

# Role of preemptive tapentadol in reduction of postoperative analgesic requirements after laparoscopic cholecystectomy

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## Abstract

**Background and Aims:** Poorly managed acute postoperative pain may result in prolonged morbidity. Various pharmacotherapies have targeted this, but research on an ideal preemptive analgesic continues, taking into account drug-related side effects. Considering the better tolerability profile of tapentadol, we assessed its role as a preemptive analgesic in the reduction of postoperative analgesic requirements, after laparoscopic cholecystectomy.

**Material and Methods:** In a prospective-double-blinded fashion, sixty patients posted for above surgery, were randomized to receive tablet tapentadol 75 mg (Group A) or starch tablets (Group B) orally, an hour before induction of general anesthesia. Perioperative analgesic requirement, time to first analgesia, pain, and sedation score were compared for first 24 h during the postoperative period and analyzed by one-way analysis of variance test. A  $P < 0.05$  was considered significant.

**Results:** Sixty patients were analyzed. The perioperative analgesic requirement was significantly lower in Group A. Verbal numerical score was significantly lower in Group A at the time point, immediately after shifting the patient to the postanesthesia care unit. Ramsay sedation scores were similar between the groups. No major side effects were observed except for nausea and vomiting in 26 cases (10 in Group A, 16 in Group B).

**Conclusion:** Single preemptive oral dose of tapentadol (75 mg) is effective in reducing perioperative analgesic requirements and acute postoperative pain, without added side effects. It could be an appropriate preemptive analgesic, subjected to future trials concentrating upon its dose-response effects.

**Key words:** Analgesia, cholecystectomy, tapentadol

## Introduction

Among the 70 million surgeries performed worldwide every year, over 80% patients suffer from moderate to severe postoperative pain.<sup>[1,2]</sup> 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. The major limiting factor in postoperative pain management includes our dependence upon opioids as potent analgesics

and their restricted dosing to minimize the associated side effects.<sup>[3]</sup> Preemptive analgesia is a modality that reduces the development of central neuro-sensitization, by providing anti-nociceptive prophylaxis before the onset of surgical pain stimulus, and thereby minimizing postoperative pain.<sup>[4-6]</sup> This technique also reduces the postoperative analgesic requirement and allows for better pain control with minimal side effects.

Various pharmacological regimes have been attempted to achieve the above targets, but the debate on an “ideal preemptive analgesic” continues. Restrictions on drug licensing

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of analgesics together with unavailability of some drugs, further compounds this problem. Tapentadol, a centrally acting analgesic, has a unique mechanism of action, which includes  $\mu$ -opioid receptor agonism, norepinephrine reuptake inhibition, and alpha-2 adrenoceptors activation. Additional benefits include better tolerability profile and increased patient satisfaction. Various trials have shown its efficacy in relieving moderate to severe pain in both acute and chronic settings.<sup>[7,8]</sup> However, its role as a preemptive analgesic is not yet investigated. Thus, the purpose of this study was to assess the preemptive role of tapentadol in reducing postoperative analgesic requirements after laparoscopic cholecystectomy.

## Material and Methods

After ethical approval and written/informed consent, all American Society of Anesthesiologists (ASA) grade I or II patients of either gender, aged > 18 years, body mass index of  $25 \pm 20\%$ , scheduled for elective laparoscopic cholecystectomy, in between July 2013 and June 2014, were selected for this randomized, parallel group, placebo-controlled trial (registered in Indian Clinical Trial Registry No.: CTRI/2014/05/004621). Patients with current history of psychiatric illness, communication difficulties, presently on psychotropic,  $\alpha$ -2 agonists or opioid medications within 28 days before scheduled surgery, any end-organ dysfunction, pregnancy, alcohol abuse, smoking habit, drug abuse, and allergy to opioid were excluded.

A 2-operator technique was employed to maintain blinding. The cases were randomly allocated (computer generated randomization and concealed via sequentially numbered, sealed, opaque envelopes) to two equal groups by an investigator involved in administration of the studied drugs: Group A received tablet tapentadol 75 mg; Group B received identically similar starch tablets, orally with a sip of water 1 h before the scheduled surgery. Further interventions and monitoring were performed by another investigator blinded to group allocation.

Premedication was omitted. In the preoperative ward, all patients were instructed on the proper use of the verbal numerical score (VNS) and Ramsay sedation score (RSS) for assessing pain and sedation. On arrival to the operative room, standard monitors were attached and baseline parameters recorded. General anesthesia was induced with lidocaine (1 mg/kg intravenous [IV]), propofol (2 mg/kg IV), and fentanyl (2  $\mu$ g/kg IV). Supraglottic airway (I-gel) insertion was facilitated with injection vecuronium (0.1 mg/kg IV). Anesthesia was maintained with isoflurane (0.5-2%), and nitrous oxide/oxygen combination (60/40%). Any rise in mean arterial pressure (MAP) of >20% from baseline was treated by administering a bolus dose of fentanyl (1  $\mu$ g/kg IV) and raising the inspiratory

concentration of isoflurane in steps of 0.2%. Any fall in MAP of >20% from baseline was managed by reducing the inspiratory concentration of isoflurane in steps of 0.2%. Target was to maintain MAP within 20% limits of baseline values. The neuromuscular blockade was maintained by vecuronium (0.02 mg/kg IV), as required throughout the surgery. At the end of surgery, the neuromuscular block was antagonized with neostigmine (0.05 mg/kg IV) and glycopyrrolate (0.01 mg/kg IV). I-gel was taken out and patients were transferred to the postanesthesia care unit (PACU), and this time point was considered as "0 h". All patients remained in the PACU for next 24 h and thereafter shifted to the general ward. Primary outcome included the total analgesic requirement during the first 24 h of postoperative period. Acute postoperative pain was assessed using the 11-point VNS on which "0" indicated "no pain" while "10" represented "maximal unbearable pain." The sedation score was assessed using the RSS (1 = anxious or restless, 2 = cooperative and orientated, 3 = responding to commands, 4 = asleep but strong response to stimulus, 5 = sluggish response to stimulus, and 6 = no response to stimulus).<sup>[9]</sup> Data for pain and sedation scores were recorded at 0 h, ½ h, 1 h, 2 h, 4 h, 24 h, postoperatively. For any pain complaints (pain score  $\geq 4$ ), injection paracetamol (1 g, IV) was administered, with the shortest interval of at least 4 h between each dose. Injection tramadol (50 mg, IV) was administered as a rescue analgesic, as per requirement. Time to first postoperative analgesia, the number of patients requiring rescue analgesia, and any possible side effects, were also recorded for the period of stay in PACU.

To detect a 20% difference in the primary outcome among the groups with a standard deviation of 27% estimated from initial pilot observations, with 80% power and 5% alpha error (two-sided), a sample size of 30 per group was required. The sample size was calculated using the power and sample size calculator of Department of Biostatistics, Vanderbilt University, USA. Taking into account a dropout rate of 5% estimated from initial pilot observations, we selected 64 cases (32 in each group) for our study.

Statistical analysis was performed using IBM SPSS statistics for windows, Version 17.0, (IBM Corp, Armonk, NY). The continuous variables were compared using the one-way analysis of variance test. Discrete variables were compared using Fisher's exact test/Chi-square test, whichever was appropriate.  $P < 0.05$  was considered significant.

## Results

In total, 60 candidates were included; 4 cases declined to participate [Figure 1]. Thus, 30 cases in each group

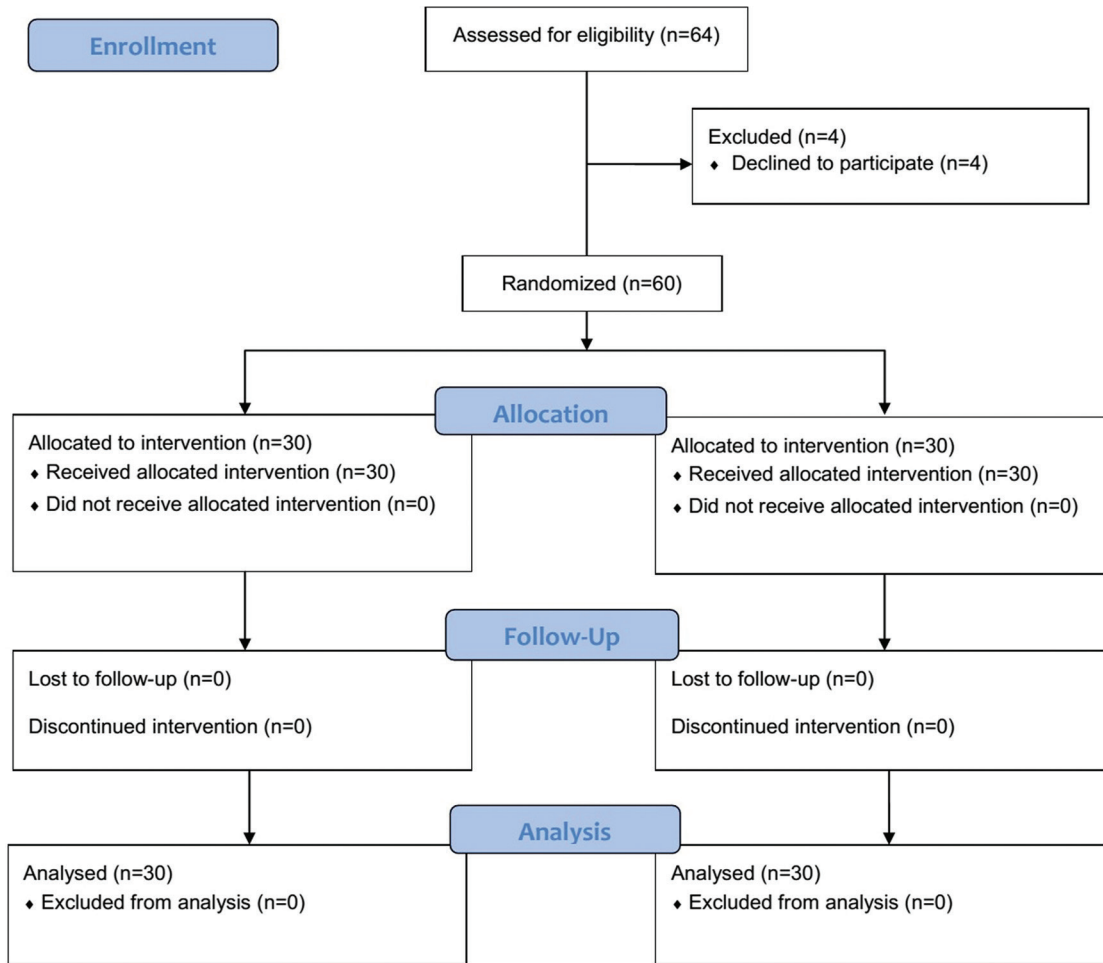


Figure 1: Flow chart of patients studied

completed the study successfully. The study groups were comparable in terms of demographic profile, ASA health status; IV fluid infused, estimated blood loss, and the duration of surgery. Intraoperative isoflurane and fentanyl requirement in Group A was significantly lower than Group B ( $P < 0.001$ ,  $P = 0.03$ , respectively) [Table 1].

The time to first analgesia in PACU was significantly longer in Group A as compared to Group B ( $P < 0.001$ ). Number of patients requiring rescue analgesia, and the total dose requirement of paracetamol and tramadol was significantly lower in Group A than that in Group B [Table 2]. The VNS was statistically lower in Group A as compared to Group B at “0 h” point (insignificant afterward), assessed in the PACU after surgery ( $P < 0.001$ ) [Figure 2]. RSS were similar at all data points between the studied groups [Figure 3]. None of the patients developed any major postoperative complication except for nausea and vomiting in 26 cases (10 in Group A; 16 in Group B), managed successfully by ondansetron (8 mg IV).

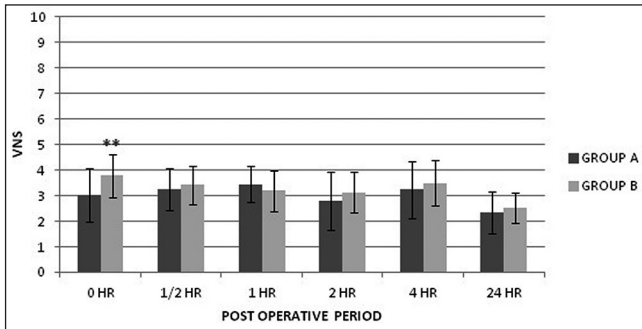
Table 1: Comparison of demographic and intra-operative parameters among the groups

Parameters	Group A (n = 30)	Group B (n = 30)	P
Age (years)	38.0±12.6	39.3±11.2	0.66
Sex distribution - male (%)	13/3 (43.3)	14/3 (46.7)	0.79
Intra-operative parameters			
Duration of anesthesia (min)	72.0±26.3	78.5±23.9	0.37
Fentanyl (µg)	115.6±21.8	129.0±28.2	0.03
Average isoflurane (%)	0.7±0.1	1.0±0.2	<0.001
IV fluid (mL)	857.5±126.5	896.3±101.5	0.18
Estimated blood loss (mL)	54.7±14.0	49.4±15.8	0.13

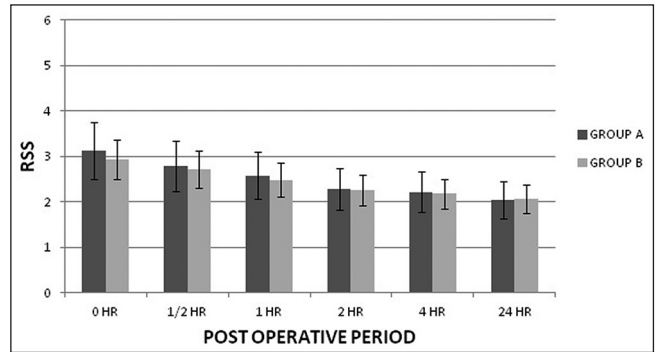
Data are expressed as mean ± SD or numbers, A  $P < 0.05$  was considered significant, SD = Standard deviation, IV = Intravenous

## Discussion

This study indicates a significant role of tapentadol as a preemptive analgesic in reducing postoperative pain scores and the corresponding analgesic requirement during the first 24 h of observation, after laparoscopic cholecystectomy. Tapentadol, though a weak  $\mu$ -opioid agonist, provides highly



**Figure 2:** Comparison of postoperative pain scores between the groups. Data expressed as mean ± standard deviation  $P < 0.05$  considered significant ( $*P < 0.05$ ,  $**P < 0.001$ ). Group A = Tapentadol group, Group B = Control group, VNS = Verbal numerical score



**Figure 3:** Comparison of postoperative sedation scores between the groups. Data expressed as mean ± standard deviation. Group A = Tapentadol group, Group B = Control group, RSS = Ramsay sedation score

**Table 2: Comparison of postoperative parameters among the groups**

Parameters	Group A (n = 30)	Group B (n = 30)	P
Time to first analgesia in PACU	96.5 ± 22.5	16.9 ± 7.0	<0.001
Paracetamol injection (g) POD1	2.7 ± 0.4	3.1 ± 1.1	0.01
Tramadol injection (mg) POD1	13.3 ± 22.5	33.3 ± 33.0	0.008
Patients requiring rescue analgesia (%)	8/3 (26.6)	17/3 (56.7)	0.01
Side effects			
Nausea and vomiting	10	16	0.11

Data are expressed as mean ± SD or n (%), A  $P < 0.05$  was considered significant, PACU = Postanesthesia care unit, POD = Postoperative day, SD = Standard deviation

effective analgesia equivalent to one-third of that observed with equianalgesic dosage of morphine. Its selective norepinephrine reuptake inhibition and alpha-2-adrenoceptor agonism inhibits the pain transmission through dorsal horn neurons, by modulating spinal interneurons, and descending inhibitory fibers from periaqueductal gray matter and rostral ventromedial medulla.<sup>[10,11]</sup> Several advantages over tramadol include its action as a single enantiomer, with a time-dependent parallel change in opioid and monoaminergic receptor dynamics, potentiating its analgesic activity under minimal adverse effects. Though, lack of action on CYP450 receptors could negatively affect its analgesic activity.<sup>[12]</sup>

Postoperative pain after laparoscopic surgery is primarily due to visceral injury by intraoperative electrocauterization or a result of gaseous distension of parietal peritoneum by the infused carbon dioxide.<sup>[13]</sup> Electrophysiology tests on various animal models indicate the specificity of tapentadol for selective inhibition of mechanical and thermal noxious stimuli.<sup>[14]</sup> This could have contributed to augmented decrease in the postoperative analgesic requirement by preemptive tapentadol, administered as per protocol of our study.

The analgesic efficacy of tapentadol has been investigated over a dose range of 50-200 mg.<sup>[7,8,10,11]</sup> Kleinert *et al*

showed that single oral dose of tapentadol 75 mg or higher efficiently reduces moderate-to-severe postoperative dental pain in a dose-related fashion and are well-tolerated relative to morphine.<sup>[7]</sup> However, a recent report of cardiovascular abnormalities after intake of tapentadol (100 mg, single dose) raised the need for a dose-response study to evaluate the safety and efficacy profile of tapentadol.<sup>[15]</sup> While the usual initiating dose of tapentadol is reported as 50-75 mg, higher doses are currently considered for patients having opioid tolerance or severe pain.<sup>[10]</sup> As the severity of postoperative pain is lower in patients operated by laparoscopic technique, we preferred a dose of 75 mg tapentadol as a preemptive analgesic, to minimize any side effects. After oral administration, tapentadol is absorbed rapidly and completely with a peak plasma concentration achieved within 1.25-1.5 h, and an elimination half-life of about 4.5 h.<sup>[16,17]</sup> We chose to administer the studied drug an hour before the scheduled surgery, to envelop the time point of maximal pain stimulus for the period of the surgical procedure. This is evident by reduced dose requirement of intraoperative isoflurane, fentanyl, and postoperative analgesics (paracetamol and tramadol) in the tapentadol group. Though, a reflection of the weak antimuscarinic activity of tapentadol might have been masked under the utilized methodology.

Several researchers have evaluated the role of tapentadol as a postoperative analgesic. Daniel *et al.* observed a significant improvement in postoperative pain scores by administering it in patients following bunionectomy surgery.<sup>[18]</sup> A similar decrease in postoperative VNS scores was observed by Hartrick *et al* in patients undergoing joint replacement surgery.<sup>[19]</sup> We also observed a similar reduction in the postoperative VNS (at “0” time point) by tapentadol; albeit administered as a preemptive analgesic. Higher postoperative analgesic requirement in the placebo group could have resulted in adequate pain control, noticed as insignificant differences in VNS at other time points between the compared groups.

Observed side effect included postoperative nausea and vomiting in both the groups; no such episodes occurred preoperatively. Thus, above complication was possibly a consequence of laparoscopic surgery or rescue analgesic (tramadol) rather than a side effect of tapentadol. Furthermore, the lower affinity of tapentadol for  $\mu$ -opioid receptors could have resulted in better gastrointestinal tolerability in this group.<sup>[7,10,11]</sup> Besides this, no ST-segment changes were observed in any of the patients, and vital parameters remained stable for the period of observation. This underscores the good tolerability profile of preemptive tapentadol, although we acknowledge that our study was not powered to access this secondary outcome.

The limitations of our study include a relatively small sample size in proportion to the burden of this postoperative morbidity. Our results may vary from studies done on other ethnic groups owing to variations in body mass, dose requirement, and the 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. Future trails could investigate these aspects or utilize multimodal drug approach for preemptive analgesia.

## Conclusion

Our study has outlined an understanding about the preemptive analgesic effects of tapentadol in the management of acute postoperative pain. Our investigation indicates that tapentadol is an appropriate choice as a preemptive analgesic having favorable safety profile, although the hunt for an ideal combination still continues.

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## Conflict of interest

There are no conflicts of interest.

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