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RESEARCH

Effect of ondansetron on the analgesic efficacy of tramadol used for postoperative analgesia: a randomised controlled study

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Background: Ondansetron is used to reduce tramadol induced postoperative nausea and vomiting (PONV). Studies on patient-controlled analgesia (PCA) found that ondansetron reduces the analgesic efficacy of tramadol. Drug requirement in PCA and in conventional intravenous analgesia without PCA device may differ. This study evaluated the effect of ondansetron on analgesic efficacy of tramadol for postoperative analgesia without a PCA device.
Methods: A prospective, randomised, placebo-controlled, double-blind parallel group study was conducted on 126 euthyroid patients of ASA I and II, aged between 30 and 65 years undergoing hemithyroidectomy under general anaesthesia. Patients were divided into group O and group C. At the time of closure of strap muscles, patients in group O received tramadol 1.5 mg/kg IV and ondansetron 0.1 mg/kg (diluted to 4 ml) IV and those in group C received tramadol 1.5 mg/kg IV and normal saline 4 ml IV. Duration of analgesia, pain score (VAS), PONV and sedation scores were analysed.
Results: Duration of analgesia was longer in group C compared with group O (164.1 min vs. 76.3 min, $p < 0.05$). Postoperative VAS score was higher in group O ($p < 0.001$). Group C showed higher PONV and sedation score.
Conclusion: Ondansetron reduces the duration and quality of analgesia of tramadol administered conventionally without a PCA device.

Keywords: ondansetron, pain, postoperative nausea and vomiting, sedation, tramadol

Introduction

Adequate postoperative pain management is of utmost importance in anaesthesia practice. Good postoperative analgesia results in quicker resumption of normal pulmonary function, early ambulation, shortened hospital stay and reduced hospital cost. Tramadol, a moderately potent partial opioid agonist, is commonly used for intraoperative as well as postoperative analgesia. However, its use has been associated with a higher incidence of postoperative nausea and vomiting (PONV).[1] For this reason, the antiemetic ondansetron is often co-administered. Some studies[2–5] on patient-controlled analgesia (PCA) have found that the analgesic efficacy of tramadol was reduced by concurrent administration of ondansetron. Conversely, few studies[6,7] showed no reduction of analgesic efficacy of tramadol when ondansetron was co-administered. Drug requirement in PCA and in conventional intravenous opioid analgesia without using a PCA device may differ,[8] but studies evaluating the effect of ondansetron on conventionally delivered tramadol are lacking. Hence, we conducted this study to evaluate the effect of intravenous ondansetron on the analgesic efficacy of intravenous tramadol administered conventionally without a PCA device for postoperative analgesia.

Methodology

This prospective, randomised, placebo-controlled, double-blind parallel group study was conducted at IPGME&R, Kolkata after receiving approval from the Institutional Ethical Committee. Euthyroid patients belonging to ASA physical status I and II, aged between 30 and 65 years and undergoing hemithyroidectomy under general anaesthesia, were included in the study. Patients with severe cardiovascular, pulmonary, hepatic, renal and neurological diseases (ASA Grade III and IV), with anticipated difficult airway, with hypothyroidism or hyperthyroidism, with known hypersensitivity to study drugs, with a history of alcohol or drug abuse, morbidly obese, pregnant and lactating patients and those receiving monoamine oxidase inhibitors, study drugs or any other antiemetic medication within 24 hours were excluded from the study.

Sample-size calculation was done using the PS Power and Sample Size Calculations (Version 2.1.30, February 2003; Department of Biostastics, Vanderbilt University, Nashville, TN, USA). The time duration between the intraoperative injection of tramadol and the requirement for rescue analgesia in the postoperative period was taken as the primary study parameter. A pilot study was done on 10 patients undergoing surgery under general anaesthesia to obtain the mean and standard deviation values for the time of requirement of rescue analgesic in the postoperative period. It was calculated that to accept or reject the null hypothesis with a power of 80% and a 5% probability of type I error, 63 patients were required per group in order to detect a time difference of 30 minutes between the groups, this calculation assume a standard deviation of 45 minutes for the primary outcome measure.

Complete pre-anaesthetic evaluation was performed in each patient including detailed history-taking, thorough physical examination including airway examination and routine preoperative investigations including complete haemogram, serum urea, creatinine, fasting & post-prandial blood sugar, thyroid profile, chest X-ray PA view and electrocardiogram (ECG).

Written informed consent was taken from each patient. All patients received oral alprazolam 0.5 mg the night before surgery. Peripheral intravenous access was secured with an 18-G IV cannula in a forearm vein. Standard intraoperative monitoring

was applied including pulse rate, non-invasive blood pressure, oxygen saturation (SpO_2) capnography and ECG. All patients received glycopyrrolate 0.2 mg IV 30 minutes preoperatively and fentanyl 2mcg/kg IV 5 minutes before induction of anaesthesia. After proper pre-oxygenation, anaesthesia was induced with thiopentone sodium 5 mg/kg IV. Tracheal intubation was done with a PVC cuffed endotracheal tube of appropriate size after achieving adequate relaxation with vecuronium 0.1 mg/kg IV. Anaesthesia was maintained with 66% nitrous oxide, 33% oxygen, isoflurane 0.9–1% and vecuronium 0.02 mg/kg IV. All patients received diclofenac 75 mg IV infusion at the time of surgical incision. Boluses of fentanyl IV were given to the patients requiring further intraoperative analgesia and these patients were dropped from the study.

The study population was randomly divided into two groups, group O and group C, with the help of a computer-generated random-number list. At the time of closure of the strap muscles, patients in group O ($n = 63$) received tramadol 1.5 mg/kg IV and ondansetron 0.1 mg/kg (diluted to 4 ml) IV and those in group C ($n = 63$) received tramadol 1.5 mg/kg IV and normal saline 4 ml IV. Residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg IV and glycopyrrolate 0.01 mg/kg IV. Patients were extubated after fulfilling the criteria for adequate reversal.

Pain was evaluated using a visual analogue scale (VAS) where 0 represents no pain and 10 represents the worst imaginable pain. PONV[9] and degree of sedation[3] were assessed postoperatively by a four-point ordinal scale (Table 1).

Rescue analgesic was given in the form of paracetamol 1 g IV when VAS score was >3. This was the primary end point of the study. The time duration between administration of intraoperative tramadol and rescue analgesic was noted and compared between two groups. VAS score, PONV score, degree of sedation, heart rate, blood pressure, respiratory rate and oxygen saturation were evaluated at an interval of 30 minutes until the patient received rescue analgesia.

Table 1: Scoring criteria for PONV and sedation

Condition	Scoring criteria
PONV	0 = No nausea or vomiting
	1 = Nausea, no vomiting
	2 = Vomiting
	3 = Persistent vomiting
Sedation	0 = Patient fully awake
	1 = Patient slightly drowsy
	2 = Patient sleeping but easily arousable
	3 = Patient unconscious, not arousable

Patients with a PONV score of 3 were treated with metoclopramide 10 mg IV as a rescue antiemetic and were dropped from the study. Any adverse event in the first 24 hours postoperatively was also recorded.

The time duration between the intraoperative injection of tramadol and the requirement for rescue analgesia in the postoperative period was considered as the primaryoutcome. The VAS score in the postoperative period in the two groups was taken as the secondary outcome.

Statistical analysis was done using the software Statistica version 6 (StatSoft Inc., Tulsa, OK, USA, 2001). Comparison of parametric data was done by Student's unpaired *t*-test. Nonparametric data were compared between two groups with the Mann–Whitney U test. Degree of sedation was compared with a chi-square test. A *p*-value of <0.05 was considered statistically significant.

Results

Three patients in group O and two patients in group C required additional fentanyl for intraoperative analgesia. Two patients in group C required metoclopramide as rescue antiemetic in the postoperative period. One patient in group O needed urgent re-exploration of the wound postoperatively due to a haematoma. All these patients were excluded from the study. Finally, 126 patients (63 patients in each group) were included for statistical analysis.

The groups were comparable in terms of demographic profile, duration of surgery and dose of tramadol administered intraoperatively (Table 2).

Duration of analgesia was longer in the control group in comparison with the study group. Figure 1 shows a statistically significant time difference between intraoperative tramadol administration and postoperative rescue analgesia requirement in group C compared with group O (*p*-value < 0.05), with group C reporting longer analgesia.

Table 3 shows statistically significant higher VAS score in the immediate postoperative period and after 30 and 60 minutes in group O compared with group C (Table 3).

In comparison with group O, group C showed (Table 4) a higher PONV score in the immediate postoperative period and after 30 and 60 minutes.

The sedation score in the immediate postoperative period was higher in group C compared with group O (Table 5).

Table 2: Demographic profile and operative details

Factor	Group O ($n = 63$) (Mean ± SD)	Group C ($n = 63$) (Mean ± SD)	*p*-value
Age (years)	41.3 ± 8.90	42.4 ± 9.78	>0.05
Sex (M:F)	19:44	13:50	>0.05
Bodyweight (kg)	56.4 ±. 6.87	58.3 ± 5.13	>0.05
ASA class (I/II)	50/13	52/11	>0.05
Duration of surgery (minutes)	129.92 ± 19.25	131.75 ± 20.06	>0.05
Dose of tramadol given intraoperatively (mg)	84.6 ± 10.30	87.4 ± 7.70	>0.05

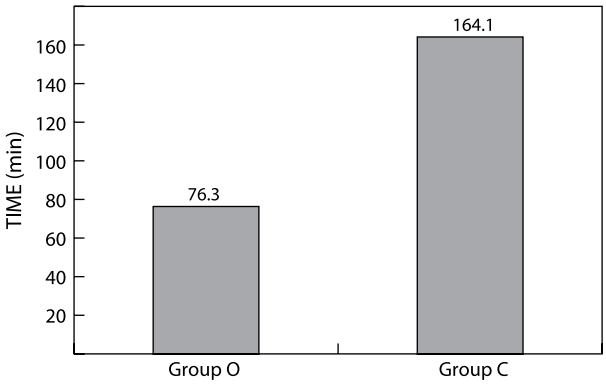

Figure 1: Time duration (minutes) between intraoperative tramadol administration and postoperative rescue analgesic requirement.

found between the two groups in respect of other postoperative monitoring parameters.

Discussion

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine.[10] It is a centrally acting analgesic which shows moderate affinity for μ receptors and weak affinity for κ and δ opioid receptors.[11] It also exerts analgesic effect by inhibiting serotonin and norepinephrine reuptake thereby blocking the nociceptive impulses at the spinal level.[10] In the liver, tramadol undergoes O-demethylation, mediated by an isoenzyme CYP2D6 to form an active metabolite, O-demethyl tramadol (M1derivative). This metabolite exhibits higher affinity for μ receptors than the parent drug.[10] Tramadol is frequently used for intraoperative as well as postoperative analgesia. However, its use is associated with a

Table 3: Postoperative VAS score

Postoperative VAS	Group O (*n* = 63) (Mean ± SD)	Group C (*n* = 63) (Mean ± SD)	*p*-value
At 0 minutes	0.86 ± 0.82	0.35 ± 0.54	<0.001
At 30 minutes	1.44 ± 0.99	0.43 ± 0.56	<0.001
At 60 minutes	2.51 ± 0.66	1.16 ± 0.68	<0.001

Table 4: Postoperative PONV score

Factor	Group O (*n* = 63) (Mean ± SD)	Group C (*n* = 63) (Mean ± SD)	*p*-value
Postoperative PONV score at 0 minutes	0.06 ± 0.24	0.73 ± 0.74	< 0.001
Postoperative PONV score at 30 minutes	0.03 ± 0.18	0.44 ± 0.53	< 0.001
Postoperative PONV score at 60 minutes	0.09 ± 0.35	0.25 ± 0.47	< 0.05

Table 5: Postoperative sedation score

Degree of sedation in postoperative period	Group O (*n* = 63)			Group C (*n* = 63)		
	At 0 min	At 30 min	At 60 min	At 0 min	At 30 min	At 60 min
0	41	55	57	5	53	56
1	14	7	6	32	10	7
2	8	1	0	26	0	0
3	0	0	0	0	0	0

Note: *p*-value < 0.001 at 0 minutes.

Table 6: Postoperative monitoring parameters

Factor	Group O (*n* = 63) (Mean ± SD)	Group C (*n* = 63) (Mean ± SD)	*p*-value
Heart rate (per minute)	83.9 ± 7.23	79.7 ± 7.03	< 0.05
SBP (mm Hg)	126.8 ± 8.29	127.6 ± 6.67	> 0.05
DBP (mm Hg)	80.8 ± 6.92	81.7 ± 6.83	> 0.05
SpO_2 (%)	98.5 ± 0.72	98.5 ± 0.80	> 0.05
Respiratory rate (per minute)	12.6 ± 0.91	12.4 ± 0.82	> 0.05

In the postoperative period, heart rate, blood pressure, respiratory rate and oxygen saturation remained within the clinical range (Table 6). Postoperative heart rate was significantly higher in group O compared with group C. No difference was

higher incidence of PONV.[12] Ondansetron is a highly selective $5HT_3$ receptor antagonist that is an effective agent in reducing PONV.[1] It reduces PONV by blocking 5-HT3 receptors centrally at the area postrema and peripherally at vagus nerve terminals.[13]

Previous studies[2–5] on PCA found that ondansetron reduces the analgesic efficacy of tramadol. A few studies also showed contradictory results.[6,7] However, most of the previous studies used a PCA device for drug administration. Controversy exists regarding the total amount of opioid requirement with a PCA device and the conventional method of opioid analgesia without a PCA device. Studies have produced conflicting results; some authors[14–16] reported significantly higher opioid use with a PCA, some[17–19] concluded significantly higher use with conventional methods. A few studies[20,21] found no difference between the two groups. There may be a number of reasons for a high demand rate other than pain, including anxiety, patient confusion and inappropriate patient use.[8] Patients may press the button of a PCA device in anticipation of pain, particularly during movement.[22] Conversely, patients may be reluctant to use this device due to fear of addiction and drug overdose.[23] Previous literature also revealed its doubtful efficacy for evaluation of pain.[22] Moreover, a PCA device is expensive and its use may not be possible in young children, patients with altered sensorium, psychological disturbances and during equipment malfunction.[8]

We evaluated the effect of ondansetron on conventional tramadol administration in a bolus dose for postoperative analgesia without the use of a PCA pump. The duration of analgesia following a bolus dose of tramadol was significantly longer in group C compared with group O (76.3 versus 164.4 minutes, $p < 0.001$). Postoperative VAS score was also significantly higher in group O compared with group C. The slightly lower heart rate in group C in the postoperative period may also be indicative of better analgesia. Tramadol causes increased release of serotonin, which affects nociception through $5HT_{1A\text{-}D}$, $5HT_{2A\text{-}C}$, $5HT_3$ and $5HT_4$ receptors.[3] Thus, the analgesic effect of tramadol mediated by release of serotonin can be attenuated by concurrent administration of ondansetron, which is a $5HT_3$ receptor antagonist. There is also a possibility of pharmacokinetic interaction. Ondansetron is partly metabolised by the CYP2D6 iso-enzyme, which is also responsible for formation of an active metabolite of tramadol, O-demethyl tramadol, which exerts an analgesic effect by binding to the μ receptor.[24] The analgesic action of tramadol may be reduced due to decreased formation of the active metabolite as the enzyme responsible for its metabolism also takes part in the metabolism of ondansetron.

In this study, PONV score was found to be less in group O ($p < 0.001$). Arcioni et al.[3] and Hammonds et al.[24] reported contradictory results. The higher vomiting score in the study conducted by Arcioni et al.[3]may be due to higher consumption of tramadol as a continuous background infusion of tramadol was used. A study conducted by De Witte et al.[2] found no difference in the PONV score. However, Rauers et al.[7] reported less vomiting in patients given tramadol who received ondansetron when compared with a placebo.

In the immediate postoperative period, the sedation score was significantly less in group O compared with group C (p-value < 0.001). This may be due to lower production of M1 metabolites in group O as the same isoenzyme, CYP2D6, is needed for metabolism of ondansetron and tramadol. This M1 metabolite is responsible for tramadol-induced sedation.[25] The low sedation score in group O may also be due to the poorer quality of analgesia. Previous studies using a PCA device did not find any significant difference in the sedation score; however, these findings may differ from the findings of our study because patients using a PCA device remain more sleepy.[22]

In summary, administration of ondansetron with tramadol is better avoided due to the potential for reduction in the analgesic effect of tramadol. Consideration should be given to using an alternative antiemetic like metoclopramide in the presence of tramadol to reduce the incidence of PONV.[26] Randomised controlled studies evaluating the effect of granisetron, tropisetron and palanosetron on the analgesic efficacy of tramadol are lacking. Further studies may be conducted in this field. In future, similar studies may be conducted using different doses of tramadol and ondansetron.

Conclusion

Administration of ondansetron with tramadol is better avoided as it reduces the duration and quality of analgesia with tramadol administered conventionally without using a PCA device.

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