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Original Research Article

ROLE OF PRE-EMPTIVE TAPENTADOL IN REDUCTION OF POSTOPERATIVE ANALGESIC REQUIREMENTS AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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Abstract

Background: Pre-emptive analgesia is the modality that reduces development of the central neuro-sensitization by providing the anti-nociceptive prophylaxis before onset of the surgical pain stimulus and thus minimizing post-operative pain. The present study was conducted to assess the pre-emptive efficacy of tapentadol in reduction of postoperative analgesic requirements after laparoscopic cholecystectomy. **Materials and Methods:** 120 patients of American Society of Anaesthesiologists (ASA) Grade 1 and 2 of age group more than 18 years of either gender with body mass index 25±20% admitted and scheduled for undergo laparoscopic cholecystectomy surgery under General Anaesthesia was included after ethical approval and written/ informed consent. The hemodynamic variables with postoperative pain and sedation was assessed using visual numerical score (VNS) and Ramsay Sedation Score (RSS). **Result:** Rescue analgesia at baseline (mean Time for first analgesic requirement) was higher in Group B (84.98 ±21.85) than Group A and C ($p<0.001$). In the present study, at base line (0 min) Mean Visual Numerical Score (VNS) was high in Group C (3.35±0.95) followed by Group A (0.40±0.49) and Group B (0.15±0.36) ($p<0.001$). At 30 min mean Visual Numerical Score (VNS) increased in all three groups. At the final observational time 1440 min Mean Visual Numerical Score (VNS) decreased with respect to baseline time (0 min) in all groups and was high in Group C (0.15±0.36) followed by Group A (0.03±0.16) ($p<0.001$). In the present study, Ramsay Sedation Score (RSS) at different time interval was found to be statistically significant in all groups ($p<0.001$). **Conclusion:** Tapentadol is appropriate choice as the pre-emptive analgesic having favourable safety profile, although hunt for the ideal combination still continues.

INTRODUCTION

Cholecystectomy is among common intra-abdominal surgeries executed in the hospitals of India.[1] Now laparoscopic surgery is considered as gold standard in treatment of cholelithiasis.[2]

The laparoscopic surgery has an advantage of having less postoperative pain and shorter hospital stay. Further, it has good cosmetic results and faster recovery with minor complications. As far as surgeon is concerned it has less operating time. It has been believed to have economic advantage.[3]

Among the 70 million surgeries performed worldwide every year, over 80.0% patients suffer from moderate to severe postoperative pain.[4] It has a huge impact upon the quality of life, as poorly controlled acute postoperative pain can lead to central neuronal sensitization precipitating chronic pain. Pre-emptive analgesia is the modality that reduces development of the central neuro-sensitization by providing the anti-nociceptive prophylaxis before onset of the surgical pain stimulus and thus minimizing post-operative pain.[5,6] Also, this technique reduces requirement of post-operative analgesic and allows better pain control along with minimal side-effects.

Pre-emptive analgesia is the preventive measure to escape such hypersensitisation caused by the incision, and inflammatory injuries through the chronic activation of the nociceptors. The wide

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range of the medications been inspected for their possible pre-emptive analgesic effects including opioids, and non-steroidal anti-inflammatory drugs (NSAIDS) through systemic, or oral route. Choice of analgesic is based on its efficacy, complications, pharmacokinetics, and cost-effectiveness.[7]

Tapentadol represents the new class of the centrally acting analgesic, μ-opioid receptor agonist-norepinephrine reuptake inhibitor (MOR-NRI), with analgesic activity that results from the contribution of both mechanisms of action.[8,9] The tolerability and efficacy of tapentadol have been demonstrated for management of both nociceptive neuropathic and types of chronic pain.[10,11] Various trials have shown its efficacy in relieving moderate-severe pain in both the acute and chronic settings.[12] However, its role as a preemptive analgesic is not yet investigated especially in India.

We hypothesized that Tapentadol is the centrally acting analgesic and has the exclusive mechanism of action that includes norepinephrine reuptake inhibition, μ-opioid receptor agonism, and the alpha-2 adrenoceptors activation. Additional benefits include better tolerability profile and increased patient satisfaction and it helps in relieving moderate/severe pain in acute, and chronic settings. Therefore, we commenced this study to assess the pre-emptive efficacy of tapentadol in reduction of postoperative analgesic requirements after laparoscopic cholecystectomy.

MATERIALS AND METHODS

This double blinded prospective study was performed at Shri Mahant Indresh Hospital, Dehradun. 120 patients of American Society of Anaesthesiologists (ASA) Grade 1 and 2 of age group more than 18 years of either gender with body mass index 25±20% admitted and scheduled for undergo laparoscopic cholecystectomy surgery under General Anaesthesia was included after ethical approval and written/ informed consent. However, the patients with history of psychiatric illness. communication difficulties, presently on Psychotropic, alpha 2 agonists or opioid medications in 28 days before scheduled surgery, any end organ disorder, pregnancy and lactational women, alcohol Abuse, smoking habit, drug abuse or allergic to opioids were excluded from the study. The study includes 120 patients which were divided randomly into equal groups using sealed, opaque envelopes. A sealed opaque envelope randomly selected, and opened by investigator, with instruction to draw the relevant drug.

GROUP A –50mg Tapentadol

GROUP B – 75mg Tapentadol orally with sip of water 1 hour before scheduled surgery.

GROUP C - Placebo

Preanesthetic check-up of the patients selected for study was carried-out a day before the surgery and was recorded on patients performa. In each case, detailed history and physical examination was carried out.

General physical examination along with cardiovascular and respiratory system examination was also done. Respiratory rate, pulse rate and blood pressure were recorded preoperatively. Local examination of study drug injection site was done to exclude any sign of sepsis, previous injury or previous deformity.

Premedication was done with tablet alprazolam 0.25 mg one night prior to the surgery. On the day of surgery, premedication with injection midazolam 0.04 mg/kg for anxiolysis. Patients were kept nil by mouth at least six hours before operation. The patient was assured, the procedure was explained and a written informed consent obtained from them. After securing intravenous line the patient was preloaded with 10 ml / kg body weight of the ringer lactate solution over 15 to 20minutes. Multipara monitor was applied and baseline respiratory rate, pulse rate, NIBP, SpO2 and ECG were recorded.

Laparoscopic cholecystectomy (LC) was done under general anaesthesia. General anaesthesia was induced with the lidocaine (1mg/kg intravenous), Propofol (2mg/kg IV) and fentanyl (2mcg/kg IV). Supraglottic airway (I-Gel) insertion was facilitated with the injection vecuronium (0.1mg/kg IV). Anaesthesia maintained with Isoflurane (0.5-2%) and Nitrous oxide /Oxygen (60/40%). Any size in MAP>20% from baseline was treated by administering the bolus dose of fentanyl (1mcg/kg IV) and raising the inspiratory concentration of isoflurane in steps of 0.2%. Any fall in MAP>20% from the baseline was accomplished by reducing inspiratory concentration of the isoflurane in steps of 0.2%. The target is to maintain the MAP below 20.0% limits of the baseline values. The neuromuscular blockade was maintained by vecuronium (0.02mg/kg IV), as required throughout surgery. At end of surgery, neuromuscular block was antagonized with neostigmine (0.05mg/kg IV) and glycopyrrolate (0.01mg/kg IV).

Postoperatively vital signs, pain and sedation parameter were noted as 0 hour, ½ hour, 1hour, 2-hour, 4-hour, 6-hour,12 hour and 24hours by an observer who was unaware of drug given. Intensity of pain at rest (irrespective of location and type of pain) using visual numerical scale (VNS) score, total analgesic requirement during first 24hr of postoperative period.

Postoperatively, the selected patient was assessed for pain, and sedation by the use of visual numerical score (VNS) and Ramsay Sedation Score (RSS). The patient was also enquired about nausea, vomiting, number of times end dose of rescue analgesia, time recorded to first postoperative analgesia; baseline (0 hour), 0.5 hour, 1 hour, 2 hour, 4 hour, 6 hour, 12 hour and 24 hour postoperatively.

Injection paracetamol 1 gram intravenous was administered if pain score was more than or equal to 4 (for pain complaints) with shortest interval of

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minimum 4 hours between each dose. The tramadol Injection 50mg intra-venous was administered as rescue analgesia, as per requirement.

Rescue analgesia was given at VNS>6 in the form of NSAIDS (injection tramadol 50mg IV). Injection ondansetron was given for post-operative nausea, and vomiting. Patient was monitored for side effects throughout the postoperative period.

Side effects and complications were noted and if any occurred was treated. The adverse effects of study drugs were looked including convulsions, cardiovascular collapse and arrhythmias.

Statistical analysis

Data was analysed using Statistical Package for Social Sciences, version 23 (SPSS Inc., Chicago, IL). Discrete (categorical) data were summarized as in proportions and percentages (%) while quantitative data were summarized as mean (SD), median or mode. Comparisons of numerical variables between the groups were analysed by Student's unpaired t test for normally distributed data, intergroup comparison was done by repeated measures analysis of variance ANOVA test. All p-value <0.05 considered as statistically significant.

RESULTS

In our study total 120 patients were divided into three groups. Group A 40 (33.3%) patients were given Tapentadol 50mg, Group B 40 (33.3%) were treated by Tapentadol 75mg and in Group C 40 (33.3%) patients were treated by placebo. On comparing the demographic characteristics among the patients, no statistical significance was observed [Table 1].

Table 1: Demographic profile of the studied patients

Patient's Characteristics	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
Age	37.45±10.91	35.65±11.12	36.33±10.26	0.752
Gender (M/F)	28/12	31/9	27/13	0.321
BMI	25.02±1.33	25.24±3.49	24.55±1.85	0.427
ASA Score (I/II)	26/14	25/15	27/13	0.567
Duration of Surgery (min)	78.45±12.1	78.80±12.1	74.9±7.73	0.209

In our study, the mean Heart Rate (HR) of Group A, Group B, Group C patients was 89.35±5.2, 86.75±8.55, 89.63±5.2 bpm respectively (p=0.097). Similiarly, insignificant results were obtained on comparing the baseline systolic, diastolic and mean arterial pressure (p>0.05) [Table 2]. The mean SPO2 of Group A, Group B, Group C patients was 96.50±1.92, 96.40±20.2, 96.55±2.21 respectively (P=0.94) [Table 2].

Table 2: Baseline hemodynamic parameters of the patients among groups

Hemodynamic Details (Pre-operative	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
HR (bpm)	89.35±5.2	86.75±8.55	89.63±5.2	0.097
SBP (mmHg)	112.05±7.1	112.75±7.22	113.25±7.21	0.755
DBP (mmHg)	78.20±5.65	77.80±5.27	77.13±5.34	0.665
MAP (mmHg)	94.18±3.77	93.30±4.07	92.59±4.47	0.228
SPO2 (%)	96.50±1.92	96.40±20.2	96.55±2.21	0.946

In our study a decrease in mean HR was observed in all three groups at different observation time intervals. Mean HR was higher at 0 min and was lower at 1440 min in all groups. Heart rate at different time interval among the group showed insignificant correlation in all groups (Group A, Group B, Group C) [Table 3].

Table 3: Distribution on the basis of their heart rate at different time interval among the group

Heart Rate (bpm)	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
0 min	89.35±5.2	86.75±8.55	89.63±5.2	0.097
30 min	88.05±5.12	85.45±6.89	88.43±5.04	0.045
60 min	86.20±4.67	83.70±8.77	86.55±4.46	0.091
120 min	85.10±4.22	83.63±7.56	85.55±4.1	0.269
240 min	84.35±4.62	83.25±7.29	84.73±4.52	0.478
360 min	83.63±4.95	81.83±3.3	83.43±4.99	0.149
720 min	82.73±4.63	80.63±4.74	82.33±4.90	0.116
1440 min	81.53±4.67	79.75±4.41	81.88±4.86	0.095

In our study, at baseline 0 min Mean MAP was higher in Group A (94.18±3.77) and was lower in Group C (92.59±4.47). In Group B mean MAP was 93.30±4.07 at 0 min. Further it was observed that it showed a decrease at 60 min observation time interval in each group (Group A, Group B and Group C Mean MAP was 83.28±5.71, 82.40±5.28 and 81.74±5.29 respectively) and again showed an increase in mean MAP of all groups. At the final observational time interval at 1440 min mean MAP

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of Group A (91.91±4.09) was higher than mean MAP of Group B (90.93±3.93) and Group C (90.43±4.62). Mean MAP at different time interval among the group showed insignificant correlation in all groups (Group A, Group B, Group C) [Table 4].

Table 4: Distribution on the basis of their Mean Arterial Pressure at different time interval among the group

MAP (mmHg)	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
0 min	94.18±3.77	93.30±4.07	92.59±4.47	0.228
30 min	89.88±4.39	88.90±4.36	88.19±5.08	0.263
60 min	83.28±5.71	82.40±5.28	81.74±5.29	0.450
120 min	85.45±6.05	84.56±4.97	83.86±5.51	0.441
240 min	87.1±5.2	85.12±4.82	85.68±4.56	0.178
360 min	89.74±4.72	88.31±3.51	87.74±4.13	0.089
720 min	90.86±4.09	90.46±4.16	90.82±4.37	0.897
1440 min	91.91±4.09	90.93±3.93	90.43±4.62	0.283

In our study, rescue Analgesia at baseline (mean Time for first analgesic requirement) was higher in Group B (84.98 ±21.85) than Group A and C (p<0.001) [Table 5].

Post-operative Rescue Analgesia (Total Number of Patients requiring rescue analgesic in post-operative) was higher in Group C 14 (35%) followed by Group A 12 (30%) and was lower in Group B 9 (22.5%) (p=0.216) [Table 5].

Table 5: Comparison of time for first analgesic and rescue analgesic in three groups

Rescue Analgesia	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
Time for first analgesic requirement (in minutes)	73.83 ±20.43	84.98 ±21.85	49.9 ± 12.4	<0.001
Total Number of Patients requiring rescue analgesic in post-operative	12 (30%)	9 (22.5%)	14 (35%)	0.216

In the present study, at base line (0 min) Mean Visual Numerical Score (VNS) was high in Group C (3.35±0.95) followed by Group A (0.40±0.49) and Group B (0.15±0.36) (p<0.001) [Table 6].

At 30 min mean Visual Numerical Score (VNS) increased in all three groups.

At the final observational time 1440 min Mean Visual Numerical Score (VNS) decreased with respect to baseline time (0 min) in all groups and was high in Group C (0.15±0.36) followed by Group A (0.03±0.16) (p<0.001) [Table 6].

In the present study, Ramsay Sedation Score (RSS) at different time interval was found to be statistically significant in all groups (p<0.001) [Table 7].

Table 6: Distribution on the basis of their pain score at different time interval among the group

Visual numerical score (VNS)	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
0 min	0.40±0.49	0.15±0.36	3.35±0.95	<0.001
30 min	1.55±0.68	1.30±1.18	3.08±0.99	<0.001
60 min	2.83±0.67	2.65±0.89	2.73±0.93	0.648
120 min	3.05±0.78	2.60±0.93	2.58±1.19	0.056
240 min	2.18±0.90	1.40±0.81	1.60±0.84	<0.001
360 min	1.70±0.61	1.15±0.48	1.0±0.56	<0.001
720 min	0.25±0.49	0.28±0.45	0.45±0.50	0.136
1440 min	0.03±0.16	0.0±0.0	0.15±0.36	0.008

Table 7: Distribution on the basis of their sedation score at different time interval among the group.

Ramsay Sedation Score (RSS)	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
0 min	4.90±0.30	4.55±0.50	0.0±0.0	<0.001
30 min	4.30±0.46	4.25±0.44	0.0±0.0	<0.001
60 min	3.40±0.59	3.35±0.58	0.0±0.0	<0.001
120 min	3.15±0.36	3.15±0.36	0.0±0.0	<0.001
240 min	3.05±0.22	3.08±0.28	0.0±0.0	<0.001
360 min	2.85±0.53	3.0±0.0	0.0±0.0	<0.001
720 min	2.50±0.88	2.85±0.53	0.0±0.0	<0.001
1440 min	1.15±0.53	1.15±0.53	0.0±0.0	<0.001

In our study, majority of patients of Group A had adverse events of hypotension 7 (17.5%) followed by Nausea 4 (10.0), Bradycardia 2 (5.0) and vomiting 1 (2.5). In Group B (40 patients) majority of patients had nausea 4 (10.0) followed by hypotension 3 (7.5) and 1 patient of Bradycardia. In Group C, majority of patients had adverse events of hypotension 11 (27.5%) followed by Nausea 4

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(10.0%), Bradycardia 3 (7.5%) and vomiting 1 (2.5%). However, no statistical significance was obtained on comparing between the groups (p>0.05) [Table 8].

Table 8: Adverse Effects/Complication among groups

Adverse events	Group A (n=40) Tapentadol 50mg	Group B (n=40) Tapentadol 75mg	Group C (n=40) Placebo	p-value
Hypotension	7 (17.5)	3 (7.5)	11 (27.5)	0.063
Bradycardia	2 (5.0)	1 (2.5)	3 (7.5)	0.591
Nausea	4 (10.0)	4 (10.0)	4 (10.0)	0.905
Vomiting	1 (2.5)	0 (0.0)	1 (2.5)	0.601

DISCUSSION

The current study was undertaken to evaluate the Role of Preemptive Tapentadol In Reduction Of Post-operative Analgesic Requirements After the Laparoscopic Cholecystectomy. In context of demographic profile, mean age of Group-A, Group-B, Group C patients was 37.45±10.91, 35.65±11.12, 36.33±10.26 years respectively, difference between them was not significant statistically. Intra-operative hemodynamic parameters showed non-significant correlation among all three groups similarly Kulkarni VR et al observed intraoperative vital parameters which were found to be comparable and statistically non-significant.[13] In our present study time for first rescue Analgesia was recorded lower and was statistically significant in Group-C compared to Group-A & B. The present study documented the intra-operative VNS scores at different observational time intervals (at 0 min, 30 min, 240min and 360 min), significant corelation among the groups was observed. Kulkarni VR et al in their study founded that quality and duration of postoperative analgesia was found to be superior in tapentadol group.[13] In agreement with this literature, they did observe a significant analgesic effect Tapentadol ER significantly reduced average pain intensity versus placebo.[14]

Tapentadol-IR 50 and 75mg and the oxycodone HCl IR 10mg were related with significant decreases in the pain intensity than placebo was observed by Hartrick et al in patients undergoing joint replacement surgery.[15] The more favourable safety, and tolerability profile of the tapentadol than oxycodone was concluded by Cochrane review.[16]

Our study observed significant Ramsay Sedation Score (RSS) at different time intervals, it was higher in Group-B as compared to Group-A which was comparable with Kulkarni VR et al, concluded RSS were similar at all points between the studied groups (Tapentadol & Control).[13]

The synergistic contribution of the noradrenaline reuptake inhibition mechanism to the analgesic effect allows for a reduced μ-opioid load, which is reflected in significantly lower occurrences of the opioid-typical side effects nausea, vomiting, and constipation as shown in randomized controlled trials.[17,18] In our present study hypotension was dominant followed by Nausea and Bradycardia. Lower incidence of nausea is noted in Tapentadol and the duration of these side effects was also shorter, Wild et al found that patients treated by tapentadol-ER 100–250mg BID experienced less vomiting, nausea, pruritus, and constipation than with oxycodone CR (20–50mg).[11,13] Crain SM et al concluded commonest side-effects of tapentadol are nausea (30.0%), dizziness (24.0%), vomiting (18.0%), and somnolence (15.0%).[19]

Limitations of the study

- The limitations of present study include, relatively smaller sample size in proportion to burden of this post-operative morbidity.
- Our results might vary from the studies performed on the other ethnic groups due to variations in the dose requirement, body mass, and subjective analgesic effects with studied drug.
- A dose response study could provide better insight into the preemptive analgesic efficacy and any corresponding increase in side effects by tapentadol.

CONCLUSION

The time for rescue Analgesia at baseline (mean Time for first analgesic need) was higher in patients where 75mg Tapentadol was given. Moreover, the mean VNS Score was also better with the patients received Tapentadol. In the light of above points, our study has drew understanding about pre-emptive analgesic effects of the tapentadol in management of the acute post-operative pain. Our investigation indicates that the tapentadol is appropriate choice as the pre-emptive analgesic having favourable safety profile, although hunt for the ideal combination still continues.

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