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The effect of palonosetron on postoperative nausea and vomiting in supratentorial craniotomy patients

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Aim: Postoperative nausea and vomiting (PONV) is a condition that adversely affects postoperative patient comfort. Supratentorial craniotomy patients were therefore monitored to establish the therapeutic efficiency of 2 different doses of palonosetron.

Materials and methods: Patients scheduled for elective supratentorial craniotomy were randomly assigned to 3 groups: a control group (n = 30), a 0.05 mg palonosetron group (n = 30), and a 0.075 mg palonosetron group (n = 30). The drugs were given intravenously at the commencement of dura mater closure. Anesthesia maintenance was provided with 1 MAC sevoflurane in a 50% air and O_2 mixture. After the extubation, the patients were monitored for 72 h with respect to postoperative nausea and vomiting.

Results: In the first 6 h, nausea was significantly lower in the 0.075 mg palonosetron group compared to the control group (P = 0.019). The incidences of nausea, retching, and vomiting at 0–72 h postoperatively were significantly lower in the 0.075 mg palonosetron group than in the 0.05 mg palonosetron or saline groups (P < 0.001).

Conclusion: In supratentorial craniotomy cases, PONV was reduced more effectively in the 0.075 mg palonosetron group than in the 0.05 mg palonosetron and control groups.

Key words: Supratentorial craniotomy, postoperative nausea and vomiting, palonosetron

Introduction

Postoperative nausea and vomiting (PONV) are frequent and distressing complications after neurosurgical procedures (1). The reported incidence of PONV after elective craniotomy has been found to be between 44% and 70% in different studies (2–5). Vomiting may increase intracranial and/or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion, and may cause an electrolyte imbalance like hyponatremia (5,6).

The area postrema of the brain stem, which is where the chemoreceptor trigger zone is located, is rich in dopamine, opioid, and serotonin (or 5-hydroxytryptamine; 5-HT_3) receptors (7–9). These receptors may play an important role in the transmission of impulses to the emetic center (10). The new generation of antiemetic agents, called 5-HT_3 receptor antagonists (ondansetron, granisetron, ramosetron, and dolasetron), are superior to conventional antiemetics for the prevention and treatment of PONV (11). Palonosetron, a second-generation 5-HT_3 receptor antagonist, has provided better PONV results, has higher receptor affinity, and has a much longer half-life (approximately 40 h) than other 5-HT_3 receptor antagonists (12). However, there are no reports about the efficacy of different doses of palonosetron in elective craniotomy for supratentorial tumor resection. This prospective, randomized, double-blinded study was designed to evaluate the efficacy and safety of different doses of palonosetron for the prevention of postoperative nausea and vomiting in patients undergoing supratentorial craniotomy.

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Materials and methods

After approval by the ethics committee, we obtained written informed consent from 90 American Society of Anesthesiologists (ASA) status I–III patients aged between 18 and 76 years old who were scheduled for elective supratentorial craniotomy for resection of mass lesions. The patients were randomly assigned into 3 groups to be administered 0.05 mg palonosetron (group P1), 0.075 mg palonosetron (group P2), or saline (group S) in a double-blinded fashion. The exclusion criteria were a history of vomiting such as motion sickness, antiemetic use preoperatively, allergy to palonosetron, pregnancy, breast-feeding, morbid obesity, cardiac dysrhythmia, clinical symptoms (hypertension, bradycardia, nausea–vomiting, confusion, and papilledema), radiological images due to increased intracranial pressure, mental retardation, or psychiatric illness. All patients in the 3 groups received corticosteroid therapy (dexamethasone: 4 mg/6 h) during the preoperative and postoperative periods. Patients were monitored with electrocardiography and for heart rate, noninvasive blood pressure, pulse oximetry, airway gas levels, and end-tidal CO2 concentration using a Datex–Engstrom AS/3 monitor (Datex–Engstrom, Helsinki, Finland). Saline was given to all patients at an hourly rate of 5 mL/kg during the study period. Anesthesia was induced with 2–2.5 mg/kg propofol (13) and 2 μg/kg fentanyl. Endotracheal intubation was facilitated by 0.1 mg/kg vecuronium. After orotracheal intubation with an armored tube resistant to kinking, general anesthesia was maintained with 1 MAC sevoflurane in a 50% air and oxygen mixture and intermittent bolus doses of 1 μg/kg fentanyl. At the end of the operation, residual neuromuscular blockade was antagonized with intravenous atropine (0.015 mg/kg) and neostigmine (0.04 mg/kg). The patient was extubated after adequate spontaneous ventilation and movement.

The patients in group P1 (n = 30) received 0.05 mg of palonosetron (Aloxi, 250 μg/5 mL, Helsinn Birex Pharmaceuticals Ltd., Dublin, Ireland) diluted to 5 mL with 0.9% saline (1 mL palonosetron, 4 mL 0.9% saline), the patients in group P2 (n = 30) received 0.075 mg of palonosetron diluted to 5 mL with 0.9% saline (1.5 mL palonosetron, 3.5 mL 0.9% saline), and the patients in group S (n = 30) received 5 mL of 0.9% saline. The drugs were prepared and administered by anesthesia staff not involved in collecting the data. The drugs were given intravenously at the commencement of dural closure.

Postoperatively, the patients were transferred to the neurosurgical intensive care unit, and trained nursing staff recorded each episode of nausea and vomiting that occurred for 72 h. Although the nurses were aware of the nature of the study, they were blinded to the drug administered. Patient age, weight, and height; the duration of surgery; anesthesia; and intraoperative narcotic consumption were recorded. Episodes of nausea and vomiting and requests (plus time of request) for rescue antiemetic medication were recorded at 0 min and 6, 24, 48, and 72 h. Nausea was defined as a feeling of the urge to vomit as solicited by the investigators during assessments. Vomiting was defined as expulsion of stomach contents through the mouth. Retching was defined as an attempt to vomit that was not productive of stomach contents. An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Metoclopramide (10 mg) was given intravenously to the patients as a rescue antiemetic after more than 2 episodes of emesis within 30 min or persistent nausea lasting more than 10 min. All patients received 1 g of paracetamol (Perfalgan, Bristol-Myers Squibb Pharmaceuticals Ltd., New York, USA) intravenously every 8 h for postoperative pain management.

The primary outcome evaluated in this study was the efficacy (and safety) of using different doses of palonosetron to prevent postoperative nausea and vomiting in patients undergoing supratentorial surgery.

Statistical analyses were performed using SPSS (version 15.0, SPSS Inc., Chicago, IL, USA) software. The Kolmogorov–Smirnov test was used to assess the normal distribution of the data. One-way ANOVA was used to compare differences between the groups for parametric data with normal distribution. Statistical significance was determined by the Scheffe test, which is a post hoc multiple comparison test. Differences between measurements carried out before and after the drug administration or procedure were compared with paired t-tests. Pearson's chi-square test was used to compare the differences between groups for categorical variables. A P-value less than 0.05 was accepted as statistically significant.

Results

There was no intergroup difference with regard to age, height, weight, sex, or ASA classification of the cases (P > 0.05) (Table 1).

The mean duration of surgery was 172.3 min in the control group, whereas it was 199 and 182 min in the 0.05 mg and 0.075 mg palonosetron groups, respectively. There was no statistically significant difference between the groups with regard to duration of surgery (P = 0.216) (Table 1).

The mean intraoperative fentanyl consumption was 246 μg in the control group, whereas it was 275 μg and 248 μg in the 0.05 mg and 0.075 mg palonosetron groups, respectively. There was no statistically significant difference between the groups with regard to mean intraoperative fentanyl consumption (P = 0.248) (Table 1).

Intergroup comparisons showed no difference with regard to mean blood pressure or heart rate (P > 0.05) (Tables 2 and 3).

Although group P2 demonstrated statistically significantly lower nausea rates at 0–6 h compared with group P1 and the control group (P < 0.043), no intergroup difference was observed at 6–24 or 24 –72 h (P > 0.05) (Table 4). There was no statistically significant difference between the groups in terms of

Table 1. Demographic and clinical data.

	Group S (n = 30) (mean ± SD)	Group P1 (n = 30) (mean ± SD)	Group P2 (n = 30) (mean ± SD)	P
Age (years)	49.8 ± 10.4	49.3 ± 14.1	47.8 ± 14.5	0.820
Weight (kg)	75.9 ± 11.6	72.7 ± 10.8	72.4 ± 13.3	0.450
Height (cm)	164.8 ± 88	166.3 ± 7.8	166.8 ± 7.8	0.620
Sex (M/F)	17/13	15/15	14/16	0.733
No. of patients with ASA physical status (I/II/III)	10/17/3	18/9/3	16/14/0	0.099
Duration of surgery (min)	172.3 ± 47.6	199 ± 64.8	182 ± 63.5	0.216
Total intraoperative fentanyl (μg)	246 ± 64	275 ± 87	248 ± 64	0.248

P < 0.05 indicates statistical significance. S = control group, P1 = 0.05 mg palonosetron, P2 = 0.075 mg palonosetron.

Table 2. Mean blood pressure (mmHg).

	Group S (n = 30) (mean ± SD)	Group P1 (n = 30) (mean ± SD)	Group P2 (n = 30) (mean ± SD)	P
MBP before induction	108.7 ± 17.3	101.1 ± 14.0	100.3 ± 13.8	0.067
MBP before intubation	85.0 ± 15.2	79.5 ± 12.2	82.7 ± 19.0	0.401
MBP after intubation	112.0 ± 20.9	104.1 ± 18.1	109.5 ± 19.3	0.283
MBP before medication	90.8 ± 12.5	92.3 ± 15.8	90.2 ± 10.7	0.815
MBP after medication	90.7 ± 14.6	90.7 ± 16.9	89.6 ± 12.4	0.947
MBP before extubation	110.8 ± 16.8	109.7 ± 19.4	110.5 ± 15.4	0.938
MBP 30 min after extubation	104.4 ± 23.5	98.9 ± 10.9	100.7 ± 16.6	0.335

MBP: Mean blood pressure. P < 0.05 indicates statistical significance. S = control group, P1 = 0.05 mg palonosetron, P2 = 0.075 mg palonosetron.

Table 3. Heart rate (beats/min).

	Group S (n = 30) (mean ± SD)	Group P1 (n = 30) (mean ± SD)	Group P2 (n = 30) (mean ± SD)	P
HR before induction	83.2 ± 15.2	77.9 ± 12.5	83.0 ± 20.1	0.364
HR before intubation	79.1 ± 15.3	72.7 ± 10.5	74.1 ± 15.6	0.186
HR after intubation	86.7 ± 14.8	83.3 ± 13.8	84.6 ± 17.5	0.689
HR before medication	76.7 ± 10.5	71.8 ± 10.0	73.9 ± 12.6	0.234
HR after medication	76.0 ± 14.4	72 .6 ± 12.3	75.1 ± 13.1	0.599
HR before extubation	95.0 ± 19.2	88.0 ± 14.5	91.1 ± 14.5	0.253
HR 30 min after extubation	87.4 ± 11.0	83.2 ± 12.4	84.3 ± 12.1	0.368

HR: Heart rate. P < 0.05 indicates statistical significance. S = control group, P1 = 0.05 mg palonosetron, P2 = 0.075 mg palonosetron.

Table 4. Postoperative retching, nausea, and vomiting.

	Group S (n = 30) n (%)	Group P1 (n = 30) n (%)	Group P2 (n = 30) n (%)	P
0–6 h:				
Retching	9 (30)	5 (16.7)	3 (10)	0.131
Nausea	14 (46.7)	11 (36.7)	5 (16.7)*	0.043
Vomiting	9 (30)	9 (30)	3 (10)	0.107
6–24 h:				
Retching	5 (16.7)	3 (10)	2 (6.7)	0.455
Nausea	5 (16.7)	4 (12.3)	2 (6.7)	0.484
Vomiting	4 (13.3)	4 (12.3)	2 (6.7)	0.638
24–72 h:				
Retching	4 (13.3)	3 (10)	0 (0)	0.133
Nausea	5 (16.7)	3 (10)	0 (0)	0.074
Vomiting	2 (6.7)	3 (10)	0 (0)	0.227
0–72 h: Retching, nausea, or vomiting	17 (56.7)	12 (40)	5 (16.7)*	0.006

P < 0.05 indicates statistical significance. S = control group, P1 = 0.05 mg palonosetron, P2 = 0.075 mg palonosetron.
*Significantly reduced relative to control group (P < 0.05).

vomiting or retching at 0–6, 6–24, or 24–72 h (P > 0.05) (Tables 4). However, the incidence of retching, nausea, or vomiting was significantly lower in the 0.075 mg palonosetron group than in the control group (P = 0.003). There was no statistically significant difference between the 0.05 mg palonosetron and control group (P = 0.301) (Table 4).

Discussion

In this study, 0.075 mg of palonosetron was observed to reduce the incidence of nausea within the first 6 h postoperatively. Kathirvel et al. (14) found the incidence of nausea–vomiting among elective craniotomy cases at 24 h postoperatively to be 44%, whereas it was 24% in patients treated with 4 mg of

ondansetron. The need for an antiemetic was reported to decrease from 15% to 5%. Fabling et al. (3) conducted a retrospective study of 199 adult cases with a history of elective craniotomy, among which the incidence of nausea at 48 h was 50% and the incidence of vomiting at 48 h was 39%. Postoperatively, 61% of the cases required an antiemetic (used intraoperatively in 7%). However, infratentorial craniotomy, female sex, and young age have been reported to be important risk factors for this complication. Madenoglu et al. (15) maintained anesthesia with isoflurane and nitrous oxide in oxygen in their earlier supratentorial craniotomy procedures, and they reported the incidence of nausea and vomiting as 46.7% and 56.%, respectively, while noting a drop in these values down to 30% and 26.7%, respectively, due to delivery of 2 mg of tropisetron.

In the present study, anesthesia was maintained with sevoflurane and an oxygen–air mixture. Known emetic potentials of opioids probably did not affect the rate of nausea and vomiting between the 3 groups because there was no statistically significant difference between the groups with regard to mean intraoperative fentanyl consumption.

In the current study, only nausea presented a statistically significant decline at 0–6 h in the 0.075 mg palonosetron group. The incidences of retching, nausea, or vomiting were 56% in the control group, 40% in the 0.05 mg palonosetron group, and 16.7% in the 0.075 mg palonosetron group at 0–72 h postoperatively. These incidences were lower in the 0.075 mg palonosetron group than in the other groups, which suggests that palonosetron is more effective at reducing PONV when used at 0.075 mg compared to 0.05 mg.

White et al. (16) compared the effect on PONV of 0.1–30 μg/kg palonosetron versus a placebo in 381 patients who underwent major gynecological surgery, and they found that palonosetron at doses of ≥1 μg/kg successfully decreased the incidence of nausea 0–24 h postoperatively.

Kovac et al. (17) conducted a study on 544 patients with a history of gynecological or breast surgery. They delivered 0.025, 0.050, and 0.075 mg doses of palonosetron for PONV prophylaxis, and 0.075 mg palonosetron was found to be significantly more effective than a placebo at preventing nausea and vomiting at both early (0–24 h) and late (24–72 h) postoperative periods.

Candiotti et al. (18) assessed the prophylactic effect of palonosetron at doses of 0.025, 0.050, and 0.075 mg in 574 patients who underwent laparoscopic day surgery, and the total incidence at 0–72 h of retching, nausea, and vomiting and early vomiting and the severity of nausea were found to be lower in the 0.075 mg palonosetron group than in the placebo group.

In our study, similarly to the above-mentioned studies, 0.075 mg of palonosetron reduced nausea episodes at 0–6 h and decreased the incidence of nausea and vomiting at other times. We observed no significant change in hemodynamics following delivery of the drug. None of the patients demonstrated postoperative side effects (such as constipation or bradycardia) due to palonosetron. Based on this study, we can recommend palonosetron as a safe agent with regard to hemodynamics and postoperative side effects at the aforementioned doses. In the present study, 51.1% of the patients were female and 48.9% were male. There was no statistically significant difference between the groups in terms of sex or age. Similarly, analgesic consumption and duration of surgery were almost the same in the groups in our study.

Due to the increasing cost of treatment for PONV, cost-effectiveness continues to be a major concern when choosing therapeutic agents. However, there is a large cost difference between palonosetron and other 5-HT_3 receptor antagonists. With respect to palonosetron, it is difficult to decide how much extra cost the added benefit is worth. A limitation of this study is that sample size calculation was not performed.

In conclusion, we suggest that intraoperative palonosetron is more effective at 0.075 mg than at 0.05 mg; therefore, it would be more appropriate to use palonosetron at 0.075 mg for the prevention of PONV in supratentorial craniotomy cases.

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