Effects of sugammadex versus neostigmine on postoperative nausea and vomiting in adult patients after general anesthesia: A single-center retrospective study

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Abstract

Background: We aimed to compare the use of sugammadex to that of neostigmine in association with the occurrence of postoperative nausea and vomiting (PONV) during the first 24 h following general anesthesia.

Methods: This retrospective cohort study included 10,912 patients who underwent elective surgery under general anesthesia in 2020 at an academic medical center in Seoul, South Korea. The exposure groups were determined according to whether the patient received sugammadex or neostigmine as a reversal agent. Demographic and perioperative variables, including PONV occurrence, were collected from the electronic medical records. The primary outcome was PONV occurrence during the first 24 h postoperatively (overall). Secondary outcomes were PONV occurrence during 0–2 h (early) and 2–24 h (delayed) postoperatively, and antiemetic use during the first 24 h postoperatively. The associations between the type of reversal agent and primary and secondary outcomes were investigated using logistic regression, while adjusting for confounding variables using stabilized inverse probability of treatment weighting (sIPTW). An interaction analysis was also performed to investigate whether the type of general anesthesia influenced the association between sugammadex use and PONV occurrence.

Results: Of the 10,912 patients included in this study, 5,918 (54.2%) received sugammadex. Sugammadex (vs. neostigmine) was found to be significantly associated with the occurrence of overall PONV (15.8 vs. 17.7%; odds ratio [OR], 0.87; 95% confidence interval [CI], 0.79–0.97; P = 0.010), the occurrence of early PONV (7.6 vs. 9.7%; OR, 0.77; 98.7% CI, 0.65–0.91; P < 0.001), and antiemetic use within 24 h postoperatively (11.8 vs. 14.3%, OR, 0.80; 98.3% CI, 0.70–0.92; P < 0.001) after sIPTW. There was no evidence of interactions between sugammadex use and type of anesthesia for the primary and secondary outcomes.

Conclusions: Compared with neostigmine/glycopyrrolate, sugammadex use was associated with a lower occurrence of PONV during the first 24 h following general anesthesia. Additionally, there was no significant interaction between the type of reversal agent and type of general anesthesia related to overall PONV occurrence. However, our retrospective study design precludes a firm conclusion regarding the effect of sugammadex on PONV after general anesthesia.

Trial registration: not applicable

Background

After general anesthesia, 20–30% of patients experience postoperative nausea and vomiting (PONV) (Kooij et al. 2012). This complication could cause patient discomfort, delayed resumption of postoperative oral intake, delayed discharge, and increased medical costs (Hirsch 1994; Macario et al. 1999). Efforts have been made to prevent PONV (Gan et al. 2020), but complete prevention has thus far failed.

The recent guidelines for PONV management have proposed using sugammadex for neuromuscular blockade (NMB) reversal as a strategy to reduce the baseline risk of PONV (Gan et al. 2020). This recommendation was based on a recent meta-analysis comparing sugammadex with neostigmine, which found that PONV incidence after treatment with sugammadex was significantly lower [odds ratio (OR) 0.52; 95% confidence interval (CI), 0.28–0.97, $P = 0.04$] (Hristovska et al. 2017). A large population-based multicenter retrospective study comparing sugammadex with neostigmine reported a similar reduction in PONV incidence after treatment with sugammadex, before and after propensity-score matching (Kim et al. 2020).

However, all six randomized-controlled trials (RCTs) analyzed in the aforementioned meta-analysis monitored PONV only during the early postoperative period (until discharge from recovery room) (Hristovska et al. 2017) and did not cover a 24-h postoperative period, which corresponds to the minimum observation period recommended (Apfel et al. 2002b). Besides, the effect of neostigmine on PONV has been controversial (Cheng et al. 2005); therefore, we have cautiously

cast doubt on whether using sugammadex instead of neostigmine could be an effective strategy to reduce the occurrence of PONV during the first 24 h postoperatively (Gan et al. 2020). Moreover, of these six RCTs, only one in a small number of patients was conducted under propofol-based total intravenous anesthesia (TIVA), finding no advantage of sugammadex over neostigmine (Schaller et al. 2010). Similarly, most patients (95.6%) in the retrospective study received inhalation anesthesia (Kim et al. 2020). Taken together, there is a paucity of data on the impact of the general anesthesia type (inhalation anesthesia vs. propofol-based TIVA) on the association between sugammadex use and PONV occurrence.

The primary objective of this retrospective study was to investigate the association between the type of reversal agent (sugammadex vs. neostigmine) and PONV occurrence during the first 24 h postoperatively in patients after elective surgery under general anesthesia. We hypothesized that sugammadex use would not be significantly associated with the occurrence rate of PONV during the first 24 h postoperatively. The secondary objective was to investigate whether the type of general anesthesia affects the association between sugammadex use and the occurrence of PONV during the first 24 h postoperatively.

Methods

Study Design and Population

The Institutional Review Board (IRB) of the Seoul National University Hospital approved this retrospective observational study on July 8, 2021 (Approval No. 2107–014–1233). The requirement for informed consent was waived because of the study retrospective design. The study followed the principles of the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Von Elm et al. 2007).

This study included adult patients (≥ 18 years) who underwent elective surgery under general anesthesia in 2020. The exclusion criteria were as follows: 1) underwent reoperation within 24 h after anesthesia; 2) was discharged within 24 h after anesthesia; 3) was transferred to the intensive care unit after anesthesia; 4) did not receive a reversal agent; 5) received cisatracurium for NMB; 6) received both sugammadex and neostigmine; 7) received inhalational anesthetic and TIVA during the same surgery; 8) had American Society of Anesthesiologists (ASA) physical status 4 or higher; 9) had missing covariate values for the propensity score calculations. Only the first surgery was included if the same patient underwent more than one surgery under general anesthesia during 2020. The study recruited all patients meeting the inclusion criteria.

Anesthetic Management

Patients were anesthetized with either inhalation anesthetics or propofol-based TIVA. The attending anesthesiologists decided on the anesthesia type. Sevoflurane or desflurane was used as the inhalation anesthetic. Nitrous oxide was not used during the study period at our institution. TIVA was performed using target-controlled propofol and remifentanil infusion. NMB was achieved to facilitate intubation and maintained using intravenous rocuronium administration. During anesthesia, 5-hydroxytryptamine receptor (5-HT_3R) antagonist (0.3mg ramosetron or 0.075mg palonosetron) and/or 5 mg dexamethasone were administered intravenously for PONV prophylaxis. The patients received 2–4 $mg.kg^{-1}$ sugammadex or 20–40 $mcg.kg^{-1}$ neostigmine and 0.4 mg glycopyrrolate intravenously to reverse NMB at the end of the surgery. Pyridostigmine was not used as a reversal agent in our institution during the study period. The type of reversal and PONV prophylaxis agents were determined according to the attending anesthesiologists. The patients were extubated following neuromuscular recovery and transferred to the post-anesthesia care unit. Rescue antiemetics, such as 5-HT3R antagonists or metoclopramides, were administered at the attending physician's discretion.

Study Outcomes, Study Groups, and Data Collection

The primary outcome was PONV during the first 24 h postoperatively (overall PONV). Secondary outcomes were PONV during the first 0–2 h and 2–24 h postoperatively, defined as the early and the delayed postoperative period, respectively (Apfel et al. 2002a), and antiemetic use during the first 24 h postoperatively. Nurses in the post-anesthesia care unit and general wards in our institution regularly evaluated and recorded postoperative nausea and vomiting in a binary form (yes/no). The exposure groups were determined according to whether the patient received sugammadex or neostigmine as a reversal agent.

Demographic, medical history, and perioperative variables data, including PONV occurrence and antiemetic use, were retrieved from electronic medical records using the Seoul National University Hospital Patients Research Environment (SUPREME) system. PONV data were extracted from the nursing records. The following covariates previously known to influence PONV incidence were analyzed: age, sex, body mass index, current smoking status, ASA physical status, history of PONV, cholecystectomy or gynecological or laparoscopic surgery (Apfel et al. 2012), extent of surgery (minor, intermediate, or major), type of general anesthesia (TIVA or inhalation anesthesia), use of intraoperative steroids, 5-HT_3R antagonists, or opioids, duration of anesthesia (h), and opioid use during the first 24 h postoperatively. Extent of surgery was classified according to the authors' judgment based on a previous study (**Supplementary Table 1**: see Additional file 1) (Myles et al. 2016). Postoperative opioid use included intravenous patient-controlled analgesia with opioids and rescue opioids.

Statistical Analysis

The language and environment for statistical computing R (ver. 4.0.0; R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. The quantile-quantile plot and Shapiro–Wilk test determined the normal distribution of continuous data, which are presented as means (standard deviation [SD]) or medians (interquartile range [IQR]) based on the outcome. Categorical data are presented as numbers (%). Missing-value imputation was not performed.

The following analyses were the main statistical approaches used to evaluate the association between the type of reversal agent and PONV occurrence. First, we investigated the association between reversal agent (sugammadex vs. neostigmine) and primary and secondary outcomes using logistic regression, while adjusting for confounding variables using stabilized inverse probability of treatment weighting (sIPTW) (Schulte and Mascha 2018). We estimated the propensity score for each patient in a logistic regression model predicting sugammadex use (vs. neostigmine) as a function of the following variables: age, sex, body mass index, current smoking status, ASA physical status, history of PONV, extent of surgery, cholecystectomy or gynecological or laparoscopic surgery, type of general anesthesia, use of intraoperative steroids, 5-HT3R antagonists, or opioids, and duration of anesthesia. Since the evidence is lacking regarding the association between PONV occurrence and type of volatile agent (Macario et al. 2005; Wallenborn et al. 2007), we integrated desflurane and sevoflurane anesthesia into inhalation anesthesia. The weights were calculated as 1/(probability of sugammadex use) for patients who received sugammadex and 1/(1-probability of sugammadex use) for patients who received neostigmine. The weights were stabilized by multiplying the proportion of patients who received sugammadex or neostigmine, respectively. We excluded patients with a probability value of 0 or 1 for receiving sugammadex based on the positivity assumption. Additionally, extreme weights smaller than the 1st percentile or larger than the 99th percentile were replaced with the 1st or 99th percentile value, respectively (Schulte and Mascha 2018). We used the standardized mean difference (SMD) to evaluate the between-group variable balance before and after performing sIPTW. The groups were considered well balanced when the SMD was < 0.10 for all covariates. An SMD < 0.15 was also considered acceptable. Subsequently, we performed a binary logistic regression to investigate the association between sugammadex use and the primary and secondary outcomes before and after performing sIPTW. The significance level for the secondary outcomes was adjusted for multiple comparisons using the Bonferroni correction ($P < 0.05/3 = 0.017$).

Second, multivariable binary logistic regression analyses for the occurrence of early and overall PONV were used for sensitivity analysis with the following variables included: sugammadex use, sex, age, ASA physical status, history of PONV, body mass index, current smoking status, cholecystectomy or gynecological or laparoscopic surgery, extent of surgery, type of general anesthesia, use of intraoperative steroids or 5-HT_3R antagonists, and duration of anesthesia. Postoperative opioid use, which could not be included in the sIPTW, was additionally included in the regression analysis for the occurrence of overall PONV. We used variance inflation factor (VIF) to evaluate multicollinearity between the variables included in the logistic regression analyses. We did not perform univariable regression analyses to select variables for the multivariable analysis model.

Third, we also performed an interaction analysis to investigate whether the type of general anesthesia influences the association between sugammadex use and PONV occurrence. The covariates included in the aforementioned multivariable logistic regression analysis were adjusted.

Because of the retrospective design of the study, a priori power calculation was not performed. In our institution, there were changes in the regimen of intravenous patient-controlled analgesia (Jung et al. 2020), and intraoperative non-opioid analgesics were introduced during 2019. We determined that these changes could affect the PONV occurrence rate and decided to include in this study only patients who underwent surgery in 2020. With the PONV occurrence rate of patients who received neostigmine assumed to be 18%, based on our acute pain service team's data (Jung et al. 2020), the group sample sizes of 5918 for sugammadex and 4994 for neostigmine could achieve 90% power to reveal a difference in proportion between the groups of -2.3%.

Results

Of the 20,017 adult patients who underwent elective surgery under general anesthesia during the study period, 10,912 patients were found eligible and included in the analysis (Fig. 1). Among them, 5,918 (54.2%) received sugammadex and 4,994 (45.8%) received neostigmine and glycopyrrolate for NMB reversal.

Table 1 presents the baseline characteristics between-group comparisons before and after performing sIPTW. The groups differed significantly in age, sex, ASA physical status, cholecystectomy or gynecological or laparoscopic surgery, type of general anesthesia, use of intraoperative steroids and 5-HT_3R antagonists, duration of anesthesia, and postoperative opioid use before performing sIPTW (SMD > 0.1) but not after, except for sex, whose SMD was considered acceptable (SMD = 0.101).

Table 1
Baseline characteristics and perioperative parameters compared between patients treated with sugammadex or neostigmine, before and after adjusting for confounding by inverse probability of treatment weighting (IPTW) in the total cohort.

Characteristics	Before IPTW			After IPTW[a]		
	Sugammadex (n = 5918)	Neostigmine (n = 4994)	SMD	Sugammadex (n = 5928)	Neostigmine (n = 4736)	SMD
Age, years	61 (49–69)	54 (42–64)	0.363	59 (46–68)	57 (45–67)	0.070
Female	3047 (51.5)	3527 (70.6)	0.400	3531.7 (59.6)	3053.4 (64.5)	0.101
Body mass index, $kg \cdot m^{-2}$	23.9 (21.8–26.3)	23.8(21.6–26.3)	0.025	23.8 (21.6–26.3)	23.8 (21.6–26.2)	0.024
Current smoker	435 (7.4)	328 (6.6)	0.031	434.5 (7.3)	318.7 (6.7)	0.023
History of PONV	151 (2.6)	104 (2.1)	0.031	150.3 (2.5)	121 (2.6)	0.001
ASA physical status I/II/III	752 (12.7)/4505 (76.1)/661 (11.2)	913 (18.3)/3773 (74.7)/348 (7.0)	0.200	918 (15.5)/4422 (74.6)/589 (9.9)	761 (16.1)/3534 (74.6)/441 (9.3)	0.025
Cholecystectomy or gynecological or laparoscopic surgeries	2733 (46.2)	800 (16.0)	0.689	1934 (32.6)	1552 (32.8)	0.003
Extent of surgery			0.830			0.037
Minor	487 (8.2)	1303 (26.1)		1055 (17.8)	856 (18.1)	
Intermediate	384 (6.5)	1225 (24.5)		861 (14.5)	746 (15.7)	
Major	5047 (85.3)	2466 (49.4)		4012 (67.7)	3134 (66.2)	
Type of general anesthesia			0.321			0.027
Total intravenous anesthesia	1446 (24.4)	1958 (39.2)		1927 (32.5)	1600 (33.8)	
Inhalation anesthesia	4472 (75.6)	3036 (61.1)		3902 (67.5)	3136 (66.2)	
Intraoperative steroid use	2994 (50.6)	965 (19.3)	0.694	2066 (34.9)	1500 (31.7)	0.068
Intraoperative 5-HT_3R antagonist use	5537 (93.6)	3847 (77.0)	0.480	5198 (87.7)	4029 (85.1)	0.076
Intraoperative opioid use	5902 (99.7)	4940 (98.9)	0.099	5887 (99.3)	4704 (99.3)	0.004

The values are presented as medians (interquartile range) or numbers (%). ASA, American Society of Anesthesiologists; SMD, standardized mean difference; 5-HT_3R, 5-hydroxytryptamine receptor

[a] Stabilized weights were used to adjust for confounding. The following variables were used as contributors to the propensity score: age, sex, body mass index, current smoker, ASA physical status, cholecystectomy or gynecological or laparoscopic surgeries, type of general anesthesia, intraoperative steroid use, intraoperative 5-HT_3R antagonist use, intraoperative opioid use, and duration of anesthesia. Postoperative opioid use was not used for propensity score calculation.

[b] during the first 24 h postoperatively.

Characteristics	Before IPTW			After IPTW[a]		
	Sugammadex (n = 5918)	Neostigmine (n = 4994)	SMD	Sugammadex (n = 5928)	Neostigmine (n = 4736)	SMD
Duration of anesthesia, hour	2.65 (1.93–3.83)	2.40 (1.67–3.50)	0.172	2.43 (1.65–3.60)	2.55 (1.77–3.58)	0.025
Postoperative opioid use[b]	5208 (88)	3230 (64.7)	0.571	4517 (76.2)	3552 (75)	0.028

The values are presented as medians (interquartile range) or numbers (%). ASA, American Society of Anesthesiologists; SMD, standardized mean difference; 5-HT_3R, 5-hydroxytryptamine receptor

[a] Stabilized weights were used to adjust for confounding. The following variables were used as contributors to the propensity score: age, sex, body mass index, current smoker, ASA physical status, cholecystectomy or gynecological or laparoscopic surgeries, type of general anesthesia, intraoperative steroid use, intraoperative 5-HT_3R antagonist use, intraoperative opioid use, and duration of anesthesia. Postoperative opioid use was not used for propensity score calculation.

[b] during the first 24 h postoperatively.

Table 2 presents the ORs of using sugammadex for the primary and secondary outcomes before and after sIPTW. Patients who received sugammadex had a significantly lower rate of overall and early PONV than those who received neostigmine before sIPTW. After sIPTW, sugammadex (vs. neostigmine) was associated with a significantly lower rate of overall PONV (15.8 vs. 17.7%, respectively; OR, 0.87; 95% CI, 0.79–0.97; $P = 0.010$). Sugammadex (vs. neostigmine) was also associated with a significantly lower rate of early PONV (7.6 vs. 9.7%, OR, 0.77; 98.3% CI, 0.65–0.91; $P < 0.001$) and antiemetic use within 24 h postoperatively (11.8 vs. 14.3%, OR, 0.80; 98.3% CI, 0.70–0.92; $P < 0.001$) after sIPTW.

Table 2

Odds ratios of sugammadex use on the primary and secondary outcomes compared with neostigmine, before and after adjusting for confounding by inverse probability of treatment weighting (IPTW), in the total cohort.

	Before IPTW				After IPTW[a]			
Primary outcome	Sugammadex (n = 5918)	Neostigmine (n = 4994)	Odds ratio[b] (95% CI)	*P*-value	Sugammadex (n = 5928)	Neostigmine (n = 4736)	Odds ratio[b] (95% CI)	*P*-value
Overall PONV (within 24h)	964 (16.3)	898 (18.0)	0.89 (0.80–0.98)	0.019	936 (15.8)	837 (17.7)	0.87 (0.79–0.97)	0.010
Secondary outcome	Sugammadex (n = 5918)	Neostigmine (n = 4994)	Odds ratio[b] (98.3% CI)	*P*-value[c]	Sugammadex (n = 5928)	Neostigmine (n = 4736)	Odds ratio[b] (98.3% CI)	*P*-value[c]
Early PONV (0–2h)	427 (7.2)	499 (10)	0.7 (0.59–0.83)	< 0.001	453 (7.6)	460 (9.7)	0.77 (0.65–0.91)	< 0.001
Delayed PONV (2–24h)	687 (11.6)	592 (11.9)	0.98 (0.85–1.13)	0.691	655 (11)	563 (11.9)	0.92 (0.80–1.06)	0.171
Antiemetic use (within 24h)	732 (12.4)	680 (13.6)	0.9 (0.78–1.03)	0.053	700 (11.8)	679 (14.3)	0.80 (0.70–0.92)	< 0.001

CI, confidence interval; PONV, postoperative nausea and vomiting

[a] Stabilized weights were used to adjust for confounding.

[b] Odds ratios estimate the odds of the given outcome in patients who received sugammadex versus patients who received neostigmine for each outcome.

[c] Statistical significance corrected by the Bonferroni correction to adjust for increased type I error by multiple testing ($P < 0.05/3 = 0.017$).

Interaction analysis revealed that there were no significant interactions among sugammadex use and type of general anesthesia for the primary and secondary outcomes except antiemetic use during the first 24 h postoperatively (Table 3).

Table 3
Interaction of primary and secondary outcomes between the use of sugammadex (vs neostigmine) and total intravenous anesthesia (vs inhalation anesthesia)

	Interaction *P*-value
Primary outcome	
Overall PONV (within 24h)	0.966
Secondary outcome	
Early PONV (0–2h)	0.984
Delayed PONV (2–24h)	0.502
Antiemetic use (within 24h)	0.036

Multivariable logistic regression analysis showed that sugammadex use was significantly associated with overall and early PONV occurrence (overall: OR, 0.87; 95% CI, 0.77–0.98; $P = 0.023$; early: OR, 0.81; 95% CI, 0.68–0.96; $P = 0.013$; Table 4). Since there were no significant interactions among sugammadex use and type of general anesthesia for the overall and early PONV occurrence, their interaction term was not included in these models.

Table 4
Predictive factors associated with postoperative nausea and vomiting during the first and 24 h after general anesthesia (GA) based on binary multivariable logistic regression analyses.

	During the first 2h after GA		During the first 24h after GA	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Sugammadex (vs. neostigmine)	0.81 (0.68–0.96)	0.013	0.87 (0.77–0.98)	0.023
Female (vs. male)	2.41 (2.03–2.86)	< 0.001	2.58 (2.27–2.92)	< 0.001
Age. year	0.99 (0.98–0.99)	< 0.001	0.99 (0.98–0.99)	< 0.001
ASA physical status (vs. Class I)				
Class II	1.04 (0.86–1.26)	0.658	0.96 (0.83–1.11)	0.550
Class III	0.87 (0.63–1.20)	0.394	0.87 (0.69–1.10)	0.237
History of PONV	1.51 (1.02–2.25)	0.040	1.54 (1.14–2.09)	0.005
Body mass index, $kg \cdot m^{-2}$	1.00 (0.99–1.02)	0.624	0.98 (0.96–0.99)	0.003
Current smoker	0.84 (0.60–1.17)	0.311	0.68 (0.53–0.88)	0.003
Cholecystectomy or gynecological or laparoscopic surgeries	1.16 (0.98–1.37)	0.090	0.82 (0.73–0.93)	0.002
Extent of surgery (vs. minor)				
Intermediate	1.05 (0.83–1.32)	0.702	1.02 (0.83–1.24)	0.867
Major	0.83 (0.67–1.03)	0.091	1.67 (1.40–2.01)	< 0.001
Total intravenous anesthesia (vs. inhalation anesthesia)	0.33 (0.27–0.39)	< 0.001	0.49 (0.43–0.55)	< 0.001
Intraoperative steroid use	0.81 (0.69–0.95)	0.008	0.86 (0.76–0.96)	0.010
Intraoperative 5-HT_3R antagonist use	0.83 (0.67–1.03)	0.090	0.98 (0.83–1.15)	0.768
Duration of anesthesia, hour	1.20 (1.16–1.25)	< 0.001	1.13 (1.10–1.17)	< 0.001
Postoperative opioid use			1.23 (1.05–1.44)	0.010

CI, confidence interval; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting; 5-HT_3R, 5-hydroxytryptamine receptor

Discussion

We found a significant association between sugammadex use and a decrease in overall PONV occurrence compared to the use of neostigmine with glycopyrrolate. Additionally, there was no significant interaction between sugammadex use and type of general anesthesia on overall PONV occurrence. Further randomized trials are required to investigate the effect of sugammadex use on PONV during the first 24 h postoperatively.

Our findings are consistent with previous studies, in which sugammadex was more effective than neostigmine in reducing immediate postoperative PONV (Hristovska et al. 2017; Koyuncu et al. 2015; Ledowski et al. 2014). The observation period for PONV in the six studies included in the meta-analysis was the immediate postoperative phase (Hristovska et al. 2017). Similar results were found in a retrospective study, in which sugammadex was more effective than neostigmine in reducing PONV in the recovery room (Ledowski et al. 2014).

However, we also showed that the significant association between sugammadex and PONV remained during the early postoperative period but disappeared during the delayed period. Previous studies reported conflicting results regarding the effect of sugammadex on PONV during the first 24 h postoperatively. An RCT with patients undergoing extremity surgery found a significant negative association between sugammadex use and PONV upon arrival in the recovery room, but not at subsequent time points (Koyuncu et al. 2015). Conversely, a large multicenter retrospective study reported sugammadex to be significantly associated with a decrease in PONV during the first 24 h postoperatively (Kim et al. 2020). However, considering the low rate of propofol-based TIVA and prophylactic steroid use, the reported PONV occurrence rate was likely underestimated. Although we also used retrospective data, the incidence of PONV in our study was similar to the recently reported early PONV incidence in a hospital in Sweden (Johansson et al. 2021) and data from our acute pain service team (Jung et al. 2020). Regression analysis also revealed previously well-known predictors for PONV, supporting the reliability of our data. Additionally, considering the increasing use of sugammadex in our institution (Ju et al. 2021), we only included patients from 2020 to minimize the effect of possible changes in perioperative management during the study period. A recent meta-analysis reported that compared with neostigmine, sugammadex was significantly associated with a reduction in PONV (Hurford et al. 2020a). However, the PONV observation periods in the 17 included studies varied considerably, and we investigated the association between sugammadex and PONV during different time windows. Future research in the effect of sugammadex on PONV would need to consider changes over time.

The rationale that sugammadex use could be associated with a decrease in PONV is based on evidence regarding the effect of neostigmine on PONV; however, the evidence is controversial (Cheng et al. 2005; Tramèr and Fuchs-Buder 1999). Although anticholinesterase has been reported to contribute to PONV by several central and peripheral mechanisms (Hood et al. 1995; Paech et al. 2018), a recent meta-analysis found no association between neostigmine and PONV occurrence rate during the first 24 h postoperatively (Cheng et al. 2005). The low-dose neostigmine (20–40 $mcg.kg^{-1}$) used in our institution would also have affected our inconclusive results (Tramèr and Fuchs-Buder 1999). However, in our analyses, sugammadex was significantlyassociated with a lower early PONV rate than was neostigmine and glycopyrrolate, possibly because of the use of glycopyrrolate. Unlike atropine, glycopyrrolate does not have antiemetic properties as it cannot cross the blood-brain barrier (Fuchs-Buder and Mencke 2001); therefore, glycopyrrolate could not offset the emetogenic effect of neostigmine. Furthermore, neostigmine has a short effect duration (20–30 min) (Priya Nair and Hunter 2004), well below 24 h postoperatively.

We also investigated the effect of sugammadex on PONV according to the type of general anesthesia. The meta-analysis used as a reference in the recent PONV guidelines (Gan et al. 2020) also assessed the effect of sugammadex on PONV according to the type of general anesthesia (Hristovska et al. 2017); however, the results were inconclusive because the TIVA subgroup included only one study (Hristovska et al. 2017). We found no significant interaction for the primary and secondary outcomes between sugammadex use and type of general anesthesia. Therefore, the power to reveal a significant effect of sugammadex use on PONV may vary depending on the difference in PONV occurrence according to the type of general anesthesia; however, its effect on PONV may not vary depending on the type of general anesthesia.

Our study had several limitations. First, regarding limitations inherent to the study's retrospective design, unmeasured or unknown covariates, including a history of motion sickness, intraoperative hypotension, and fluid administration, might have biased our results. Second, as a study at a single tertiary university hospital, the generalizability of our findings is

impeded. Differences in perioperative management could affect the PONV occurrence rate. Third, the number of antiemetic agents administered and type of general anesthesia were determined by the attending anesthesiologists rather than the predicted risk of PONV. Especially, 5-HT_3R antagonists were not used in patients at low risk of PONV in our hospitals, and the regression analysis found no association between 5-HT_3R antagonists and overall PONV. Fourth, since we could not investigate post-discharge nausea and vomiting because of our retrospective design, several patients were excluded from discharge within 24 h postoperatively, possibly causing selection bias. However, given that the association between sugammadex use and PONV was significant only in the early postoperative period, by the time period of our primary outcome, the selection bias might have been insignificant. Lastly, because of the absence of cost-effectiveness analysis, our results could not justify the use of sugammadex to reduce PONV. Concern over the expense of sugammadex was reported as the primary barrier to its use in a worldwide survey (O'Reilly-Shah et al. 2017). A recent cost analysis study opposed its routine use to reduce only PONV (Hurford et al. 2020b).

Conclusions

In conclusion, we found a significant association between sugammadex use and decrease in PONV during the first 24 h after general anesthesia, compared to use of neostigmine with glycopyrrolate, possibly because of a decrease in PONV during the early postoperative period rather than the delayed period. Additionally, there was no significant interaction for overall PONV occurrence between sugammadex use and type of general anesthesia, suggesting that the association between sugammadex use and PONV did not vary depending on the type of general anesthesia. However, our retrospective study design precludes a firm conclusion regarding the effect of sugammadex on PONV after general anesthesia.

Abbreviations

5-HT_3R
5-hydroxytryptamine receptor
ASA
American Society of Anesthesiologists
CI
confidence interval
IQR
interquartile range
IRB
Institutional Review Board
NMB
neuromuscular blockade
OR
odds ratio
PONV
postoperative nausea and vomiting
RCT
randomized-controlled trial
SD
standard deviation
sIPTW
stabilized inverse probability of treatment weighting

SMD
standardized mean difference
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
SUPREME
Seoul National University Hospital Patients Research Environment
TIVA
based total intravenous anesthesia
VIF
variance inflation factor

Declarations

Ethics approval and consent to participate

The requirement for informed consent was waived because of the study retrospective design.

Consent for publication

Not applicable

Availability of data and materials

Data are available from the authors upon reasonable request and with permission of the Institutional Review Board of the Seoul National University Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J-WJ contributed to study design/planning, data collection, data analysis, and drafting the manuscript. IEH contributed to data collection and data analysis. H-YC contributed to data collection and drafting the manuscript. SMY contributed to data collection and revising the manuscript. WHK contributed to data analysis and drafting the manuscript. H-JL contributed to study design/planning, data collection, data analysis, and revising the manuscript. All authors read and approved the final manuscript

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Figures

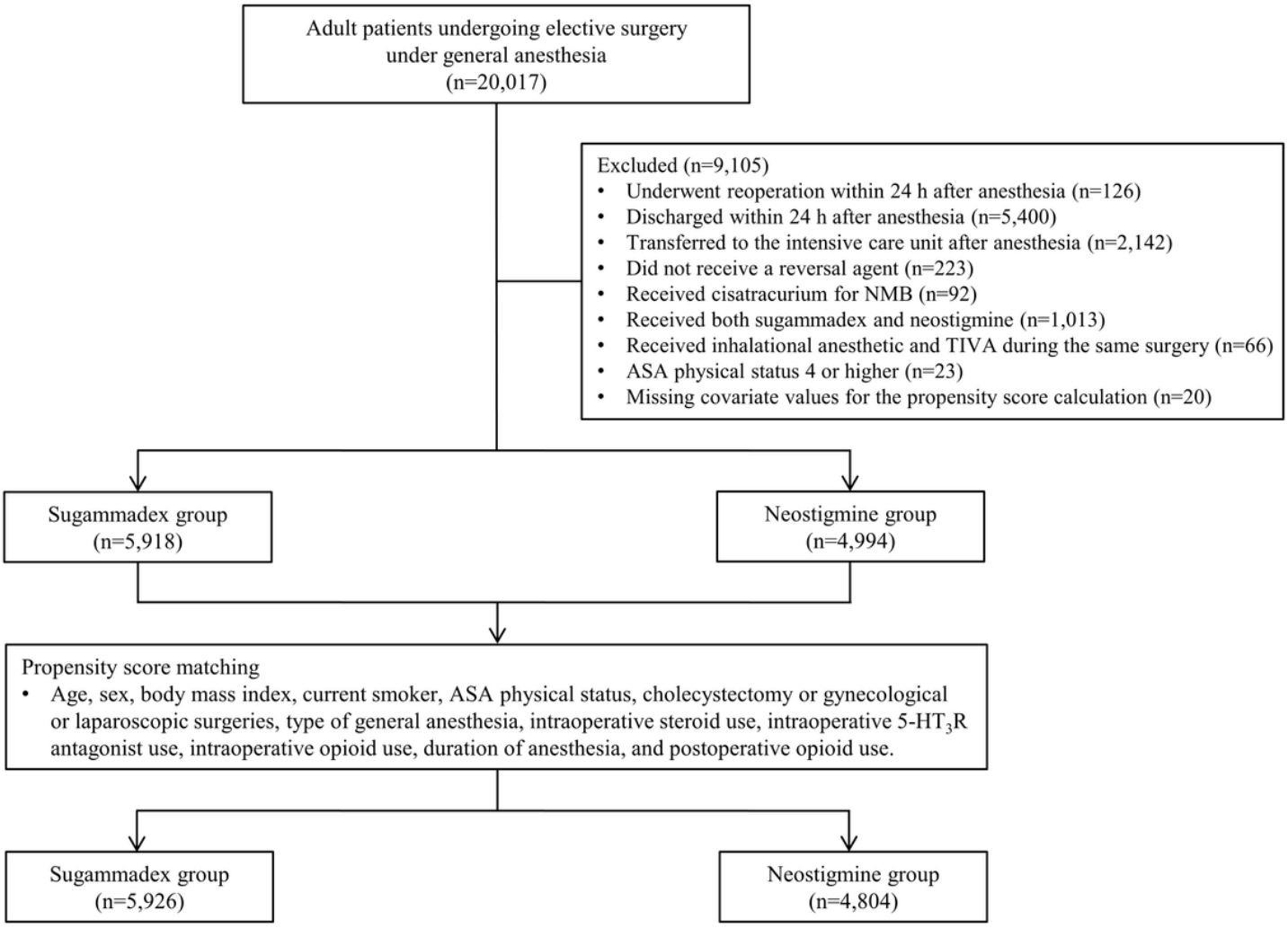

Figure 1

Flow diagram of the study. ASA, American Society of Anesthesiologists; NMB, neuromuscular blockade; TIVA, total intravenous anesthesia; 5-HT3R, 5-hydroxytryptamine receptor

Supplementary Files

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