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REPORTS OF ORIGINAL INVESTIGATIONS

Comparison of remimazolam and sevoflurane for general anesthesia during transcatheter aortic valve implantation: a randomized trial

Comparaison du rémimazolam et du sévoflurane pour l'anesthésie générale lors de l'implantation valvulaire aortique via cathéter : une étude randomisée

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Abstract

Purpose *Safe perioperative management of patients undergoing transcatheter aortic valve implantation (TAVI) is crucial. Remimazolam is a newly developed short-acting benzodiazepine. We hypothesized that combining remimazolam and flumazenil would reduce emergence time compared with sevoflurane in patients undergoing general anesthesia for TAVI.*

Methods *We conducted a prospective, randomized, parallel-design, open-label, single-centre clinical trial between June 2022 and August 2023 at Kagoshima University Hospital. We allocated patients randomly to either the remimazolam/flumazenil group or the sevoflurane group. Patients in the remimazolam group received iv remimazolam whereas patients in the sevoflurane group received sevoflurane for general anesthesia maintenance. Patients in both groups received a remifentanil infusion throughout the TAVI procedure (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv). Remimazolam and sevoflurane were adjusted to maintain a Bispectral Index™ (Covidien/Medtronic, Minneapolis, MN, USA) of 40–60. In the remimazolam group, flumazenil (0.2 mg iv) was administered immediately after remimazolam discontinuation. The primary outcome was time to extubation. Secondary outcomes included intraoperative variables (hemodynamic variables and vasopressor dose), rate of intra- and postoperative complications, and recovery of muscle strength.*

Results *Overall, 60 patients were enrolled, and data from 56 were included. The median [interquartile range] time to extubation was significantly shorter in the remimazolam group than in the sevoflurane group (6.5 [5.1–8.1] min vs 14.2 [10.9–15.9] min; difference in medians, −6.9 min; 95% confidence interval, −8.7 to −5.0; $P < 0.001$). Statistically significant differences were observed in the perfusion index ($P = 0.03$) and regional cerebral oxygen saturation ($P = 0.03$) between the groups. No significant differences between the two groups were seen in other secondary outcomes.*

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Conclusions *Compared with sevoflurane, a combination of remimazolam and flumazenil significantly reduced the time to extubation in patients undergoing general anesthesia for TAVI. Therefore, remimazolam may be a suitable choice for general anesthesia in patients undergoing TAVI.*

Study registration *UMIN.ac.jp (UMIN000047892); first posted 30 May 2022.*

Résumé

Objectif *Une prise en charge périopératoire sécuritaire de la patientèle bénéficiant d'une implantation valvulaire aortique via cathéter (TAVI) est cruciale. Le rémimazolam est une benzodiazépine à courte durée d'action nouvellement développée. Nous avons émis l'hypothèse que l'association du rémimazolam et du flumazénil réduirait le temps d'émergence par rapport au sévoflurane chez les personnes bénéficiant d'une anesthésie générale pour une TAVI.*

Méthode *Nous avons réalisé une étude clinique prospective, randomisée, en parallèle, ouverte et monocentrique entre juin 2022 et août 2023 à l'hôpital universitaire de Kagoshima. Nous avons aléatoirement assigné les patient·es au groupe rémimazolam/flumazénil ou au groupe sévoflurane. Les patient·es du groupe rémimazolam ont reçu du rémimazolam iv tandis que les patient·es du groupe sévoflurane ont reçu du sévoflurane pour le maintien de l'anesthésie générale. Les deux groupes ont reçu une perfusion de rémifentanil tout au long de la procédure TAVI (0,2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv). Le rémimazolam et le sévoflurane ont été ajustés pour maintenir un indice bispectral (Covidien/Medtronic, Minneapolis, MN, États-Unis) de 40 à 60. Dans le groupe rémimazolam, le flumazénil (0,2 mg iv) a été administré immédiatement après l'arrêt du rémimazolam. Le critère d'évaluation principal était le délai d'extubation. Les critères d'évaluation secondaires comprenaient les variables peropératoires (variables hémodynamiques et dose de vasopresseurs), le taux de complications peropératoires et postopératoires, et la récupération de la force musculaire.*

Résultats *Au total, 60 patient·es ont été recruté·es et les données de 56 ont été incluses. Le délai médian [écart interquartile] jusqu'à l'extubation était significativement plus court dans le groupe rémimazolam que dans le groupe sévoflurane (6,5 [5,1–8,1] min vs 14,2 [10,9 à 15,9] min; différence entre les médianes, −6,9 min; intervalle de confiance à 95 %, −8,7 à −5,0; $P < 0{,}001$). Des différences statistiquement significatives ont été observées dans l'indice de perfusion ($P = 0{,}03$) et la saturation cérébrale régionale en oxygène ($P = 0{,}03$) entre les groupes. Aucune différence intergroupe significative n'a été observée dans les autres critères d'évaluation secondaires.*

Conclusion *Par rapport au sévoflurane, une combinaison de rémimazolam et de flumazénil a considérablement réduit le temps d'extubation chez les patient·es bénéficiant d'une anesthésie générale pour une TAVI. Par conséquent, le rémimazolam peut être un choix approprié pour l'anesthésie générale chez les patient·es bénéficiant d'une TAVI.*

Enregistrement de l'étude *UMIN.ac.jp (UMIN000047892); première mise en ligne le 30 mai 2022.*

Keywords aortic stenosis · general anesthesia · remimazolam · sevoflurane · transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) has become an important alternative to surgical aortic valve replacement for treating severe aortic stenosis, especially in older patients.[1] Transcatheter aortic valve implantation can be safely managed with general anesthesia or moderate sedation.[2,3] Meta-analyses indicate that moderate sedation is associated with lower 30-day mortality and stroke rate compared with general anesthesia.[3] Although the use of moderate sedation is increasing, general anesthesia is preferable in some patients; for example, patients with atrial fibrillation, myocardial infarction, or cardiac failure might need transesophageal echocardiography and/or total immobility for precise valve positioning.[3,4] General anesthesia also facilitates the use of 2D or 3D transesophageal echocardiography to prevent prosthetic paravalvular regurgitation.[5,6] Patients undergoing TAVI are at moderate-to-high risk of perioperative stroke (incidence, 2–4%),[7,8] which is associated with a higher risk of complications.[8] Thus, early detection of stroke symptoms is crucial for preventing permanent neurologic dysfunction.[9]

Remimazolam, a newly developed anesthetic drug,[10] is a short-acting benzodiazepine with a context-sensitive half-life of around 12 min.[11,12] Acting via cerebral γ-aminobutyric acid receptors, flumazenil can counter its sedative effect,[13] potentially aiding emergence from general anesthesia.[14] While several meta-analyses suggest that remimazolam moderately reduces hypotension during sedation or general anesthesia induction compared with propofol, absolute blood pressure differences are minimal.[15–17] Nevertheless, the effects of combining remimazolam and flumazenil on emergence time and intraoperative hemodynamics remain unclear.

We hypothesized that combining remimazolam and flumazenil shortens emergence time compared with

sevoflurane in patients undergoing general anesthesia for TAVI. We also hypothesized that remimazolam may help maintain blood pressure during general anesthesia compared with sevoflurane.

Materials and methods

Study design and ethics approval

This manuscript adheres to the Consolidated Standards of Reporting Trials guidelines (Electronic Supplementary Material [ESM] eAppendix).[18] This prospective, randomized, parallel-design, open-label, single-centre clinical trial was approved by the ethics committee of Kagoshima University Hospital (Kagoshima, Japan; reference number, 210312). It was conducted from June 2022 to August 2023 at Kagoshima University Hospital. This trial was prospectively registered in a publicly accessible database (UMIN.ac.jp [UMIN000047892]; first posted 30 May 2022). Written informed consent was obtained from all patients before enrolment.

The inclusion criteria were patients with acquired severe aortic stenosis[19] (age $\geq$ 18 yr) undergoing TAVI under general anesthesia. The exclusion criteria were allergy to remimazolam, sevoflurane, midazolam, or flumazenil; a history or family history of malignant hyperthermia; and difficulties in participation because of psychological conditions.

Intraoperative management

The patients were randomly allocated to one of the two groups using internet-based software in a simple randomized manner (Research Randomizer version 4.0).[A] Patients in the remimazolam group received intravenous remimazolam for maintenance of general anesthesia whereas patients in the sevoflurane group received inhaled sevoflurane. As complete blinding was not possible because sevoflurane administration requires the use of a vaporizer, intraoperative anesthesia care team members were not blinded to group allocation. Two anesthesiologists provided anesthetic management. One anesthesiologist with experience in procedures and perioperative care of patients undergoing TAVI (> 30 patients) supervised anesthesia care and recorded intraoperative variables. Cardiac surgeons and intensivists were responsible for postoperative intensive care. Preoperative patient data were extracted from hospital medical records.

No preoperative sedatives or analgesics were administered in either group. In the operating room, standard perioperative monitoring was initiated per American Society of Anesthesiologists guidelines. The Life Scope J patient monitoring system (Nihon Kohden Corp., Tokyo, Japan) was used to continuously monitor heart rate (HR), direct arterial blood pressure, electrocardiogram, peripheral oxygen saturation measured by pulse oximetry (SpO_2), perfusion index (PI) derived from the plethysmographic waveform, end-tidal carbon dioxide tension ($EtCO_2$), and bladder or rectal temperature. The PI was calculated from the pulse oximeter's infrared signal using the following formula: PI = (pulsatile signal / non-pulsatile signal) $\times$ 100. Invasive arterial pressure monitoring was initiated before anesthesia induction. Bispectral Index^{TM} (BIS^{TM}) values were monitored using a BIS^{TM} Quatro Sensor (Covidien/Medtronic, Minneapolis, MA, USA). Regional cerebral oxygen saturation (rSO_2) was continuously monitored using an INVOS^{TM} 5100C cerebral/somatic oximeter (Covidien/Medtronic).

Intraoperative transesophageal echocardiography was performed after tracheal intubation. A temporary 5-Fr pacemaker wire and a central venous catheter were inserted through the internal jugular vein for rapid ventricular pacing. In the remimazolam group, general anesthesia was induced with remimazolam (6 $mg \cdot kg^{-1} \cdot hr^{-1}$ *iv*), remifentanil (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *iv*), and rocuronium (0.6–0.9 $mg \cdot kg^{-1}$ *iv*). The remimazolam infusion rate was reduced to 1 $mg \cdot kg^{-1} \cdot hr^{-1}$ *iv* after loss of consciousness and adjusted to maintain a BIS of 40–60. In the sevoflurane group, general anesthesia was induced with midazolam (0.05 $mg \cdot kg^{-1}$ *iv*), remifentanil (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *iv*), and rocuronium (0.6–0.9 $mg \cdot kg^{-1}$ *iv*). Anesthesia was maintained using sevoflurane (0.5–1.0 age-adjusted minimum alveolar concentration), adjusted to maintain a BIS of 40–60. In both groups, the remifentanil infusion rate was reduced to 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *iv* after tracheal intubation and maintained throughout the TAVI procedure. The infusion rate was adjusted at the attending anesthesiologist's discretion to ensure adequate analgesia. Considering the high-risk nature of the selected population, remifentanil dose adjustments were permitted for patient safety. The remifentanil infusion rate was reduced to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *iv* after completing the TAVI procedure. Neuromuscular blockade (train-of-four [TOF] count < 3; TOF-Watch® SX, Organon, Ireland) was maintained with a rocuronium infusion (1–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *iv*); the infusion was discontinued after valve implantation. Acetaminophen (1 g *iv* for weight $\geq$ 50 kg, 0.015 $g \cdot kg^{-1}$ *iv* for weight < 50 kg) was administered at skin closure. Then, 10 mL of 0.75% ropivacaine was administered via local infiltration.

[A] *Urbaniak GC, Plous S*. Research Randomizer (Version 4.0); 2013. Available from URL: http://www.randomizer.org/ (accessed August 2024).

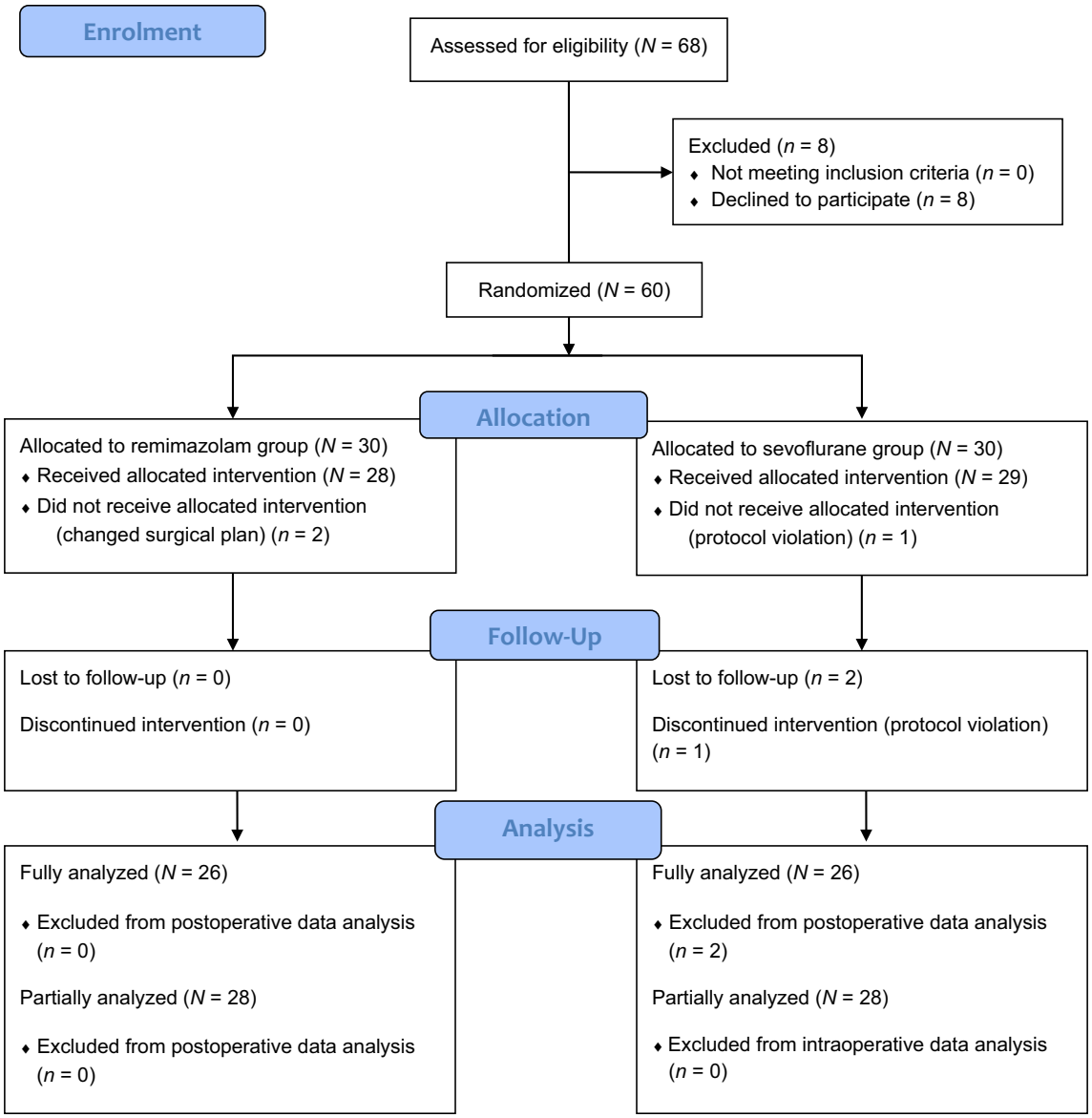

Fig. 1 Flow diagram presenting patient selection and analysis. One patient in the sevoflurane group did not receive the intervention because of protocol violation (only verbal consent was obtained). We discontinued intervention in one patient in the sevoflurane group because of a protocol violation (another sedative was used). We excluded the postoperative data of two patients in the sevoflurane group because of loss to follow-up.

No analgesics other than remifentanil and acetaminophen were used in the operating room. All anesthetic drugs were discontinued after completing postoperative radiography. After confirming a TOF count of > 2, sugammadex (2 mg·kg^{-1}) was administered. In the remimazolam group, flumazenil (0.2 mg *iv*) was administered immediately after remimazolam discontinuation and was repeated every minute (0.1 mg *iv*) until the patient responded to verbal stimulation.

In both groups, continuous norepinephrine infusion (0.05–0.08 μg·kg^{-1}·min^{-1} *iv*) was started when remifentanil started during induction, and it was adjusted to maintain the mean arterial pressure (MAP) at $\geq$ 60 mm Hg. Intraoperative hypotension (MAP $<$ 60 mm Hg) was treated with a single intravenous bolus of phenylephrine (50–100 μg *iv*) or ephedrine (4–8 mg *iv*), depending on the HR. If the HR was $<$ 60 min^{-1}, ephedrine was administered. Other vasopressors or inotropes were used at the discretion of the anesthesia care provider. A colloid bolus (Voluven; Otsuka Pharmaceutical, Tokyo, Japan) of 10 mL·kg^{-1} *iv* was infused during induction, followed by continuous infusion of a balanced crystalloid (Bicanate; Otsuka Pharmaceutical, Tokyo, Japan) at a rate of 2–8 mL·kg^{-1}·hr^{-1} *iv*. The attending anesthesiologists were allowed to administer three boluses (30 mL·kg^{-1} *iv*) of the colloid if needed. Red blood

Table 1 Preoperative baseline characteristics of participants

Characteristic	Remimazolam $N = 28$	Sevoflurane $N = 28$
Age (yr), median [IQR]	86 [83–89]	85 [83–90]
Female, *n*/total *N* (%)	21/28 (75%)	15/28 (54%)
BMI ($kg \cdot m^{-2}$), median [IQR]	23 [20–27]	23 [21–26]
ASA-PS, *n*/total *N* (%)		
III	24/28 (86%)	24/28 (86%)
IV	4/28 (14%)	4/28 (14%)
Aortic valve area (cm^2), median [IQR]	0.55 [0.49–0.66]	0.56 [0.45–0.73]
Mean pressure gradient aortic valve (mm Hg), median [IQR]	48 [38–59]	47 [41–65]
NYHA, *n*/total *N* (%)		
I	3/28 (11%)	0/28 (0%)
II	16/28 (57%)	25/28 (89%)
III	9/28 (32%)	3/28 (11%)
EuroSCORE II (%), median [IQR]	3.6 [2.7–6.1]	3.5 [2.3–4.4]
STS mortality score (%), median [IQR]	4.8 [3.8–6.7]	4.8 [3.1–8.2]
JapanSCORE (%), median [IQR]	4.0 [2.3–8.8]	5.1 [2.6–8.3]
Clinical Frailty Scale, median [IQR]	4 [3–5]	3 [3–4]

ASA-PS = American Society of Anesthesiologists Physical Status; BMI = body mass index; IQR = interquartile range; NYHA = New York Heart Association heart failure classification; STS = Society of Thoracic Surgeons

cells were transfused to maintain hemoglobin concentrations of 8–10 $g \cdot dL^{-1}$. Fresh-frozen plasma or platelets were transfused if blood loss exceeded 1,000 mL and if clinically insufficient hemostasis was suspected by surgeons or anesthesiologists. Vasodilator use was at the discretion of the anesthesia care provider. During anesthesia induction and after cessation of anesthetic drug administration, the lungs were ventilated with an inspired oxygen fraction (F_IO_2) of 1.0 with a fresh gas flow of 6 $L \cdot min^{-1}$. After tracheal intubation, the lungs were ventilated with an F_IO_2 of 0.4 with a fresh gas flow of 3 $L \cdot min^{-1}$ and a tidal volume (TV) of 6–8 $mL \cdot kg^{-1}$ of ideal body weight. The respiratory rate was adjusted to maintain an $EtCO_2$ of 35–45 mm Hg and a positive end-expiratory pressure of 5–8 cm H_2O. Intraoperative data were recorded every 20 sec. The patients were warmed using a forced-air warming system (Cocoon™ Connective Warming System, Care Essentials Pty Ltd., North Geelong, VIC, Australia) to maintain normal core temperature.

Primary and secondary outcomes

The primary outcome was time to extubation, defined as the time from cessation of remimazolam or sevoflurane administration to extubation. The extubation criteria were eye opening with verbal stimulation, presence of spontaneous ventilation with a TV of > 5 $mL \cdot kg^{-1}$ of ideal body weight and a respiratory rate of 10–20 min^{-1}, hemodynamic stability (MAP of 60–140 mm Hg and HR of 50–120 min^{-1}), and recovery of TOF ratio to > 1.0. The patients were verbally stimulated every 20 sec after anesthetic drugs were discontinued.

The secondary outcomes were MAP, HR, SpO_2, PI, rSO_2, BIS, and core body temperature during general anesthesia; vasopressor doses during general anesthesia; and intra- and postoperative complication rates, as defined by the Valve Academic Research Consortium 3 (VARC-3).[20] We compared intraoperative variables at seven timepoints: baseline (before induction), 120 sec after tracheal intubation, 30 sec before the start of the operation, 30 sec before valve implantation, minimal values during valve implantation (except HR), 30 sec before the end of the operation, and 120 sec after extubation.

Intra- and postoperative complications

Intraoperative complications included conversion to open surgery, unplanned use of mechanical circulatory support, valve malpositioning, and severe paravalvular regurgitation. The patients were followed up for 30 days postoperatively. Postoperative data were obtained from hospital medical records. The extracted postoperative

Table 2 Intraoperative data

Variable	Remimazolam $N = 28$	Sevoflurane $N = 28$	Difference in mean or median (95% CI)	P value
Operative time (min), mean (SD)	75 (23)	77 (19)	−2 (−13 to 10)	0.77†
Anesthesia time (min), mean (SD)	178 (24)	185 (29)	−7 (−21 to 7)	0.33†
Blood loss (mL), median [IQR]	0 [0–29]	0 [0–25]	0 (0 to 10)	0.39‡
Urine output (mL), mean (SD)	321 (287)	338 (246)	−17 (−160 to 127)	0.82†
Colloid administration (mL), median [IQR]	900 [685–1,000]	900 [800–988]	0 (−130 to 70)	0.81‡
Crystalloid administration (mL), median [IQR]	540 [408–750]	570 [313–715]	0 (−130 to 150)	0.93‡
Transfusion (mL), median [IQR]	180 [0–280]	0 [0–280]	0 (0 to 280)	0.14‡
Fluid balance (mL), mean (SD)	1,236 (470)	1,185 (426)	51 (−189 to 291)	0.67†
Remimazolam induction dose (mg), median [IQR]	6 [5–7]	0 [0–0]	6 (5 to 7)	< 0.001‡
Remimazolam maintenance dose ($mg \cdot kg^{-1} \cdot hr^{-1}$), median [IQR]	0.68 [0.59–0.78]	0 [0–0]	0.68 (0.64 to 0.74)	< 0.001‡
EtSev (%), median [IQR]	0 [0–0]	0.89 [0.75–1.03]	−0.89 (−0.99 to −0.79)	< 0.001‡
Flumazenil dose (mg), median [IQR]	0.4 [0.3–0.5]	0 [0–0]	0.4 (0.3 to 0.5)	< 0.001‡
Midazolam dose (mg), median [IQR]	0 [0–0]	3.0 [3.0–3.0]	−3.0 (−3.0 to −3.0)	< 0.001‡
Remifentanil dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$), mean (SD)	0.17 (0.02)	0.16 (0.01)	0.009 (0.00 to 0.02)	0.04†
Rocuronium dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$), mean (SD)	5.3 (1.2)	4.9 (1.6)	0.3 (−0.4 to 1.1)	0.10†
Sugammadex dose (mg), mean (SD)	106 (36)	122 (36)	−16 (−35 to 3.3)	0.10†
BIS during anesthesia, mean (SD)	51 (6)	50 (6)	1 (−3 to 4)	0.68†
Intraoperative VARC-3 complications,* n/total N (%)	0/28 (0%)	0/28 (0%)	0% (−0.15 to 0.15)	0.99‡

Differences are calculated as (remimazolam − sevoflurane)

*Intraoperative VARC-3 complications included conversion to open surgery, unplanned use of mechanical circulatory support, valve malposition, and severe paravalvular regurgitation

†Student's t test

‡Mann–Whitney U test; differences in medians and their 95% CIs were calculated using the Hodges–Lehmann method

BIS = bispectral index; CI = confidence interval; EtSev = end-tidal sevoflurane concentration; IQR = interquartile range, SD = standard deviation; VARC-3 = Valve Academic Research Consortium 3

complications were length of stay in the intensive care unit (ICU), length of stay in the hospital, postoperative nausea and vomiting (PONV), neurologic events (stroke and delirium), hospitalization (except for pre-existing conditions), bleeding (overt bleeding that required a transfusion of 1 unit of whole blood/red blood cells), vascular/access-related complications, cardiac structural complications (cardiac structure perforation/injury/compromise, new pericardial effusion, or coronary obstruction), new conduction disturbances and arrhythmias, acute kidney injury (meeting at least one of the following criteria: a 150–200% increase in serum creatinine compared with that at baseline, or an increase of > 0.3 $mg \cdot dL^{-1}$ [26.4 $mmol \cdot L^{-1}$] within 48 hr of the index procedure), myocardial infarction (requiring treatment), bioprosthetic valve dysfunction (including nonstructural valve dysfunction, thrombosis, and endocarditis), leaflet thickening and reduced motion, clinically significant valve thrombosis, technical success at exit from operating room, device success at 30 days, and all-cause mortality at 30 days. The aortic valve area, aortic regurgitation, and mean aortic valve pressure gradient were also extracted from hospital medical records.

Intensive care unit admission and management was determined at the discretion of cardiac surgeons and intensivists. Postoperative nausea and vomiting and delirium were recorded at least twice daily in the ICU. Attending ICU nurses recorded delirium using the Confusion Assessment Method for the ICU.[21]

Statistical analysis

Categorical data are presented as absolute and relative frequencies. Group comparisons were performed using the Chi square or Fisher's exact test depending on the expected cell counts of corresponding contingency tables.

Table 3 Primary and secondary outcomes

Outcome	Remimazolam $N = 28$	Sevoflurane $N = 28$	Difference in means, medians, or proportions (95% CI)	P value
Extubation time (min), median [IQR]	6.5 [5.1–8.1]	14.2 [10.9–15.9]	−6.9 (−8.7 to −5.0)	< 0.001‡
MAP during anesthesia (mm Hg), mean (SD)	77 (7)	74 (6)	3 (−0 to 7)	0.07†
HR during anesthesia (min^{-1}), mean (SD)	72 (10)	69 (13)	3 (−3 to 9)	0.32†
SpO_2 during anesthesia (%), median [IQR]	100% [99–100]	99% [99–100]	0 (−0 to 1)	0.35‡
Norepinephrine dose ($ng \cdot kg^{-1} \cdot min^{-1}$), mean (SD)	39 (29)	47 (23)	−8.1 (−22 to 6.1)	0.26†
Phenylephrine bolus dose (mg), median [IQR]	0.10 [0.05–0.19]	0.20 [0.00–0.15]	0 (−0.05 to 0.05)	0.79‡
Ephedrine bolus dose (mg), median [IQR]	5 [1–8]	12 [8–14]	−4 (−8 to −2)	0.0006‡
Other vasopressors/inotropes use, *n*/total *N* (%)	4/28 (14%)	6/28 (21%)	7% (−15 to 30)	0.73§
Postoperative VARC-3 complications, *n*/total *N* (%)	8/28 (29%)	10/26 (38%)*	10% (−16 to 37)	0.57§

Differences are calculated as (remimazolam − sevoflurane)

*Complications were not recorded in two patients in the sevoflurane group because of loss to follow-up

†Student's *t* test

‡Mann–Whitney *U* test; differences in medians and their 95% CIs were calculated using the Hodges–Lehmann method

§Fisher's exact test

HR = heart rate; IQR = interquartile range; MAP = mean arterial pressure; SD = standard deviation; CI = confidence interval; SpO_2 = oxygen saturation measured by pulse oximetry; VARC-3 = Valve Academic Research Consortium 3

Continuous data are presented as mean and standard deviation (SD) or median and interquartile range [IQR], depending on the distribution. The unpaired *t* test or Mann–Whitney *U* test was performed to assess differences between groups. Differences in medians and their 95% confidence intervals (CIs) were calculated using the Hodges–Lehmann method. We analyzed the time course of intraoperative variables using a mixed model. This model uses a compound symmetry covariance matrix and is fitted using restricted maximum likelihood. In the absence of missing values, this method provides the same *P* values and multiple comparisons tests as repeated-measures two-way analysis of variance, followed by Sidak's multiple comparison test. We conducted additional analysis to examine the time course of MAP, HR, PI, and rSO_2 by adjusting for baseline values. The values at each timepoint were normalized by dividing them by the baseline values. All statistical tests were performed with a two-sided 5% significance level. Statistical analyses were performed using Prism version 10.2.3 (GraphPad Software, San Diego, CA, USA). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[22]

One of the most important complications after TAVI is stroke (reported incidence, 2–4%), which is associated with adverse outcomes.[7,8] Further, more than half of perioperative strokes occur within 24 hr after TAVI.[23] The American Heart Association and American Stroke Association recommend that a stroke alert should be initiated within 5 min from symptom discovery.[9] We thus determined that a 5-min difference in time to extubation was clinically important to minimize permanent neurologic dysfunction after stroke. To detect a 5-min difference in time to extubation with a two-sided approximation while accepting an α error of 5% and a β error of 20%, we calculated the required study size as 48 patients based on preliminary data using Power and Sample Size Calculation version 3.1.2 (Dupont WD and Plummer WD, Vanderbilt University, Nashville, TN, USA). Preliminary data were calculated from patients who underwent TAVI at our institution (number of patients, 20; mean [SD] time to extubation, 12 [6] min). To account for patient dropout, we added 25% more patients, resulting in a final sample size of 60 patients.

Results

During the study period, 68 patients underwent TAVI, with 60 patients enrolled in the study (30 each in the remimazolam and sevoflurane groups; Fig. 1). Two patients in the remimazolam group did not undergo intervention because of changes in the surgical plan. In the sevoflurane group, the intervention was not initiated for one patient as only verbal consent was obtained, and the intervention was discontinued for another patient because

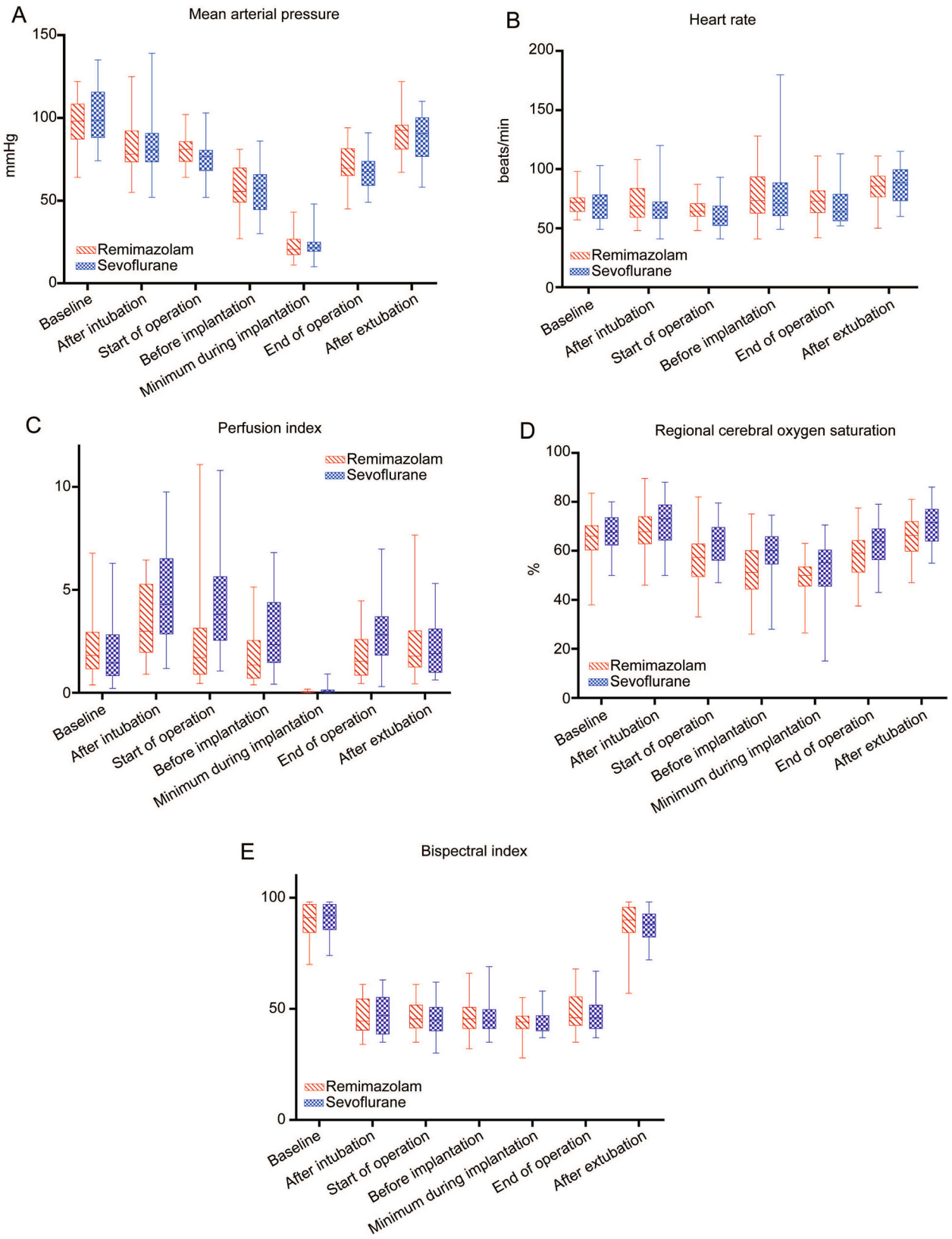

Fig. 2 Time course of hemodynamic variables. Boxes show medians (horizontal middle lines) and interquartile ranges (top and bottom parts of the boxes); whiskers show the lowest and highest values.

other sedatives were used. We excluded postoperative data from two patients in the sevoflurane group because they did not complete follow-up visits, despite our attempts to contact them.

Participants' preoperative baseline characteristics are shown in Table 1. All patients were aged > 75 yr, and over half were female. All patients underwent transfemoral TAVI. One patient in the remimazolam group received an Evolut FX valve (Medtronic, Minneapolis, MA, USA), while the remaining patients received a Sapien3 valve (Edwards Lifesciences, Irvine, CA, USA).

Intraoperative data

Intraoperative data are shown in Table 2. Operative time, blood loss, and fluid balance were comparable between the groups. The remifentanil dose was slightly higher in the remimazolam group than in the sevoflurane group (difference, 0.009 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 95% CI, 0.0003 to 0.018). The signal quality index of the electroencephalogram was higher in the sevoflurane group (median difference, 1.2). The remifentanil infusion rate was adjusted slightly in five patients in the remifentanil group and in four patients in the sevoflurane group. Owing to severe hypotension after valve implantation, chest compressions (< 3 min) were performed in one patient in the remimazolam group and in three patients in the sevoflurane group. Acetaminophen was not administered by attending anesthesiologists to two patients from each group, totalling four patients.

Primary and secondary outcomes

The primary and secondary outcomes are summarized in Table 3. The time to extubation was significantly shorter in the remimazolam group compared with the sevoflurane group (difference in medians, −6.9 min). The median ephedrine bolus dose was lower in the remimazolam group than in the sevoflurane group (difference in medians, −4 mg). There were no significant differences in other secondary outcomes between the groups. Figure 2 shows a time course of the intraoperative variables. There were no differences in the time course of repeated measurements for MAP (P = 0.46), HR (P = 0.33) or BIS (P = 0.78). The PI after intubation (difference in means, −1.3%; 95% CI, −2.5 to −0.1) and the PI before the start of operation (difference in means, −1.7%; 95% CI, −2.8 to −0.4) were significantly lower in the remimazolam group than in the sevoflurane group (Fig. 2, ESM eTables 1 and 2). Before valve implantation, rSO_2 was significantly lower in the remimazolam group than in the sevoflurane group (difference in means, 7.3%; 95% CI, 0.4 to 14.3). Detailed results of the mixed-effects model are shown in ESM eTables 1 and 2. The results were similar even after adjusting for baseline values (ESM eFigure and ESM eTable 3).

Valve Academic Research Consortium-3 complications and other postoperative data

The incidence of PONV and delirium was not recorded in three patients in the sevoflurane group because they did not stay in the ICU. There were no intraoperative VARC-3 complications in either group (Table 4). One patient in each group required a temporary pacemaker and one in the remimazolam group required permanent pacemaker implantation postoperatively.

Discussion

In this prospective, randomized, parallel-design, open-label, single-centre clinical trial, we found that using a combination of remimazolam and flumazenil shortened the time to extubation compared with sevoflurane in patients undergoing general anesthesia for TAVI. Although patients in the remimazolam group required a lower ephedrine bolus dose than those in the sevoflurane group, the MAP, HR, and use of other vasopressors did not differ between the groups. Significant differences were observed in PI and rSO_2 between the groups. There were no differences in intra- or postoperative complications between the groups.

Remimazolam combined with flumazenil reduced the time to extubation by approximately 7 min compared with sevoflurane. Few studies have compared remimazolam combined with flumazenil and volatile anesthetics.[24] A previous study, employing propensity-score matching, reported that time to extubation was shorter with a remimazolam/flumazenil combination than with sevoflurane.[24] No difference in time to extubation has been reported between anesthesia using remimazolam without flumazenil and sevoflurane.[25,26] Routine administration of flumazenil to reverse remimazolam may pose some risks. Resedation after flumazenil reversal may occur.[27] A meta-analysis showed that resedation occurred in 9% of patients in whom remimazolam was used in combination with flumazenil.[28] Flumazenil-based reversal of sedation induced by remimazolam increased PONV after gynecological surgery compared with no reversal.[29]

Mean arterial pressure, HR, norepinephrine and phenylephrine doses, and the use of other vasopressors/inotropes did not differ between the groups. We observed that the sevoflurane group required more ephedrine than the remimazolam group. These results were unexpected because remimazolam has been reported to induce less

Table 4 Valve Academic Research Consortium 3 complications and other postoperative data

	Remimazolam	Sevoflurane	Difference in medians or proportions (95% CI)	*P* value
Length of stay in the ICU (hr), median [IQR], (total patients)	19 [16–22] (*N* = 28)	19 [17–22] (*N* = 25)*	0 (−2 to 2)	0.92§
Length of stay in the hospital (day), median [IQR], (total patients)	9 [8–11] (*N* = 28)	9 [8–11] (*N* = 28)	0 (−1 to 1)	0.72§
PONV in the ICU, *n*/total *N* (%)	4/28 (14%)	0/25 (0%)*	14% (−5 to 34)	0.11‖
Delirium in the ICU, *n*/total *N* (%)	5/28 (18%)	5/25 (20%)*	2% (−22 to 25)	0.99‖
Stroke, *n*/total *N* (%)	2/28 (7%)	0/26 (0%)†	7% (−10 to 25)	0.49‖
Hospitalization, *n*/total *N* (%)	1/28 (4%)	0/26 (0%)†	4% (−13 to 20)	0.99‖
Bleeding, *n*/total *N* (%)	1/28 (4%)	0/26 (0%)†	4% (−13 to 20)	0.99‖
New conduction disturbances and arrhythmias, *n*/total *N* (%)	3/28 (11%)	5/26 (19%)†	9% (−14 to 31)	0.46‖
Bioprosthetic valve dysfunction, *n*/total *N* (%)	0/28 (0%)	1/26 (4%)†	4% (−14 to 19)	0.47‖
Valve thrombosis, *n*/total *N* (%)	0/28 (0%)	1/26 (4%)†	4% (−14 to 19)	0.47‖
Other postoperative complications, *n*/total *N* (%)‡	0/28 (0%)	0/26 (0%)†	0% (−16 to 15)	0.99‖
Device success at 30 days, *n*/total *N* (%)	26/28 (100%)	26/26 (100%)†	0% (−16 to 15)	0.99‖
All-cause mortality at 30 days, *n*/total *N* (%)	0/28 (0%)	0/26 (0%)†	0% (−16 to 15)	0.99‖

*Three patients in the sevoflurane group did not stay in the ICU

†Postoperative complications were not recorded in two patients of the sevoflurane group because of loss to follow-up

‡Other postoperative complications included vascular or access-related complications, cardiac structural complications, acute kidney injury, myocardial infarction, leaflet thickening, and reduced motion

§Mann–Whitney *U* test; differences in medians and their 95% CIs were calculated using the Hodges–Lehmann method

‖Fisher's exact test

CI = confidence interval; ICU = intensive care unit; IQR = interquartile range; PONV = postoperative nausea and vomiting; VARC-3 = Valve Academic Research Consortium 3

hypotension than propofol during anesthesia induction and sedation.[15,17,30] Since MAP during anesthesia has been reported to be similar between propofol and sevoflurane, we expected that remimazolam may reduce hypotension compared with sevoflurane.[31] Nevertheless, there are conflicting results regarding hypotension during the maintenance of general anesthesia.[24–26,32,33] No difference in hypotension between remimazolam and sevoflurane was reported in patients undergoing gynecological laparoscopic surgery in a randomized trial.[32] Nevertheless, remimazolam reduced hypotension events compared with sevoflurane in another randomized trial.[25,26] Further, remimazolam reduced hypotension and vasopressor use in observational studies using propensity-score matching.[24,33]

Comparing hemodynamic effects between remimazolam and sevoflurane is worthwhile because patients undergoing TAVI may experience significant hemodynamic fluctuation with induction of anesthesia, rapid pacing, and valve implantation.[4] Given that remimazolam is a recently developed drug, there is minimal clinical information related to high-risk patients.[34] Remimazolam can be used for sedation.[35] Although sedation with local anesthesia may become standard management in TAVI, our study reinforced the notion that maintenance with remimazolam does not compromise hemodynamics in high-risk patient populations. Although significant differences were observed in PI and rSO_2 between the groups, the effect sizes were small. Nevertheless, we do not consider these differences to be clinically significant.

Limitations

Our study has several limitations. First, allocation was not fully blinded as a vaporizer was used in the sevoflurane group. Anesthesiologists may have selected drug doses in favour of a single group. Second, this was a single-centre study, and the results may not apply to other situations. Third, we did not record resedation after flumazenil administration. Although we realize that resedation may occur after flumazenil administration,[27] the corresponding caution was published after our study protocol was approved.[13] Flumazenil has a half-life of 50–60 min whereas remimazolam has a context-sensitive half-life of around 12 min.[11,12,36]

Conclusions

Our results show that the combination of remimazolam and flumazenil significantly reduced time to extubation compared with sevoflurane. Although patients in the remimazolam group received a lower ephedrine bolus dose than those in the sevoflurane group, MAP, HR, and the use of other vasopressors were similar between the groups. These results indicate that remimazolam may be a suitable choice for general anesthesia in patients undergoing TAVI.

Author contributions *So Harimochi* conducted the study and wrote the manuscript. *Kohei Godai* conducted the study, analyzed the data, and wrote the manuscript. *Mayumi Nakahara* conducted the study and critically revised the manuscript. *Akira Matsunaga* supervised the study and critically revised the manuscript.

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