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Research Article

EFFICACY AND TOLERABILITY OF FLUPIRTINE MALEATE VERSUS DICLOFENAC IN MECHANICAL LOW BACK PAIN – A PROSPECTIVE COMPARATIVE STUDY

RAMYA R[1]*, RAJARAM S[1], LEENA RANJINI V[2], NATHIYA S[3]

[1]Department of Pharmacology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamil Nadu, India. [2]Department of Pharmacology, Shri Sathya Sai Medical College and Research Institute, Chengalpattu, Tamil Nadu, India. [3]Department of Pharmacology, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu, India.

***Corresponding author: Ramya R; Email: ramyavishal1595@gmail.com**

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ABSTRACT

Objective: Low back pain (LBW) is one of the most common reasons for adults visiting orthopedic outpatient clinics in our country. The objective of the study was to compare the safety and efficacy of flupirtine, a selective neuronal potassium channel opener, with diclofenac, a widely used NSAIDs analgesic, in patients with mechanical LBW (MLBP).

Methods: This prospective, open-labeled, and randomized comparative clinical study included 100 patients with MLBP for more than 6 weeks. Fifty patients received flupirtine 100 mg, and 50 patients received diclofenac 100 mg for 7 days. Follow-up was done on day 8 and day 30. Assessments of functional improvement by the Oswestry Disability Index (ODI), pain relief by the Visual Analog Scale (VAS), Numerical Rating Scale (NRS), and Pain Relief Rate (PRR) were recorded. Safety and tolerability were also assessed. Data were analyzed using the Chi-square and Paired student t-tests.

Results: VAS, NRS, and ODI scores were assessed for each visit (0, 1, and 2), and PRR was assessed on visits 1 and 2. VAS ($p<0.05$), NRS ($p<0.05$) scores, and sustained effect after stoppage of the drug were found to be better in the flupirtine group compared to the diclofenac group. Flupirtine was well tolerated. More patients reported adverse events in diclofenac than in the flupirtine group.

Conclusion: Flupirtine may have a superior sustained effect compared to diclofenac in MLBP.

Keywords: Flupirtine, Diclofenac, SNEPCO, Oswestry disability index, Visual analog scale, Pain relief rate, Numerical rating scale.

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INTRODUCTION

Low Back Pain (LBW) is one of the major musculoskeletal problems that are often associated with loss of work productivity and thus having a huge impact on the economic burden on individuals and on societies. Based on the Global Burden of Disease Study, LBW is considered as a leading cause of disability globally. An estimated 619 million people suffer with LBP worldwide [1]. Around 90% of the cases of back pain are idiopathic and in 5–10% specific causes such as degenerative conditions, inflammation, infection, neoplasm, metabolic bone disease, referred pain, psychogenic pain, trauma, or congenital disorders may be identified [2]. It is usually non-specific or mechanical. Mechanical LBW (MLBP) arises intrinsically from the spine, intervertebral disks, or surrounding soft tissues. Causes of mechanical back pain include lumbar strain, herniated discs, spondylitis, spondylolisthesis, spinal stenosis, and fractures. The symptoms of MLBP are usually aggravated by day-to-day physical activities such as bending, extending, twisting, and lifting, whereas avoidance of pain-producing activities results in temporary improvement. Non-steroidal anti-inflammatory drugs, muscle relaxants, benzodiazepines, corticosteroids, and opioid analgesics are commonly prescribed in MLBP [3].

NSAIDs are the most used analgesic medication worldwide. However, the NSAIDs use is associated with serious gastrointestinal adverse effects such as gastritis, gastrointestinal bleeding, and gastric and intestinal ulcers [4]. NSAIDs are also associated with renal complications including interstitial nephritis and glomerulopathy and may cause salt and water retention in patients with renal, cardiac, or hepatic comorbidities. Even some individuals may have hypersensitivity reactions to NSAIDs, with symptoms that ranging from vasomotor rhinitis, angioedema, generalized urticaria, and bronchial asthma to even laryngeal edema, bronchoconstriction, flushing and hypotension [5,6].

Diclofenac sodium is one of the commonly used non-steroidal anti-inflammatory drugs having both analgesic and anti-inflammatory actions [7]. It is used in the treatment of various acute and chronic pain and inflammation. It also has an increased risk of gastrointestinal side effects such as gastric ulcers and bleeding. [8].

Flupirtine is a centrally acting non-opioid analgesic without antipyretic activity that has potential applications in pain management. Flupirtine is consistent with its unique mechanism of action, selective neuronal potassium channel opener and NMDA receptor antagonist has rapidly evolved as the most preferred analgesic for the treatment of musculoskeletal pain [9-11]. It modulates neuronal potassium channels, causing hyperpolarization of neurons and reducing their excitability. This mechanism of action is different from traditional analgesics, such as NSAIDs and opioids, making it a valuable alternative for pain relief. The pharmacological properties of flupirtine include analgesic, muscle relaxant, and antioxidant activity that favors its therapeutic benefits [12]. Unlike NSAIDS, it is generally considered to have a tolerable safety profile and lack gastric acidity, renal side effects, thrombotic events, and bleeding [13,14]. The most common adverse effects noted were nausea, vomiting, heartburn, abdominal discomfort, sleep disturbances, diarrhea, and constipation [15]. Furthermore, it is not associated with the risk of addiction or respiratory depression, making it a safer choice in certain pain management scenarios. Hence, this study was conducted to compare the safety and efficacy of flupirtine maleate with diclofenac sodium in patients with MLBP.

METHODS

Study design

This prospective, open-labeled, and randomized comparative clinical study was designed and conducted by the Departments of Orthopedics and Pharmacology. All patients attending orthopedic OPD with MLBP of more than 6 weeks were screened and recruited to the study based on the following inclusion and exclusion criteria.

Inclusion criteria

The following criteria were included in the study:

- Adult men and women between 35 and 45 years of age with MLBP of more than 6 weeks.

Exclusion criteria

The following criteria were excluded from the study:

- History of hypersensitivity
- Pain associated with fractures/head injury
- Patients with kidney, liver, heart, thyroid, osteoporosis, or malignancy disorders
- Patients on corticosteroids or those who had undergone any other clinical trial participation within the past 1 month
- Inflammatory back pain and secondary causes (excluded by history, clinical examination, and investigations such as CRP and ESR, plain radiograph of lumbosacral spine and sacroiliac (SI) joints in all cases).

The study protocol received clearance from the Institutional Ethics Committee (VMKVMC/IEC/14/45) before the start of the study. This study was conducted according to the declaration of Helsinki for Biomedical Research Involving Human Subjects and principles of good clinical practice. Mandatorily, the written informed consent was obtained from all the patients recruited for the study after explaining the objective of the study. The patients who were included in the study were assured of confidentiality.

Fig. 1 is the flowchart depicting the study design. About 119 patients were screened and 100 patients were recruited for the study. The patients were divided into two groups. It was done in a 1:1 ratio as per their register number. Fifty patients received tablet flupirtine maleate 100 mg and fifty patients received tablet diclofenac sodium 100 mg. The treatment period was about 7 days for both groups and each group took medications twice daily. Every patient had three visits during the study. Visit 0, that is, baseline visit on the day of recruitment, visit 1 on day 8, and visit 2 on day 30 as a follow-up visit 3 weeks after stoppage of treatment to evaluate the after-effect of the drugs. The complete study period was 30 days for the individual patient. Adverse effects, if any, were also noted. Height, body weight, baseline resting pulse rate, and blood pressure were also recorded on Visit 0. The participants were not allowed to use any other analgesics including other NSAIDs, 5-HT3 receptor antagonists, corticosteroids, or medications that alter the response of the study drugs.

Outcome measures

The disability index was scored for individual patients using an Oswestry Disability Index (ODI) assessment questionnaire. The patient's pain perception was noted on Visual Analog Scale (VAS) and Numerical Rating Scale (NRS) scores, and the degree of pain relief was assessed by the Pain Relief Rate (PRR) score. VAS is a 10 cm scale ("10"=worst pain imaginable; "0"=no pain), NRS-no pain-"0" and worst pain imaginable-"10". PRR: "<25%" as unrelieved, "25–49%" as mere relief, "50–74%"=moderate relief, "75–99%"=significant relief, and "100%" as complete relief were also assessed. During each visit, the VAS score, NRS score, and ODI score were assessed, and on visits 1 and 2, PRR was assessed. Safety and tolerability were also assessed at the end of the study.

Statistical analysis

The acquired data were analyzed with SPSS software version 17.0. Data were analyzed using the Chi-square (χ^2) and Paired student's t-test. For VAS, NRS, ODI, PRR, and adequate pain relief, descriptive statistics (Means and standard deviations) were calculated for each group. $p<0.05$ was considered statistically significant.

RESULTS

We analyzed the data of 100 patients who were recruited for the study. All the participants completed the study. None of them discontinued

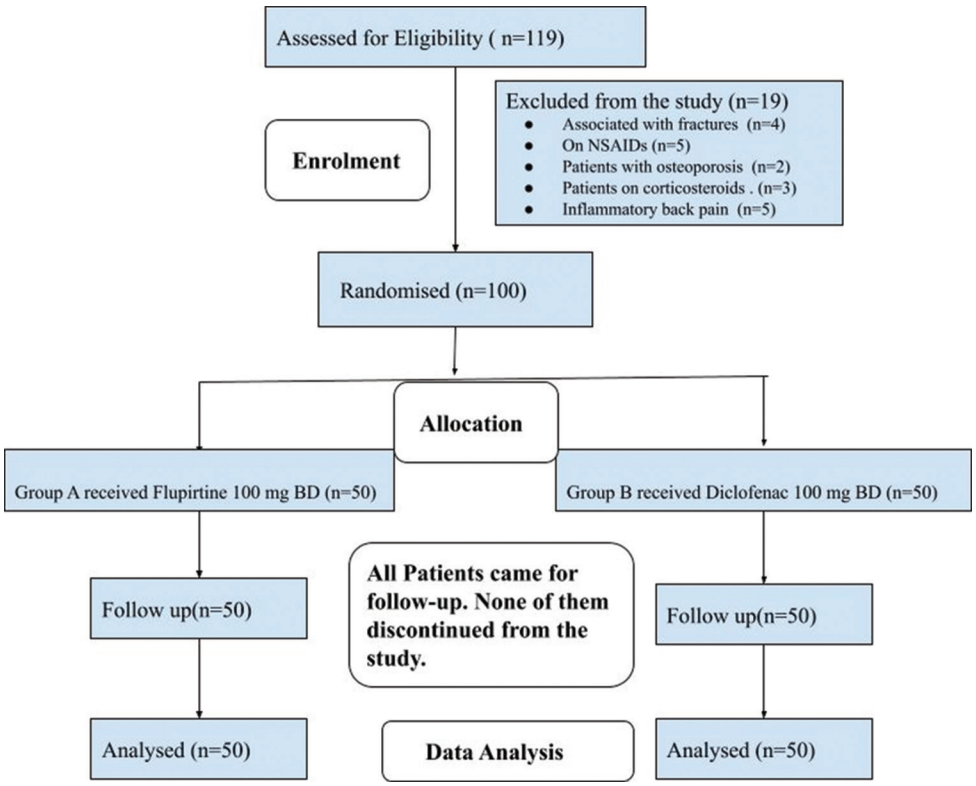

Fig. 1: Flowchart depicting the study design

the study or lost the follow-up. Fifty received Flupirtine maleate and 50 received diclofenac sodium.

Demographic and baseline characteristics

There were more females (56%) than males (44%) (Table 1). Study participants belong to the age range from 35 to 47 years (Table 1). The two treatment groups were balanced for these demographic and baseline characteristics. Before the initiation of treatment, there are no significant differences in the duration of pain between both study groups (Table 2).

Efficacy evaluation

The baseline mean VAS score of 7.76±0.7 was decreased to 1.66±0.93 (−76%, p<0.05) at visit 1 and further to 1.22±0.72 at visit 2 in the flupirtine group. The VAS score of 7.80±0.8 at baseline was decreased to 3.1±1.4 (−59%, p<0.05) at visit 1 and 2.04±1.1 at visit 2 in the diclofenac group. A similar trend was noted for the NRS score and ODI score as mentioned in Table 2. The baseline NRS score of 7.73±0.65 was decreased to 1.54±0.83 (−77%, p<0.05) at visit 1 and 1.44±0.74 at visit 2 in the flupirtine group. The NRS score of 7.73±0.6 at baseline was decreased to 2.3±1.5 (−70%, p<0.05) at visit 1 and 2.10±1.2 at visit 2 in the diclofenac group. At baseline, the mean ODI score was 52±5.4, it was reduced to 11.56±6.4 (−78%, p<0.05) at visit 1 and 10.54±4.83 at visit 2 in the flupirtine group. At baseline, the mean ODI score was 51.68±5.44, it was reduced to 15.1±8.8 (−72%, p<0.05) at visit 1 and 15.24±4.3 at visit 2 in the diclofenac group. At visit 1 (day 8, after treatment completion), the mean PRR score was 81.1±12.27, and at visit 2 (day 30) 85.0±9.4 in the flupirtine group. At visit 1, the mean PRR score was 72.3±17.1, and at visit 2 to 76.94±12.5 in the diclofenac group.

As mentioned in Table 2, at visit 1, VAS, NRS, and ODI scores were significantly (p>0.05) lower in the flupirtine group when compared to the diclofenac group and PRR was higher (p>0.05) in the flupirtine group compared to diclofenac group after 7 days of initiation of treatment. At visit 2, VAS (p<0.001) and NRS (p<0.05) scores were found to be better in the flupirtine group compared to the diclofenac group, and the difference was statistically significant (Table 2). Pain relief after 23 days of treatment assessed by ODI (p<0.001) and PRR (p<0.05) was found to be better in the flupirtine group compared to the diclofenac group (Table 2) and the difference was statistically significant. The sustained effect 4 weeks after stoppage of treatment was better in the case of flupirtine, as evidenced by better scores at visit 2. The PRR measurement showed that the total number of patients achieving significant to complete pain relief 4 weeks after discontinuation of treatment (i.e., in Visit 2) was more in the flupirtine group compared to diclofenac.

Table 1: Basic demographic data of both groups

Parameters	Flupirtine maleate Mean±SD	Diclofenac sodium Mean±SD
Age	40.52±3.699	40.46±3.67
Sex		
Males	23 (46%)	22 (44%)
Females	27 (54%)	28 (56%)
Height	67.98±6.88	70.6±8.49
Weight	156.41±3.070	154.94±5.607
Duration of pain	9.88±1.97	9.8±2.01

Safety evaluation

Both the treatment regimens were well tolerated and none of the patients withdraw due to adverse events. More patients reported adverse events in the diclofenac group than in the flupirtine group (Table 3 and Fig. 2). The adverse events were only mild or moderate in intensity; hence, no patients withdrew from the study. With flupirtine, most of the adverse events were related to the gastrointestinal system (epigastric pain, nausea, and vomiting) and headache but more so with diclofenac.

DISCUSSION

The results of this study demonstrate that flupirtine maleate exhibits superior efficacy in several important aspects of LBP management. The observed reductions in VAS and NRS scores indicate that patients in the flupirtine group experienced more significant pain relief compared to those receiving diclofenac. Several studies have compared flupirtine with traditional NSAIDs, such as diclofenac, in the context of LBW management. These studies have indicated that flupirtine may offer superior efficacy and sustained pain relief, with fewer adverse events [15-17]. However, more research is needed to confirm and generalize these findings. Hence, this study was conducted to contribute valuable insights to the management of MLBP and may assist health-care providers and patients in making informed therapeutic decisions. Beyond LBW, flupirtine has been explored for its potential in post-operative pain, posttraumatic pain, and other conditions requiring pain management. These applications suggest a broad range of possibilities for its clinical use [5].

Furthermore, this study showed sustained effect of flupirtine maleate even after discontinuation of the drug. This indicates that flupirtine maleate may provide longer-lasting pain relief, which can be of significant benefit to patients dealing with chronic LBP. Flupirtine is an effective analgesic in acute, sub-acute, and chronic musculoskeletal pain, post-operative pain, migraine, tension headaches, and in many chronic pain states. It is found to be effective in neuropathic pain in cancer patients when given along with opioids [18,19] Flupirtine can be used safely and effectively in patients with MLBP. This might be due to the analgesic and muscle relaxant properties of flupirtine that inhibit the spinal mono and polysynaptic flexor reflexes. These reflexes are mediated through NMDA receptors is inhibited [13]. Flupirtine maleate is a prototype drug of selective centrally acting, non-opioid analgesics. Since the pathophysiology of pain includes a component of neuronal hyperexcitability, flupirtine acts by inducing hyperpolarization of the resting membrane potential and inhibiting action potential generation [20]. It is effective for pain conditions where the primary requirement is only analgesic action without sedation or anti-inflammatory effects. In addition, the findings related to tolerability are important. However, the responses at the end also showed greater tolerability compared to diclofenac. Flupirtine maleate was associated with fewer adverse events compared to diclofenac, suggesting that it is a well-tolerated option, which may improve patient compliance with treatment regimens. In our study, the most common adverse effects associated with flupirtine use were headache, epigastric pain, nausea, and vomiting, which are usually well tolerated. Patients in the diclofenac group experienced more epigastric pain, drowsiness, nausea, and vomiting when compared to the Flupirtine group. The tolerability was superior in the Flupirtine group due to its minimal side effects. Our study results are like that of a study by Sharma *et al*., [13], a

Table 2: Comparison of VAS, NRS, ODI, and PRR scores at visits 0, 1, and 30 between study groups

Score	Visit 0 (Mean±SD)			Visit 1 (Mean±SD)			Visit 2 (Mean±SD)		
	Flupirtine	Diclofenac	p-value	Flupirtine	Diclofenac	p-value	Flupirtine	Diclofenac	p-value
VAS	7.76±0.7	7.80±0.8	0.796	1.66±0.93	3. 1±1.4	0.206	1.22±0.72	2.04±1.1	0.048
NRS	7.73±0.65	7.73±0.6	0.496	1.54±0.83	2.3±1.5	0.179	1.44±0.74	2.10±1.2	0.04
ODI	52±5.44	51.68±5.4	0.534	11.56±6.43	15.1±8.8	0.166	10.54±4.83	15.24±4.3	0.206
PRR	-	-		81.1±12.27	72.3±17.1	0.155	85.0±9.4	76.94±12.5	0.112

Table 3: Comparison of adverse drug reactions between study groups

Adverse reactions	Flupirtine No. (%)	Diclofenac No. (%)
No reaction	21 (34.43)	9 (11.11)
Epigastric pain	10 (16.40)	26 (32.09)
Headache	8 (13.11)	12 (14.81)
Constipation	3 (4.91)	1 (1.24)
Diarrhea	6 (9.82)	5 (6.17)
Colic	4 (6.60)	1 (1.24)
Drowsiness	0 (0)	8 (9.88)

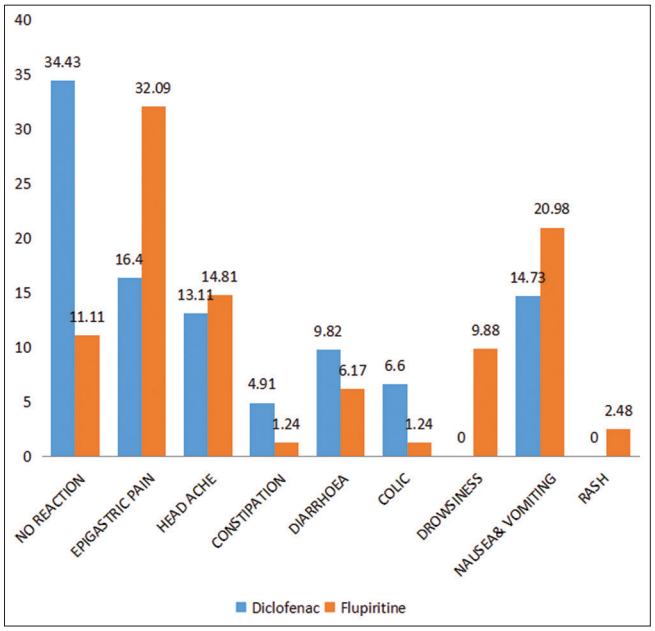

Fig. 2: Comparison of adverse drug reactions between study groups

prospective open-labeled study conducted on 60 patients. The efficacy parameters did not show any significant differences, but the adverse events were of mild-to-moderate intensity in both groups. None of the adverse events necessitated dose modification or withdrawal from the study. This shows that Flupirtine has better tolerability with low side effects when compared to NSAIDs Piroxicam.

The efficacy of flupirtine maleate with pentazocine in the treatment of pain after orthopedic hip surgery showed better patient satisfaction with flupirtine than with pentazocine treatment [21]. There were minimal CNS side effects such as dizziness and lightheadedness in the flupirtine group when compared to pentazocine. Banerjee et al. [1], studied the efficacy and tolerability of flupirtine with tramadol in 240 patients with NSAIDs intolerant to MLBP. In their study, the VAS and NRS scores improved significantly in both treatment groups in the last visit but were more observed with flupirtine. PRR was higher with flupirtine and adverse effects were less with flupirtine. Another study by Li et al. [17] proved that flupirtine reduced the pain and showed improvement in functional capacity compared to opioid analgesic tramadol in patients with subacute back pain for one week.

Limitations

It is essential to acknowledge the limitations of this study. First, this unicenter study's sample size was relatively small, and it is hard to generalize these findings in the general population and for making conclusions in a much broader way, multicenter studies including larger sample size are warranted to draw conclusions. Furthermore, further research is warranted to explore the full range of applications for flupirtine maleate in pain management. This includes investigating its efficacy in different pain conditions, identifying patient subgroups that may benefit the most, and establishing optimal dosing regimens. In addition, the potential interactions of flupirtine maleate with other medications and its long-term safety profile should be examined more thoroughly.

Despite its potential, there are a limited number of well-designed clinical trials specifically examining flupirtine for LBW. Hence, this study supports the existing literature, with flupirtine use for better efficacy and tolerability.

CONCLUSION

The present clinical comparative study showed that flupirtine maleate is a promising alternative to traditional NSAIDs like diclofenac, especially in LBW. The outcomes of this study have several clinical implications for health-care providers and patients dealing with mechanical LBP.

ETHICAL APPROVAL

The institutional Ethics Committee approved the study.

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None.

CONFLICTS OF INTEREST

No authors declare any conflicts of interest.

SOURCE OF FUNDING

None.

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