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ORIGINAL ARTICLE

Postoperative nausea and vomiting after artificial joint replacement surgery: comparison between remimazolam and sevoflurane, a propensity score analysis

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Abstract

Purpose Remimazolam, a newly synthesized ultrashort-acting benzodiazepine, has not been previously compared with sevoflurane with regard to postoperative nausea and vomiting (PONV). The aim of this study is to investigate the incidence of PONV between remimazolam and sevoflurane among patients undergoing artificial joint replacement surgery.

Methods We conducted a retrospective analysis of the electronic medical records of patients who underwent artificial joint replacement surgery at Kobe City Medical Center General Hospital from 2020 to 2022, with a focus on comparing the incidence of PONV among those who received sevoflurane versus remimazolam anesthesia. To control for confounding factors, we employed a propensity score-matching technique to pair patients who received sevoflurane anesthesia with those who received remimazolam anesthesia.

Results The records of 292 patients receiving general anesthesia for artificial joint replacement surgery were collected and categorized into group sevoflurane ($n=241$) or group remimazolam ($n=51$). Before propensity score matching, age and ASA-PS exhibited significant differences between two groups. There was no significant difference in the incidence of PONV between them ($p=0.461$). After matching, there were 51 patients in each group. However, there is no significant difference in the incidence of PONV between the two matched cohorts ($p=0.243$).

Conclusions This study demonstrated that there was no difference in the prevalence of PONV between remimazolam and sevoflurane anesthesia in patients undergoing artificial joint replacement surgery.

Keywords Remimazolam · Postoperative nausea and vomiting · Propensity score matching

Introduction

Postoperative nausea and vomiting (PONV) is usually defined as nausea and/or vomiting in the post-anesthesia care unit (PACU) or in the immediate 24 postoperative hours. It has reported to occur in 30% of all post-surgical patients and up to 80% in high-risk patients [1–4]. Patients often rate PONV as worse than postoperative pain [5]. In addition, it may require unanticipated hospital admission and delay recovery room discharge [6, 7] and it is important to prevent or reduce PONV in perioperative management.

Remimazolam is a newly developed ultrashort-acting benzodiazepine that acts on central GABAA receptors to produce sedation and amnesia. It was approved as a general anesthetic in Japan firstly in the world [8]. Hari et al. reported in their prospective randomized double-blinded study that remimazolam reduced the incidence of PONV after laparoscopic gynecological surgery compared to general anesthesia with desflurane during the early postoperative period [9]. However, no study has compared the incidence of PONV between remimazolam and sevoflurane. In this propensity score-matched, retrospective, observational study, we aimed to compare the rates of PONV between remimazolam and sevoflurane in patients undergoing artificial joint replacement surgery.

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Methods

Study design

The present study was approved by the ethics review boards of our hospital (zn220615). All data were anonymized and de-identified at the start of the study. We analyzed the electronic medical records of 292 patients receiving artificial joint replacement surgery in Kobe City Medical Center General Hospital from January 1, 2020 to October 31, 2022 with sevoflurane and remimazolam anesthesia. Artificial joint replacement surgery included hip, knee, shoulder, and other surgeries. All surgeries were performed under general anesthesia. Most of cases received peripheral nerve block with a single dose of ropivacaine after the induction of general anesthesia. In addition to the maintenance anesthetics (sevoflurane or remimazolam), remifentanil, rocuronium, and fentanyl were administered during operation. Most patients received intravenous patient-controlled analgesia (IV-PCA) with fentanyl after the operation. In cases where blood transfusion was conducted, exclusively red blood cell transfusion and autologous blood transfusion were implemented, with no administration of fresh frozen plasma or platelet products.

We excluded cases where two or more general anesthetics are used in combination, cases with missing data for variables or outcome measures, cases in which remimazolam was used only for the induction of anesthesia. We categorized the patients according to maintenance anesthetic agents used: group sevoflurane ($n = 241$) and group remimazolam ($n = 51$).

Data collection

We collected data associated with risk factors for PONV related to patient characteristics (age, gender, height, weight, body mass index, Apfel score, and American Society of Anesthesiologists physical status: ASA-PS), risk factors related to operation (operation time, anesthesia time, and total fluid volume), and risk factors related to medications (dose of intravenous fentanyl, dexamethasone, droperidol, granisetron, and fentanyl in IV-PCA) from institutional anesthesia database (ORSYS, PHILIPS, Amsterdam, Netherlands). There were no cases where metoclopramide was administered intraoperatively. Apfel score is a PONV prediction score [2] and was calculated from four factors: female gender, nonsmoking status, postoperative use of opioids, and history of PONV or motion sickness. Data regarding the occurrence of PONV were abstracted from the record of postoperative round by anesthesiologists in electronic medical charts.

Statistical analysis

This is a retrospective study and did not involve any statistical power analysis. All characteristics and measured outcomes were demonstrated as mean and standard deviation for continuous variables and as numbers and percentages for categorical variables. The Mann–Whitney U test was used for group comparisons of continuous variables when data were abnormally distributed; otherwise, Student's t test was applied. Pearson's χ^2 and Fisher's exact test were used for group comparisons of categorical variables. Because this was a retrospective cohort study, patients were not randomized before the statistical analysis. Therefore, we used a propensity score matching method to minimize the effect of selection bias on the outcomes. Individual propensity scores were generated through multivariable logistic regression model, accounting for covariates such as age, gender, height, weight, body mass index, Apfel score, ASA-PS, operation time, anesthesia time, and total infusion volume, dosage of administered fentanyl, dexametazone, droperidol, granisetron, and contents of IV-PCA. Patients with sevoflurane or remimazolam anesthesia were matched with a ratio 1:1 on these propensity scores using a caliper size of 0.2. We matched 51 patients anesthetized by remimazolam with 51 patients anesthetized by sevoflurane. All p values were two-sided, and a p value < 0.05 was considered indicative of statistical significance. Statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) modified to add statistical functions [10].

Results

The records of 292 patients receiving general anesthesia for artificial joint replacement surgery at Kobe City Medical Center General Hospital from January 1, 2020 to October 31, 2022 were collected and categorized into group sevoflurane ($n = 241$) or group remimazolam ($n = 51$). Their baseline characteristics are listed in Table 1. Before propensity score matching, age and ASA-PS exhibited significant differences between two groups. There was no significant difference in the incidence of PONV between them ($p = 0.461$). After matching, there were 51 patients in each group. The clinical characteristics of the two matched groups extracted by a propensity analysis are presented in Table 2. The covariates were well balanced after matching. However, there is no significant difference in the incidence of PONV between the two matched cohorts ($p = 0.243$).

Table 1 Patient characteristics

	Sevoflurane ($n=241$)	Remimazolam ($n=51$)	p value
Administration of flumazenil		49/51	
Artificial joint replacement			
Hip (%)	143 (59.3)	34 (66.7)	0.349
Knee (%)	83 (34.4)	16 (31.4)	0.746
Shoulder (%)	15 (6.2)	1 (2.0)	0.322
Others (%)	1 (0.4)	0 (0.0)	1
Postoperative analgesia			
PNB (%)	188 (78.0)	41 (80.4)	0.852
Epidural (%)	32 (13.3)	3 (5.9)	0.161
Others (%)	21 (8.7)	7 (13.7)	0.294
Sex, female (%)	173 (71.8)	35 (68.6)	0.734
Age (yr)	70.79 ± 9.54	77.82 ± 8.31	< 0.001
Height (cm)	154.85 ± 9.49	150.34 ± 23.11	0.024
Weight (kg)	59.53 ± 13.05	56.35 ± 10.25	0.104
Body mass index (kg/m^2)	24.75 ± 4.61	23.53 ± 5.01	0.093
Operation time (min)	176.30 ± 62.15	170.12 ± 62.20	0.519
Anesthesia time (min)	256.15 ± 65.93	253.47 ± 67.34	0.793
Fluid volume (mL)	1638.77 ± 650.77	1583.28 ± 569.42	0.573
Transfusion (%)	29 (12.0)	13 (25.5)	0.026
Transfusion volume (mL)	33.22 ± 109.14	42.49 ± 94.19	0.574
Reversal of muscle relaxation			
Neostigmine (%)	55 (22.8)	8 (15.7)	0.349
Sugammadex (%)	187 (77.6)	44 (86.3)	0.189
ASA-PS	2.29 (0.52)	2.59 (0.54)	< 0.001
Risk factors of PONV			
Apfel score	2.61 ± 0.72	2.69 ± 0.85	0.493
Remifentanil (mg)	0.98 ± 0.63	1.04 ± 0.76	0.549
Intraoperative fentanyl (mcg)	219.29 ± 108.74	232.35 ± 95.17	0.427
Dose of fentanyl in IV-PCA (mcg/h)	20.27 ± 8.97	19.12 ± 7.29	0.391
Preventive factors of PONV			
Dexamethasone (mg)	2.38 ± 2.55	2.73 ± 2.75	0.386
Droperidol (mg)	0.11 ± 0.15	0.11 ± 0.17	0.919
Granisetron (mg)	0.30 ± 0.56	0.37 ± 0.56	0.397
PONV (%)	56 (23.2)	9 (17.6)	0.461
No PONV (%)	185 (76.8)	42 (82.4)	0.461
Mild nausea (%)	29 (12.0)	3 (5.9)	0.321
Severe nausea (%)	3 (1.2)	1 (2.0)	0.538
Vomitting (%)	24 (10.0)	5 (9.8)	1

Values are shown as mean ± SD or number (%)

PNB peripheral nerve block, *ASA-PS* American Society of Anesthesiologists physical status, *PONV* postoperative nausea and vomiting, *IV-PCA* intravenous patient-controlled analgesia

Discussion

In this study, we investigated whether remimazolam anesthesia could decrease the incidence of PONV compared with sevoflurane anesthesia. However, there was no difference in the incidence of PONV between sevoflurane anesthesia and remimazolam anesthesia. After propensity score matching, the results were essentially unchanged.

Remimazolam is a novel, ultrashort-acting benzodiazepine that exerts its sedative and amnesic effects via interaction with central GABAA receptors [11]. It was approved as a general anesthetic in Japan firstly in the world [8], and recently approved for procedural sedation in the United States, China, and Europe. Remimazolam is metabolized by tissue esterases to an inactive metabolite [12], and the half-time of arterial remimazolam concentration for 3-h constant

Table 2 Patient characteristics after propensity score matching

	Sevoflurane ($n=51$)	Remimazolam ($n=51$)	p value
Artificial joint replacement			
Hip (%)	25 (49.0)	34 (66.7)	0.108
Knee (%)	24 (47.1)	16 (31.4)	0.155
Shoulder (%)	2 (3.9)	1 (2.0)	1
Postoperative analgesia			
PNB (%)	42 (82.4)	41 (80.4)	1
Epidural (%)	2 (3.9)	3 (5.9)	1
Others (%)	7 (13.7)	7 (13.7)	1
Sex, female (%)	14 (27.5)	16 (31.4)	0.828
Age (yr)	76.86 ± 7.97	77.82 ± 8.31	0.553
Height (cm)	152.73 ± 9.02	150.34 ± 23.11	0.493
Weight (kg)	57.92 ± 13.41	56.35 ± 10.25	0.508
Body mass index (kg/m^2)	24.73 ± 4.90	23.53 ± 5.01	0.223
Operation time (min)	166.61 ± 47.82	170.12 ± 62.20	0.75
Anesthesia time (min)	250.67 ± 47.23	253.47 ± 67.34	0.808
Fluid volume (mL)	1471.61 ± 553.55	1583.28 ± 569.42	0.318
Transfusion (%)	9 (17.6)	13 (25.5)	0.471
Transfusion volume (mL)	33.73 ± 95.27	42.49 ± 94.19	0.641
Reversal of muscle relaxation			
Neostigmine (%)	7 (13.7)	8 (15.7)	1
Sugammadex (%)	44 (86.3)	44 (86.3)	1
ASA-PS	2.59 ± 0.50	2.59 ± 0.54	1
Risk factors of PONV			
Apfel score	2.65 ± 0.66	2.69 ± 0.85	0.791
Remifentanil (mg)	1.02 ± 0.67	1.04 ± 0.76	0.869
Intraoperative fentanyl (mcg)	239.71 ± 107.49	232.35 ± 95.17	0.715
Dose of fentanyl in IV-PCA (mcg/h)	18.78 ± 8.61	19.12 ± 7.29	0.833
Preventive factors of PONV			
Dexamethasone (mg)	2.43 ± 2.50	2.73 ± 2.75	0.563
Droperidol (mg)	0.15 ± 0.17	0.11 ± 0.17	0.297
Granisetron (mg)	0.41 ± 0.70	0.37 ± 0.56	0.756
PONV (%)	15 (29.4)	9 (17.6)	0.243
No PONV (%)	36 (70.6)	42 (82.4)	0.243
Mild nausea (%)	3 (5.9)	3 (5.9)	1
Severe nausea (%)	0 (0.0)	1 (2.0)	1
Vomitting (%)	12 (23.5)	5 (9.8)	0.109

Values are shown as mean ± SD or number (%)

ASA-PS American Society of Anesthesiologists physical status, *PONV* postoperative nausea and vomiting, *IV-PCA* intravenous patient-controlled analgesia

rate infusion is approximately 7.5 min [13]. In addition, as remimazolam belongs to the benzodiazepine class of drugs, the benzodiazepine antagonist flumazenil can reverse the effects of remimazolam in the event of adverse reactions and further abbreviate recovery times [13].

There have been few studies that have contrasted the incidence of PONV between remimazolam and other inhaled anesthetics. A study by Hari et al. found that remimazolam was effective in reducing the incidence of early postoperative nausea and vomiting in comparison to desflurane in gynecological laparoscopic surgery, with no significant difference observed in the incidence of PONV 24 h after surgery [9]. Song et al. also reported in their parallel-group, single-blind randomized controlled trial that remimazolam significantly reduced the incidence of PONV compared to the desflurane group in patients undergoing laparoscopic cholecystectomy or robotic gynecological surgery [14].

Several studies have compared the incidence of PONV between remimazolam and propofol. Suzuki et al. reported that, in their retrospective, observational study employing

propensity score matching, remimazolam anesthesia was associated with a higher incidence of postoperative nausea and vomiting compared to propofol [15]. Similarly, Mao et al. reported in their prospective, double-blinded, randomized controlled trial that the incidence of PONV was higher in the remimazolam group than in the propofol group in patients undergoing urological surgery [16]. On the other hand, Choi et al. reported in their prospective, double-blind, randomized controlled, non-inferiority trial that there were no significant differences in PONV between remimazolam and propofol anesthesia in patients undergoing open thyroidectomy [17]. The findings derived from these studies will inevitably be influenced by the nature of the surgical procedure, the individual characteristics of the patient, and study populations. At present, no expansive and conclusive prospective studies exist with regard to the impact of remimazolam on PONV. The prevalence of PONV in the context of remimazolam anesthesia is currently undetermined.

There are several reports indicating that midazolam, a benzodiazepine similar to remimazolam, may be effective in preventing PONV. Lee et al. reported in their randomized controlled trial that midazolam 2 mg when administered 30 min before the end of surgery was as effective against PONV as ondansetron 4 mg [18]. Ahn et al. conclude in their systematic review and meta-analysis that midazolam is effective in preventing PONV [19]. Given that midazolam has been shown to have a preventive effect on PONV, it was expected that remimazolam would exhibit a similar effect. However, This study found no significant difference in the frequency of PONV between remimazolam and sevoflurane, although the use of volatile anesthetics was reported to be the primary cause of early postoperative vomiting [20]. Remimazolam exhibits a brief duration of action, and even if it demonstrated a prophylactic effect on PONV, this effect may be rapidly lost. Furthermore, most cases in which remimazolam was used in this study were reversed with flumazenil, suggesting that any potential prophylactic effect on PONV may have been negated by reversal. The precise impact of flumazenil on PONV remains indeterminate. The drug's labeling identifies vomiting as a potential adverse reaction, though our exhaustive research has yet to uncover any reports suggesting flumazenil as a causative agent of PONV.

This study had several limitations. Firstly, it is worth noting that, as with many retrospective studies, our data was imperfect and may have included missing or incomplete information. For example, data regarding the incidence of postoperative nausea and vomiting (PONV) was extracted from the anesthesiologists' postoperative notes recorded in electronic medical charts. This method of data collection may have resulted in an underestimation of the frequency of PONV in our study, as some patients may not have remembered experiencing PONV. Recall bias may have been present. Additionally, we were unable to obtain detailed information on the occurrence of PONV at various time points. It was determined, however, that our data met the criteria for PONV due to most postoperative rounds occurring within 24 h after the surgical procedure.

Secondly, while we used propensity score matching to mitigate the influence of confounding factors in both study groups, it is important to recognize that observational studies can only partially control for measured variables and unmeasured variables may still confound the results. However, the anesthesia practices during artificial joint replacement surgery were similar throughout the study period, leading us to conclude that the impact of unmeasured variables was likely minimal.

Thirdly, this is a retrospective study and no statistical sample size calculations were conducted. In a prospective study involving groups of 51 participants, a sample size of 134 individuals would be necessary to achieve statistical significance for a reduction in PONV from 30 to 15%. While sample size determination is not an imperative in retrospective studies, it cannot be overlooked that the limited sample size may have contributed to the absence of statistically significant disparities observed in the current study.

Finally, it is important to exercise caution when extrapolating the findings of our study, as the data was derived from a single medical center. Further randomized controlled trials are necessary to validate the results presented in our study.

Conclusions

This single-center, propensity score-matched, retrospective, observational study demonstrated that there was no difference in the prevalence of PONV between remimazolam and sevoflurane anesthesia in patients undergoing artificial joint replacement surgery.

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Data availability The data that support the findings of this study are available on request from the corresponding author, KY. The data are not publicly available due to restrictions e.g. their containing information that could compromise the privacy of research participants.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. Anesth Analg. 1994;78:7–16.

2. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91:693–700.
3. Koivuranta M, Läärä E, Snåre L, Alahuhta S. A survey of postoperative nausea and vomiting. Anaesthesia. 1997;52:443–9.
4. Kranke P, Eberhart LH, Toker H, Roewer N, Wulf H, Kiefer P. A prospective evaluation of the POVOC score for the prediction of postoperative vomiting in children. Anesth Analg. 2007;105:1592–7.
5. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg. 1999;89:652–8.
6. Fortier J, Chung F, Su J. Unanticipated admission after ambulatory surgery–a prospective study. Can J Anaesth. 1998;45:612–9.
7. Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS, Gan TJ. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. Anesthesiology. 2000;92:958–67.
8. Masui K. Remimazolam besilate, a benzodiazepine, has been approved for general anesthesia!! J Anesth. 2020;34:479–82.
9. Hari Y, Satomi S, Murakami C, Narasaki S, Morio A, Kato T, Tsutsumi YM, Kakuta N, Tanaka K. Remimazolam decreased the incidence of early postoperative nausea and vomiting compared to desflurane after laparoscopic gynecological surgery. J Anesth. 2022;36:265–9.
10. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
11. Sneyd JR. Remimazolam: new beginnings or just a me-too? Anesth Analg. 2012;115:217–9.
12. Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. Anesth Analg. 2012;115:284–96.
13. Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent. Front Pharmacol. 2021. https://doi.org/10.3389/fphar.2021.690875.
14. Song SW, Jang YN, Yoon MW, Jeon YG. Quality of recovery in patients administered remimazolam versus those administered an inhalant agent for the maintenance of general anesthesia: a randomized control trial. BMC Anesthesiol. 2022;22:226.
15. Suzuki Y, Kawashima S, Makino H, Doi M, Nakajima Y. A comparison of remimazolam and propofol for postoperative nausea and vomiting: a propensity score-matched, observational, single-center cohort study. Korean J Anesthesiol. 2022. https://doi.org/10.4097/kja.22441.
16. Mao Y, Guo J, Yuan J, Zhao E, Yang J. Quality of recovery after general anesthesia with remimazolam in patients' undergoing urologic surgery: a randomized controlled trial comparing remimazolam with propofol. Drug Des Devel Ther. 2022;16:1199–209.
17. Choi JY, Lee HS, Kim JY, Han DW, Yang JY, Kim MJ, Song Y. Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: a randomized non-inferiority trial. J Clin Anesth. 2022;82: 110955.
18. Lee Y, Wang JJ, Yang YL, Chen A, Lai HY. Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a andomized controlled trial. Anaesthesia. 2007;62:18–22.
19. Ahn EJ, Kang H, Choi GJ, Baek CW, Jung YH, Woo YC. The effectiveness of midazolam for preventing postoperative nausea and vomiting: a systematic review and meta-analysis. Anesth Analg. 2016;122:664–76.
20. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR, Society for Ambulatory Anesthesia. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118:85–113.