의학석사 학위논문

경피적 대동맥 판막 치환술의 감시마취 관리에서 레미마졸람과 덱스메데토미딘이 술 후 회복에 미치는 영향 비교

The Effects of Remimazolam versus Dexmedetomidine on Recovery after Transcatheter Aortic Valve Replacement under Monitored Anesthesia Care : A Propensity Score-Matched Analysis

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이 논문을 의학석사학위 논문으로 제출함

2024년 2월

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Abstract

Background: A recent trend of minimalist transcatheter aortic valve replacement (TAVR) under monitored anesthesia care (MAC) emphasizes early recovery and faster discharge from the hospital. Remimazolam besylate is a newer benzodiazepine with a short recovery time, but concerns about its potential to increase the risk of postoperative delirium have been raised. Thus, the authors hypothesized that remimazolam is non-inferior to dexmedetomidine in terms of recovery after TAVR.

Methods: This retrospective cohort study aimed to compare remimazolam versus dexmedetomidine in patients undergoing TAVR under MAC at a tertiary academic hospital between July 2020 and July 2022. The primary endpoint was timely recovery after TAVR, defined as discharge from the intensive care unit within the first day following the procedure. The secondary endpoints were time to be fully awake, oxygen supplementation duration, intubation, need for vasopressor/inotropes, need for temporary pacemakers (TPMs), and incidence of delirium.

Results: The study included 464 patients, of whom 218 received remimazolam and 246 received dexmedetomidine. After propensity matching, 164 patients were included in each group. Patients in the remimazolam group showed no significant difference in terms of timely recovery (risk difference [RD] -0.6; 95% confidence interval [CI] -6.1 to 4.9; p=0.827). Remimazolam usage was associated with a shorter duration of being fully awake (2 [0–4] hours vs. 3 [2–5] hours, p-value=0.011) and a lesser need for postoperative vasopressors/inotropes (12.8% vs. 23.8%, p=0.013) and TPMs (46.3% vs. 65.9%, p<0.001) compared to dexmedetomidine usage. The remimazolam and dexmedetomidine groups showed no significant difference in the incidence of delirium (18.3% vs. 18.9%, p=0.886).
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Conclusions: In patients undergoing TAVR, remimazolam was associated with non-inferior intensive care unit stay when compared to dexmedetomidine. Additionally, remimazolam was associated with a more favorable recovery profile, including a shorter duration to be fully awake and reduced postoperative requirements for vasopressors/inotropes and TPMs.

Table of Contents

Introduction

Transcatheter aortic valve replacement (TAVR) is an alternative to surgical interventions with comparable efficacy and safety.[1,2] Recently, a notable shift towards a minimalist approach in TAVR has been observed. Minimalist TAVR consists of less invasive procedures to promote early discharge, such as minimal procedural sedation and protocolized perioperative management.[3,4]

Monitored anesthesia care (MAC) is an essential component of the minimalist approach,[5] Although consensus is lacking on the optimal anesthetic agent for patients undergoing TAVR. Propofol and dexmedetomidine are widely used, each with distinct limitations. Propofol is associated with hemodynamic instability and respiratory depression,[6,7] while dexmedetomidine is associated with hypotension and bradycardia, particularly during prolonged infusions.[8]

Remimazolam, a newly developed ultrashort-acting benzodiazepine, has demonstrated outstanding hemodynamic and respiratory stability.[9,10] Remimazolam may be a potential sedative for procedural sedation in settings such as bronchoscopy[11,12] and endoscopy.[13,14] Remimazolam is rapidly hydrolyzed to an inactive metabolite by tissue esterase,[15] and its hypnotic effect can be reversed using flumazenil,[16] allowing for rapid recovery and minimal residual sedation. However, since benzodiazepine administration is associated with an increased risk of postoperative delirium,[17] the potential of remimazolam to increase the risk of postoperative delirium is concerning.

Considering these potential advantages and disadvantages, we hypothesized that remimazolam is non-inferior to dexmedetomidine in terms of recovery in patients undergoing TAVR. This study aimed to i) demonstrate the non-inferiority of remimazolam in terms of timely recovery, defined as intensive care unit (ICU) discharge within the first day following TAVR, in comparison to dexmedetomidine, and ii) compare specific recovery profiles associated with timely recovery.

Methods

Study design and patients

This observational cohort study was conducted on patients who underwent TAVR at a tertiary care center in Seoul, South Korea. All patients who underwent TAVR between July 2020 and July 2022 were evaluated for eligibility. The patients who underwent emergent or valve-in-valve TAVR and those scheduled for general anesthesia were excluded. The study data was obtained from the ASAN Medical Center Aortic Valve Replacement Registry (NCT03298178) and a medical record review. The study was approved by the Institutional Review Board (AMC IRB 2022-1098), and the requirement for informed consent was waived, considering the retrospective nature of the study.

Study exposure and perioperative management

The primary exposure in the study was remimazolam, and the comparative exposure was dexmedetomidine. TAVR procedures were typically performed under MAC unless the patient's overall condition was unstable or transapical TAVR was performed. Before July 2021, dexmedetomidine and remifentanil were the agents used for MAC with dexmedetomidine dosages ranging from 0.3 to 0.7 μg/kg/hr after loading of 1 μg/kg for 10 minutes and remifentanil target-controlled infusion (TCI) dosages ranging from 0.3 to 0.7 ng/mL. After its introduction in July 2021, remimazolam was the primary sedative in most TAVR procedures in the center. Remimazolam was administered in conjunction with remifentanil with remimazolam dosages ranging from 0.2 to 0.6 mg/kg/hr after a bolus of 2.5 to 5 mg and remifentanil TCI dosages ranging from 0 to 0.3 ng/mL. The target level of sedation aimed to achieve a Modified Observer's Assessment of Alertness and Sedation score of ≤ 3. When dexmedetomidine was administered, the use of rescue sedatives, such as 1 mg of midazolam, was allowed in cases where the intended level of sedation was not achieved. All sedatives were discontinued upon confirming the integrity of the prosthetic aortic valve. At the end of the procedure, remimazolam was reversed with 0.2 mg of flumazenil. Perioperative management adhered to institutional standards involving multidisciplinary risk stratification and optimal management planning through collaboration with the cardiology team. The interventionist adopted a minimalist approach by simplifying the procedure, enabling TAVR without using transesophageal echocardiography, and relying on meticulous computed tomography measurement. The anesthesiologist performed arterial cannulation for perioperative monitoring and 18-gauge venous cannulation for massive bleeding. The postoperative care objectives were to minimize the cardiac ICU stay duration to less than a day, followed by discharge on the third day. A cardiac rehabilitation program was implemented if deemed necessary.

Outcomes

The primary outcome of the study was timely recovery after TAVR, defined as ICU discharge within the first day following TAVR. The criteria for discharge from the ICU in our center included several factors: the patient should be alert and conscious, hemodynamically stable, and not require vasopressors or inotropes, or if needed, they should be on minimal doses. Secondary outcomes included factors that may affect the patient's timely recovery, such as the duration to be fully awake (the duration from ICU admission until the first instance when the Richmond Agitation-Sedation Scale score reaches 0, evaluated by ICU nurses), duration of postoperative oxygen supplementation, need for intubation at the ICU, infusion of vasopressor/inotropes (inclusive of drug infusion initiated in the operating room and continued in the ICU, as well as instances where a new infusion was initiated in the ICU), need for temporary pacemaker (TPM), and occurrence of delirium assessed with the Confusion Assessment Method for the Intensive Care Unit; ICU nurses assessed delirium immediately upon arrival and at each nursing shift. Tertiary outcomes included all-cause mortality within 30 days after surgery, occurrence of stroke, need for cardiopulmonary resuscitation/extracorporeal membrane oxygenation, and need for permanent pacemakers.

Statistical analysis

We anticipate that approximately 90% of the patients undergoing TAVR will achieve timely recovery based on the data from our TAVR registry. Remimazolam would be considered non-inferior with a margin of -10%. Based on these assumptions, 142 patients per group would be required to

demonstrate non-inferiority, with an alpha of 0.025 and a power of 0.8. The study duration was expected to achieve this sample size.

The analysis employed propensity-score matching to compare remimazolam and dexmedetomidine. A multivariable logistic regression model was utilized for estimating the propensity score, incorporating potential confounders such as age, sex, body mass index, smoking history, New York Heart Association functional classification, hypertension, diabetes mellitus, myocardial infarction, atrial fibrillation, stroke, peripheral vascular disease, pulmonary disease, chronic kidney disease, previous cardiac surgery, left ventricular ejection fraction, hemoglobin, B-natriuretic peptide, troponin I, albumin, and Society of Thoracic Surgeons score. A complete-case analysis was conducted in the logistic regression modeling due to relatively few participants with missing variables. After determining the propensity score, 1:1 Greedy matching was conducted with a caliper width of 0.1. Matching balance was assessed using the standardized mean difference (SMD), considering it well-balanced when the SMD was < 0.1. In the matched-cohort analysis, McNemar's test was used for comparing categorical outcomes and paired t-test or Wilcoxon signed-rank test, as appropriate, for continuous outcomes. Categorical outcomes were reported with risk differences and 95% confidence intervals.

To enhance the robustness of our primary findings, we conducted three sensitivity analyses. First, to address missing values of baseline characteristics in the propensity model, we performed single-value imputation using median or mode. Second, a multivariable logistic regression analysis was executed on the unmatched cohort. Third, recognizing the possible confounding effect of the date of TAVR, which could not be balanced between the two groups in our study, we conducted sensitivity analyses to assess its impact on the study results. To investigate the potential time-dependent pattern of the timely recovery rate, we utilized logistic regression with a restricted cubic spline to plot the estimated timely recovery rate by the month of TAVR. This analysis aimed to determine whether there was an overall correlation between the timing of TAVR and the observed timely recovery rate. Furthermore, the multivariable logistic regression analysis was repeated, treating the month of TAVR as a continuous variable and the six-month interval as a categorical variable. This approach helped ascertain whether there was a discernible effect of time on the outcomes.

The results regarding secondary and tertiary outcomes were not adjusted for multiple comparisons. Therefore, all results, apart from the primary outcome, should be viewed as exploratory. All analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population and characteristics

The medical records of 492 consecutive patients who underwent TAVR under MAC between July 2020 and July 2022 were reviewed retrospectively. Patients who underwent emergent TAVR (n=5), valve-in-valve TAVR (n=7) or had planned general anesthesia (n=16) were excluded. After exclusion, a total of 464 patients were included in the analytic cohort (Figure 1). The baseline characteristics of the unmatched and matched cohorts are summarized in Table 1. The median age was 81 (interquartile

range [IQR], 77–84) years, and 195 (56.7%) were women. Among them, 218 (47.0%) received remimazolam as a sedative for MAC. After 1:1 propensity-score matching, the analysis included a total of 328 patients (164 in each group). Propensity matching resulted in a well-balanced baseline characteristic between the two groups with SMD < 0.1.

Intraoperative characteristics

Intraoperative characteristics are outlined in Table 2. Rescue sedative requirements were not observed in the remimazolam group and were observed in 33.5% of the dexmedetomidine group ($p < 0.001$). No significant difference was observed in the need for vasopressor/inotropes during TAVR between the remimazolam and dexmedetomidine groups (30.5% vs. 24.4%; $p = 0.216$).

Primary and secondary outcomes

The primary and secondary outcomes are shown in Table 3. Of the 464 unmatched patients undergoing TAVR, 91.7% (200 of 218) in the remimazolam group were discharged from the ICU within the first day compared to 91.5% (225 of 246) in the dexmedetomidine group. The median [IQR] duration of ICU stay was 25.5 [23 to 27] hours and 26 [24 to 28] hours in the remimazolam and dexmedetomidine groups, respectively. The timely recovery rate remained consistent in the propensity score-matched cohort with 92.7% (152 of 164) in the remimazolam group and 93.3% (153 of 164) in the dexmedetomidine group (p=0.827). The median [IQR] duration of ICU stay was 25.5 [23 to 27] hours in the remimazolam group and 26 [25 to 28] hours in the dexmedetomidine group. Non-inferiority was met as the difference in the proportion [95% CI] of patients with timely recovery was -0.6% [-6.1 to 4.9], which was within the prespecified non-inferiority margin of -10%. Regarding secondary outcomes, the remimazolam group exhibited a significantly shorter duration to be fully awake and lower need for vasopressor/inotrope support and TPM support. The incidence of postoperative delirium showed no significant difference between the groups.

Tertiary outcomes and sensitivity analyses

Among tertiary outcomes, no significant differences were observed in terms of all-cause mortality within 30 days after surgery, incidence of stroke, need for cardiopulmonary resuscitation/extracorporeal membrane oxygenation, or need for permanent pacemakers (Table 4). The results of sensitivity analyses were consistent with those of the primary analysis as presented in Supplementary Tables 1 and 2 and Supplementary Figure 1.

Discussion

This study evaluated the timely recovery rate of remimazolam and dexmedetomidine after TAVR and compared the associated recovery profiles. Remimazolam exhibited a non-inferior association compared to dexmedetomidine in terms of timely recovery in patients undergoing TAVR under MAC. Remimazolam was associated with a more favorable recovery profile, including a shorter

duration to be fully awake and reduced postoperative requirement for vasopressors/inotropes and TPMs.

Remimazolam, a novel benzodiazepine known for its rapid metabolism, hemodynamic stability, and minimal bradycardia, was considered a suitable option for TAVR. However, concerns about a potential increase in the incidence of delirium led us to cautiously hypothesize that remimazolam might be non-inferior in terms of timely recovery. The study outcomes supported our hypothesis, establishing remimazolam as non-inferior to dexmedetomidine regarding timely recovery following TAVR. Moreover, several secondary outcomes, including duration to be fully awake and postoperative vasopressor/inotrope and TPM use, generally aligned with our hypothesis. In contrast, the incidence of delirium did not correspond with our initial hypothesis. Therefore, secondary outcomes require a detailed review to comprehensively assess the overall impact of remimazolam on recovery profiles after TAVR.

The remimazolam group exhibited a lower postoperative incidence of inotrope/vasopressor use and TPM requirement. Although the comprehensive impact of remimazolam on blood pressure and heart rhythm remains unexplored, previous studies have shown its hemodynamic stability relative to alternative anesthetic agents.[18,19] This study also presents an association between remimazolam administration and decreased requirement for vasopressors/inotropes, evident in the postoperative rather than the intraprocedural period. This observation can be explained by the known biphasic effects of dexmedetomidine on the cardiovascular system. Dexmedetomidine induces hypertension and tachycardia shortly after the initial bolus injection, while hypotension and bradycardia become prevalent during prolonged infusion.[20] This may explain why the hemodynamic stability induced by remimazolam was not significantly different during the operative period compared with that during the postoperative period. Regarding the use of pacemakers, dexmedetomidine's tendency to induce bradycardia and arrhythmias may explain why the remimazolam was less likely to retain TPMs.[21,22] However, the lower incidence of inotrope/vasopressor use and the need for TPM in the remimazolam group does not appear to be linked to the increase in the timely recovery rate. No significant differences were observed between the two groups concerning inotrope/vasopressor use on postoperative day 1 or the need for TPM on postoperative day 2. Consequently, the favorable outcomes associated with remimazolam may be transient and not have significantly contributed to ICU discharge on the first postoperative day. Nevertheless, remimazolam usage might be related to faster ICU discharge in a more rapid recovery protocol.

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The duration to be fully awake was advantageous in the remimazolam group, consistent with the findings from a previous study.[11] One significant factor contributing to the shorter recovery duration of remimazolam may be attributed to its pharmacokinetics. The majority of patients undergoing TAVR are in their 80s, have multiple comorbidities, and are in a frail condition[1]. Nevertheless, the duration to be fully awake would not have been affected considerably by these patient factors since the metabolism and excretion of remimazolam may not be influenced by age, sex, body weight, race, and kidney function.[10] Furthermore, flumazenil usage could also have played a role in achieving a shorter duration to be fully awake.

The incidence of delirium within two days after TAVR in this study was 18.3% in the remimazolam group and 18.9% in the dexmedetomidine group and showed no significant difference. Although benzodiazepines are generally known to be associated with an increased risk of delirium, our

results were contradictory. The findings of a recent study suggest that, unlike other benzodiazepines, remimazolam may not be associated with an increased risk of delirium. Aoki et al. demonstrated that the use of remimazolam in cardiac surgery showed no significant association with increased postoperative delirium compared to that of other anesthetic agents.[23] Additionally, a randomized controlled trial in orthopedic surgery showed that remimazolam did not significantly increase delirium compared to propofol.[24] However, interpreting the effects of remimazolam on delirium incidence in our study should be approached with caution for the following reasons. Considering that 33.5% of individuals in the dexmedetomidine group received midazolam as a rescue sedative, midazolam may have played a role in the increased delirium in this group. It is prudent not to overly extrapolate and interpret these findings since delirium incidence is a secondary outcome in this study, and the data was not prospectively collected. Waiting for the results of ongoing randomized controlled trials (such as KCT0007245 at https://cris.nih.go.kr/) is warranted.

Limitations

The retrospective design and the single-center setting at a tertiary university hospital may limit the generalizability of the results. In addition, although the sensitivity analyses in this study revealed no significant trend and effect in the primary outcome over time, we cannot completely rule out the possibility that the temporal difference in the use of remimazolam and dexmedetomidine could have acted as a confounding factor.

Conclusion

In patients undergoing TAVR, remimazolam demonstrated a non-inferior association with timely recovery compared to dexmedetomidine. Additionally, remimazolam was associated with a more favorable recovery profile, including a shorter duration to be fully awake and reduced postoperative requirements for vasopressors/inotropes and TPMs.

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Table 1. Baseline characteristics

	Before matching			After matching		
	Remimazolam (n=218)	Dexmedetomidine (n=246)	SMD	Remimazolam (n=164)	Dexmedetomidine (n=164)	SMD
Age (yr)	81 [77 to 84]	81 [77 to 84]	0.015	80.5 [76.5 to 84]	81 [77 to 84]	0.004
Female sex	119 (54.6)	144 (58.5)	0.08	99 (60.4)	96 (58.5)	0.037
Body mass index	23.7 ± 3.9	24.5 ± 4.3	0.195	24.0 ± 3.99	23.8 ± 3.6	0.033
Ever smoker	44 (20.2)	59 (24.0)	0.092	32 (19.5)	36 (22.0)	0.06
NYHA class ≥ III	22 (10.1)	57 (23.2)	0.357	21 (12.8)	21 (12.8)	<0.001
Hypertension	159 (72.9)	181 (73.6)	0.014	120 (73.2)	124 (75.6)	0.056
Diabetes mellitus	91 (41.7)	103 (41.9)	0.003	70 (42.7)	75 (45.7)	0.061
Myocardial infarction	5 (2.3)	5 (2.0)	0.018	3 (1.8)	5 (3.0)	0.079
Atrial fibrillation	28 (12.8)	33 (13.4)	0.017	22 (13.4)	20 (12.2)	0.037
Stroke	14 (6.4)	31 (12.6)	0.212	12 (7.3)	13 (7.9)	0.023
Peripheral vascular disease	5 (2.3)	6 (2.4)	0.01	3 (1.8)	4 (2.4)	0.042
Pulmonary disease	14 (6.4)	20 (8.1)	0.066	11 (6.7)	10 (6.1)	0.025
Chronic kidney disease	146 (67.0)	179 (72.8)	0.126	113 (68.9)	115 (70.1)	0.026
Previous cardiac surgery	2 (0.9)	6 (2.4)	0.119	2 (1.2)	2 (1.2)	<0.001
Ejection fraction (%)	62.5 [58 to 66]	63 [57 to 66]	0.018	63 [58 to 66]	62.5 [57 to 66]	0.02
Hemoglobin (g/dl)	11.5 ± 1.6	11.4 ± 1.8	0.095	11.4 ± 1.6	11.3 ± 1.7	0.041
Albumin (g/dl)	3.6 [3.3 to 3.8]	3.5 [3.3 to 3.7]	0.204	3.5 [3.3 to 3.8]	3.5 [3.3 to 3.8]	0.015
B-type natriuretic peptide (pg/ml)	165.5 [79 to 441])	181.5 [90 to 417]	0.054	161 [77.5 to 378.5]	170.5 [87.5 to 382]	0.065
Troponin-I (ng/ml)	20 [11 to 49]	19 [11 to 40]	0.089	20 [10 to 49]	17.5 [10 to 36.5]	0.072
STS score	3.32 [2.12 to 4.62]	3.22 [2.18 to 5.09]	0.069	3.41 [2.13 to 4.71]	3.17 [2.06 to 5.02]	0.026

Data are presented as number of patients (%), mean ± standard deviation, or median [interquartile range].

Abbreviations: NYHA : New York Heart Association, SMD: standardized mean difference, STS : Society of Thoracic Surgeons.

Table 2. Intraoperative characteristics

	Before matching		After matching		
	Remimazolam (n=218)	Dexmedetomidine (n=246)	Remimazolam (n=164)	Dexmedetomidine (n=164)	P-value
Conversion to general anesthesia					0.184
Due to the anesthetic reasons	3 (1.4)	2 (0.8)	3 (1.8)	0 (0.0)	
Due to the procedural reasons	2 (0.9)	2 (0.8)	2 (1.2)	1 (0.6)	
Mask ventilation	0 (0)	2 (0.8)	0 (0)	0 (0)	
Rescue sedatives	0 (0)	80 (32.5)	0 (0)	55 (33.5)	<0.001
Remifentanil (μg)	60 [40 to 100]	140 [100 to 200]	60 [40 to 100]	140 [100 to 200]	<0.001
Vasopressor/inotropes	68 (31.2)	63 (25.6)	50 (30.5)	40 (24.4)	0.216
Duration of the procedure (min)	62.5 [55 to 73]	55 [47 to 67]	62.5 [55 to 71.5]	55 [47 to 67]	0.007

Data are presented as number of patients (%) or median [interquartile range].

Table 3. Primary and secondary outcomes

	Before matching		After matching			
	Remimazolam (n=218)	Dexmedetomidine (n=246)	Remimazolam (n=164)	Dexmedetomidine (n=164)	Risk difference (95% CI)	P-value
Primary outcome						
Timely recovery	200 (91.7)	225 (91.5)	152 (92.7)	153 (93.3)	-0.6 (-6.1 to 4.9)	0.827
Duration of ICU stay (hr)	25.5 [23 to 27]	26 [24 to 28]	25.5 [23 to 27]	26 [25 to 28]		0.172
Secondary outcomes						
Time to be fully awake (hr)	2 [0 to 4]	3 [2 to 6]	2 [0 to 4]	3 [2 to 5]		0.011
Oxygen supplement duration (hr)	5 [4 to 6]	5 [4 to 6]	5 [4 to 6]	6 [5 to 6]		0.518
Intubation	1 (0.5)	2 (0.8)	1 (0.6)	2 (1.2)	-0.6 (-2.7 to 1.5)	0.571
Vasopressor/inotropes*	27 (12.4)	64 (26.0)	21 (12.8)	39 (23.8)	-11.0 (-19.3 to -2.7)	0.013
On POD 1**	17 (7.8)	19 (7.7)	11 (6.7)	9 (5.5)	1.2 (-1.8 to 4.2)	0.617
On POD 2***	5 (2.3)	4 (1.6)	3 (1.8)	1 (0.6)	1.2 (-4.2 to 6.6)	0.803
Need for TPM*	100 (45.9)	155 (63.0)	76 (46.3)	108 (65.9)	-19.5 (-30.0 to -9.0)	<0.001
On POD 1**	88 (40.4)	10 (52.9)	63 (38.4)	90 (54.9)	-16.5 (-27.8 to -5.3)	0.004
On POD 2***	11 (5.1)	12 (5.0)	8 (4.9)	6 (3.7)	1.2 (-3.9 to 6.3)	0.789
Delirium	38 (17.4)	43 (17.6)	30 (18.3)	31 (18.9)	-0.6 (-9.6 to 8.4)	0.886

Data are presented as number of patients (%) or median [interquartile range].

* Overall incidence during ICU stay.

** Participants who need support on postoperative day 1.

*** Participants who need support on postoperative day 2.

Abbreviations: CI: confidence interval, ICU: intensive care unit, POD: post-operative days, TPM: temporary pacemaker.

Table 4. Tertiary outcomes

	Before matching		After matching			
	Remimazolam (n=218)	Dexmedetomidine (n=246)	Remimazolam (n=164)	Dexmedetomidine (n=164)	Risk difference (95% CI)	P-value
All-cause mortality within 30 days	3 (1.4)	2 (0.8)	3 (1.8)	2 (1.2)	0.6 [-2.7 to 3.9]	0.657
Stroke	0 (0)	9 (3.7)	0 (0)	4 (2.4)	- 2.4 [-5.4 to 0.5]	1.000
Cardiopulmonary resuscitation or ECMO	1 (0.5)	6 (2.4)	1 (0.6)	2 (1.2)	-0.6 [-3.3 to 2.1]	0.571
Permanent pacemaker	10 (4.6)	12 (4.9)	8 (4.9)	5 (3.0)	1.9 [-2.7 to 6.4]	0.372

Data are presented as number of patients (%) or median [interquartile range].

Abbreviations: CI: confidence interval, ECMO: extracorporeal membrane oxygenation.

Table 5. Sensitivity analysis: single value imputation for missing covariables

	After matching		
	Remimazolam (n=182)	Dexmedetomidine (n=182)	P-value
Timely recovery	166 (91.2)	170 (93.4)	0.451
Length of ICU stay (hr)	25 [23 to 27]	26 [24 to 28]	0.110
Time to be fully awake (hr)	2 [0 to 4]	3 [2 to 6]	<0.001
Oxygen supplement time (hr)	5 [4 to 6]	6 [5 to 6]	0.264
Intubation	0 (0)	2 (1.1)	
Vasopressor/inotropes	25 (13.7)	43 (23.6)	0.018
Need for TPM	82 (45.1)	116 (63.7)	<0.001
Delirium	31 (17.0)	36 (19.8)	0.501

Data are presented as number of patients (%) or median [interquartile range].

Abbreviations: CI: confidence interval, ICU: intensive care unit, TPM: temporary pacemaker.

Table 6. Sensitivity analysis: multivariable logistic regressions

	Odds ratio (95% CI)	P-value
Model 1*	0.87 (0.41 to 1.84)	0.076
Model 2**	0.55 (0.17 to 1.78)	0.325
Model 3***	0.88 (0.25 to 3.08)	0.836

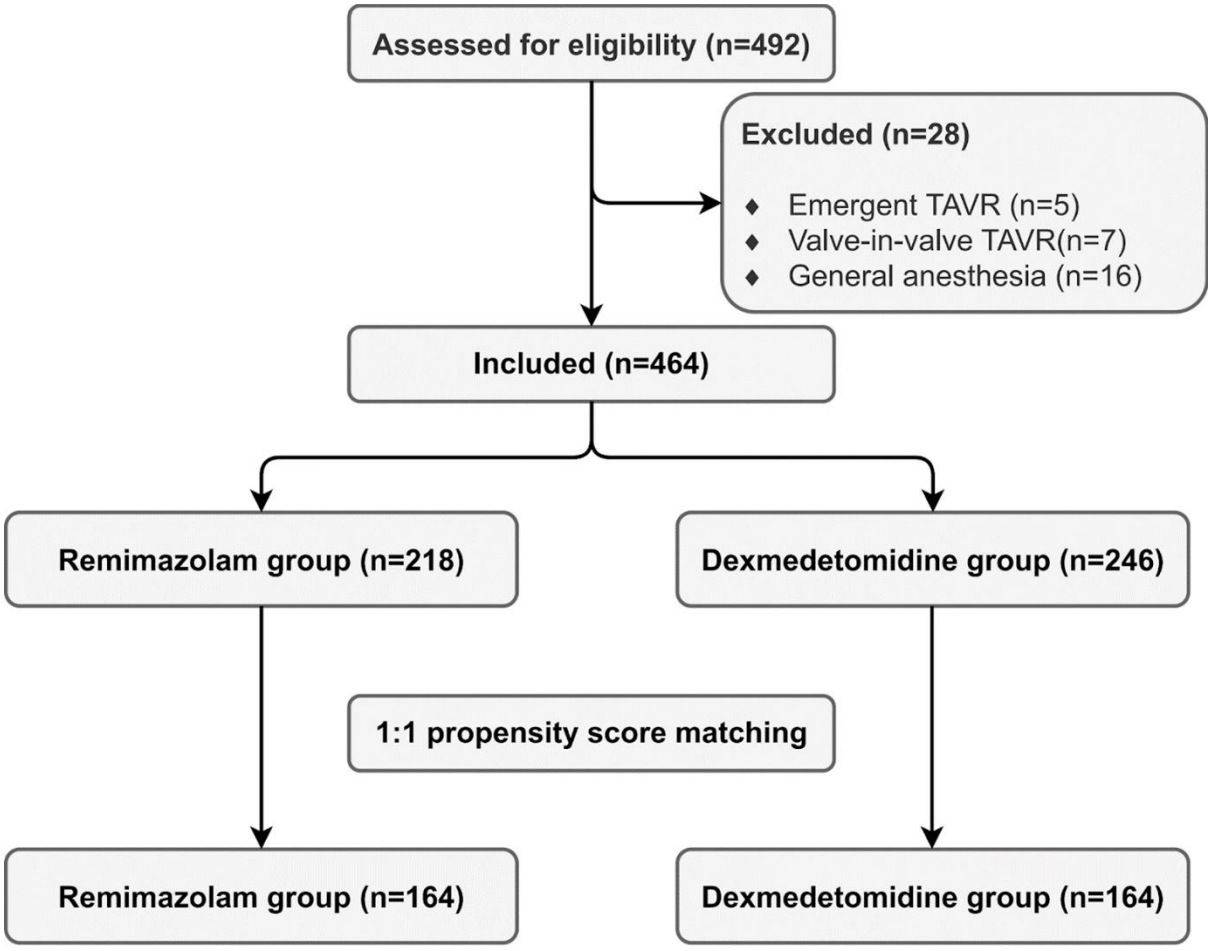
*Adjusted with all covariables included in the propensity model.

**Adjusted with all covariables in the Model 1 plus month of the TAVR procedure as continuous variable.

***Adjusted with all covariables in the Model 1 plus categorized TAVR months d in 6-month intervals.

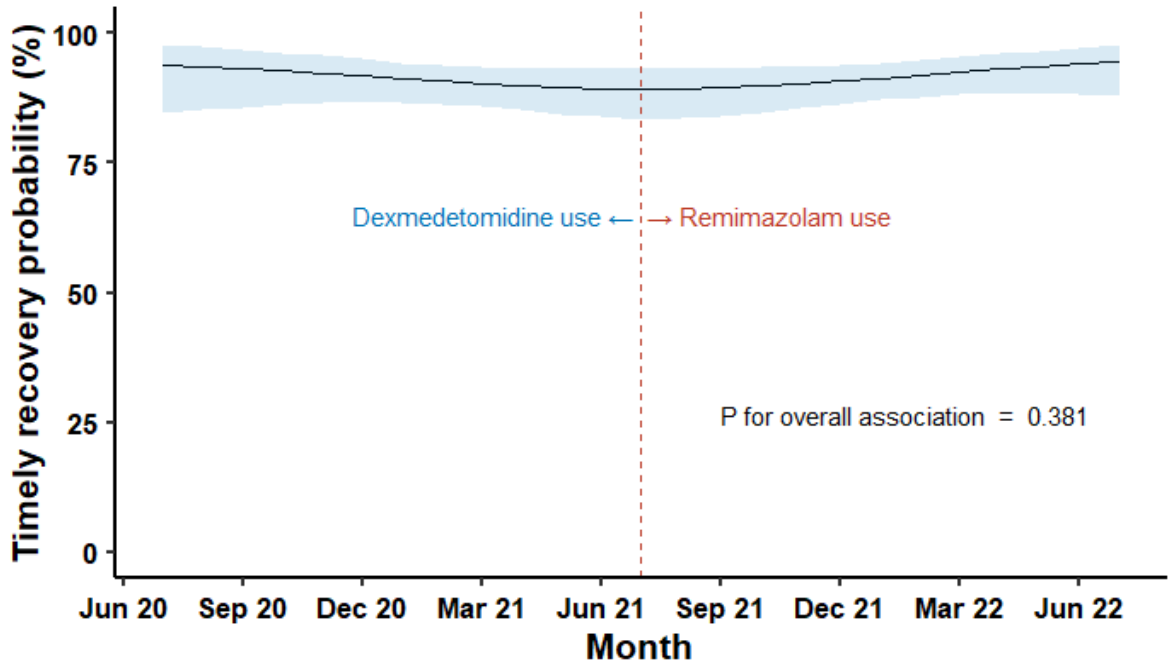
Abbreviations: CI: confidence interval.

Figure 1. Flow diagram



Abbreviations: TAVR: transcatheter aortic valve replacement.

Figure 2. Estimated timely recovery probability according to TAVR months



The solid line indicates the estimated probability of timely recovery according to TAVR months, with the shaded area representing the 95% confidence interval. The vertical dashed line denotes the introduction of remimazolam in July 2021. Before July 2021, dexmedetomidine was the primary sedative, and after July 2021, remimazolam became the primary sedative in most TAVR procedures. Abbreviations: TAVR: transcatheter aortic valve replacement.

Korean abstract (국문요약)

서론: 최근 감시마취관리(monitored anesthesia care, 이하 MAC) 하에 시행되는 경피적 대동맥 판막 치환술(transcatheter aortic valve replacement, 이하 TAVR)은 환자의 빠른 회복과 퇴원을 강조하고 있다. 레미마졸람 베실레이트는 벤조디아제핀 계열의 신약으로, 회복 시간이 짧다는 장점이 있지만 수술 후 섬망 발생 위험이 증가할 수 있다는 우려가 있다. 이에 따라, 본 연구진은 TAVR 후 회복 측면에서 레미마졸람이 덱스메데토미딘에 비해 열등하지 않을 것이라는 가설을 세웠다.

방법: 본 연구는 단일 기관 후향적 연구로, 2020년 7월부터 2022년 7월까지 MAC 하에 TAVR을 시행 받은 환자들에게서 레미마졸람과 덱스메데토미딘을 비교하였다. 연구의 일차 결과지표는 TAVR 후 적시 회복률이고, 수술 후 하루 이내에 중환자실에서 퇴실한 경우로 정의하였다. 연구의 이차 결과지표는 완전히 깨어나는데 걸리는 시간, 산소 보충 기간, 기도 삽관 여부, 혈관수축제/강심제 필요 여부, 임시 심박동기(TPM) 필요 여부, 그리고 섬망 발생률이다.

결과: 464명의 환자 중에서 218명은 레미마졸람, 246명은 덱스메데토미딘을 진정제로 사용하였고, 성향매칭 후 최종분석에는 각 그룹에 164명씩 포함되었다. TAVR 이후 적시 회복률 측면에서, 레미마졸람은 덱스메데토미딘에 비해 열등하지 않은 것으로 나타났다(리스크 차이 [RD] −0.6; 95% 신뢰구간 [CI] −6.1에서 4.9; p=0.827). 레미마졸람 사용은 덱스메데토미딘 사용과 비교했을 때 환자가 완전히 깨어나는데 걸리는 시간이 더 짧았고(2[0−4] 시간 대 3[2−5] 시간, p=0.011), 수술 후 혈관수축제/강심제 사용이 적었으며(12.8% 대 23.8%, p=0.013), TPM 사용이 적었다(46% 대 65.9%, p<0.001). 레미마졸람과 덱스메데토미딘 군은 섬망 발생률에서 유의한 차이가 없었다(18.3% 대 18.9%, p=0.886).

결론: TAVR을 시행 받는 환자들에서, 레미마졸람은 중환자실 재원일 측면에서 덱스메데토미딘에 비해 열등하지 않다고 간주되며, 수술 후 의식회복 시간, 혈관수축제/강심제 투여율 및 TPM 필요성 측면에서 보다 더 유리한 회복 양상과 관련이 있었다.