Research Article

Comparision of Analgesic Efficacy of Tramadol Infusion Versus Tramadol Plus Ondansetron Infusion In Medical Intensive Care Unit

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Abstract

Background: Tramadol, a preferred analgesic due to its less respiratory depression. It also has a central action that blocks the reuptake and enhances the release of serotonin at spinal antinociceptive pathways. Ondansetron, an antiemetic is a serotonin receptor antagonist. Due to the contradictory actions of the two drugs, co-administration of these drugs resulted in higher usage of tramadol. All these studies were done in the postoperative period. **Aim:** The aim of this study is to evaluate the analgesic efficacy of tramadol infusion versus tramadol plus ondansetron infusion in Medical Intensive Care Unit (ICU) patients. **Materials and Methods:** After Institutional Ethical Committee approval, 50 patients who experience pain other than postoperative pain were enrolled and randomized into two groups. Both the groups initially received 50 mg of tramadol intravenously over 10 min followed by Group T+O received 10 mg/h tramadol + 0.4 mg/h ondansetron as an infusion. Group T received 10 mg/h tramadol as infusion. Hemodynamic parameters along with pain assessment using Verbal Rating Scale (VRS) were analyzed at 0, 3, 6, 12, and 24 h. Rescue analgesia was administered if VRS >4. Side effects were noted by condition scoring criteria (CSC) scale. **Results:** Rescue analgesia was administered at 3 h, for three patients in T+O Group and 1 patient in T Group, but this is not statistically significant ($P = 0.153$). No rescue analgesia was required in both the groups at any other point of time. There was fall in heart rate, systolic and diastolic blood pressures, respiratory rate at 0, 3, 6, 12, and 24 h in both the groups but not statistically significant. Grade 1 sedation of CSC scale was observed in two patients of Group T+O and one patient in Group T but not statistically significant ($P = 0.153$). No nausea and vomiting were seen. **Conclusions:** We conclude that co-administration of tramadol and ondansetron can be practiced in medical ICU patients without any higher requirement in dosage of tramadol.

Keywords: Analgesia, ondansetron, tramadol

Introduction

Tramadol is one of the commonly preferred analgesics due to its less incidence of respiratory depression.[1,2] It is an opioid analgesic that not only acts as the mu opioid receptor agonist for its analgesic action but also has a central analgesic action that blocks the reuptake and enhances the release of serotonin at spinal antinociceptive pathways.[3-5] Ondansetron is a serotonin 5-HT3 receptor antagonist. Its usage as an antiemetic in the postoperative period, chemotherapy drugs, radiation therapy is well established.[6]

Due to the contradictory actions of tramadol and ondansetron on serotonin receptors, few earlier studies stated coadministration of ondansetron along with tramadol decreased the analgesic efficacy of tramadol, and there was a higher requirement of tramadol.[7,8] On the contrary, there were also studies stating that coadministration of these drugs neither increased analgesic consumption nor emesis.[9] Neither of these studies was conducted in medical intensive care patients.

We conducted a randomized prospective study in Medical Intensive Care Unit (ICU) whether there is decreased analgesic

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efficacy of tramadol when co-administered with ondansetron. We have also observed for any other side effects such as nausea, vomiting, and sedation.

Aim of the study

The aim is to evaluate the analgesic efficacy of tramadol infusion versus tramadol plus ondansetron infusion and any side effects.

Materials and Methods

After taking approval from the Institutional Ethics Committee, we conducted a randomized prospective study in our medical ICU enrolling 50 patients after obtaining an informed consent who are experiencing pain other than postoperative pain. Patients were divided into two groups 25 of each.

Group T+O received 50 mg of injection tramadol slow intravenously over 10 min followed by 10 mg/h tramadol +0.4 mg/h ondansetron as an infusion.

Group T received 50 mg of injection tramadol slow intravenously over 10 min followed by 10 mg/h tramadol as an infusion.

Inclusion criteria

- Age: 18–70 years.

Exclusion criteria

- Age <18 years
- Pregnant patients, lactating patients
- Known seizure disorder increased intracranial pressure
- Patient on antidepressants
- Patient with substance abuse
- Renal or hepatic impairment patients
- Postoperative patients
- Mechanically ventilated patients
- Known allergic to tramadol or ondansetron.

Hemodynamic parameters along with pain assessment using Verbal Rating Scale (VRS) ranging from 0 to 10 were analyzed in both the groups at 0, 3, 6, 12, and 24 h. At any time if VRS >4, rescue analgesic in the form of paracetamol 1 g intravenously was supplemented. Side effects such as nausea, vomiting, and degree of sedation were assessed by a four-point ordinal scale [Table 1]. Data were analyzed using SPSS 24.0 IBM Analytic software [SPSS Inc.,Chicago, Illinois, USA]. We used unpaired *t*-test to know the difference between two groups.

Results

Fifty patients with various organ involvements requiring analgesia were enrolled into the study [Table 2]. Both the groups were demographically comparable [Table 3].

At 3 h, 3 patients in T+O Group and 1 patient in T Group required rescue analgesia, but this is not statistically significant (P = 0.153) [Figure 1]. No rescue analgesia was required among the groups at any other point in time as their VRS among the groups were never >4 [Table 4 and Figure 2].

Table 1: Scoring for nausea, vomiting, and sedation

	Condition scoring criteria
Nausea	0 -No nausea
	1 - Mild nausea, not requesting pharmacological rescue
	2 - Nausea, requesting pharmacological rescue
	3 - Nausea resistant to pharmacological treatment
Vomiting	0 - No vomiting
	1 - Vomiting, single event
	2 - Vomiting, repeated events requesting pharmacological rescue
	3 - Vomiting resistant to pharmacological treatment
Sedations	0 - Patient fully awake
	1 - Patient slightly drowsy
	2 - Patient sleeping but easily arousable
	3 - Patient unconscious, not arousable

Table 2: Number of patients based on disease system involved

Disease	Number of cases in percentage
Acute pancreatitis	17 (34%)
Pulmonary - pneumonitis	12 (24%)
Polytrauma	9 (18%)
Carcinomas	12 (24%)

Table 3: Demographic profiles

Factor	Group T + O	Group T	*P*
Age (years) mean±SD	44.2±9.88	44.72±8.97	0.470
Sex (M:F)	11/14	15/10	0.257

Table 4: Mean VRS variation among the groups

Hours	VRS mean±SD		*P*
	T + O	T	
0	9.96±0.2	9.84±0.37	0.8187
3	2.68±1.21	2.4±0.81	0.1718
6	1.68±0.62	1.64±0.56	0.4071
12	1.16±0.62	1.08±0.27	0.2804
24	1.08±0.57	1±0.5	0.3004
48	0.96±0.61	0.84±0.47	0.2205

Among the groups, there was fall in heart rate, systolic blood pressures, diastolic blood pressures, respiratory rate at 0, 3, 6, 12, and 24 h but no statistical significance was seen [Tables 5 and 6].

No nausea and vomiting were observed among the groups at any period. Grade 1 sedation condition scoring criteria (CSC) was observed in 2 patients of Group T+O and 1 patient in Group T, but this is not statistically significant (P = 0.153).

Discussion

Tramadol, a synthetic 4-phenyl-piperidine analog of codeine exerts its analgesic effect by possessing moderate affinity at

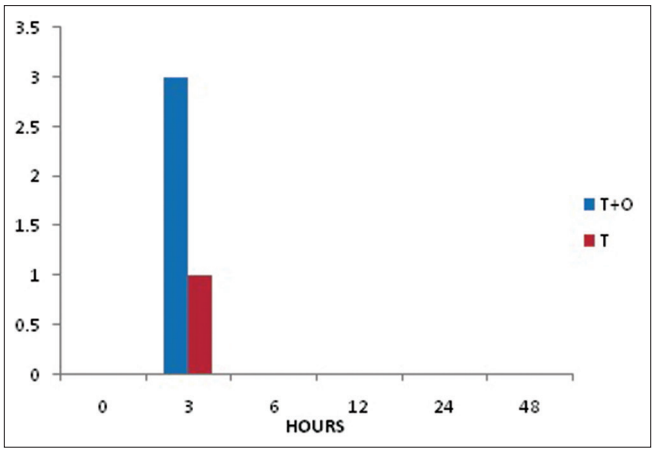

Figure 1: Rescue analgesia requirement

Table 5: Mean Heart rate and respiratory rate variations in both groups

Hours	Heart rate mean±SD		*P*	Respiratory rate mean±SD	
	T + O	T		T + O	T
0	104.32±3.90	104.28±4.16	0.4861	29.36±1.15	29±1.52
3	94.4±3.34	93.04±3.20	0.07431	25.64±1.22	24.96±1.96
6	88.04±2.96	87.04±2.82	0.11387	21.76±1.64	21.32±1.62
12	82.68±2.39	82.36±2.95	0.33793	18.52±1.12	18.4±1.70
24	79.56±1.26	79.36±3.21	0.38664	16.72±0.89	16.64±0.75
48	79.6±1.55	79±1.73	0.10179	16.32±0.85	16.24±0.92

Table 6: Mean SBP and DBP variations in both groups

Hours	SBP Mean±SD		*P*	DBP Mean±SD	
	T + O	T		T + O	T
0	154±6.58	152.56±10.99	0.2883	89.92±3.53	87.92±7.15
3	125.52±4.51	125.04±5.60	0.3701	80.24±2.10	78.68±5.49
6	123.12±4.16	123.04±5.03	0.4753	78.48±1.55	76.88±5.50
12	121.52±3.01	121.44±3.97	0.4684	78±1.63	76.16±5.71
24	120.24±1.73	120.08±4.37	0.4329	77.76±2.25	76.56±5.95
48	119.84±1.72	119.76±2.90	0.4532	77.44±2.32	76.48±3.42

receptor and a weak affinity at κ and δ opioid receptors.[10,11] Recent studies also stated a central analgesic action of tramadol at spinal level by inhibiting serotonin and nor epinephrine reuptake and blocks nociceptive impulses.[10] Tramadol is metabolized in the liver by demethylation to an active metabolite O-demethyl tramadol, mediated by an isoenzyme CYP2D6 of cytochrome P450. This active metabolite possess a higher affinity for μ receptors.[10] Higher plasma levels of tramadol are seen in individuals who carry two inactive copies of CYP2D6 and are known as poor metabolizers. Intermediate metabolizers are people who carry one or more inactive copies, and ultra-rapid metabolizers are people who carry more than two active copies of CYP2D6.[12]

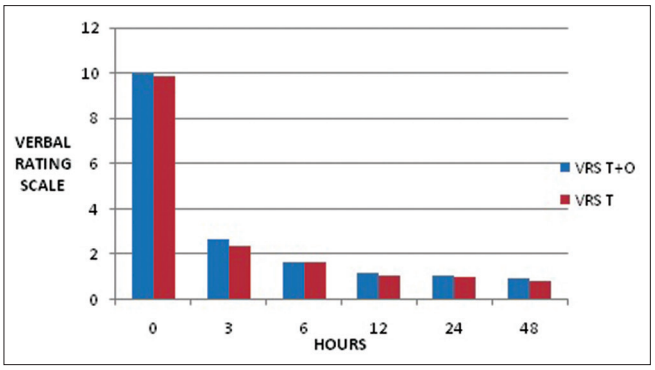

Figure 2: Mean verbal rating scale variation among the group

Ondansetron, a serotonin 5-HT3 receptor antagonist exerts its antiemetic property by blockage of chemoreceptor trigger zone and enteric neuron 5hydroxytryptamine-3 (5HT3) receptors. Similar receptors are present on nociceptive primary afferent fibers not only on peripheral free terminal but also centrally on the spinal terminal, and these receptors are also present on neurons of the dorsal horn.[13,14] According to Ye *et al*., ondansetron has an anti-nociceptive effect similar to local anesthetics by blocking sodium channels.[15] Peripheral 5HT3 receptors, by binding to the opioid receptor are responsible for this anti-nociceptive action.[16] Cui *et al*. stated that there could be the release of 5-HT in dorsal horns of the spinal cord by stimulation of periaqueductal gray matter and results in inhibition of nociception of dorsal horn neurons.[17] These statements prove that serotonin has a role in nociceptive pathways.

Studies compared tramadol as an analgesic in the postoperative period with either oral or intravenous intermittent boluses versus infusion and concluded infusion of tramadol was efficacious than oral or intravenous intermittent boluses as an analgesic.[18,19]

On the postoperative period, co-administration of ondansetron with tramadol by patient-controlled analgesia resulted in the decreased analgesic effect of tramadol probably due to blocking of 5-HT3 spinal receptors.[7] Another study also in postoperative period by patient-controlled analgesia and stated ondansetron acutely decreases the analgesic efficacy of tramadol in humans.[8]

A study stated coadministration of ondansetron neither increased tramadol consumption nor frequency of postoperative nausea and vomiting in the postoperative setting. Whereas plasma concentrations of O-desmethyltramadol were significantly correlated to CYP2D6 genotype, no influence was detected for ondansetron.[9]

We conducted the study in medical intensive care patients experiencing pain other than postoperative pain. As we are not enrolling patients with postoperative pain in this study, we preferred lower infusion doses of tramadol and ondansetron in this study with one group receiving tramadol and ondansetron infusion and the other group receiving only

tramadol infusion as an analgesic after a bolus dose of 50 mg of tramadol in both the groups. At 0, 3, 6, 12, 24, and 48 h, pain assessment was done by VRS and patients were substituted rescue analgesia in the form of intravenous paracetamol when required. Hemodynamic variations were also monitored at these intervals. There was definite fall in mean hemodynamic values in our study at various time intervals, providing indirect evidence of the analgesic action of tramadol. The mean VRS in both groups was high (9.96 in Group T+Z and 9.84 in Group T) at the 0-time interval and came down at 3 h interval (2.68 in Group T+Z and 2.4 in Group T) and mean VRS was never >4 at any other point of evaluation. Three patients in T+Z Group and 1 patient in T Group required rescue analgesia at 3 h as their VRS score was >4. No patient had nausea or vomiting in both groups according to CSC. Three patients had Grade 1 sedation in Group T+Z and 1 patient had Grade 1 sedation in Group T which were not statistically significant ($P = 0.153$).

Conclusions

We conclude that co-administration of ondansetron with tramadol can be practiced in medical ICU patients with lesser doses without any side effects such nausea, vomiting, and sedation. More number of studies with large study population along with the determination of plasma concentrations of O-demethyltramadol is required before a conclusion can be elucidated.

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Conflicts of interest

There are no conflicts of interest.

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