COMPARATIVE EFFICACY AND SAFETY OF TAPENTADOL AND TRAMADOL IN PATIENTS WITH MODERATE TO SEVERE CHRONIC LOW BACK PAIN: A PROSPECTIVE, RANDOMIZED, OPEN-LABELTRIAL AT TERTIARY CARE TEACHING HOSPITAL IN NORTH INDIA

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ABSTRACT

BACKGROUND

Chronic Low back pain is one of the leading causes of disability and has a major socioeconomic impact. Despite the availability of numerous treatment options, pain continues to be under-treated, indicating a need for a potent analgesic with a low side-effect profile. The use of opioids has been strongly recommended in chronic low back pain but are underutilised due to potential risk of adverse effects. The present study was conducted to compare the efficacy and safety of atypical opioids tapentadol and tramadol in patients with moderate to severe chronic low back pain.

MATERIALS AND METHODS

It was randomized, prospective, open label, comparative and parallel group study. 96 patients suffering from moderate to severe chronic low backache were included in the study. They were randomised to receive either tapentadol ER (50 -250 mg twice a day orally) or tramadol ER (100-300 mg, twice a day, orally.) for 6 weeks. Patients in both the groups were followed up for a period of 6 weeks. Two patients were lost to follow-up with one patient in each group. Henceforth, 48 patients in Group I and 46 patients in Group II completed the study. Efficacy and safety of tapentadol and tramadol was assessed by visual analogue scale, finger to floor distance test and straight leg raising test and by noticing ADRs in both the groups. The data was analyzed with the help of computer software MS Excel and SPSS version 17.0 for Windows. Statistical significance was assessed by paired and unpaired Student 't' test.

RESULTS

The mean baseline VAS score was 9.66 ± 0.69 in Group I patients, which decreased to 8 ± 0.54, 6.39 ± 0.64 and 4.45 ± 0.58 respectively and the mean baseline VAS score was 9.65 ± 0.70 in Group II patients, which decreased to 8.15 ± 0.36, 6.45 ± 0.69 and 4.47 ± 0.54 respectively at follow up visits in chronic low backache patients. Both the groups showed statistically highly significant reduction in pain at all levels on VAS scale and finger to floor distance parameter at all levels but the results of straight leg raising test were not statistically significant. Patients on tapentadol reported less adverse drug reactions with better gastrointestinal tolerability as compared to tramadol.

CONCLUSION

Both the drugs tapentadol ER and tramadol ER provided significant analgesic efficacy for management of moderate to severe chronic low backache. However tapentadol ER with better gastrointestinal tolerability profile, may represent a better alternative to other strong opioids for such patients.

KEYWORDS

Chronic Low Backache, Tapentadol, Tramadol, Efficacy, Safety.

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BACKGROUND

Chronic low backache is a major cause of disability adjusted life years worldwide.[1] In India, occurrence of low back pain is also alarming. Nearly 60-80% of people in India have significant back pain at some time in their lives.[2,3] Low back pain prevalence has been found to range from 6.2% to 92% with increase of prevalence with age and female preponderance. The most common causes of low back pain are injury and stress, resulting in musculoskeletal and neurological disorders (e.g. muscle spasm and sciatica). Back pain may also result from infections, degenerative

diseases (e.g. osteoarthritis), rheumatoid arthritis, spinal stenosis, tumors and congenital disorders. Approximately 9 to 12% of people (632 million) have low back pain at any given point in time, and nearly one quarter (23.2%) report having it at some point over any one-month period.[4] The first-line treatment for chronic low backache include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids, and strong opioids.[5] Compounds that activate opioid receptors have been used for decades in the treatment of moderate to severe pain.[6] Studies of long-acting opoids like oxymorphone, oxycodone, morphine, hydromorphone, fentanyl, and buprenorphine confirm the analgesic efficacy in patients with chronic low back pain.[7]

Tramadol is a commonly used opioid drug for chronic low backache patients, has a low abuse potential, possesses no clinically relevant respiratory or cardiovascular effects, lacks pharmacodynamics tolerance, has little effect on gastrointestinal motility and is well tolerated with a low incidence of adverse effects in humans.[8]

Tapentadol represents a new class of centrally acting analgesic, mu-opioid receptor agonist and norepinephrine reuptake inhibitor, with analgesic activity that results from the contribution of both the mechanisms. An extended release formulation was approved by Food and Drug Administration in 2011 for management of moderate to severe chronic low back pain and in 2012 FDA widened its indication for neuropathic pain associated with diabetes mellitus in adult patients requiring continuous round the clock opioid therapy over an extended period of time.[9] Tapentadol might be a valuable alternative to commonly prescribed opioids for management of chronic low back pain as it has dual mechanism of action, less gastrointestinal side effects and has less abuse potential. The data about tapentadol is scanty in our Indian setup and head-on-head comparison between tapentadol and tramadol is very scarce. So, the present study was undertaken to study and compare efficacy and safety of tapentadol extended release with that of tramadol extended release in patients with moderate to severe chronic low back pain so that more robust data is generated.

Aims and Objectives-

The aim and objective of study was to assess and compare the efficacy and safety of tapentadol extended release (ER) and tramadol extended release (ER) in patients with moderate to severe chronic low back pain.

MATERIALS AND METHODS

Study Centre- Postgraduate Department of Pharmacology and Therapeutics in collaboration with the Postgraduate Department of Orthopaedics in a tertiary care teaching hospital Jammu and Kashmir.

Study Design-

Open label comparative, randomised, parallel group and prospective study.

Study Duration-

6 weeks**.**

Study Sample-

96 participants taken and 94 completed the study.

Inclusion Criteria

1. Participants with diagnosis of moderate to severe chronic low back pain; chronic pain defined as pain lasting for at least three months prior to enrolment.
2. Participants must require a strong analgesic (defined as World Health Organization Step 3) as judged by the investigator.
3. Either sex from 18 years and above.

Exclusion Criteria

1. Patients with severe respiratory depression, severe asthama or severe COPD.
2. Severe cardiac impairment.
3. Deranged LFTs and RFTs.
4. Acute intoxication with alcohol, hypnotics, etc.,
5. Low back pain caused by cancer, bony deformity and arthritis.
6. Other musculoskeletal disabilities.
7. Presence of paralytic ileus.
8. H/o epilepsy, pregnancy, abuse potential and hypersensitivity to tapentadol or tramadol.
9. Spinal infections, fractures, spondylolisthesis.

Study Procedure- The study was conducted after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from the patients after explaining them the nature, purpose and procedures of the study. The demographic data, contact number and address of each patient was recorded. They were screened by medical history, physical examination and laboratory investigations. All patients were clinically evaluated and laboratory investigations were done at regular interval with follow-up visits of patients at 2 weeks, 4 weeks and 6 weeks of maintenance period. The randomized, prospective, open-label, comparative study was conducted on 94 patients with moderate to severe chronic low back pain as per WHO guidelines, aged 18 years or more of either sex after excluding 2 patients who were lost to follow-up. The patients were randomized into two groups. Group I comprised of patients (n=48) who were put on tapentadol ER (100-250 mg, twice a day, orally), while Group II comprised of patients (n=46) who were put on tramadol ER (100-300 mg, twice a day, orally), with follow-up at 2, 4, and 6 weeks.

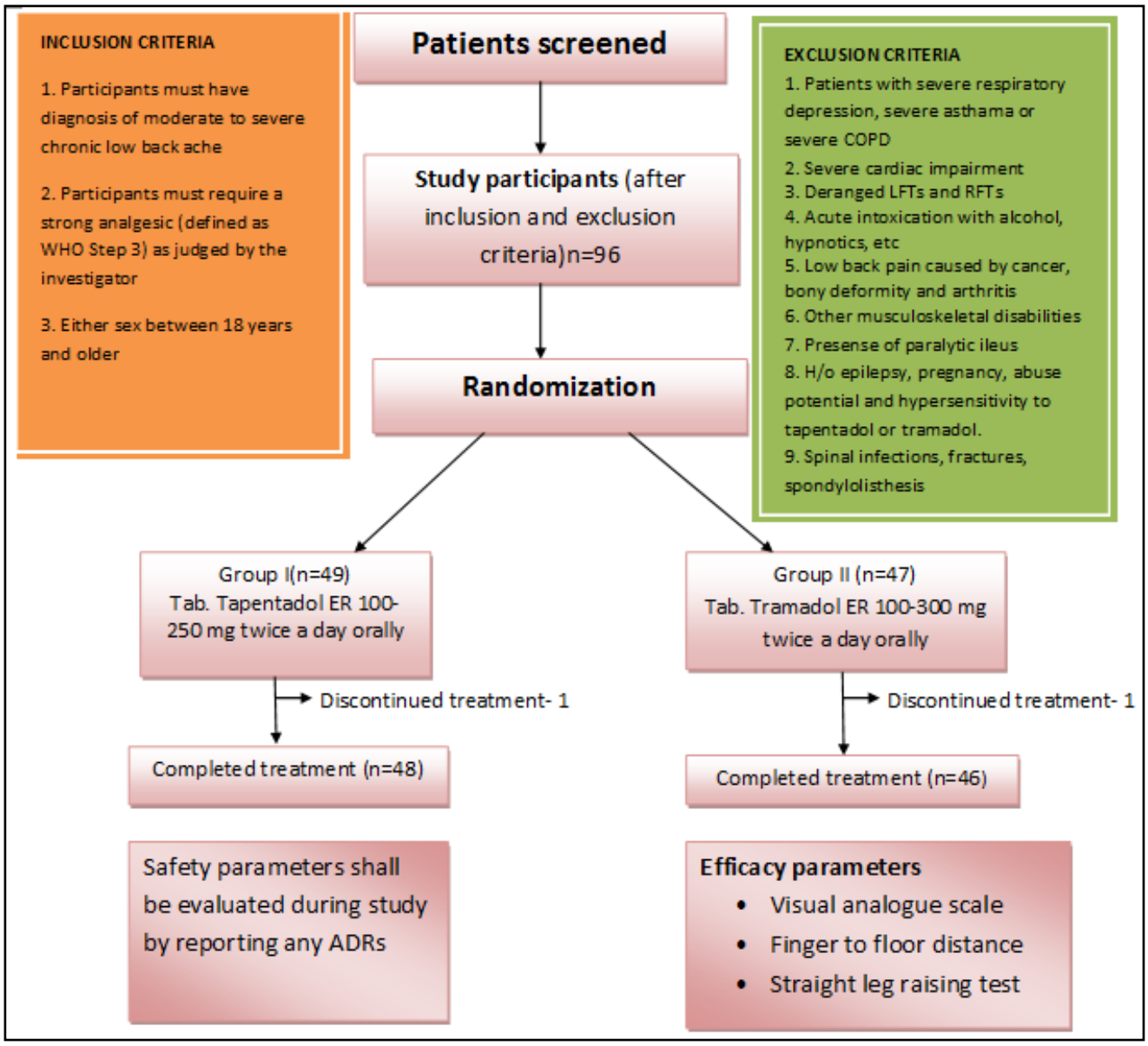

Figure 1. Flow Chart

Efficacy Parameters were Evaluated by the following Scales-

Visual Analogue Scale (VAS)-

This was used as the main subjective measure of pain. Patients were explained that pain might be represented by a straight line 10 cm long. The extremes of which correspond to '0' (no pain) at one end and '10' (worst pain) on the other end. Patients were asked to rate their pain. A higher score indicated greater pain intensity.[10]

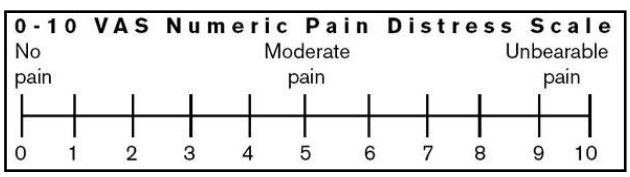

Chart 2. Visual Analogue Scale with Grading from '0' Indicating 'No Pain' tos'10' Indicating 'Worst Pain'

Finger to Floor Distance Test-

Fingertip-to-floor (FTF) test as an outcome measure on the great majority of patients presenting with lumbo-pelvic pain, for the simple reason that forward bending is one of the more painful and limited movements, especially in those with neural symptoms. Forward flexion of the spine was recorded by measuring the distance between fingertips and floor. Most normal people can reach within 7 cm of the floor.[11] This test has good reliability, validity and responsiveness. Therefore, this outcome measure in clinical practice is strongly recommended in chronic low backache patients.

Straight Leg Raising-

This was measured on both sides. The patient was asked to lie supine. The examiner elevated the leg slowly with the knee maintained in the fully extended position by the examiner's hands. The examiner continued to lift the patient's leg by flexing at the hip until pain was elicited or end range was reached. Neurologic pain which reproduced

in the leg and low back between 30-70 degrees of hip flexion is a positive result of lumbar disc herniation at the L4-S1 nerve roots. Pain at less than 30 degrees of hip flexion indicated acute spondylolisthesis, gluteal abscess, disc protrusion or extrusion, tumor of the buttock, an acute dural inflammation. Pain at greater than 70 degrees of hip flexion indicated tightness of the hamstrings, gluteus maximus, hip capsule or pathology of the hip or sacroiliac joints.[2]

Safety Assessment-

The safety profile of the drugs was studied and compared on the basis of adverse drug reactions which were documented in ADR reporting forms provided by the Central Drug Standard Control Organization.

Statistical Analysis-

The data was analysed with the help of computer software MS Excel and SPSS version 17.0 for Windows. Data reported as mean ± standard deviation and proportions as deemed appropriate for quantitative and qualitative variables respectively. Statistical significance was assessed by paired and unpaired Student's'-test. All analysis was carried out in accordance with intention to treat basis. A 'p'-value of <0.05 was considered as statistically significant. All p-values reported are two-tailed.

RESULTS

All patients attending orthopaedics OPD with chronic low backache were screened for their eligibility to participate in the study. A total of 96 patients who fulfilled the inclusion criteria were enrolled for the study and 94 patients completed the study in which there were 38 males and 56 females. One patient dropped out in each group. The present study revealed that most of the subjects (30.85%) were in the age group of 45-54 years. Mean age of the subjects in Group I was 47.14 years, whereas in Group II it was 49.93 years. Chronic low backache was more prevalent in females (59.57%) than males (40.43%) with a ratio of 1.47:1 in favour of females. In Group I and Group II, females outnumbered males with a ratio of 1.82:1 and 1.19:1 respectively (Table 1).

Sex	Group I No. (%)	Group II No. (%)	Total No. (%)
Male	17 (35.42)	21 (45.65)	38 (40.43)
Female	31 (64.58)	25 (54.35)	56 (59.57)
Total	**48 (100.00)**	**46 (100.00)**	**94 (100.00)**

Table 1. Gender Distribution of Patients in Group I (Tapentadol ER) and Group II (Tramadol ER)

The VAS score showed statistically significant reduction in pain at all levels in both the groups (p<0.0001) s but on comparison no significant differences were seen at baseline, at 2 weeks, 4 weeks and 6 weeks (p>0.05) (Table 2; Figure 2).

Visual Analogue Scale	Group I (n=48) Mean ± SD	Group II (n=46) Mean ± SD
Baseline	9.66 ± 0.69	9.65 ± 0.70
2 weeks	8 ± 0.54**	8.15 ± 0.36**
4 weeks	6.39 ± 0.64**	6.45 ± 0.69**
6 weeks	4.45 ± 0.58**	4.47 ± 0.54**

Table 2. Effect of Tapentadol ER (Group I) and Tramadol ER (Group II) on Visual Analogue Scale (VAS) for Assessment of Pain

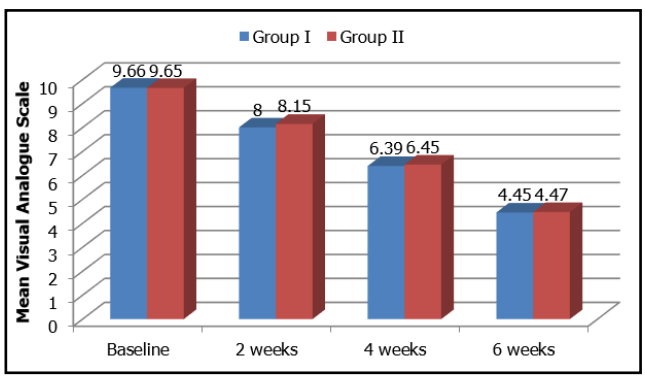

Figure 2. Comparison of Mean Values of Visual Analogue Scale (VAS) of Patients in Group I (Tapentadol ER) vs Group II (Tramadol ER)

The finger to floor distance decreased from base line to 6 wks. and show statistically highly significant improvement at all levels but again on comparison no significant difference was seen. (Table 3, Figure 3).

Finger to Floor Distance	Group I (n=48) Mean ± SD	Group II (n=46) Mean ± SD
Baseline	11.43 ± 2.10	11.80 ± 3.64
2 weeks	10.08 ± 1.31**	9.73 ± 2.52**
4 weeks	8.83 ± 1.07**	8.28 ± 1.74**
6 weeks	6.66 ± 0.88**	6.86 ± 1.24**

Table 3. Effect of Tapentadol ER (Group I) and Tramadol ER (Group II) on Finger to Floor Distance

**Highly significant (p<0.0001).

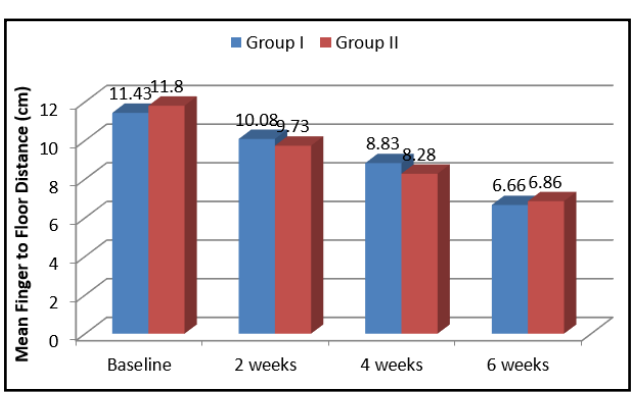

Figure 3. Comparison of Mean Values of Finger to Floor Distance Parameter of Patients in Group I (Tapentadol ER) vs Group II (Tramadol ER)

The Results of straight leg raising test were found to be statistically non-significant at all follow-up visits (p>0.05) in both the groups and on comparing two groups of treatment for right as well as for left leg, straight leg raising test showed statistically non-significant results (p>0.05) at 2 weeks, 4 weeks and 6 weeks, though clinically there was some improvement at 6 weeks. (Table 4, figure 4).

Straight Leg Raising Test		Group I Mean ± SD (Degree)	Group II Mean ± SD (Degree)
Baseline	Right Leg	88.54 ± 5.83	86.52 ± 8.74
	Left Leg	84.79 ± 10.10	84.78 ± 11.10
2 weeks	Right Leg	88.75 ± 5.30	86.52 ± 8.74
	Left Leg	84.79 ± 10.10	84.78 ± 11.10
4 weeks	Right Leg	89.16 ± 3.47	88.04 ± 5.81
	Left Leg	85.83 ± 8.20	86.08 ± 8.55
6 weeks	Right Leg	89.58 ± 2.01	88.26 ± 4.85
	Left Leg	87.29 ± 5.73	87.39 ± 5.74

Table 4. Effect of Tapentadol ER (Group I) and Tramadol ER (Group II) on Straight Leg Raising Test (Left)

Not significant (p>0.05).

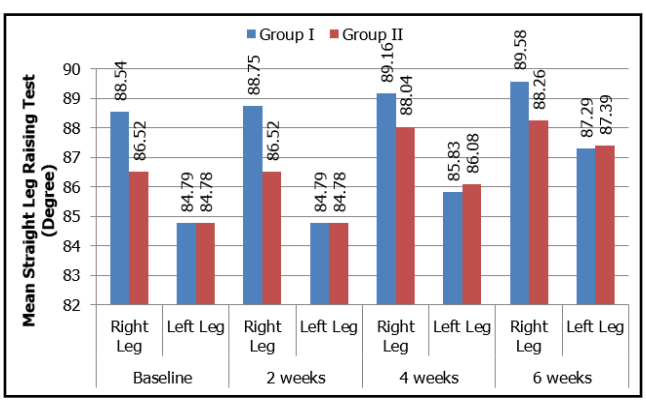

Figure 4. Comparison of Mean Values of Straight Leg Raising Test Parameter of Patients in Group I (Tapentadol ER) vs. Group 11

A total of 10 adverse drug reactions (ADRs) were reported in the study. In Group I, there were 3 (6.25%) cases of ADRs. One patient had vertigo (2.08%), while 2 complained of dizziness (4.17%) after taking tapentadol ER. In Group II, there were 7 (15.22%) cases of ADRs. The most common adverse drug effect reported in tramadol group was nausea (8.70%) followed by vomiting (6.52%). On comparison, tapentadol ER showed better gastrointestinal tolerability then tramadol ER. No severe ADRs were reported in both the groups. All ADRs were mild and subsided without medication. (Figure 5)

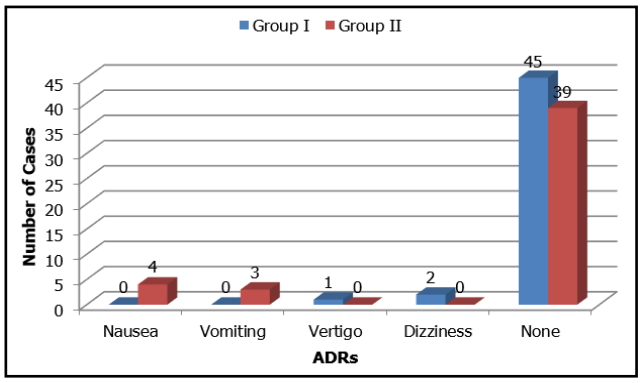

Figure 5. Adverse Drug Reaction Profile of Study Drugs

DISCUSSION

Chronic low back pain represents a major healthcare problem which seriously impairs the quality of sufferer's working and social lives. It also poses a major economic problem due to the frequent use of health services and absence from work.[12]

Pharmacotherapy, including NSAIDs and opioid analgesics, is an important cornerstone in the multi-modal management of pain.[13] Opioids are considered as gold standard for treatment of moderate to severe pain. However, opioids are underutilized due to potential risk of adverse effects, abuse, tolerance and withdrawal which limit their usefulness in cases of chronic pain.[14] Atypical opioids like tapentadol and tramadol seem to be promising drugs in this regard. Since there was scanty data available in the review of literature regarding comparison between these two drugs, we took up the present study.

The average age of the patients with moderate to severe low back pain enrolled in the study was 48.51 ± 12.58 years.[15] These results are similar to other studies where mean age of patients who had chronic low back pain was 49.9 ± 13.83 years. Females outnumbered males with a ratio of 1.47:1. Some studies showed that females had higher incidence rate of chronic low back pain and it increased with age.[16,17] In the present study, a total of 59.57% females and 40.43% males were having chronic low back pain. These findings are similar to other studies as well where 60% females and 40% males were suffering from chronic low back pain.[18] After menopause women have more severe disc space narrowing than age matched men. This may be associated with physiological changes caused by relative lower level of sex hormones after menopause in females and the accelerated lumbar disc degeneration.[19]

Tapentadol represents a new class of centrally acting analgesic. It is a novel drug used for moderate to severe chronic pain like osteoarthritis and low back pains. In the present study, in Group I, tapentadol ER showed significant reduction in pain intensity from baseline to 6 weeks in patients of chronic low back pain as signified by VAS scores. This shows that tapentadol ER is very effective in reducing pain. These findings were similar to Afilalo M et al. (2010) and Buyank R et al. (2010), studies in which tapentadol ER showed effective decrease in pain intensity using VAS.[20] The analgesic activity of tapentadol is attributed to dual

mechanism of action as mu opioid receptor agonist and norepinephrine reuptake inhibitor.[21]

Tramadol also is a centrally acting synthetic opioid analgesic that has dual mechanism of action, binding to mu-opioid and weakly inhibiting the neuronal uptake of both nor-epinephrine and serotonin, which contribute to its efficacy. It is commonly used opioid analgesic in conditions like osteoarthritis and low back pain.

The tramadol ER in the study showed a significant reduction in the pain intensity from baseline to 6 weeks in patients of chronic low back pain by showing statistically significant improvement in pain on VAS scores. Various studies have compared tramadol with placebo intensity. Tramadol ER formulations have consistently demonstrated significant improvements in pain scores compared to placebo in patients with moderate to moderately severe chronic pain.[22]

A research trial was conducted using tapentadol and tramadol as study drugs which showed that both the drugs have significant effect in reducing the osteoarthritic pain using VAS and WOMAC scores.[23] The results of our study are consistent with the observations shown in this study in which tapentadol was found to be as efficacious as tramadol in patients of chronic low backache.[18]

Since finger to floor distance test has exhibited good reliability and validity, this outcome measure is commonly used in clinical practice in patients of low backache. In the present study, both the drugs tapentadol and tramadol showed significant decrease in finger to floor distance from baseline to 6 weeks, but on comparison, there was no significant difference between the two ($p>0.05$). While reviewing the literature, we found very few studies wherein finger to floor distance parameter was used to judge the efficacy of tapentadol or tramadol.[24]

In straight leg raising test, clinically there was some improvement in leg raising at 6 weeks of treatment from baseline, but statistically the results were not significant in both groups ($p>0.05$). However, in a study straight leg raising after Back School Therapy was significantly better than conservative treatment in patients of chronic low back pain.[11]

In the present study, a total of 10 adverse drug reactions were reported, 3 (6.25%) in tapentadol group and 7 (15.22%) in tramadol group, indicating that more adverse drug reactions were reported in tramadol group patients particularly gastrointestinal side effects.

Two patients in our study discontinued the treatment with one patient in each group due to development of adverse drug reaction during treatment period and both were excluded from the study.

Various studies showed that there is better gastrointestinal tolerability of tapentadol when compared with oxycodone, opioids which are commonly used in the past in patients with low back pain or osteoarthritis). Very few head to head studies are available comparing safety of tramadol and tapentadol in patients with moderate to severe pain. The various studies have reported that tapentadol is more tolerable than tramadol with less adverse drug reactions.[25] Lesser incidence of nausea and vomiting has been reported with tapentadol as compared to that by tramadol in the literature which holds true in our study as well. Better gastrointestinal tolerability of tapentadol is due the fact that tapentadol is a weak inhibitor of serotonin reuptake whereas, tramadol is a potent inhibitor.[25] The Small sample size and short duration are some of the limitations of present study.

CONCLUSION

The results of the current study indicate that Tapentadol ER provides analgesic efficacy that is similar to that provided by Tramadol ER for management of moderate to severe chronic low backache with a better gastrointestinal tolerability profile. Given that gastrointestinal side effects have substantial negative impact on patient's outcome, Tapentadol ER may represent a better alternative to other strong opioid for such patients. However, more robust studies are needed to substantiate these findings.

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