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Research Article

COMPARISON OF THE EFFICACY AND SAFETY OF TRAMADOL VERSUS TAPENTADOL IN ACUTE OSTEOARTHRITIC KNEE PAIN: A RANDOMIZED, CONTROLLED TRIAL

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ABSTRACT

Objectives: Osteoarthritis of knee, a common disorder of elderly, has multifaceted pain mechanisms. Newer opioids such as tramadol and tapentadol target those multiple pain mechanisms, with few studies that compare them. We compared the efficacy and safety of tramadol versus tapentadol in acute episodes of osteoarthritic knee pain on 100 patients, 50 in each group.

Methods: Group A received tramadol 50 mg twice daily for a period of 1-week, and Group B received tablet tapentadol 50 mg twice daily for a period of 1-week. Pain and function were evaluated by numerical pain rating scale (NPRS) and Western Ontario and McMaster Universities (WOMAC) questionnaire and scored during the initial baseline visit before the start of treatment. The efficacy of the drugs was evaluated at the end of 1st week follow-up by repeating the NPRS and WOMAC questionnaire. Adherence to medication was emphasized, and side effects of the drugs were evaluated by Naranjo's scale. The data were analyzed statistically using descriptive statistics, namely, mean, standard deviation, and median. Non-parametric tests, namely, Mann–Whitney test, Wilcoxon signed rank test, and parametric tests such as unpaired t-test and paired t-test were used wherever applicable. All patients completed the study.

Results: There was no statistically significant difference in the total WOMAC scoring between the two groups: Tramadol and tapentadol. However, tapentadol provided statistically significant pain relief compared to tramadol as measured by the NPRS. Both the groups tolerated the drugs well. There was no incidence of any adverse effects.

Conclusion: Hence, both the drugs are efficacious in treating an acute painful episode of osteoarthritic knee pain and can be safely prescribed to the patients.

Keywords: Tapentadol, Tramadol, Newer opioids.

INTRODUCTION

Osteoarthritis (OA) [1] is one of the common orthopedic disorders in the elderly, characterized by progressive destruction of the articular cartilage, usually involving knee and hip. Pain is the main presenting symptom. Managing osteoarthritic pain is a herculean task due to the multiple pain mechanisms involved and the presence of comorbidities in this age group. Although wide options of analgesics are available, the efficacy and safety profile of the medications is of special concern in this patient population.

The use of non-steroidal anti-inflammatory drugs is limited due to doubtful efficacy and side effects such as peptic ulcer and bleeding tendency. The use of opioids is limited by the risk of adverse effects (AE) and dependence liability.

Newer opioids such as tramadol and tapentadol target the multiple pain mechanisms and aim for good efficacy and safety profile.

Tapentadol [2] is a centrally acting μ opioid agonist approved by FDA, in 2008, and also inhibits reuptake of noradrenaline. Previous studies comparing tapentadol with oxycodone in OA knee reveal tapentadol to be equally efficacious with good gastrointestinal tolerability.

Tramadol [3] with the same mechanism of action is already in use for treating acute episodes, but the use is limited by its side effects and is considered a weak opioid by the WHO analgesic ladder.

Although both have the same mechanism of action, they have their own limitations, and there are only a few studies that compare the efficacy and safety of tramadol versus tapentadol. Hence, we planned to study and compare the efficacy, tolerability, and safety of tramadol versus tapentadol in acute episodes of osteoarthritic knee pain.

METHODS

After approval from the Institutional Human Ethics Committee, a randomized, prospective, comparative, single-blinded study was conducted on patients with OA knee attending the Outpatient Department of Orthopedics in a tertiary care teaching hospital for a study period of 8-week on 100 patients with 50 patients in each group. Patients aged 40-65 years of either sex with acute pain episodes due to chronic OA of knee unilateral or bilateral and are willing to give consent and come for follow-up will be included in the study.

Pregnant and lactating mothers, patient with kidney, liver, and heart disease, malignancy, patients not willing to give informed consent and follow-up, patients with bronchial asthma and paralytic ileus, patients with known hypersensitivity to any of the drug; patient already on analgesic medications, monoamine oxidase inhibitors, and corticosteroids for past 2 weeks will be excluded from the study.

A detailed history regarding age, sex, duration of the disease, presence of comorbid conditions, medication history was obtained using case study proforma. A validated Western Ontario and McMaster Universities (WOMAC) questionnaire available in the local vernacular language was given to the patient for answering. The severity of knee pain was assessed by the numerical pain rating scale (NPRS). The primary investigator was blinded during the study. Then, randomization was done by block randomization by the orthopedic surgeon and the coinvestigator, and each patient was assigned to one of the two treatment groups. Group A received tablet tramadol 50 mg twice daily

orally for 1 week, and Group B received tablet tapentadol 50 mg twice daily orally for 1 week.

Tramadol [4] was procured from Ranbaxy Laboratories Limited under the trade name of tablet trambax 50 mg (10 tablets costing 99 Rs.). Tapentadol was procured from Ranbaxy Laboratories Limited under the trade name of tablet tydol 50 mg (10 tablets costing 99 Rs.). No other medications were given during the study period. If the pain severity demands additional analgesic use, then such patients were treated as dropouts and included in the intention to treat analysis.

The patients were advised about the treatment plan and the side effects of the drugs. If any intolerable side effect occurs, the patient was advised to report to the hospital at any time for treatment. At the end of 1 week, the patient was asked to come for follow-up. The importance of adherence to treatment was explained to each patient and checked during the follow-up visit by pill count method.

During the follow-up visit, the WOMAC questionnaire [5] was given for answering and NPRS [6] was used to assess the severity of pain. The questionnaire was read by the investigator for illiterate patients, and answers were noted. The WOMAC questionnaire and pain scale was scored for each patient and the average scores of each group were compared.

Outcome measures

Efficacy assessment parameters

Primary efficacy measure

The WOMAC OA index, a disease-specific self-administered health status measure that is widely accepted as reflective of OA disease activity was used. The 3.1 Likert version consists of 24 questions (5 questions to assess pain, 2 for joint stiffness, and 17 questions to assess difficulty in physical function). Individual question response was assigned a score of between 0 (none) to 4 (extreme) and summed to form a score ranging from 0 (best) to 96 (worst). The sum of the scores divided by 96 gives the percentage of the score.

Secondary efficacy measure

11-point numeral pain rating scale, a scale to assess pain severity that starts with the end point "0" that describes no pain and "10," the worst pain imaginable was used. The patient was asked to tell the severity of pain using number 0-10.

Safety and tolerability parameters

Naranjo's [7] adverse drug reaction probability scale, a widely accepted was used to assess the incidence of AEs such as nausea, vomiting, constipation, dizziness, and respiratory depression.

Statistical analysis

Mean ± standard deviation was used for the description of data. Student's t-test, Mann–Whitney test, Wilcoxon signed rank test, paired t-test, and unpaired t-test were employed for comparing both the groups according to the appropriate situation. $p<0.05$ was considered as statistically significant. SPSS computer software was used for statistical analysis.

RESULTS

Demographic details

The demographic details regarding age and gender were compared between the two groups and found to be statistically insignificant.

Assessment of primary efficacy variables

NPRS

The difference is pain intensity and stiffness in the WOMAC scoring between the baseline visit and the 1st week visit in Group 1 was calculated by Wilcoxon signed rank test. Similar test was used in Group 2. Difference between Group 1 (tramadol) and Group 2 (tapentadol) was calculated by Mann–Whitney test and compared. The subsets of WOMAC scoring namely pain, difficulty in function and the total scoring between the baseline visit and the 1st week visit in Group 1 was calculated by paired t-test. Similar test was used in Group 2. Difference between Group 1 (tramadol) and Group 2 (tapentadol) was calculated by unpaired t-test and compared.

All the relevant data are summarized in Tables 1 and 2. From our study, we found that the pain intensity difference as measured by NPRS between the baseline visit and at the end of 1st week follow-up visit in Group 1 (tramadol) was statistically significant. Similar results were obtained in Group 2 (tapentadol). There was the significant statistical difference in pain intensity by NPRS between the two groups ($p<0.05$) and tapentadol significantly lowered the pain as compared to tramadol.

WOMAC scoring

Pain

We found that there was statistically significant reduction in pain between the baseline visit and at the end of 1st week. $p<0.05$ in tramadol group (Group 1). Similar results were obtained in tapentadol group, i.e., Group 2. On comparison between Group 1 and Group 2, it was evident that there was no statistically significant difference between tramadol and tapentadol (Group 1 and 2).

Stiffness

We found that there was statistically significant reduction in pain between the baseline visit and at the end of 1st week. $p<0.05$ in tramadol group (Group 1). Similar results were obtained in tapentadol group, i.e., Group 2 ($p=0.05$). On comparison between Group 1 and Group 2, it was evident that there was statistically significant difference between tramadol and tapentadol (Group 1 and 2) with tapentadol reducing the stiffness better than tramadol ($p<0.05$).

Function

We found that there was statistically significant reduction in pain between the baseline visit and at the end of 1st week. $p<0.05$ in tramadol group (Group 1). Similar results were obtained in tapentadol group, i.e., Group 2. On comparison between Group 1 and Group 2, it was evident that there was no statistically significant difference between tramadol and tapentadol (Group 1 and 2).

Total WOMAC scoring

We found that there was statistically significant reduction in pain between the baseline visit and at the end of 1st week. $p<0.05$ in tramadol group (Group 1). Similar results were obtained in tapentadol group, i.e., Group 2. On comparison between Group 1 and Group 2, it was evident that there was no statistically significant difference between tramadol and tapentadol (Group 1 and 2).

From the results, it is evident tapentadol produces significant pain relief as rated by NPRS when compared to tramadol. On the other hand, there was no statistically significant difference between the tramadol and tapentadol with reference to the total WOMAC scoring. However, stiffness was significantly reduced in the tapentadol group (Group 2) compared to tramadol group (Group 1).

DISCUSSION

The results of our study revealed that there was no statistically significant difference in the total WOMAC scoring between the two groups. However, tapentadol provided statistically significant pain relief compared to tramadol as measured by the NPRS. Both the groups tolerated the drugs well, and there was no incidence of any AEs such as nausea, vomiting, giddiness, constipation, and respiratory depression.

The probable reason for the significant pain relief caused by tapentadol is due to the dual nature in the mechanism of action causing μ opioid agonistic action and norepinephrine reuptake inhibition. Similar

Table 1: Comparison of the efficacy variables between the groups

Study parameters	Group 1 (tramadol)			Group 2 (tapentadol)			Group 2 versus Group 1 (tapentadol vs. tramadol)		
	Baseline visit	End of 1st week	p value	Baseline visit	End of 1st week	p value	Baseline visit	End of 1st week	p value
NPRS median	7.00	5.00	2.0000	8.00	5.00	3.00	8.00	5.00	3.00
WOMAC score									
Pain (mean±SD)	15.42±2.492	9.68±3.787	5.74±3.756	15.90±2.225	11.56±1.680	4.34±2.560	15.66±2.362	10.62±3.064	5.04±3.275
Stiffness (median)	4.00	3.00	1.0000	7.00	4.00	3.00	6.00	4.00	2.00
Difficulty in function (mean±SD)	49.70±7.702	30.24±10.613	19.46±9.424	54.04±9.887	35.58±6.661	18.04±10.341	51.85±9.072	32.91±9.215	18.75±9.869
Total WOMAC score (mean±SD)	69.50±9.038	43.64±13.951	25.86±13.075	77.90±7.285	51.33±8.029	26.60±9.324	73.70±9.193	47.47±11.961	26.23±11.304

SD: Standard deviation, WOMAC: Western Ontario and McMaster Universities, NPRS: Numerical pain rating scale

Table 2: Comparison of the efficacy variables between the groups

Study parameters	Baseline visit versus end of 1st week		Group 2 versus Group 1 (tapentadol vs. tramadol)
	Group 1 (tramadol)	Group 2 (tapentadol)	
NPRS	0.001+a	0.454a	0.037b
WOMAC score			
Pain	0.312c	0.002+c	0.058d
Stiffness	0.000+a	0.454a	0.000+b
Difficulty in function	0.017+c	0.003+c	0.740d
Total score	0.000+c	0.001+c	0.131d

+Statistically significant p<0.05. aWilcoxon signed rank test, bMann–Whitney test, cPaired t-test, dUnpaired t-test. WOMAC: Western Ontario and McMaster Universities, NPRS: Numerical pain rating scale

results were obtained by Lange *et al*. [8,9], who evaluated the efficacy and tolerability of tapentadol prolonged release (PR) 100-250 mg and compared with placebo and oxycodone 25-50 mg over 12-week period using NPRS. He performed the study on around 2500 patients with chronic OA of knee and low back ache. He found that the efficacy of tapentadol PR was non-inferior to oxycodone controlled release (CR) (p<0.001), and tapentadol PR had superior gastrointestinal tolerability compared with oxycodone CR (p<0.001) and with few treatment discontinuations.

Regarding the WOMAC scoring, our study revealed no statistically significant difference between the groups in the mean WOMAC score. The probable reason would be due to the inclusion of pain, stiffness, and difficulty in function subsets of WOMAC scoring. Moreover, our study was limited to 1 week period. There was significant pain relief between the baseline visit and at the end of the 1st week with tapentadol. Similar results are obtained by Hartrick *et al*. [10-12], who evaluated efficacy and tolerability of tapentadol immediate release (IR) in patients who were candidates for joint replacement surgery due to end-stage joint disease and compared tapentadol IR with oxycodone HCI IR. Tapentadol IR 50 and 75 mg and oxycodone HCI IR 10 mg were associated with significant reductions in pain intensity compared with placebo, based on 2- and 10-day sum of pain intensity difference and 2-, 5-, and 10-day total pain relief (TOTPAR) and sum of TOTPAR and pain intensity difference (p<0.001). The efficacy of tapentadol IR 50 and 75 mg was non-inferior to that of oxycodone HCI IR 10 mg; however, the incidence of selected gastrointestinal AEs (nausea, vomiting, and constipation) was significantly lower for both doses of tapentadol IR compared with oxycodone HCI IR 10 mg (p<0.001).

Our study revealed no side effects with any of the drugs and none withdrew the treatment medications which in turn ensure good tolerability profile. Our study had a sample size of 50 patients with 50 mg of both the drugs over 1-week period. Previous studies have revealed tapentadol to have a good gastrointestinal tolerability and tramadol within few incidences of vomiting and dizziness. Hence, both the treatment regimens can be safely prescribed to the patients. The limitation of our study was that we did not include chronic osteoarthritic knee pain and just included only the acute painful episode. Furthermore, the evaluation of NPRS and WOMAC scoring was a subjective one which may vary.

Furthermore, research on a long period is required in this area to find the efficacy and safety of these drugs to render the best treatment to the patient population.

CONCLUSION

Our study revealed that there was no statistically significant difference in the total WOMAC scoring between the two groups: Tramadol, and tapentadol. However, tapentadol provided statistically significant pain relief compared to tramadol as measured by the NPRS. Both the groups tolerated the drugs well and there was no incidence of any AEs such as nausea, vomiting, giddiness, constipation, and respiratory depression. Hence, both the drugs are efficacious in treating acute painful episode of osteoarthritic knee pain and can be safely prescribed to the patients.

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