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Effect of prophylactic palonosetron and sugammadex on postoperative nausea and vomiting in patients undergoing microvascular decompression under propofol-maintained anesthesia

A retrospective observational study

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Abstract

Microvascular decompression (MVD) is associated with a particularly high risk of postoperative nausea and vomiting (PONV) among craniotomy patients. However, there is no information regarding the effect of prophylactic palonosetron and sugammadex on PONV in patients undergoing MVD under propofol-maintained anesthesia.

Medical records of 274 adults who had undergone MVD under propofol-maintained anesthesia were reviewed. Patients were classified into 4 groups, based on the reversal agent used (sugammadex/pyridostigmine) and whether or not prophylactic palonosetron was used. The PONV incidence and risk factors were analyzed according to the use of these agents.

The overall incidence of PONV was 30.7% during the first 24 hours postoperatively. The incidence of PONV was lower in the group using combination of prophylactic palonosetron and sugammadex (19.3%) compared with the group not using both agents (37.2%). The combined use of the prophylactic palonosetron and sugammadex was identified as a factor affecting the occurrence of PONV in both univariable (OR = 0.40, 95% CI: 0.21–0.77, $P = .006$) and multivariable (OR = 0.38, 95% CI: 0.20–0.75, $P = .005$) logistic regression analyses. In multivariable logistic regression analysis, female sex was also significant independent risk factor in PONV (OR = 2.62, 95% CI: 1.35–5.08, $P = .004$).

In this retrospective observational study, the combined use of prophylactic palonosetron before anesthetic induction and sugammadex as a reversal of neuromuscular blockade are associated with a reduction in the incidence of PONV in patients undergoing MVD under propofol-maintained anesthesia.

Abbreviations: ASA = American Society of Anesthesiologists, MVD = microvascular decompression, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting.

Keywords: microvascular decompression, palonosetron, postoperative nausea and vomiting, propofol, sugammadex

1. Introduction

Postoperative nausea and vomiting (PONV) are common after general anesthesia and may cause patient discomfort, dehydration, electrolyte imbalance, pulmonary aspiration, and prolonged hospital stay.[1] The incidence of PONV has been reported to vary from 20% to 73%,[2–4] but relatively high incidence of PONV ranged from 40% to 80% have been reported in neurosurgical patients within 24 hours after craniotomy.[5–7] Furthermore, a recent retrospective study reported that microvascular decompression (MVD), which is the most popular surgical treatment for patients with trigeminal neuralgia and hemifacial spasm, is associated with a particularly high risk of PONV among craniotomy patients.[8]

It is well known that the incidence of PONV is lower under propofol-maintained anesthesia than under volatile-maintained anesthesia in patients undergoing craniotomies.[9–11] In addition, antiemetic drugs such as palonosetron and ramosetron have well-established roles in the prophylaxis and treatment of PONV.[12,13] Sugammadex is a new gamma-cyclodextrin drug that binds to rocuronium.[14] It is a fast-onset drug that reverses neuromuscular blockade without the muscarinic side effects like PONV that occur with traditional anticholinergic-cholinesterase inhibitor mixtures. Sugammadex has been associated with a lower rate of PONV than neostigmine and pyridostigmine that cause the muscarinic side effects.[15–17]

Previous studies that aimed to reduce PONV in patients undergoing MVD were based on the use of inhalation anesthetics,[8,18] and no study has investigated the effects of sugammadex and palonosetron on PONV in patients using

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propofol for anesthetic maintenance. Therefore, we conducted this study to determine the effect of prophylactic palonosetron and sugammadex on the incidences of PONV among patients who underwent MVD during propofol-maintained anesthesia.

2. Methods

After obtaining approval from the Institutional Review Board of Kyung Hee University Hospital, we retrospectively reviewed the electronic medical records of 274 adults who had undergone MVD under propofol-maintained anesthesia between January 2014 and December 2017. The medical history, anesthesia records, nursing records, and medication administration records for the first 24 postoperative hours were reviewed. The following patient data were collected: demographic data, diagnosis, American Society of Anesthesiologists (ASA) physical status, and smoking history. The anesthetic data that was collected included total intraoperative propofol dose, administration of neuromuscular blocking and reversal agents, total intraoperative remifentanil dose, prophylactic palonosetron administration, and anesthesia time. The postoperative data included the presence of PONV in the postoperative 24 hours, postoperative opioids, administration of antiemetics, and the length of hospital stay.

We classified patients into 4 groups based on the reversal agent and prophylactic palonosetron that was used. Group NONE was defined by the use of pyridostigmine for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL was defined by the use of pyridostigmine for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction. Group SUGA was defined by the use of sugammadex for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL-SUGA was defined by the use of sugammadex for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction. None of the patients in group NONE and SUGA received any type of 5-HT3 receptor inhibitors during surgery, and patients in group PAL and PAL-SUGA received only palonosetron.

Anesthesia was induced by 2 mg/kg of propofol and 0.8 mg/kg of rocuronium, and maintained with propofol (effect site concentration: 2.0–4.0 μg/mL) and remifentanil (effect site concentration: 3.0–7.0 ng/mL) via a target-concentration infusion pump, while maintaining the bispectral index between 40 and 50. A mixture of 50% oxygen and air was used to maintain anesthesia. Palonosetron (0.075 mg) was not administered or administered at the discretion of the anesthesiologist prior to induction of general anesthesia. At the end of the surgery, a sugammadex (2 mg/kg) or pyridostigmine (15 mg)-glycopyrrolate (0.4 mg) mixture was administered to reverse neuromuscular blockade. The choice of reversal agent was decided based on the preference of the anesthesiologist. Patient-controlled analgesia (PCA) was not used.

2.1. Statistical Analysis

Continuous variables were expressed as mean ± SD, and categorical variables were expressed as absolute number (%). Continuous variables were compared using a Student's t test or the Mann–Whitney *U* test. Categorical variables were compared using Fisher's exact test or the χ^2 test. The relationship between each variable and PONV was analyzed through a univariable logistic regression analysis. A multivariable logistic regression analysis was conducted with variables that had *P*-values of .05 or less in the univariable logistic regression. *P*-values $< .05$ were considered statistically significant. All statistical analyses were carried out using IBM SPSS Statistics for Windows/Macintosh, Version 23.0 (IBM Corp., Armonk, NY).

3. Results

There were 274 patients who had undergone MVD under propofol-maintained anesthesia during the 4 years and were analyzed (group NONE, n = 145; group PAL, n = 19; group SUGA, n = 32; and group PAL-SUGA, n = 78).

The demographic and clinical characteristics of the patients in each group are shown in Table 1. There was a significant difference in the proportion of smokers (group NONE = 21.4%, group PAL = 5.3%, group SUGA = 0%, group PAL-SUGA = 12.8%) among the 4 groups (*P* = .004). The overall incidence of PONV was 30.7% (84/274), and the incidence of PONV in each of the 4 groups differed (group NONE = 37.2%, group PAL = 26.3%, group SUGA = 31.3%, group PAL-SUGA = 19.3%; *P* = .048).

Table 2 shows the demographic and clinical characteristics according to the development of PONV. The proportion of

Table 1

Comparison of patient characteristics by each group.

Variable	Group NONE (n = 145)	Group PAL (n = 19)	Group SUGA (n = 32)	Group PAL-SUGA (n = 78)	*P*-value
Age, years	54.7 ± 10.1	56.1 ± 9.5	57.3 ± 10.1	58.5 ± 9.9	.062
Sex (Female)	100 (69.0%)	14 (73.7%)	26 (81.3%)	58 (74.4%)	.519
BMI, kg/m^2	23.8 ± 3.2	25.1 ± 3.7	23.7 ± 3.1	24.7 ± 3.3	.058
Diagnosis (TN/HFS)	25/120 (17.2%/82.8%)	5/14 (26.3%/73.7%)	6/26 (18.8%/81.2%)	15/63 (19.2%/80.8%)	.815
Smoking	31 (21.4%)	1 (5.3%)	0 (0.0%)	10 (12.8%)	.004
Anesthetic time, minutes	235.0 ± 22.3	233.7 ± 34.3	237.8 ± 35.1	230.4 ± 38.6	.390
ASA physical status (I/II/III)	31/113/1 (21.5%/77.9%/0.7%)	3/16/0 (15.8%/84.3%/0%)	9/23/0 (28.1%/71.9%/0%)	13/64/1 (16.7%/82.1%/1.3%)	.745
Dose of propofol, mg	1814.3 ± 455.4	1769.5 ± 408.7	1856.3 ± 509.5	1869.7 ± 488.5	.768
Dose of remifentanil, mg	5.2 ± 0.7	5.8 ± 1.9	5.0 ± 1.8	5.5 ± 1.53	.227
Postoperative fentanyl use, μg	0.5 ± 4.6	5.3 ± 15.8	3.1 ± 12.3	4.5 ± 16.5	.065
The incidence of PONV	54 (37.2%)	5 (26.3%)	10 (31.3%)	15 (19.3%)	.048
Hospital length of stay, days	9.8 ± 3.5	10.2 ± 2.0	10.2 ± 2.9	10.6 ± 3.4	.363

Data are expressed as number (%) or mean ± SD. Group NONE was defined as the use of pyridostigmine for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL was defined as the use of pyridostigmine for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction. Group SUGA was defined as the use of sugammadex for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL-SUGA was defined as the use of sugammadex for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction.

ASA = American Society of Anesthesiologists physical status classification, BMI = body mass index, HFS = hemifacial spasm, PONV = postoperative nausea and vomiting, TN = trigeminal neuralgia.

Table 2

Comparison of patient characteristics according to PONV occurrence.

	PONV (−) (n = 190)	PONV (+) (n = 84)	*P*-value
Age, years	56.2 ± 10.0	56.0 ± 10.3	.793
Sex (Female)	128 (67.4%)	70 (83.3%)	.007
BMI, kg/m^2	24.4 ± 3.3	23.6 ± 3.1	.057
Diagnosis (TN/HFS)	39/151 (20.5%/79.5%)	12/72 (14.3%/85.7%)	.221
Smoking	33 (17.4%)	9 (10.7%)	.159
Anesthetic time, minutes	234.4 ± 31.6	232.8 ± 26.5	.681
ASA physical status (I/II/III)	38/152/0 (20.0%/80.0%/0%)	18/64/2 (21.4%/76.2%/2.4%)	.125
Prophylactic palonosetron	77 (40.5%)	20 (23.8%)	.008
Dose of propofol, mg	1836.7 ± 489.6	1820.8 ± 414.0	.625
Dose of remifentanil, mg	5.3 ± 1.3	5.3 ± 1.2	.919
Postoperative fentanyl use, μg	2.5 ± 10.8	1.8 ± 12.1	.627
Hospital length of stay, days	10.2 ± 3.8	9.8 ± 2.1	.323
Sugammadex	85 (44.7%)	25 (29.8%)	.020
Group (NONE/PAL/SUGA/PAL-SUGA)	91/14/22/63 (47.9%/7.4%/11.6%/33.2%)	54/5/10/15 (64.3%/6.0%/11.9%/17.9%)	.048

Data are expressed as number (%) or mean ± SD. Group NONE was defined as the use of pyridostigmine for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL was defined as the use of pyridostigmine for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction. Group SUGA was defined as the use of sugammadex for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL-SUGA was defined as the use of sugammadex for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction.

ASA = American Society of Anesthesiologists physical status classification, BMI = body mass index, HFS = hemifacial spasm, PONV = postoperative nausea and vomiting, TN = trigeminal neuralgia.

female in the group with PONV was high ($P = .007$). The proportion of patients who used sugammadex for the reversal of neuromuscular blockers was higher when PONV did not occur (44.7%) than when PONV occurred (29.8%) ($P = .020$). The proportion of patients who used prophylactic palonosetron was also higher when PONV did not occur (40.5%) than when PONV occurred (23.8%) ($P = .008$). The proportion of using both prophylactic palonosetron and sugammadex was higher in the group without PONV than in the group with PONV (33.2% vs 17.9%). The univariable logistic regression analysis indicated that female sex, prophylactic palonosetron administration, use of sugammadex for neuromuscular blockade reversal, and the PAL-SUGA group were associated with PONV (Table 3). In the multivariable logistic regression analysis, female sex (OR = 2.62, $P = .004$) and the PAL-SUGA group (OR = 0.38, $P = .005$) were associated with PONV.

4. Discussion

A recent retrospective study has reported that MVD is associated with a particularly high risk of PONV among craniotomy patients.[8] Our study showed that combined use of prophylactic

Table 3

Result of the univariable logistic regressions and multivariable logistic regressions for PONV in 24 hours.

	Univariable		Multivariable	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age	1.00 (0.97–1.02)	.868		
Sex (female)	2.42 (1.27–4.64)	.008	2.62 (1.35–5.08)	.004
BMI, kg/m^2	0.92 (0.85–1.00)	.058		
Diagnosis (HFS)	1.55 (0.77–3.14)	.224		
Smoking	0.57 (0.26–1.25)	.163		
Anesthetic time	1.00 (0.99–1.01)	.998		
ASA				
I	Reference			
II	0.88 (0.47–1.65)	.692		
III	10.42 (0.24–448.23)	.222		
Prophylactic palonosetron	0.46 (0.26–0.82)	.008	0.56 (0.27–1.14)	.108
Dose of propofol	1.00 (1.00–1.00)	.795		
Dose of remifentanil	0.94 (0.86–1.03)	.188		
Postoperative Fentanyl use	0.99 (0.97–1.02)	.628		
Hospital length of stay	0.96 (0.88–1.06)	.432		
Sugammadex	0.52 (0.30–0.91)	.021	0.67 (0.34–1.33)	.255
Group				
NONE	Reference		Reference	
PAL	0.60 (0.21–1.76)	.355	0.57 (0.19–1.71)	.317
SUGA	0.77 (0.34–1.74)	.524	0.65 (0.28–1.50)	.310
PAL-SUGA	0.40 (0.21–0.77)	.006	0.38 (0.20–0.75)	.005

Group NONE was defined as the use of pyridostigmine for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL was defined as the use of pyridostigmine for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction. Group SUGA was defined as the use of sugammadex for the reversal of neuromuscular blockade and no prophylactic palonosetron. Group PAL-SUGA was defined as the use of sugammadex for the reversal of neuromuscular blockade and prophylactic palonosetron before anesthesia induction.

ASA = American Society of Anesthesiologists physical status classification, BMI = body mass index, HFS = hemifacial spasm, PONV = postoperative nausea and vomiting, TN = trigeminal neuralgia.

palonosetron and sugammadex was associated with lower the incidence of PONV in patients undergoing MVD under propofol-maintained anesthesia.

A systematic review reported that the incidence of PONV is lower under propofol-maintained anesthesia than under volatile-maintained anesthesia in patients undergoing craniotomy.[11] Our study showed the overall incidence of PONV was 30.7%, which was the lower than the incidences of 40% to 80% that was observed in previous studies.[5–7] However, the additional inhibitory effect of PONV of prophylactic palonosetron and sugammadex has not been studied in patients with propofol-maintained anesthesia. Although each agent (palonosetron and sugammadex) has been reported to significantly reduce PONV under volatile anesthesia,[15–17,19] our study showed that each single agent did not decrease PONV under propofol-maintained anesthesia but decreased PONV when used in combination through multivariable logistic regression analysis.

Many studies have investigated how to prevent and treat PONV. These studies examined the use of serotonin antagonists, dexamethasone, droperidol, scopolamine, acupuncture, dimenhydrinate, propofol, regional anesthesia, and general anesthesia without nitrous oxide.[20] Pyridostigmine, which has been used to reverse neuromuscular blockade, can cause PONV due to muscarinic side effects. Previous study has shown that the prevalence of PONV can be reduced by using sugammadex instead of pyridostigmine.[15] Sugammadex is a recently developed drug, and there have not been enough investigations of its effect on PONV in patients undergoing MVD.[20,21] In our study, the incidence of PONV was reduced when sugammadex was used instead of pyridostigmine, which causes muscarinic side effects such as PONV, and synergistic effects were demonstrated by using sugammadex with prophylactic palonosetron. The use of sugammadex should also be considered in future studies for prevention of PONV.

Palonosetron is a 5-HT_3 receptor antagonist that effectively prevents PONV during the 0–24 hours period after the operation. Palonosetron was shown to be more effective than ramosetron, when administered during the early phase of the surgery,[13] and this may be due to the peak concentration time (5 hours) and the long duration of action (40 hours) of palonosetron. Prophylactic palonosetron was used before anesthetic induction in our study, and the incidence of PONV in the group treated with prophylactic palonosetron was lower than that in the untreated group, which is consistent with previous results.[12,13]

A multicenter study was conducted to determine the extent to which efficacy could be improved by combining interventions (antiemetic drug [ondansetron, dexamethasone, or droperidol], propofol instead of a volatile anesthetic, reduction of nitrous oxide concentration, and the substitution of remifentanil for fentanyl) to reduce the incidence of PONV.[21] The incidence of PONV in patients with the propofol-maintained anesthesia decreased as the number of combined interventions increased, but the 95% confidence intervals overlapped between the no antiemetic agent and only one antiemetic agent subgroups. Several other studies have also shown that a combination of antiemetics is more effective than the use of single agents.[22,23] Although the univariable logistic regression showed a significant association in our study, there were no significant association between the PONV and each prophylactic palonosetron or sugammadex used alone in the multivariable logistic regression analysis. However, the incidence of PONV was significantly reduced when prophylactic palonosetron and sugammadex were used together (group PAL-SUGA) compared to group NONE in the both univariable and multivariable logistic regression. Our results are consistent with previous studies that combining intervention is more effective at preventing PONV than single antiemetic intervention.

Although the exact etiology of PONV is unknown, many risk factors have been reported. Apfel et al[4] reported that female sex, postoperative use of opioids, history of PONV and/or motion sickness, and non-smoking status were the 4 most important independent risk factors for PONV. In patients undergoing MVD, Meng and Quinlan[24] reported that the risk factors for PONV are female sex, desflurane, and large amounts of fentanyl. In our study, the logistic regression analysis revealed that among the risk factors listed above, only female sex had a statistically significant association with PONV. Although the exact mechanism is unknown, this result may be related to the menstrual cycle and hormonal effect.[25] It has been reported that PONV increases by postoperative use of large amounts of fentanyl ($>250\,\mu g$).[24] In our study, regression analysis showed that postoperative opioid use was not significantly associated with PONV, probably because high doses of fentanyl were not used to control postoperative pain. Although smoking is known to reduce the incidence of PONV, we could not find the association between the smoking and PONV in our study. Further studies may be needed to determine whether the antiemetic effect of smoking is masked in propofol-maintained anesthesia.

There are several limitations to this study. First, due its retrospective nature, we do not have any information about the patients' past history of PONV and motion sickness, which are major risk factors for PONV. Second, this was a single-center study, which has significant inherent limitations in the generalizability of its findings. Third, the number of smoking patients was not standardized for each group. Although the smoking reduces the incidence of PONV, the rate of smoking patients in group NONE was the highest. If smoking factor is standardized through prospective study, the difference of PONV incidence rate may be more increased between groups. It is a limitation of this retrospective study.

In conclusion, the combined use of prophylactic palonosetron before anesthetic induction and sugammadex as a reversal of neuromuscular blockade are associated with a reduction in the incidence of PONV in patients undergoing MVD under propofol-maintained anesthesia. After evaluating the risk for patients scheduled for surgery, the combined use of prophylactic palonosetron and sugammadex can be considered for high-risk patients. To sufficiently evaluate this correlation, a prospective randomized controlled trial is needed.

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