

Utility of Remimazolam in Total Intravenous General Anesthesia for Extremely Obese Patients: Two Case Reports

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Abstract

Case Report

Background: Remimazolam, an ultra-short-acting benzodiazepine, is increasingly used for general anesthesia. However, systematic data on remimazolam use for the maintenance of total intravenous anesthesia (TIVA) in extremely obese patients (BMI ≥ 40 kg/m²) remain scarce, leaving the clinical feasibility of this comprehensive approach uncertain. The unique pharmacokinetic characteristics of remimazolam, including its rapid onset, swift metabolism, and ability to maintain stable vital signs and respiration, make it a promising choice for anesthesia in obese patients. **Case:** We present two case reports where remimazolam was employed for total intravenous general anesthesia in such patients. The first patient, with a BMI of 51.44 kg/m², underwent robot-assisted parathyroidectomy, whereas the second patient, with a BMI of 42.66 kg/m², underwent wound debridement for cerebrospinal fluid leakage. Both patients progressed without complications and maintained stable vital signs. **Conclusions:** These cases suggest that remimazolam may be a safe and effective option for anesthesia management in extremely obese patients. Further research is warranted to confirm these findings.

Keywords: Remimazolam; Case report; Morbid obesity; Anesthesia; General; Intravenous.

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INTRODUCTION

Remimazolam is an ultra-short-acting benzodiazepine, approved as a general anesthetic and sedative in South Korea in 2021. Its unique pharmacokinetic properties, including a small steady-state volume of distribution, high elimination clearance, and a short context-sensitive half-life, enable its use in general anesthesia through continuous intravenous administration [1]. As remimazolam undergoes rapid esterase-mediated metabolism to a pharmacologically inactive carboxylic acid metabolite (CNS 7054) and follows first-order linear pharmacokinetics, its accumulation or half-life is not prolonged by extended intravenous infusion times or increased doses [2-4]. While research on the pharmacokinetics and pharmacodynamics of remimazolam is ongoing, limited studies have focused on its use in obese patients [5]. Obese patients carry distinct anesthetic risks, including difficult airway management and pathophysiology-altering comorbidities [6]. In addition, obesity-induced changes in body composition can significantly alter the pharmacokinetics of traditional anesthetic agents [7]. Although preliminary reports have described

remimazolam usage solely for anesthetic induction in super-obese patients [5], literature evaluating its continuous infusion for sustaining anesthesia remains limited. In this study, we present two case reports providing initial evidence that a remimazolam-based total intravenous anesthesia (TIVA) regimen, spanning both induction and prolonged maintenance, can serve as a viable and stable anesthetic option for patients with class III obesity (body mass index, BMI ≥ 40 kg/m²).

CASE REPORT

This case report was reviewed and approved by the Institutional Review Board (IRB No. 2023-06-021) and conducted in accordance with the Declaration of Helsinki-2013. Written informed consent for publication was obtained from both patients.

The first case involves a super-obese patient: a 41-year-old female with a BMI of 51.44 kg/m² (height, 136.1 cm; weight, 95.3 kg) who was scheduled for a robotic-assisted parathyroidectomy for hyperparathyroidism. The patient had comorbidities, including hypertension, diabetes mellitus, a congenital

single kidney, and severe scoliosis. Pulmonary function tests revealed mild restrictive airway obstruction (forced expiratory volume in 1 s (FEV₁), 64% of the predicted value; forced vital capacity (FVC), 61% of the predicted value; and FEV₁/FVC, 87% of the predicted value). Preoperative chest radiography revealed no active lung lesions. Transthoracic echocardiography revealed a normal left ventricular function. Electrolyte, liver function tests and kidney function tests were within normal limits three weeks before the operation (BUN/Cr 23.0/0.73 mg/dl, eGFR 100.9 ml/min/1.73 m²). The Mallampati score was 4, and the patient had a short, thick neck.

Upon entering the operating room, the patient was placed in a ramped position and continuously monitored using pulse oximetry, noninvasive blood pressure, four-lead electrocardiography, and bispectral index (BIS Quatro™; BIS, Covidien, USA). The train-of-four (TOF) or post-tetanic count (PTC) was repeatedly assessed on the ulnar nerve of the left hand using a quantitative neuromuscular blockade monitor (TwitchView™, LTR Medical, Australia). Figure 1 illustrates the overall process.

The patient's pre-induction vital signs were as follows: blood pressure at 157/100 mmHg, heart rate at 79 beats/min, and oxygen saturation at 100%. Pre-oxygenation was performed using 100% O₂ at a flow rate of 8 L/min via a facial mask. General anesthesia was induced through a continuous infusion of remimazolam (Byfavo®, Hana Pharm, Korea) (6 mg/kg/h, total body weight), and remifentanyl (Remiva®, Hana Pharm, Korea) (0.75 mcg/kg/min, lean body mass). At 150 s after initiating the remimazolam infusion, the patient lost consciousness (24 mg of remimazolam was administered during the loading period). The mean BIS scores remained stable at 58. Succinylcholine (1 mg/kg) was then administered, and the remimazolam infusion dose was adjusted to a maintenance dose (1 mg/kg/h, total body weight). Intubation was performed when the TOF count reached 0, with a 50 mg bolus dose of rocuronium administered, followed by a continuous infusion of rocuronium (0.5 mg/kg/h, ideal body weight) [8]. The infusion rate of remifentanyl was adjusted to the maintenance dose, and the dosage was titrated within the following range based on changes in vital signs (0.19 mcg/kg/min to 0.21 mcg/kg/min, lean body mass). Mechanical ventilation was initiated with an end-tidal CO₂ level of 35 mmHg. The ventilation mode used was volume-controlled mode (Auto-Flow®), with FiO₂ at 1.0, a fresh gas flow of 8.0 L/min, a tidal volume of 350 ml, a breathing frequency of 16 breaths/min, and a PEEP of 10cmH₂O. A 20 G catheter was inserted into the right dorsalis pedis artery to ensure accurate and continuous blood pressure monitoring. Figure 2 shows the patient's vital signs, changes in the BIS value, and drug dosage during anesthesia induction and intubation.

The operation time and anesthesia time were 3 h and 30 min, respectively. Throughout this process, the patient's blood pressure was maintained within ±10% of the baseline values, oxygen saturation was maintained at 100%, and BIS values ranged from 43 to 64.

Forty minutes before the end of the operation, when the robotic surgical machine was removed from the surgical field, rocuronium infusion was stopped. Immediately after skin suturing, the infusions of remimazolam and remifentanyl were discontinued, and the patient's position was changed to a ramped position to secure the airway. Figure 1 shows the overall appearance of the patient. When the surgery was completed, the total doses of remimazolam, rocuronium, and remifentanyl were 325 mg, 193 mg, and 1.63 mg, respectively, and the TOF count was 2. We administered 4 mg/kg of sugammadex (BRIDION®, Merck Sharp Dohme, USA), and at that time, the blood pressure and heart rate were 122/72 mmHg and 75 beats/min, respectively. Two minutes after the administration of sugammadex, the TOF ratio recovered to 96%, and the blood pressure and heart rate increased to 162/60 mmHg and 96 beats/min, respectively. Nicardipine 0.5 mg was administered, and the blood pressure decreased but remained near 140/70 mmHg. Sixteen minutes after discontinuation of the remimazolam and remifentanyl infusion, spontaneous breathing was restored, and the patient struggled with mechanical ventilation, reducing oxygen saturation to 83% and increasing blood pressure to 190/95 mmHg. The mean BIS values were 74. Therefore, manual ventilation with 100% oxygen was performed based on the patient's spontaneous breathing, and nicardipine 0.5 mg was administered. Three minutes after the restoration of spontaneous breathing, the BIS value was 90, and the patient voluntarily opened her eyes. After confirming that her spontaneous breathing was completely restored, we performed oral suction and extubated the endotracheal tube. After extubation, the patient breathed well without airway obstruction or laryngeal spasms, and the patient's vital signs remained stable (blood pressure, 142/68 mmHg; heart rate, 98 bpm; oxygen saturation, 100%). The patient was transferred to the post-anesthesia care unit (PACU), and 30 min later, she was moved to the general ward. The patient was discharged six days later without any complications, including re-sedation, postoperative delirium, unstable vital signs, respiratory complications, or postoperative nausea and vomiting.

The second case involves a 31-year-old female with a BMI of 42.66 kg/m² (height, 150 cm; weight, 96.0 kg). She was scheduled for wound debridement due to post-craniectomy cerebrospinal fluid leakage and had pre-existing Arnold-Chiari malformation type 1. Preoperative assessments, including chest radiography, electrolyte levels, liver function tests, and kidney function tests, were all within normal limits one week before the operation. The Mallampati score was 4.

Upon admission to the operating room, the patient was positioned in a ramped posture and continuously monitored using pulse oximetry, noninvasive blood pressure measurement, four-lead electrocardiography, and bispectral index (BIS Quatro™; BIS, Covidien, USA). The train-of-four (TOF) or post-tetanic count (PTC) was repeatedly measured on the ulnar nerve of the left hand using a quantitative neuromuscular blockade monitor (TwitchView™, LTR Medical, Australia).

The initial measurements for blood pressure, heart rate, and oxygen saturation were as follows: 136/76 mm Hg, 75 beats/min, and 98%, respectively. Pre-oxygenation was performed with 100% O₂ at 8 L/min using a facial mask. General anesthesia was induced through a continuous infusion of remimazolam (Byfavo®, Hana Pharm, Korea) (3 mg/kg/h, total body weight) and remifentanyl (Remiva®, Hana Pharm, Korea) (0.75 mcg/kg/min, lean body mass). Approximately 375 s after initiating the remimazolam infusion, the patient lost consciousness (30 mg of remimazolam was administered during the loading period), and the BIS value was 51. Succinylcholine (1 mg/kg) was then administered, and the remimazolam infusion dose was reduced to a maintenance dose (1 mg/kg/h, total body weight). Sixty seconds after succinylcholine administration, the TOF count was 0, and intubation was performed immediately after the administration of rocuronium (0.6 mg/kg). The mean total remimazolam was 30 mg. The infusion rate of remifentanyl was adjusted to the maintenance dose, and the rate was regulated within the specified range in response to changes in vital signs (0.11 mcg/kg/min to 0.18 mcg/kg/min, lean body mass). Mechanical ventilation was initiated with an end-tidal CO₂ level of 31 mmHg (ventilation mode, volume-controlled mode (Auto-Flow®); FiO₂, 0.5; fresh gas flow, 4.0 L/min; tidal volume, 360 ml; frequency, 12 breaths/min; PEEP, 10

cmH₂O). A 22 G catheter was inserted into the right radial artery to monitor blood pressure. The patient's position was changed from supine to prone during the surgery. Figure 3 shows the changes in vital signs and BIS values throughout this process.

During the 4 h and 25 min of the operation, the patient's blood pressure remained well-controlled within $\pm 20\%$ of the baseline values, oxygen saturation was maintained at 100%, and BIS values ranged from 40 to 63.

When the skin suture was completed, the infusion of remimazolam, remifentanyl, and rocuronium was stopped; the TOF count was 0; and the BIS value ranged from 54 to 61. The total doses of remimazolam, remifentanyl, and rocuronium were 446 mg, 4.58 mg, and 120 mg, respectively. Subsequently, the patient's position was changed from prone to supine, and Sugammadex (BRIDION®, Merck Sharp Dohme, USA) was administered at 4 mg/kg. Three minutes after the administration of sugammadex, the TOF ratio recovered to 102%, and the patient's blood pressure and heart rate were maintained at 126/76 mmHg and 85 beats/min, respectively. Fifteen minutes after discontinuing remimazolam, spontaneous breathing and consciousness were restored, with a BIS value of 90. Subsequently, oral suctioning was performed and the endotracheal tube was extubated. The patient showed unobstructed spontaneous breathing and was free from laryngeal spasm after extubation, with stable vital signs (blood pressure, 122/71 mmHg; heart rate, 69 bpm; oxygen saturation, 100%). Following these procedures, the patient was transferred to the PACU and, 30 min later, to the general ward. The patient was hospitalized for 12 days for the evaluation of Arnold-Chiari malformation type 1, without any complications, including re-sedation, postoperative delirium, unstable vital signs, respiratory complications, or postoperative nausea and vomiting.



Fig. 1: Overall appearance at induction of anesthesia in the first case

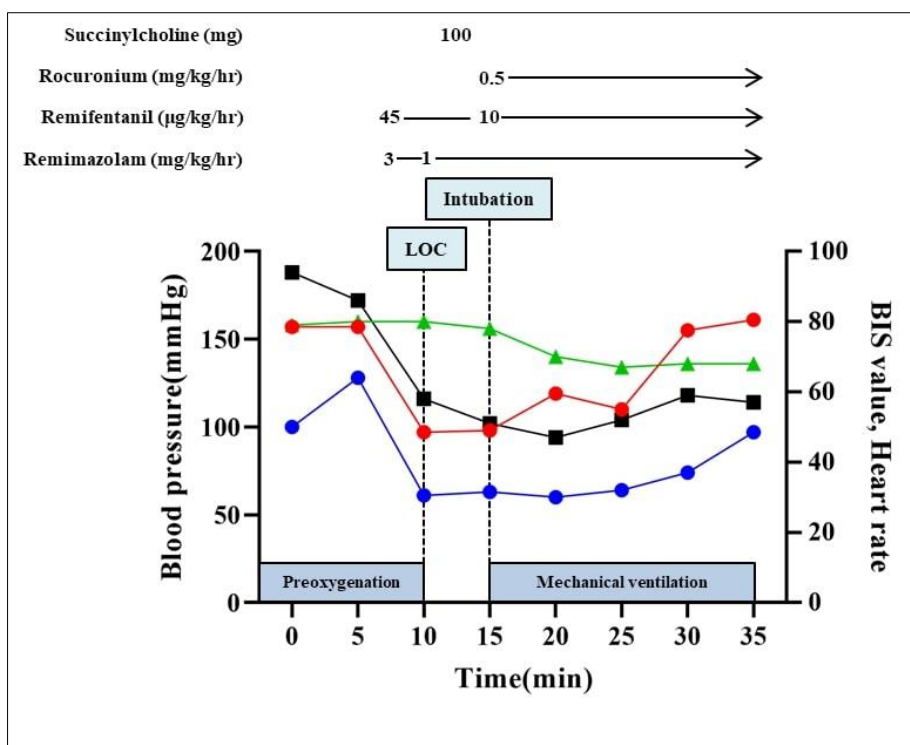


Fig. 2: Anesthesia record in the first case. Red circle: systolic blood pressure, blue circle: diastolic blood pressure, green triangle: heart rate, Black square: bispectrality index

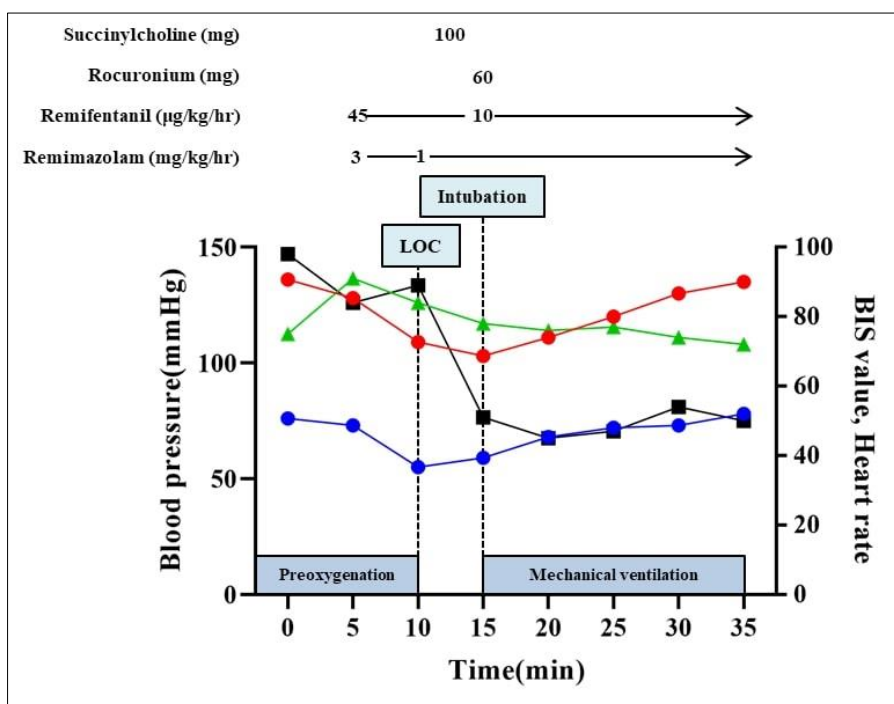


Fig. 3: Anesthesia record in the second case. Red circle: systolic blood pressure, blue circle: diastolic blood pressure, green triangle: heart rate, purple square: bispectrality index

DISCUSSION

In a world where the overweight population is soaring, selection of the best anesthetic drug for obese patients is emerging as a top priority. Several difficulties may arise when conventional anesthetic agents are used, particularly in severely obese patients. For example,

during intravenous anesthesia using propofol, the distribution of the drug within the abundant fat tissue of obese patients may be suboptimal, resulting in delayed onset and prolonged awakening. Under inhalation anesthesia with sevoflurane, the high fat distribution coefficient of the drug can lead to delayed drug elimination during the awakening phase. This

uncertainty in drug metabolism and elimination can pose issues regarding the effectiveness and awakening of obese patients during anesthesia. Several factors related to changes in body composition and metabolic disorders should be considered when using anesthetic agents in obese patients. Obese patients often exhibit a higher body fat ratio, resulting in a substantial disparity between the total body weight (TBW) and ideal body weight (IBW). For drugs with limited distribution into the adipose tissue, the loading dose should be based on the patient's IBW, whereas for drugs that are distributed significantly into the adipose tissue, the loading dose should be based on TBW [9]. In obese patients, it is essential to consider that alterations in respiratory and circulatory dynamics may lead to delayed absorption and clearance compared to normal individuals [6]. In morbidly obese patients, frequently associated comorbidities, such as diabetes, hypertension, hyperlipidemia, and non-alcoholic fatty liver disease, contribute to physiological changes, including alterations in hepatic and renal function, which, in turn, influence the absorption, metabolism, and clearance of anesthetic agents. In super-obese patients, inadequate fluid administration may increase the risk of acute renal failure, especially in the presence of preexisting renal disease, delayed surgery time, or intraoperative hypotension [10,11].

Remimazolam is a new ultrashort-acting drug that has emerged as a promising solution to these challenges. It is described by a three-compartment model (V1, 1.9 L; V2, 3.9 L; V3, 79 L) with high clearance, small distribution volumes, and a rapid onset and offset of sedation [12]. Remimazolam exhibits a rapid context-sensitive half-time compared to midazolam and propofol (after a 3-hour infusion, remimazolam, 7.5 min; midazolam, 58 min; propofol, 20 min) [1]. Remimazolam can undergo rapid hydrolysis into inactive metabolites via non-organ-dependent metabolism, and pharmacokinetic models have suggested that the total clearance of remimazolam is independent of body weight [2,3,4]. The rapid expression and wake-up characteristics of remimazolam, along with the availability of a reversal agent, provide a tool for accurately controlling the level of anesthesia. In addition, remimazolam can effectively maintain spontaneous breathing and demonstrate a reduced cardiovascular depressive effect, thereby facilitating the maintenance of stable vital signs during anesthesia [3]. Therefore, Remimazolam is suitable for use in obese patients who may be concerned about drug accumulation due to a large amount of fat tissue, difficulty in securing airways, and the need for proper anesthesia depth and drug dosage due to a large number of comorbid cardiovascular diseases. However, research on remimazolam in obese patients is limited, with no reported cases of intravenous anesthesia in super-obese patients [5].

General anesthesia with remimazolam can be induced at a rate of 6 or 12 mg/kg/h according to standard

guidelines. In the first case, induction was initiated at 6 mg/kg/h based on total body weight, whereas in the second case, the induction dose was deliberately reduced to a lower rate of 3 mg/kg/h. This clinical decision was prompted by an abundance of caution following a review of several studies reporting potential circulatory collapse or anaphylaxis associated with rapid remimazolam administration [13,14]. In the first and second cases, the time and dose of remimazolam administered until the loss of consciousness were 150 seconds and 24 mg, and 375 seconds and 30 mg, respectively. Slowing down the rate of the induction dose resulted in a longer time for the loss of consciousness; however, no anaphylaxis or other adverse reactions occurred in either case.

In a study that examined the dosage at which consciousness was lost when administering remimazolam as a bolus in patients of normal body weight, it was observed that consciousness was lost at a dosage of 0.29 mg/kg in patients in their 30s and 0.25 mg/kg in those in their 40s [15]. These values closely resembled the calculated dose at the point of loss of consciousness in our present cases. During anesthesia induction, the patient's airway and breathing were well-maintained, and blood pressure remained stable. During the operation, a maintenance dose of remimazolam was administered at a rate of 1 mg/kg/h in both cases, maintaining BIS values in the respective ranges of 43-64 and 40-63. In these cases, the total doses of remimazolam administered were 325 and 446 mg, respectively. Without the administration of flumazenil, the patient fully regained consciousness 20 and 15 min after discontinuing remimazolam. Since there have been no prior pharmacodynamic and pharmacokinetic studies on remimazolam in obese patients, we administered the drug based on total body weight and successfully induced anesthesia without any issues. Future research on the pharmacodynamics and pharmacokinetics of remimazolam in obese patients is essential to further investigate its use in these patients.

In the current report, the first patient experienced a transient episode of respiratory struggle and desaturation (SpO₂ 83%) alongside a hypertensive response (190/95 mmHg) during the early emergence phase. This event warrants careful consideration regarding the emergence characteristics of remimazolam in extremely obese populations. Severely obese patients are inherently vulnerable to rapid desaturation and upper airway obstruction during emergence due to a significantly reduced functional residual capacity (FRC) and increased chest wall resistance. Furthermore, because remimazolam features a rapid offset and context-sensitive half-life, its sedative effect diminishes swiftly upon discontinuation. If proper multi-modal analgesics are not fully established before emergence, this rapid decline in sedation can potentially precipitate acute surgical pain, leading to sympathetic overactivity and emergence agitation. In our case, the transient respiratory struggle and hypertensive response were

promptly and successfully managed with manual ventilation using 100% oxygen and the administration of nicardipine. This experience highlights that while remimazolam ensures a predictable and prompt recovery profile, a comprehensive strategy incorporating timely pain management and meticulous airway planning must be strictly established in advance to prevent emergence agitation and potential airway collapse in super-obese cohorts.

This report possesses several inherent limitations that should be acknowledged. First, as an observational study of only two cases, the findings cannot be statistically analyzed or widely generalized to the broader population of extremely obese patients. Second, the absence of a control group (such as patients receiving propofol or inhalational anesthetics) precludes direct comparative conclusions regarding the superiority of remimazolam over conventional agents. Lastly, advanced pharmacokinetic and pharmacodynamic data, such as real-time plasma concentration measurements, were not captured in this clinical setting, limiting our ability to objectively characterize remimazolam's metabolic behavior in this unique cohort. Nevertheless, these preliminary findings serve as a valuable clinical foundation advocating for larger, well-controlled prospective trials to further validate the safety and optimization of remimazolam-based TIVA in morbidly obese individuals.

In conclusion, these cases illustrate the successful anesthetic management using remimazolam for total intravenous general anesthesia in patients with very high BMI, suggesting that it may represent a promising alternative for future practice. The patients experienced no side effects, including changes in consciousness, hemodynamics, or respiratory status, or postoperative nausea, as described above. These results indicate that remimazolam can be an effective and safe choice for anesthesia management in super-obese patients, providing a novel option for anesthesia in obese patients.

Previous presentation at conferences

This case report was previously presented, in part, as an abstract at the 18th World Congress of Anaesthesiologists (WCA 2024) in Singapore, March 3–7, 2024.

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