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Research Article

EFFICACY AND TOLERABILITY OF FLUPIRTINE VERSUS TRAMADOL IN THE TREATMENT OF MODERATE CHRONIC LOW BACK PAIN

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ABSTRACT

Objective: The objective of the study was to assess and compare the efficacy and tolerability of flupirtine versus tramadol in patients with chronic moderate low back pain (LBP).

Materials and Methods: A prospective study was conducted in the outpatient department of orthopaedics at tertiary care hospital, Rajamahendravarm. After meeting the inclusion criteria, a total of 60 patients were randomly allocated to tablet flupirtine 100 mg in Group A and tablet tramadol 50 mg in Group B. The efficacy of the study drugs was assessed at baseline and the end of treatment by numerical rating scale$_{11}$, visual analog scale-100 mm, physician's, and patient's global assessment. Statistical analysis was done using paired and unpaired t-test and data were presented as mean±standard deviation. Adverse drug reactions were monitored during the treatment.

Results: The study results showed that 90% of the patients in Group A and 78% of the patients in Group B had shown a good response to their respective drugs. 30% of flupirtine group patients reported adverse drug reactions which were mild.

Conclusion: Both the drugs are effective in the treatment of moderate chronic LBP, but the advantage of flupirtine was, the incidence of adverse drug reactions was less when compared to tramadol group.

Keywords: Flupirtine, Tramadol, Chronic low back pain, Visual analog scale.

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INTRODUCTION

Low back pain (LBP) is the major health problem worldwide and it is the fifth most common reason for a physician visit, in which nearly 60–80 % of people are affected throughout their lifetime, and the prevalence of chronic LBP is 23% [1,2]. In chronic LBP, 90% of cases were non-specific, whereas 5–10% of cases were specific in origin, like degenerative conditions, inflammation, infection, and neoplasm. Studies have reported that the prevalence of chronic LBP is increasing linearly from the third decade of life to 60 years of age, and more common in women [3]. LBP is a leading cause of activity limitation and work absence which has a huge impact on economic burden [4], so medications are recommended to keep patients physically active and to restore functional abilities and participation in daily life [1]. The pharmacological agents prescribed for chronic LBP are nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, benzodiazepines, systemic corticosteroids, and opioid analgesics [5]. At present, the mainstay of the treatment for chronic LBP is NSAIDs and opioids, but long-term use of these drugs cause gastrointestinal tract disturbances and sedation. Flupirtine maleate is a centrally-acting and non-opioid analgesic. It is unique among analgesics as it has dual therapeutic effects such as analgesic and muscle relaxant properties. Flupirtine is a selective neuronal potassium channel opener (SNEPCO) which activates G-protein-coupled receptors that stimulate K+ channels of neuronal cells and it also indirectly acts as N-methyl-D-Aspartate (NMDA) antagonist and inhibits neuronal excitability and reduces calcium Ca2+ influx into the cells. This mechanism is vital for neuronal transmission of pain signals to motor neurons [6]. Flupirtine has shown mild adverse effects such as a headache, dizziness, nausea, and epigastric complaints and there were no serious adverse events (SAE) and no signs of drug dependence, tolerance, or withdrawal symptoms. A multicenter phase IV study conducted in Germany had shown that tolerability of flupirtine treatment was excellent with extremely low withdrawal and adverse event rates [7]. On the other hand, standard drug, tramadol is an atypical centrally acting opioid analgesic, most commonly used for pain relief, its analgesic effect is exerted by a dual mechanism, by weak μ opioid agonist and also acts by inhibiting reuptake of serotonin and norepinephrine (NE) [8,9]. Although both flupirtine and tramadol individually have proven their efficacy in the treatment of moderate chronic LBP; however, there is a paucity of studies comparing both the drugs. Hence, the present study was carried out to assess the efficacy and tolerability of flupirtine and tramadol in chronic LBP of moderate intensity.

MATERIALS AND METHODS

This was a prospective, randomized study conducted on 60 patients suffering from chronic LBP, who attended the Outpatient Department of Orthopaedics at GSL Medical College and General Hospital, Rajamahendravaram, Andhra Pradesh, India. After getting approval from the Institutional Ethics Committee, all the study subjects who were enrolled in the study are screened by physician and orthopedician followed by an examination. Informed and written consent was taken from the study subjects who are satisfying the selection criteria. The selection criteria included patients between the ages of 20 and 60 years with nonspecific LBP for >3 months duration. Exclusion criteria were patients with a history of hepatic or renal disease, major trauma, cancer, infection, cauda equina syndrome, fibromyalgia, osteoporosis, or vertebral compression. Pregnant and lactating women and those with a history of hypersensitivity to these drugs were also excluded from the study. After initial screening, the demographic data, history, drug history, family history, findings of general and physical examination, and blood investigations (liver function test and renal parameters) were recorded in case record form. The study subjects were randomly divided into two Groups A and B by computer-based technique. Group A was allocated with tablet flupirtine 100 mg and Group B with tablet tramadol 50 mg, twice daily, orally after food for 10 days. The efficacy of the study drugs was estimated by assessment of pain intensity at baseline and

the endpoint using visual analog scale 100 mm (VAS-100mm) [10,11] and numerical rating scale (NRS_{11}) [12,13]. At the end of the treatment, the relative pain relief was assessed by physician's global assessment and patient's global assessment (PGA) based on the verbal rating scale-5 with the expressions of very good, good, fair, poor, and very poor. Any adverse event reported by the patients or observed by the physician was monitored during the total duration of the treatment for the tolerability of drugs. The data obtained from the study subjects were tabulated and expressed as mean±standard deviation, and then analyzed using unpaired student's t-test to compare the means of two independent groups and paired t-test to compare the means within the group, $p<0.05$ is considered statistically significant.

RESULTS

Out of 65 enrolled patients, 60 patients completed the study and five patients lost to follow-up (2 from Group A and 3 from Group B). Demographic data of the study subjects revealed that the mean age of study subjects in Group A and Group B was 45.4±8.45 and 46.2±9.7, respectively (Table 1).

Efficacy assessments

The pain intensity was assessed by VAS score, it was found that there was no significant difference between the two treatment groups, but within the groups, there was a significant reduction in pain at baseline to at the end of treatment, which was statistically significant (Fig. 1 and Table 2).

Fig. 2 and Table 3 represent the pain intensity on the NRS scale at baseline and, at the end of the treatment. There was no significant mean difference between the two groups, which was statistically insignificant, but both the groups showed significant improvements in the reduction of pain.

At the end of the study, the patient's response to the drugs was assessed by the PGA (Fig. 3). It was observed that a majority number of patients in Group A (95%) experienced a good response compared to Group B (88%).

Assessment of pain relief was done by physician at the end of the study; it was observed that major part of 90% of study subjects of Group A had good response compared to Group B (78%), (Fig. 4).

Table 4 represents the adverse events (AE) experienced by the study subjects at the end of the treatment, no SAE were reported by any of the patients in both treatment groups. The majority (70%) of patients of Group B reported AE which were mild.

DISCUSSION

LBP is a common musculoskeletal symptom that may either be acute or chronic. It is caused due to a variety of diseases and disorders. Age, is one of the most common factor in the development of LBP. In most studies, it was found that the highest incidence of LBP was in the third decade of life, with the prevalence increasing until the age of 60 to 65 years. However, there is recent evidence that prevalence continues to increase with age with more severe forms of LBP. In the present study, both groups were comparable with respect to the demographic profile of the patients. The mean age of flupirtine and tramadol group was 45.4±8.45 and 46.2±9.7, respectively. A raised BMI is an established risk factor for LBP; in the present study, it was observed there was significant rise in mean body mass index (BMI) value. BMI in flupirtine group was 28.5±2.9 and in Tramadol group was 29.6±2.2. Similarly, a study conducted by Oded *et al.* found that an increase in BMI was associated with an increase in the probability of LBP [14]. Most commonly used method for the evaluation of pain severity and relief is the VAS due to its practicality, reproducibility, sensitivity to treatment effects, and ease of analysis [15]. We have also used VAS for evaluating the severity of pain. The current study results are inconsistent with those of a previously reported study on the analgesic efficacy of flupirtine versus tramadol. A phase IV study conducted by Uberall *et al.* [16] observed that there was a significant reduction of NRS_{11} scores at baseline and at the end of

Table 1: Demography and anthropometric variables of the study subjects

Variables	Group A, n=30, (%)	Group B, n=30, (%)
Gender		
Male	8 (26.6)	15 (50)
Female	22 (73.3)	15 (50)
Age (years)		
21–30	4 (13.3)	5 (16.6)
31–40	8 (26.6)	12 (40)
41–50	12 (40)	11 (36.6)
51–60	6 (20)	2 (6.6)
Weight [Kg]		
Mean±SD	76.3±9.1	77.6±8.1
BMI [Kg/m^2]		
Mean±SD	28.5±2.9	29.6±2.2

Group A: Flupirtine, Group B: Tramadol, SD: Standard deviation

Table 2: Mean VAS score changes within the Groups A and B

Groups	Mean±SD	p value
Flupirtine group (Group A)		
VAS – 100 mm at day 0	60.7±7	0.0001*
VAS – 100 mm at day 10	16.4±10.5	
Tramadol group (Group B)		
VAS – 100 mm at day 0	62.7±7.7	0.0007*
VAS – 100 mm at day 10	21.1±11.12	

VAS: Visual analog scale, SD: Standard deviation, *Statistical significant

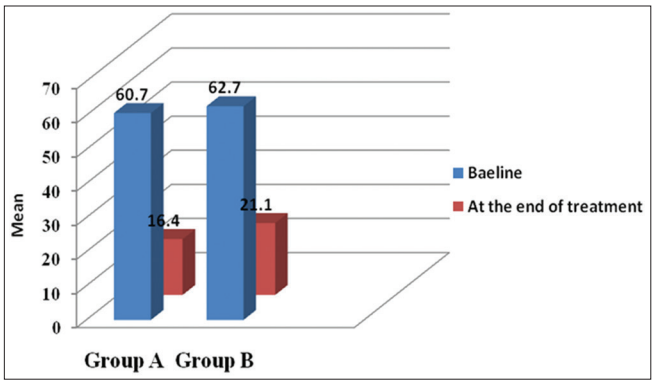

Fig. 1: Mean visual analog scale scores of study groups before and after treatment. Group A: Flupirtine, Group B: Tramadol

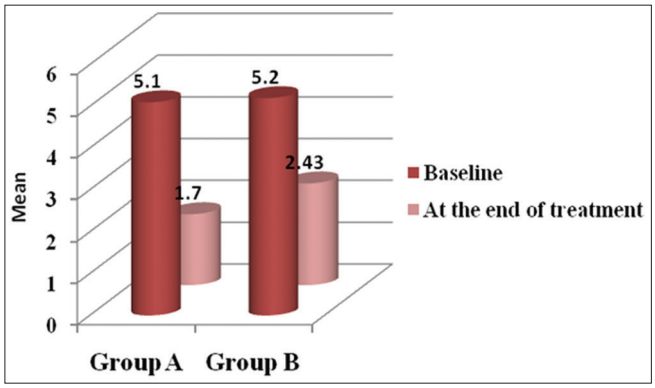

Fig. 2: Mean numerical rating scale scores of study groups before and after treatment. Group A: Flupirtine, Group B: Tramadol

4th week, which is inconsistent with the present study findings. Another study conducted by Li *et al.* [17] found that there was a significant reduction of means of VAS and NRS_{11} scores at baseline and at the end of treatment, which is in line with the mean scores of VAS and NRS_{11}

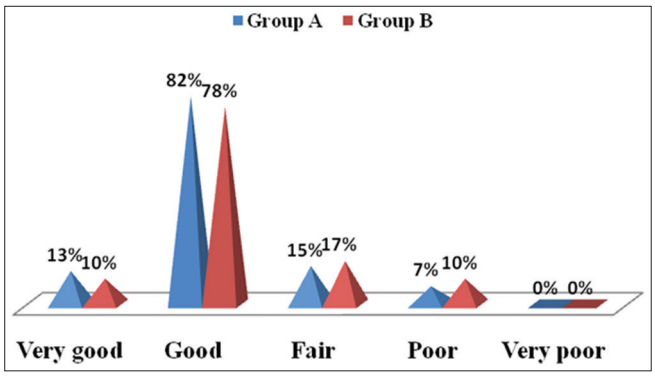

Fig. 3: Patient's global assessment at the end of the study treatment. Group A: Flupirtine, Group B: Tramadol

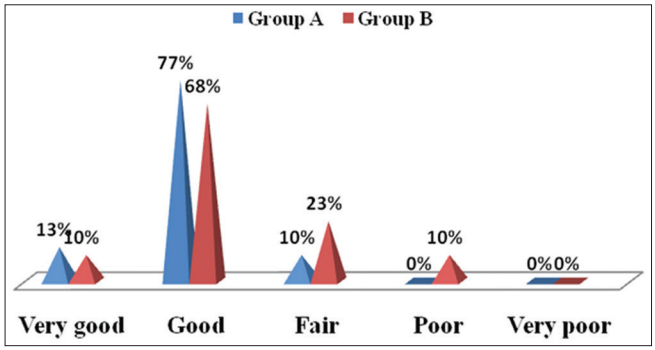

Fig. 4: Physician's global assessment at the end of the study treatment. Group A: Flupirtine, Group B: Tramadol

Table 3: Mean NRS score changes within Groups A and B

Groups	Mean±SD	p value
Flupirtine group (Group A)		
NRS – 11 at day 0	5.1±0.8	0.001*
NRS – 11 at day 10	1.7±1.14	
Tramadol group (Group B)		
NRS – 11 at day 0	5.2±0.79	0.001*
NRS – 11 at day 10	2.43±1.10	

NRS: Numerical rating scale, SD: Standard deviation, *statistical significant

Table 4: AE in both the treatment groups n (%)

Type of AE	Group A	Group B
Abdominal pain	2 (10)	0
Sedation	2 (10)	6 (30)
Nausea	1 (5)	4 (20)
Vomiting	1 (5)	1 (5)
Constipation	0	3 (15)
Total no. of AE	6 (30)	14 (70)

Group A: Flupirtinem, Group B: Tramadol, AE: Adverse event, BMI: Body mass index

in both groups ($p<0.05$) but the difference between the groups was statistically insignificant. Banerjee and Bhattacharyya [18], in a study compared the efficacy and tolerability of flupirtine versus tramadol in NSAID intolerant mechanical LBP and used VAS as an efficacy parameter. Scores in VAS improved significantly ($p<0.05$) in both groups in the last visit, but more so with flupirtine. No significant group difference in mean pain relief scores was found at any point in both groups.

The analgesic agents most commonly used in LBA are prostaglandin inhibitors (NSAIDs), COX-2 inhibitors, drugs acting by μ-receptor agonist (Opioids), and acetaminophen which has a centrally mediated action. Flupirtine is a unique analgesic, centrally acting, and a non-opioid analgesic which also has an indirect NMDA receptor antagonistic action by activating potassium 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. This unique potassium channel opening property exhibited by flupirtine has not been demonstrated by any other analgesic. Therefore, it belongs to a class of drug known as SNEPCO. The drug also possesses a GABA-A receptor modulator property [19]. In patients who received tramadol, reduction in pain was significant at the end of treatment. Tramadol exhibits μ-opioid receptor agonist as well as NE and serotonin reuptake inhibitor activity. In the present study, it was observed that nausea, vomiting, and sedation were the major adverse effects experienced by the patients who received tramadol [20]. No SAE were observed in both treatment groups. The majority (70%) of Group B patients had reported AE. Most of the AE were mild in severity. An overall good tolerability and safety profile were observed. Other previous studies also observed that oral flupirtine is an effective analgesic with the advantage of fewer central nervous system side effects as compared to opioids [21]. Limitations of the study are small in sample size and less study duration. We did not study geriatric patients (>60 years) since the safety of the drug in this age group is not established. Hence, further studies are required in a larger sample and longer study duration to evaluate better efficacy and tolerability of study drugs.

CONCLUSION

The results of the current study showed that flupirtine provided an analgesic efficacy that was not inferior to that of tramadol. Flupirtine was well tolerated, as it is devoid of adverse effects such as nausea, vomiting, and sedation, whereas these events are reported tramadol. Hence, flupirtine can be used as an alternative drug to opioids as an analgesic in the management of moderate chronic LBP.

CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest.

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REFERENCES

1. Burton AK, Tillotson KM, Main CJ, Hollis S. Psychosocial predictors of outcome in acute and subchronic low back trouble. Spine (Phila Pa 1976) 1995;20:722-8.
2. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. Lancet 2012;379:482-91.
3. Meucci RD, Fassa AG, Faria NM. Prevalence of chronic low back pain: Systematic review. Rev Saude Publica 2015;49:S0034.
4. Taimela S, Kujala UM, Salminen JJ, Viljanen T. The prevalence of low back pain among children and adolescents. A nationwide, cohort-based questionnaire survey in Finland. Spine (Phila Pa 1976) 1997;22:1132-6.
5. Chou R, Huffman LH, American Pain Society, American College of Physicians. Medications for acute and chronic low back pain: A review of the evidence for an American pain society/American college of physicians clinical practice guideline. Ann Intern Med 2007;147:505-14.
6. Devulder J. Flupirtine in pain management: Pharmacological properties and clinical use. CNS Drugs 2010;24:867-81.
7. Ringe JD, Miethe D, Pittrow D, Wegscheider K. Analgesic efficacy of flupirtine in primary care of patients with osteoporosis related pain. A multivariate analysis. Arzneimittelforschung 2003;53:496-502.
8. Schug SA. The role of tramadol in current treatment strategies for musculoskeletal pain. Ther Clin Risk Manag 2007;3:717-23.
9. Devi YB, Sumanth KS, Raju VB, Gandhi BM, Srinivas K. A new reversed-phase high-performance liquid chromatography method development and validation for the simultaneous estimation of ketorolac tromethamine and tramadol hydrochloride in pharmaceutical

dosage forms. Asian J Pharm Clin Res 2017;10:186-90.
10. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: A critical review. Psychol Med 1988;18:1007-19.
11. Huskisson EC. Measurement of pain. Lancet 1974;2:1127-31.
12. Rodriguez CS. Pain measurement in the elderly: A review. Pain Manag Nurs 2001;2:38-46.
13. Farrar JT, Young JP Jr. LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.
14. Oded H, Friedlander A, Gordon B, Arzi H. The relationship between the body mass index, body height and the prevalence of low back pain in young adults. Spine J 2013;11:92.
15. Philip BK. Parametric statistics for evaluation of the visual analog scale. Anesth Analg 1990;71:710.
16. Uberall MA, Mueller-Schwefe GH, Terhaag B. Efficacy and safety of flupirtine modified release for the management of moderate to severe chronic low back pain: Results of SUPREME, a prospective randomized, double-blind, placebo and active-controlled parallel-group phase IV study. Curr Med Res Opin 2012;28:1617-34.
17. Li C, Ni J, Wang Z, Li M, Gasparic M, Terhaag B, *et al.* Analgesic efficacy and tolerability of flupirtine vs. Tramadol in patients with subacute low back pain: A double-blind multicentre trial*. Curr Med Res Opin 2008;24:3523-30.
18. Banerjee M, Bhattacharyya K. Comparative study of efficacy and tolerability of flupirtine versus tramadol in non-steroidal anti-inflammatory drug intolerant mechanical low back pain. Indian J Rheumatol 2012;7:135-40.
19. Fabule J, Adebajo A. Comparative evaluation of cardiovascular outcomes in patients with osteoarthritis and rheumatoid arthritis on recommended doses of nonsteroidal anti-inflammatory drugs. Ther Adv Musculoskelet Dis 2014;6:111-30.
20. Nasare NV, Banerjee BD, Deshmukh PS, Mediratta PK, Ahmed RS, Saxena AK, *et al*. The impact of pharmacogenetics on adverse drug reactions to predict the efficacy of tramadol monotherapy for the treatment of post herpetic neuralgia patients. Int J Pharm Pharm Sci 2014;6:89-96.
21. Scheef W. Analgesic efficacy and safety of oral flupirtine in the treatment of cancer pain. Postgrad Med J 1987;63 Suppl 3:67-70.