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Comparison of Ramosetron and Ondansetron for Prevention of Postoperative Nausea and Vomiting in Patients on Preoperative Steroids Undergoing Supratentorial Craniotomy: A Prospective, Double-Blind, Randomized Controlled Study

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Abstract

Background: This study was designed to compare the efficacy of prophylactic ramosetron with ondansetron in preventing PONV after elective supratentorial craniotomy in adult patients on preoperative steroids.

Methods: A total of 145 American Society of Anesthesiologists (ASA) I–II patients aged 30–50 years on preoperative steroids scheduled to undergo elective supratentorial craniotomy under general anesthesia were enrolled in the study. A standard anesthesia regimen was followed in all patients. Patients were randomly allocated into two groups to receive ondansetron (4 mg/2 ml; Group O), or ramosetron (0.3 mg/2 ml; Group R) intravenously (IV) at the time of dural closure. The incidence of PONV, need for rescue antiemetics, rescue analgesics and any adverse events were recorded up to 48 hours postoperatively.

Results: During 0–24 hours after surgery, complete response (no PONV) was observed in 30 patients of the ondansetron group and in 34 patients of the ramosetron group ($p > 0.05$). Complete response i.e., no PONV between 24–48 hours after surgery was observed in 31 patients of the ondansetron group and in 45 patients of the ramosetron group and was statistically significant ($p < 0.05$). During 0–24 hours, PONV requiring rescue antiemetics were comparable in both the groups, whereas between 24–48 hours PONV requiring rescue antiemetics was higher in ondansetron group (18 patients) as compared to ramosetron group (8 patients) and was statistically significant ($p < 0.05$).

Conclusion: Ramosetron was more efficacious than ondansetron in preventing delayed PONV (24–48 hours) in patients on preoperative steroids following supratentorial craniotomy under general anesthesia. However, both the drugs were comparable in preventing early PONV (0–24 hours). The incidence of side effects was similar in ondansetron and ramosetron.

Keywords: Ondansetron; Postoperative nausea and vomiting (PONV); Ramosetron; Supratentorial craniotomy.

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Introduction

Postoperative nausea and vomiting (PONV) is one of the most commonly encountered problem after neurosurgical operations.[1] The reported incidence of PONV after elective craniotomy is 44% to 70% and is more common following posterior fossa surgery.[1,2]

PONV in neurosurgical patients causes pain, tachycardia, aspiration, patient discomfort,

dehydration, acid-base disturbances, and electrolyte imbalances like symptomatic hyponatremia.[2] It may also lead to an increase in intracranial pressure and wound dehiscence which may be deleterious to the patients.[3] PONV is a major cause of delayed discharge from recovery room and/or unanticipated hospital admission following surgery thereby increasing medical costs.[4] Hence, the aim is to provide a rational therapy for prevention of postoperative nausea and vomiting so that the patient-related distress is mitigated.

The effectiveness of ondansetron in preventing PONV has been extensively studied in various high-risk surgeries including neurosurgeries.[5] It is safe with fewer side effects, but its efficacy is limited in preventing delayed PONV (24–48 hours).[6,7]

Ramosetron is a newer, highly selective and more potent 5-HT3 receptor antagonist. It exhibits a higher affinity for the receptors with a slower dissociation, resulting in longer duration of action.[8] Ramosetron has been effectively used to prevent delayed PONV in various high-risk surgeries.[9] However, there is relative scarcity of literature on the use of ramosetron in neurosurgical patients on preoperative steroids to prevent early (0–24 hours) and delayed (24–48 hours) PONV.

We therefore designed a prospective, randomized, double-blind study with the primary objective to compare the efficacy (in terms of absence of PONV and number of rescue antiemetics required) of ramosetron with ondansetron in the prevention of early (0–24 hours) and delayed (24–48 hours) PONV in patients on preoperative steroids undergoing supratentorial craniotomy. The secondary objective was to compare the side effects of ramosetron and ondansetron.

Materials and Methods

The protocol was approved by the Institutional board of studies and passed by the Ethical Committee of the hospital and registered in the Clinical Trials Registry (CTRI/2018/01/016775). After obtaining written and informed consent, 145 adult patients of either sex ASA (American Society of Anesthesiologists) I&II aged 30 to 50 years on preoperative steroids undergoing elective craniotomy from 01 December 2015 to 30 January 2017 were included (Figure 1). Patients with a history of motion sickness, gastroesophageal reflux disease (GERD), cardiovascular disease, respiratory disease, uncontrolled diabetes mellitus, anticipated difficult intubation, history of alcohol, drug abuse, smokers, Glasgow Coma Score (GCS) less than 13 and patients who could not be extubated at the end of surgery were excluded from the study. The numeric rating scale (NRS) for pain intensity and visual analogue scale (VAS) for nausea was explained to the patient during preanesthetic visit.

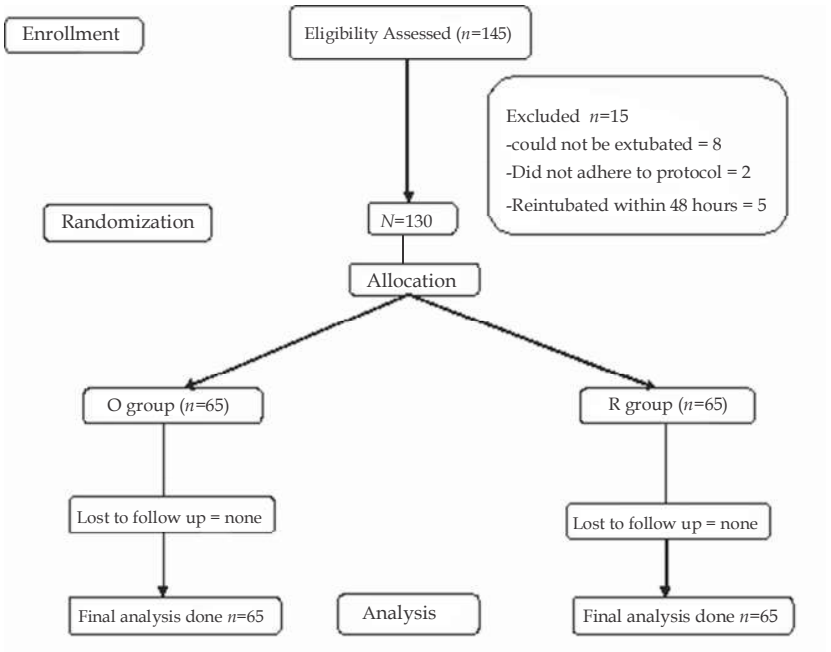

Fig. 1: Consort diagram

Patients were randomly allocated by a computer generated random number list and allocation concealment was done using serially numbered opaque envelope technique. The patients were allocated into two groups—the O group and the R group receiving ondansetron (4 mg/2 ml) and ramosetron (0.3 mg/2 ml), respectively. The medications were prepared by a pharmacist who was not involved in the study in identical 5 ml syringes and were administered by the anesthesiologist blinded to the medication. Patients receiving the relevant antiemetic were also blinded to the medication.

All the patients were administered dexamethasone intravenously (IV) in a dose of 4 mg every 6 hourly, for at least 24 hours prior to surgery and continued postoperatively for 48 hours in a dose of 4 mg every 6 hours.

The patients were administered lorazepam (0.5 mg) orally on the night before surgery and advised nil per orally (NPO) for 8 hours. Anesthesia and monitoring were standardized for all patients. Pulse oximetry (SpO_2), electrocardiogram (ECG), non-invasive blood pressure (NIBP) and end-tidal CO_2 ($ETCO_2$) were continuously monitored in the operating room. Patients were induced with propofol 2 mg/kg and fentanyl 2 mcg/kg. Intubation was facilitated by using vecuronium 0.1 mg/kg. Temperature monitoring was done with esophageal stethoscope and maintained at 36 ± 1°C. Right or left subclavian vein was cannulated for monitoring central venous pressure. Radial artery was cannulated with a 20 G arterial catheter for continuous blood pressure monitoring and arterial blood gas sampling.

Anesthesia was maintained with nitrous oxide (66%), sevoflurane (1–2%) in oxygen and vecuronium bromide with IPPV so as to maintain $ETCO_2$ level between 30 and 35 mm Hg. Intraoperatively, analgesia was supplemented with fentanyl every hourly in a dose of 1 mcg/kg. Normal saline (NS), blood and colloids were administered to maintain fluid balance.

At the end of the surgery, ondansetron (4 mg/2 ml) or ramosetron (0.3 mg/2 ml) was administered intravenously at the time of dural closure. Paracetamol 15 mg/kg IV was given during skin closure for postoperative analgesia followed by the reversal of neuromuscular blockade with neostigmine (0.04 mg/kg) and glycopyrrolate (0.01 mg/kg).

Patients were extubated and shifted to intensive care unit (ICU) or high dependency unit (HDU). The postoperative care was as per the ICU protocol and similar in all patients.

Patients were closely monitored for 48 hours postoperatively. Any complaint of nausea, retching, and vomiting or adverse drug effect was recorded by an independent observer (usually a resident doctor) who was blinded to the study between 0–24 and 24–48 hours.

Nausea was defined as subjective unpleasant sensation associated with awareness of the urge to vomit.[10] Whereas retching was defined as labored spasmodic, rhythmic contraction of the abdominal muscles without expulsion of gastric contents and vomiting was defined as forceful expulsion of gastric contents from the mouth.[11] A *complete response* was defined as the absence of PONV.

Nausea was measured using a 10-point numerical visual analogue scale (VAS)[12] with 0=no nausea and 10=nausea as bad as could be. A score of >5 was considered severe, 5 as moderate and <5 as minimal. During the period of monitoring, the vomiting/retching episodes of >2 were considered severe, 2 as moderate, and <2 as mild. Furthermore, moderate and severe nausea constituted significant nausea.

Metoclopramide (0.15 mg/kg) IV was administered as rescue antiemetic in patients with two or more than two episodes of vomiting and/or significant nausea at any time within 48 hours of operation.

Postoperative nausea and vomiting (PONV) occurring up to 24 hours after surgery was taken as *early PONV* whereas *delayed PONV* was defined as postoperative nausea and vomiting occurring during 24–48 hours after surgery.

A standard analgesic regimen of 1 gm IV paracetamol every 8 hours was given during first 48 hours to each patient. In addition, rescue analgesic (tramadol 1.5 mg/kg) was administered when numeric rating scale (NRS) score perceived by the patient was found to be 4 or more. The time to first rescue analgesic and the total dose of rescue analgesics administered were also recorded.

The patients were asked for occurrence of any adverse effects (dizziness, dyspepsia, weakness, flushing and urticaria). If present, it was diligently sought, documented and addressed appropriately.

Statistical Analysis

The sample size was estimated on the basis of differential response of PONV while using ramosetron as compared to ondansetron.

Assuming a complete response with ondansetron on PONV to be 70%, a clinical improvement of 20% was considered clinically significant, with an allowable alpha error (α) of 0.05 and power of 80%, the sample size was calculated to be a minimum of 65 patients in each group using sealed envelope sample size calculator.[13] Univariate analysis was performed using chi-square test and Fisher's exact test for non-parametric (gender, ASA physical status, incidence of PONV and complete response, rescue antiemetics, and adverse events). One-way ANOVA and Tukey post-hoc tests were used to compare parametric data (age, height, weight, duration of anesthesia and surgery, intraoperative fentanyl requirement, amount of fluid infused and blood loss, time to first dose of rescue analgesic and total amount of rescue analgesic required). A *p*-value of <0.05 was considered statistically significant. All data were recorded on standardized case report forms and were exported for analysis in SPSS version 20 (SPSS Inc., USA). The results were presented in number, percentage, mean and standard deviation as appropriate.

Results

During a period of 14 months, a total of 145 adult patients undergoing craniotomy were included in the study. Fifteen patients were excluded from the study in which eight patients could not be extubated, two patients did not adhere to study protocol and five patients were reintubated within 48 hours of admission to ICU/HDU (Figure 1).

The O Group (ondansetron) and the R Group (ramosetron) were comparable ($p > 0.05$) with respect to the patients demographic data, duration of anesthesia and surgery, the amount of fluid administered and blood loss. The total consumption of opioid (fentanyl) in the intraoperative period was also comparable among the two groups (Table 1).

Table 1: Demographical Profile of Patients

Patient Variables		O Group (Ondansetron) (*n*=65)	R Group (Ramosetron) (*n*=65)	*p*-value
Age (in years) (mean ± SD)		40.02 ± 7.62	40.78 ± 8.05	0.5814 (NS)
Gender	Males	39 (60%)	37 (56.9%)	0.7211(NS)
	Females	26 (40%)	28 (43.1%)	
ASA Grades	I	17 (26.15%)	18 (27.69%)	0.3962 (NS)
	II	48 (73.84%)	47 (72.30%)	
Height (cm) (mean ± SD)		154.25 ± 5.27	154.97 ± 8.21	0.3486 (NS)
Weight (kg) (mean ± SD)		58.2 ± 6.6	61.7 ± 5.8	0.3425 (NS)
Duration of Anesthesia (min) (mean ± SD)		217.54 ± 89.20	201.31 ± 70.96	0.2531(NS)
Duration of surgery (min) (mean ± SD)		169.62 ± 84.06	148.28 ± 64.84	0.1208 (NS)
Total Intraoperative opioid used (Inj fentanyl) (μgm)		201.6 ± 82.3	194.3 ± 62.2	0.5315 (NS)
Fluid given (mL)		2562 ± 432	2305 ± 382	0.1464 (NS)
Blood loss (mL)		254 ± 68	296 ± 46	0.1103 (NS)

NS: Not significant statistically

There was no significant difference between the two groups in terms of total dose of rescue analgesics required in the postoperative period. The time to administer the first dose of rescue analgesic was also similar in both the groups (Table 2).

Table 2: Time to First Dose and Total Dose Required of Rescue Analgesic Postoperatively

Patient Variables	O Group (Ondansetron) (*n*=65)	R Group (Ramosetron) (*n*=65)	*p*-value
Time to rescue analgesic (min) (Inj Tramadol)	164.2 ± 8.2	176.1 ± 9.7	0.8109 (NS)
Total rescue analgesic required (mg) Inj Tramadol	92.7 ± 11.2	84 ± 9.6	0.6352 (NS)

NS: Not significant statistically

During 0–24 hours, there was no significant difference in the incidence of PONV and the need for rescue antiemetic requirement. However, significant difference was observed in the incidence of PONV (52.30% vs 30.77%) and the need for rescue antiemetic requirement (27.69% vs 12.34%) among the two groups, 24–48 hours postoperatively ($p < 0.05$) (Table 3).

During 0–24 hours after surgery, the incidence of complete response i.e., no PONV was comparable in both the groups and it was not statistically significant ($p > 0.05$) (Table 3). However, during 24–48 hours after surgery, the incidence of complete response i.e., no PONV was more in patients of ramosetron group (69.23%) as compared to that of ondansetron group (47.69%) and this difference was statistically significant ($p < 0.05$) (Table 3).

Table 3: Early (0-24 Hours) and Late (24–48 Hours) Postoperative Nausea and Vomiting (PONV)

PONV	Early (0-24 Hours)		*p*-value	Late (24–48 Hours)		*p*-value
	O Group (Ondansetron) (*n* = 65)	R Group (Ramosetron) (*n* = 65)		O Group (Ondansetron) (*n* = 65)	R Group (Ramosetron) (*n* = 65)	
Nil	30 (46.15%)	34 (52.30%)	0.482(NS)	31 (47.69%)	45 (69.23%)	0.020*
Present	35 (53.85%)	31 (47.70%)	0.482(NS)	34 (52.30%)	20 (30.77%)	0.020*
Requiring rescue antiemetic	10 (15.38%)	14 (21.53%)	0.365(NS)	18 (27.69%)	8 (12.34%)	0.028*
Not Requiring rescue antiemetic	25 (38.46%)	17 (26.15%)	0.133(NS)	16 (24.61%)	12 (18.46%)	0.393 (NS)

NS: Not significant statistically *Statistically significant

During 0–24 hours postoperatively, the incidence as well as severity of nausea, vomiting and retching between the two groups was not statistically significant (*p*-value >0.05) (Table 4). The results for the 24–48 hours period suggested that the incidence as well as severity of nausea alone was not statistically significant ($p > 0.05$). Ramosetron was found to be more effective in preventing delayed vomiting as compared to ondansetron. The incidence of vomiting was

Table 4: Severity of Early (0–24 Hours) and Delayed (24–48 Hours) Nausea, Vomiting and Retching

Variable	Early (0–24 Hours)		*p*-value	Late (24–48 Hours)		*p*-value
	O Group Ondansetron (*n* = 65)	R Group Ramosetron (*n* = 65)		O Group Ondansetron (*n* = 65)	R Group Ramosetron (*n* = 65)	
Nausea						
No nausea	41 (63.07%)	45 (69.23%)	0.458 (NS)	47 (72.30%)	55 (84.61%)	0.087 (NS)
Nausea present:	24 (36.92%)	20 (30.76%)	0.458 (NS)	18 (27.69%)	10 (15.37%)	0.087 (NS)
Mild	15 (23.07%)	12 (18.46%)	0.516 (NS)	11 (16.92%)	6 (9.23%)	0.193 (NS)
Moderate	5 (7.70%)	6 (9.23%)	0.752 (NS)	5 (7.7%)	2 (3.07%)	0.243 (NS)
Severe	4 (6.15%)	2 (3.07%)	0.403 (NS)	2 (3.07%)	2 (3.07%)	1.000 (NS)
Vomiting						
No vomiting	55 (84.61%)	56 (86.15%)	0.803 (NS)	43 (66.1%)	62 (95.84%)	0.0192*
Vomiting present	10 (15.37%)	9 (13.83%)	0.803 (NS)	22 (33.83%)	3 (4.60%)	0.0192*
Mild	5 (7.69%)	5 (7.69%)	1.000 (NS)	8 (12.30%)	2 (3.07%)	0.048*
Moderate	3 (4.61%)	3 (4.61%)	1.000 (NS)	8 (12.30%)	1 (1.53%)	0.032*
Severe	2 (3.07%)	1 (1.53%)	0.559 (NS)	6 (9.23%)	0 (0.00%)	0.027*
Retching						
No Retching	54 (83.07%)	56 (86.15%)	0.626 (NS)	52 (80.0%)	61 (93.84%)	0.035*
Retching present	11(16.88%)	9 (13.83%)	0.626 (NS)	13 (19.98%)	4 (6.13%)	0.0325*
Mild	6 (9.20%)	5 (7.69%)	0.752 (NS)	3(4.61%)	2 (3.07%)	1.00 (NS)
Moderate	2 (3.07%)	3 (4.61%)	0.648 (NS)	8 (12.30%)	1 (1.53%)	0.032*
Severe	3 (4.61%)	1 (1.53%)	0.309 (NS)	2 (3.07%)	1 (1.53%)	0.612 (NS)

NS: Not significant statistically *Statistically Significant

lesser in ramosetron group (4.60%) as compared to ondansetron group (33.83%) and was statistically significant (p-value < 0.05) (Table 4). Moreover patient experiencing severe episodes of vomiting were greatly reduced in number in ramosteron group (0.00%) as compared to ondansetron group (9.23%) Retching occurred less frequently in patients of ramosetron group (6.13%) as compared to ondansetron group (19.98%) and this difference was significant among the two groups (p < 0.05) (Table 4).

The incidence of adverse events-dizziness, dyspepsia, weakness, flushing and urticaria were comparable in both the groups (Table 5).

Table 5: Adverse Drug Effects

Adverse Drug Effects	O Group (Ondansetron) (n = 65)	R Group (Ramosetron) (n = 65)	p-Value	Total (%) (n = 130)
Dizziness	3 (4.61%)	2 (3.07%)	0.648 (NS)	5 (3.84%)
Dyspepsia	2 (3.07%)	1 (1.53%)	0.559 (NS)	3 (2.30%)
Weakness	2 (3.07%)	2 (3.07%)	1.000 (NS)	4 (3.07%)
Flushing	1 (1.53%)	0	0.999 (NS)	1 (0.76%)
Urticaria	2 (3.07%)	1 (1.53%)	0.559 (NS)	3 (2.30%)
Total	**14 (21.5%)**	**10 (15.38%)**	**0.365 (NS)**	**24(18.46%)**

NS: Not significant statistically

Discussion

This prospective randomized double-blind study was performed to compare the antiemetic efficacy of ramosetron with ondansetron in patients on preoperative steroids undergoing supratentorial craniotomy.

Determinants like timing and duration of antiemetic administration following craniotomy have been subjects of conjecture since long. In our study, we too did emphasize upon these two pertinent variables and found that PONV occurred more frequently so in the first 48 hours following surgery. Our findings were in consonance with those of Sang Hee Ha *et al.*[14] who propounded this similar hypothesis in their study. The plausible mechanism of the same has been attributed to the fact that pneumocephalus and blood clots accompanying craniotomies act as additive triggers for PONV in the first 48 hours, thereby warranting antiemetic administration during this duration.[15]

Ondansetron, a selective 5-HT3 receptor antagonist 5-HT3, has been extensively studied for the prevention of PONV following different types of surgeries including neurosurgery. It prevents nausea and vomiting through its action on chemo-receptor trigger zone (CTZ). In a meta-analysis conducted among a cohort of 308 craniotomy patients, it was observed that the incidence of nausea and vomiting reduced significantly with ondansetron only in the first 24 hours.[16] The results in our study were comparable and we also observed that ondansetron was effective during the first 24 hours after craniotomy (Table 3).

Ramosetron (0.3 mg) has been found to be more effective than ondansetron (4 mg) in previous studies.[17–19] However, there are not too many studies on the use of ramosetron to prevent PONV in neurosurgical patients.

In our study, ramosetron was found to be more effective during 24–48 hours, in terms of absence of PONV and the number of rescue antiemetics required as compared to ondansetron. An important finding in our study was that although the incidence and severity of nausea alone was reduced in both the groups during the study period (0–48 hours), it was not statistically significant. However, we observed that ramosetron was more effective in preventing delayed (24–48 hours) postoperative vomiting as compared to ondansetron.

Patients in ramosetron group experienced lesser number of episodes of vomiting during 24–48 hour. In our study, the severity of nausea was measured by a 10-point visual analogue scale (VAS). Nausea being a subjective symptom, it would have been difficult to accurately judge the severity of nausea based on visual analogue scale. This could have been the reason that the intensity and severity of nausea was found to be similar in both the groups during the study duration.

Not with standing though, ramosetron is known to have a prolonged duration of action, longer half-life along with higher receptor affinities. Therefore, a strong case can be made towards superior ramosetron efficacy.[9]

In concordance with our observation that ramosetron was superior to ondansetron in the 24–48 hours postoperative period, Ryu *et al.*[20] also

observed similar results However, in our study instead of total intravenous anesthesia (TIVA) with propofol and remifentanyl, the anesthesia was maintained with inhalational agents (sevoflurane) in nitrous oxide and oxygen. Additionally, all the patients in our study were on preoperative steroids, whereas only 30% of the patients were receiving steroids in the study by Ryu *et al*.

Corticosteroids have been the mainstay of treatment to reduce Perilesional edema in patients presenting with intracranial lesions. Dexamethasone acts synergistically with 5-HT3 receptor antagonists to reduce PONV and this may have influenced the baseline incidence of PONV in our study. However, we are of the view that since dexamethasone was administered in similar doses in both the groups, the probability of bias was minimal and did not confound the interpretation of results in our study.

A contrasting study in related literature by Sang Hee Ha *et al*.[14] found a comparative efficacy of ramosetron and ondansetron in patients undergoing microvascular decompression with retromastoid craniotomy. The authors used higher dosage of ondansetron (8 mg) as compared to that in our study (4 mg). This can be explained by the possible higher efficacy of few drugs being temporally associated with slightly higher dosages. These higher doses are however fraught with higher complication rates and risks and benefits need to be weighed accordingly.

Post craniotomy pain and the amount of opioid consumption effects the occurrence of PONV, in neurosurgical patients.[21] Therefore, an important and logically determinant variable in our study setting was the total dose of opioid required intraoperatively during the study period. But it was found that its effect was largely obviated as a potential confounder/bias as no statistically significant difference was observed in ondansetron and ramosetron groups, as far as intraoperative requirement of fentanyl and postoperative rescue analgesia was concerned. Also of remark here is to state that the incidence of adverse effects (dizziness, dyspepsia, weakness, flushing, urticaria) was comparable in the two groups, not tantamounting to be statistically significant ($p < 0.05$). Headache is one of the most common side effect of 5-HT3 receptor antagonists. It was not recorded in our study since it was difficult to discriminate headache from postcraniotomy pain in patients with neurosurgery.

The discrepancies and similarities with other studies vis-a-vis ours calls for an unmet need of establishing equivalent dosages of ramosetron and ondansetron to help avert the associated potential bias when the two drugs are not considered for application with due heed to their individual pharmacokinetics and pharmacodynamics.

In our study, we did not compare the antiemetic efficacy of ramosetron to that of a placebo control because we did not consider it to be suitable and also a study design with a placebo control group would be inappropriate because the subjects were at an extremely high-risk for PONV.

The anesthesia was maintained with nitrous oxide (66%) and Sevoflurane (1–2%). Use of nitrous oxide during surgery also plays an emetogenic role[22,23] and this may have influenced the incidence of PONV in our study.

Ondansetron, in our study was used in a dose of 4 mg which was based on previous studies evaluating the dose response relationship. Ondansetron in a dose of 4–8 mg has been found to be equally effective to reduce the incidence of PONV in high-risk patients. In contrast to our study, Tramer *et al*.[24] reported that higher doses of ondansetron might be more effective in preventing delayed PONV in high-risk surgeries.

Conclusion

Ramosetron (0.3 mg) was more efficacious than ondansetron (4 mg) in preventing delayed PONV (24–48 hours) in patients on preoperative steroids undergoing supratentorial craniotomy under general anesthesia.

Recommendations: We recommend that further prospective multicentric studies be done to find out the best dose of an antiemetic drug for a particular surgery. We also recommend that studies be done to compare ramosetron with higher doses of ondansetron to prevent PONV after supratentorial craniotomy under general anesthesia.

Support: Nil.

Conflicts of interest: Nil.

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