7	12 (40.0)	12 (40.0)	1.000, NS
Day 14	6 (20.0)	5 (16.6)	0.739, NS
Tenderness of paravertebral muscles			**$\chi 2$**
Day 1	10 (33.3)	12 (40)	0.592, NS
Day 7	7 (23.3)	9 (30)	0.559, NS
Day 14	2 (6.7)	2 (6.7)	1.000, NS
Sensory disturbance of lower limbs			**$\chi 2$**
Day 1	7 (233)	8 (26.7)	0.766, NS
Day 7	5 (16.7)	3 (10)	0.448, NS
Day 14	2 (6.7)	2 (6.7)	1.000, NS
Pain in lower limbs			**'t' test**
Day 1	1.73 ± 0.78	1.75 ± 0.84	0.709, NS
Day 7	1.03 ± 0.76	0.96 ± 0.86	0.686, NS
Day 14	0.43 ± 0.50	0.37 ± 0.49	0.795, NS
Lumbar pain on visual analogue scale (VAS)			**'t' test**
Day 1	6.33 ± 1.56	6.06 ± 2.30	0.791, NS
Day 7	3.53 ± 1.38	3.16 ± 1.64	0.353, NS
Day 14	1.76 ± 0.93	1.53 ± 1.40	0.452, NS
Global assessment of response to therapy (GART)			**'t' test**
End of 14th day	1.43 ± 0.93	1.83 ± 0.79	0.079, NS

NS - Non-significant, Sig - Significant, χ^2 - Chi square

Table 3 shows the adverse events reported by the patients during the study period. In Group I patients receiving flupirtine most of the adverse events were related to the gastrointestinal system (nausea, diarrhea) and central

nervous system (drowsiness, dizziness). In Group II patients receiving piroxicam most of the adverse events were related to the gastrointestinal system (diarrhea, heartburn, dyspepsia). 13.3% in flupirtine group and 16.6% in piroxicam group reported adverse events. So, flupirtine was better tolerated than piroxicam. All the events were of mild to moderate intensity in both the groups. None of the adverse events necessitated the dose modification or withdrawal from the study.

Table 3: Safety assessment.

Parameter (n)	Flupirtine				Piroxicam			
	Baseline	Day 7	Day 14	Total points	Baseline	Day 7	Day 14	Total points
Nausea	0	1	0	1	0	0	0	0
Diarrhea	0	1	0	1	0	1	0	1
Heartburn	0	0	0	0	0	1	1	2
Dyspepsia	0	0	0	0	0	1	1	2
Drowsiness	0	0	1	1	0	0	0	0
Dizziness	0	0	1	1	0	0	0	0
Total	0	02	02	04 (13.3%)	0	03	02	05 (16.6%)

DISCUSSION

Low back pain is a common musculoskeletal symptom that may be either acute or chronic. It may be caused by a variety of diseases and disorders that affect the lumbar spine. The most frustrating aspect in the treatment of low back pain is that there is "no magic bullets".[3] Flupirtine maleate is a non-opioid drug without antipyretic and anti-inflammatory properties which is approved by European Medical Agency for acute and chronic pain especially of musculoskeletal origin.[5] It has distinctive mechanism of action exerting a dual therapeutic effect with both analgesic and musculoskeletal properties that has utility in the treatment of pain including that associated with muscle tension.[6]

NSAIDs are the most frequently prescribed medications worldwide and are widely used for patients with low back pain.[4] Piroxicam is an NSAID and is a non-selective COX inhibitor possessing both analgesic and antipyretic properties. Some of the studies have shown the beneficial role of Piroxicam in low back pain.[7] However, sufficient studies with respect to safety and efficacy are lacking.

Both flupirtine and piroxicam individually have proven their efficacy in the management of low back pain of acute onset. However, there is paucity of studies comparing both the drugs. Hence this study was undertaken to compare efficacy and tolerability of flupirtine vs. piroxicam in the low back pain and ascertain the superiority of one drug over the other, if any. The study was conducted by Department of Orthopedics & Pharmacology at Basaveshwara Medical College Hospital & Research Centre, Chitradurga.

Low back pain may be attributed to various degenerative changes of the vertebrae, strain on the dorsolumbar muscles, poor posture, herniated lumbar intervertebral disc, spondylosis deformans, and muscle sprains with spasms.[8] Manasi Banerjee et al.[9] in a study comparing the efficacy and tolerability of flupirtine vs. tramadol in NSAID intolerant mechanical low back pain used Visual Analogue Scale (VAS) as efficacy parameter. Scores in VAS improved significantly ($p<0.05$) in both groups in the last visit, but more so with flupirtine. Adverse effects were less with flupirtine [26 (24.30%) versus 41 (39.81%), $p<0.05$], minimizing drop-outs. In another study by Joginder Pal Attri et al.[11] comparing flupirtine and diclofenac for analgesia and adverse effects in elective abdominal surgeries used VAS as the efficacy parameter. VAS was comparable in both groups at all measured intervals ($p>0.05$). Oral flupirtine and diclofenac sodium were equally effective for postoperative analgesia. Patients in diclofenac group experienced significantly more heartburn, impaired taste sensation and dizziness as compared to flupirtine group. Flupirtine was better tolerated by the patients because of its minimal adverse effects. In our present study of flupirtine vs. piroxicam, showed no significant difference in VAS scores at day 7 or day 14 ($p>0.05$). Nausea, diarrhea, drowsiness, dizziness were the most common adverse events in the present study. Only 13.35% patients reported adverse events in our present study as compared to 24.30% reported by Manasi Banerjee et al.[9]

Flupirtine is a non-opioid centrally acting analgesic. Flupirtine acts indirectly as N-methyl-D-aspartate (NMDA) receptor antagonist by activation of K^+ channels. Flupirtine causes a dose-dependent reduction of NMDA receptor mediated glutamate induced rise in intracellular Ca^{++} concentration. It binds to and activates G-protein coupled inwardly rectifying K^+ channels. Activation of this channel leads to hyperpolarization of neuronal membrane and the neuron becomes less excitable; thus, there is stabilization of resting neuronal membrane.[10] The beneficial effects of

Flupirtine might be attributed to these mechanism in low back pain.

Amelie E et al.[10] in a double-blind, parallel placebo-controlled trial with piroxicam involving 278 patients with acute low back pain showed a statistically greater amount of pain relief in the lying ($p<0.001$), sitting ($p<0.01$), and standing ($p<0.01$) positions, but after 7 days the difference between treatments was no longer significant. After 1 week's therapy, however, the requirement for additional analgesic was significantly lower in the piroxicam group ($p<0.05$), and more Piroxicam than placebo patients (42 versus 28) had returned to work ($p<0.05$). Tolerance was excellent in most patients, with only 13% of the piroxicam and 17% of the placebo group reporting adverse effects of mainly mild or moderate severity. The profile of the adverse effects was similar for both treatments. In the present study of flupirtine vs. piroxicam, there was no significant difference in all the efficacy parameters like Finger to floor distance, Lasegue's sign, tenderness of paravertebral muscle, sensory disturbance of lower limbs, pain in lower limb, VAS rating of low back pain and GART ($p<0.05$). Diarrhea, heartburn, dyspepsia were the most common adverse events in our study. About 16.6% patients receiving piroxicam reported adverse events in our study as compared to 13% reported by Amelie E et al. piroxicam was well tolerated with all the events being only of mild to moderate intensity. Both efficacy and tolerability are consistent with the findings reported by Amelie E et al.[10]

To conclude, both the drugs were equally effective and well tolerated in patients of low back pain but flupirtine was better tolerated than piroxicam. It is hard to generalize these findings in the general population considering that we conducted the study on a small sample size. Further studies with larger sample size are needed to be conducted to draw conclusions.

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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