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Comparative study of analgesic efficacy and tolerability of oral tapentadol-paracetamol combination vs. oral tramadol-paracetamol combination for postoperative pain relief in patients undergoing hernia surgery

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Abstract : *Introduction* : Oral tramadol-paracetamol combination is the standard analgesic combination used in our institute for control of postoperative pain. Tapentadol is a relatively new dual-action analgesic, which, although similar to tramadol, has certain theoretical advantages over it. We are not aware of any published head-to-head comparison between these two agents for postoperative analgesia.

Methods : In this randomized double-blind controlled trial we compared the postoperative analgesic efficacy and tolerability of oral tapentadol vs. tramadol, in combination with oral paracetamol, in two groups of ASA I-II patients (60 in each group) undergoing elective inguinal hernioplasty. All patients enrolled in the study received standard spinal anesthesia with bupivacaine (heavy) 0.5% to achieve block level up to T6. At the end of surgery, when the block level receded to T10, Group I received the combination of oral paracetamol 500 mg and oral tapentadol 100 mg, repeated 6-hourly thereafter up to 24h; Group II received tramadol 100 mg along with oral paracetamol 500 mg, all other conditions remaining the same. The primary outcome was pain score at rest and on movement as measured by visual analog scale (VAS) scores 0-10. Secondary outcomes included use of rescue analgesic, tolerability and patient satisfaction.

Results : Both the groups fared well in terms of pain control from 0h till 24h (VAS scores remained under 2 at rest and under 3 on movement in both the groups) and use of rescue analgesic, as well as short-term adverse effects and tolerability. Though more patients in Group I needed rescue analgesic than Group II (16.7% vs. 3.3%, both groups only once), and reported nausea (16.7% vs. 3.3%) and vomiting (10% vs. 3.3%), these differences were not statistically significant ($P > 0.05$). Patient satisfaction was high in both groups.

Conclusion : In this first direct comparison randomized blinded trial, both oral tapentadol and oral tramadol, in combination with oral paracetamol, were found to be quite efficacious and well tolerated in pain management for patients undergoing hernia surgery. No drug combination was found to be superior to the other.

Key words : tapentadol; tramadol; postoperative pain; hernioplasty; randomized controlled trial.

Appropriate management of acute pain remains a considerable challenge for health care providers (1). Despite substantial advances in pain research in recent decades, inadequate acute pain control is still more the rule than the exception. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality (2). The advantages of effective postoperative pain management include patient comfort and therefore satisfaction, earlier mobilization, fewer pulmonary and cardiac complications, a reduced risk of deep vein thrombosis, faster recovery and reduced cost of care (2).

Pain, like many medical conditions, is multi-pathophysiologic and, therefore, from a theoretical perspective, may be best treated by drugs that act on multiple pathways (3). Paracetamol (acetaminophen) is one of the most widely used agents for the management of postoperative pain. It exerts simultaneous anti-nociception at both spinal and supra-spinal sites (4). In order to provide multi-modal analgesia, paracetamol is often used with tramadol, which is an atypical weak opioid with a dual mechanism of action: μ-opioid receptor activation along with enhancement of serotonin and noradrenaline transmission (5). The tramadol/paracetamol combination may benefit from the complementary mechanisms of action of the two compounds, as well as from the rapid onset of action of paracetamol and the long-lasting effects of tramadol (6).

At our institute, which is a tertiary care centre,

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the routine standard for postoperative pain control is a combination of paracetamol and tramadol. However, tramadol often causes severe nausea and vomiting, it is a pro-drug which needs to be metabolically activated, and its dual action depends upon two different enantiomers. These are the relative disadvantages of tramadol (7).

A novel opioid drug, tapentadol, was launched at the end of 2011 in the European market for human use. Based on its unique mechanism of action, it has been proposed as the first representative of a new pharmacological class of centrally acting analgesics: the mu-opioid receptor agonist, noradrenaline reuptake inhibitor (MORNRI) (8). Tapentadol provides highly effective analgesia (9). Studies have shown higher satisfaction rates, increased tolerability and lower discontinuation rates among the patients using tapentadol (10).

Despite their similarities and differences, no direct head-to-head comparison between tramadol and tapentadol as a component of postoperative multimodal analgesia was available at the time this study was planned. Hence this study aimed to compare the analgesic efficacy of oral tapentadol-paracetamol combination vs. oral tramadol-paracetamol combination for postoperative pain relief in patients undergoing inguinal hernia surgery (primary aim) and to compare the tolerability and side effect profiles as well (secondary aim).

Material and Methods

In this randomized double-blind controlled trial (clinical trials registry no. CTRI/2016/08/007217), following approval from Institute Ethics Committee, 120 male patients of ASA I-II aged 18-65 years posted for elective hernioplasty for primary hernia by open method by different but adequately qualified surgical faculty members were enrolled for the study after obtaining informed consent before study intake. They were randomized by computer-generated random sequence to 2 groups of 60 patients each. One group received combination of oral tapentadol-paracetamol (Group I), and the other received a combination of oral tramadol-paracetamol (Group II). Patients with the following characteristics were excluded from the study (exclusion criteria): ASA status III or more; major co-existing medical illness (especially severe asthma/COPD, repeat hernia surgery, epilepsy, uncontrolled hypertension or diabetes, liver or renal disease); patients with paralytic ileus, patients on antidepressants (to avoid risk of developing serotonin syndrome), and known hypersensitivity to any of the study medications.

The sample size was calculated as follows: pilot data from our institute showed that patients reported 1.5 average pain score at rest on visual analog scale (SD 0.5) at 4 hours after hernioplasty operation with the standard oral tramadol plus paracetamol combination. Assuming 20% as a clinically meaningful reduction of pain score with the study drug combination (i.e. mean 1.2) with same variance, 90% power and two-sided alpha as 5, the needed sample was 59 per group. Thus 60 patients were recruited for each group.

All patients enrolled in the study received standard spinal anesthesia with bupivacaine (heavy) 0.5% to achieve block level up to T6. At the end of surgery, when the block level receded to T10, Group I received the combination of oral paracetamol 500 mg and oral tapentadol 100 mg. This combination was repeated 6-hourly thereafter up to 24 hours. For Group II, similar procedure was followed using oral tramadol 100 mg instead of tapentadol, along with oral paracetamol 500 mg, all other things remaining the same. All patients received oral ondansetron 4 mg, pre-operatively then 12-hourly as a prophylactic anti-emetic. Both the patients and the raters were blinded to the group allocation, which was done by a person not involved in rating or data collection.

A structured questionnaire was used for the groups, documenting their demographic and clinical data, height and weight, co-existing diseases if any, known allergies, and the details of the operation.

Outcome measures

i. Primary outcome:

Pain rating, at rest and on movement, measured by visual analog scale (VAS), during the postoperative period at intervals of 0 hour (when the first dose of the combination is administered, i.e., when the block level recedes to T10), 2, 4, 8, 12, and 24 h. The patients were demonstrated before the operation about the use of VAS.

ii. Secondary outcomes:

a. Rescue analgesic (intravenous diclofenac sodium 75 mg, on patient's demand, for which they were instructed earlier): if, when, and how much needed.

b. Side-effect profile and adverse effects in both groups were noted on a structured format. These included: nausea, vomiting, headache, dizziness, gastritis, and drowsiness.

c. Patient satisfaction was also noted at the end of the study period as 'very satisfied', 'satisfied' and 'undecided'.

d. Pulse, blood pressure (BP) and respiratory rate were also noted.

The findings on the outcome measures were subjected to suitable parametric and non-parametric statistical analyses (descriptive statistics, Student's t and chi-squared test, using SPSS version 17, Chicago, IL).

Results

Baseline sample characteristics

The baseline characteristics of the two groups (age, education, occupation, height and weight) were all comparable, with no significant differences (Table 1).

Clinical characteristics

Groups I and II did not differ significantly on any of the baseline clinical variables studied: duration of surgery, blood loss, and baseline scores of pain at rest and on movement, heart rate, systolic and diastolic blood pressure, and respiratory rate (Table 1). They did not have any significant past or co-existing medical or surgical disease.

Pain scores at rest

Overall the postoperative pain scores were in the mild range in both the groups: out of a maximum score of 10, the mean pain scores at any time in both the groups ranged from 0.47-0.58 (at 0h) to 1.47-1.70 (at 4 h postoperative). Pain scores decreased after 4 h in both the groups ($P < 0.001$). The two groups were however comparable at all the time points of observation ($P > 0.05$) (Table 2).

Pain scores on movement

As above, overall the postoperative pain scores were in the mild range in both the groups: out of a maximum score of 10, the mean pain scores at any time in both the groups ranged from 0.61-0.79 (at 0 h) to 2.28-2.39 (at 4 h postoperative). Pain scores decreased progressively after 4h in both the groups ($P<0.001$). The two groups were however comparable at all the time points of observation ($P > 0.05$) (Table 3).

Heart rate, blood pressure and respiratory rate

Similar multivariate tests were carried out for comparing the two groups on postoperative heart rate, blood pressure (systolic and diastolic) and respiratory rate. On all these repeated measures, there was no significant difference between the groups, i.e., the two groups were comparable.

Use of rescue analgesic

Rescue analgesic was needed by more patients in Group I than Group II, though the difference was not significant (16.7% vs. 3.3%; $P > 0.05$) (Table 4). Patients who were given rescue analgesic needed it only once (intravenous diclofenac 75 mg), usually at 4 h postoperative.

Patient satisfaction

Patients in both the groups were highly satisfied. Patient satisfaction was rated as 'very satisfactory' or 'satisfactory' by almost all the subjects in both groups (100% vs. 97%; $P > 0.05$) (Table 5).

Table 1
Baseline sample and clinical characteristics

	Group I [Tapentadol] (n = 60)	Group II [Tramadol] (n = 60)	P value
Age (years) Mean ± SD	44.3 ± 17.61	45.5 ± 17.54	0.798
Height (cm) Mean ± SD	167.2 ± 6.48	167.6 ± 6.17	0.808
Weight (kg) Mean ± SD	63.7 ± 11.63	62.1 ± 8.40	0.536
Duration of Surgery (min) Mean ± SD	60.5 ± 17.43	69.0 ± 19.80	0.083
Blood loss (ml) Mean ± SD	68.0 ± 58.68	52.66 ± 36.66	0.190
Baseline pain VAS score at rest Mean ± SD	0.47 ± 1.07	0.58 ± 0.91	0.671
Baseline pain VAS score at movement Mean ± SD	0.61 ± 1.23	0.79 ± 1.15	0.560
Baseline heart rate (bpm) Mean ± SD	113.9 ± 16.70	121.2 ± 14.67	0.659
Baseline systolic blood pressure (mm Hg) Mean ± SD	125.8 ± 10.13	119.6 ± 12.71	0.263
Baseline diastolic blood pressure (mm Hg) Mean ± SD	79.7 ± 11.24	79.8 ± 7.57	0.912
Baseline respiratory rate per minute Mean ± SD	22.0 ± 4.21	19.8 ± 3.58	0.720

Table 2
Postoperative pain scores on visual analog scale (VAS): at rest.

	Group I [Tapentadol] (n = 60)	Group II [Tramadol] (n = 60)	P value
At 2 h	0.99 ± 1.29	1.03 ± 0.63	0.870
At 4 h	1.70 ± 1.96	1.47 ± 0.56	0.552
At 8 h	1.00 ± 0.96	1.34 ± 0.77	0.130
At 12 h	1.10 ± 1.59	0.92 ± 0.65	0.554
At 24 h	0.71 ± 0.82	0.75 ± 0.67	0.850

Table 3
Postoperative pain scores on visual analog scale (VAS): on movement.

	Group I [Tapentadol] (n = 60)	Group II [Tramadol] (n = 60)	P value
At 2 h	1.28 ± 1.50	1.85 ± 0.89	0.081
At 4 h	2.28 ± 2.23	2.39 ± 0.88	0.808
At 8 h	2.06 ± 1.12	2.24 ± 0.94	0.497
At 12 h	1.78 ± 1.13	1.76 ± 0.83	0.948
At 24 h	1.49 ± 1.08	1.46 ± 0.93	0.889

Table 4
Use of rescue analgesic.

Rescue Analgesic	**Group-I (Tapentadol) N = 60**	**Group-II (Tramadol) N = 60**	**P Value**
Not Needed N (%)	50 (83.3)	58 (96.7)	0.195
Needed N (%)	10 (16.7)	2 (3.3)	

Table 5
Patient satisfaction.

Patient Satisfaction	**Group-I (Tapentadol) N = 60**	**Group-II (Tramadol) N = 60**	**P Value**
Very Satisfied N (%)	24 (40.0%)	20 (33.3%)	0.546
Satisfied N (%)	36 (60.0%)	38 (63.4%)	
Undecided N (%)	0 (0%)	1 (3.3%)	

Table 6
Adverse effects.

Incidence of Adverse effect	**Group-I (Tapentadol) N = 60**	**Group-II (Tramadol) N = 60**	**P Value**
Nausea N (%)	10 (16.7)	2 (3.3)	0.195
Vomiting N (%)	6 (10.0)	2 (3.3)	0.237
Dizziness N (%)	4 (6.7)	2 (3.3)	0.492
Headache N (%)	2 (3.3)	0 (0)	1.00
Gastritis N (%)	0	0	--
Drowsiness N (%)	4 (6.7)	0 (0)	0.375

Side effects and adverse effects

Very few patients experienced side effects to these drugs in any group. The most frequently reported adverse effects was nausea in the Group I (Tapentadol), reported by 10 patients (16.7%), followed by vomiting in 6 patients (10%). These figures were higher than those seen in the Group II (Tramadol): 2 (3.3%) and 2 (3.3%) respectively. However, these differences were not statistically significant. Other infrequently reported symptoms included dizziness, drowsiness and headache, though none of these were significantly different between the two groups (Table 6).

Discussion

To the best of our knowledge, this is the first head-to-head comparison between two dual-action analgesics (in combination with paracetamol) as an oral multimodal analgesic combination to control postoperative pain in patients undergoing elective inguinal hernia operation. The two groups in our study were comparable with respect to age, height, weight, duration of surgery, blood loss, and baseline pain scores, hemodynamic measures and respiratory rate. Pain scores peaked at 4 h postoperatively but decreased significantly in both the groups from 4h postoperatively onwards ($P < 0.001$). The peak at 4h may be because duration of action of both tramadol and tapentadol is 4-6 hours; also, spinal anesthesia was wearing off and patients being shifted to their wards. There were no significant differences between the two groups in terms of VAS scores at rest or on movement at any time points of observation.

Rescue analgesic was needed by more patients in Group I than Group II, though the difference was not significant (16.7% vs. 3.3%; $P > 0.05$). Patient satisfaction was rated as 'very satisfactory' or 'satisfactory' by almost all the subjects in both groups (100% vs. 97%; $P > 0.05$). With the exception of nausea which was reported by 16.7% in the Tapentadol group, all other side effects (vomiting, headache, dizziness, drowsiness, gastritis) were infrequent (0-10%), and all side effects were comparable across the groups.

Atypical opioids such as tramadol and tapentadol have a dual mechanism of action and have been designed to overcome the issues of a limited therapeutic window and the induced opioid receptor down regulation, through an opioid-sparing effect (7). In combination with opioid analgesics, paracetamol could be used also in the management of more severe pain (such as postoperatively).

Our study has shown that combining oral tapentadol or tramadol with paracetamol significantly reduced the pain scores of patients postoperatively. Results in all the outcome parameters studied were comparable for the two groups, including pain scores, rescue analgesic utilization, tolerability and patient satisfaction. Therefore the results of our study do not allow us to conclude which is a better combination.

Although a clinical review (11) concluded that tapentadol overcomes a number of the liabilities of tramadol, some liabilities do exist, like risk of precipitating serotonin syndrome and adverse effects due to its antimuscarinic activity. It was also concluded that more data are required before its role comparative to tramadol can be assessed, like longer-term efficacy/tolerability trials in chronic pain states, additional clinical studies in elders (including frail elders in institutional settings), and studies of the effect of UDP-glucuronosyltransferase genetic polymorphisms on tapentadol pharmacokinetics (11,12).

In a recent comparative study it was observed that oral tapentadol was more effective as a multimodal analgesia approach in controlling acute postoperative pain after coronary artery bypass and graft surgery compared to intravenous tramadol (13). However, the study design and patient characteristics were different. Our head-to-head comparison study importantly adds to the current state of knowledge in this area by refuting some of the claims for tapentadol made earlier purely on theoretical considerations without validation by empirical data (11, 14).

In conclusion, this randomized controlled trial directly comparing oral tapentadol with oral tramadol, both in combination with oral paracetamol, to compare postoperative pain control and tolerability in patients undergoing elective inguinal hernioplasty, did not find any particular combination superior to the other, whereas both the combinations were found to be quite efficacious, satisfactory to the patients, and generally well tolerated. This has clinical implications for postoperative pain management especially for cost-effectiveness considerations. Thus, in view of our findings, cost rather than efficacy-tolerability should be considered relevant for choosing tapentadol vs. tramadol in combination with paracetamol in this population. This is of practical importance because there is a substantive cost difference between the two drugs in their immediate-release formulations. One-week cost of oral tramadol 400 mg/d is GBP 1.57 or Euro ~1.7, vis-à-vis that of tapentadol 300 mg/d is GBP 18.68

or Euro ~20.2 (15).

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