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Remimazolam for General Anesthesia in an Elderly Patient with Severe Heart Failure and Aortic Stenosis: A Case Report

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Abstract | **Case Report**

Background: It is challenging to perform general anesthesia in patients with severe heart failure. Remimazolam, a recently approved benzodiazepine for general anesthesia, may be very useful for these patients because of less cardiovascular depression compared to other anesthetics. ***Case:*** An 85-year-old male patient with severe heart failure (left ventricular ejection fraction, 16%) and aortic stenosis was scheduled for general anesthesia for femur fracture surgery. Anesthesia was performed with remimazolam and remifentanil, and a stable hemodynamic state was maintained with continuous administration of phenylephrine and dobutamine. He did not wake up even 30 minutes after discontinuation of remimazolam administration. Flumazenil was administered intravenously. After 5 minutes, he was awakened and recovered without any events. ***Conclusions:*** Remimazolam can be a safe anesthetic for patients with severely impaired cardiac function. For rapid awakening from anesthesia in elderly patients, lowering dose of remimazolam should be considered and flumazenil can be used as necessary.

Keywords: Heart failure; Remimazolam; General anesthesia; Aged; Flumazenil.

INTRODUCTION

Patients with severe heart failure pose difficulty during general anesthesia due to anesthetic induced myocardial depression and peripheral vasodilation. In addition, most patients with left ventricular dysfunction are very sensitive to changes in preload and sympathetic tone, which play important role in maintaining tissue perfusion and cardiac output [1]. Therefore, for patients with severely impaired cardiac function, careful management is required during anesthesia. The selection of appropriate anesthetics is the starting point for successful anesthetic management in such patients.

Remimazolam, a newly developed benzodiazepine, is an ultra-short-acting sedative. Its context-sensitive half-time after infusion for 4 hour is 6.8 ± 2.4 min [2]. Remimazolam has less effects of cardiovascular suppression than other sedatives/hypnotics [3]. In addition, unlike other intravenous anesthetics, the action of remimazolam can be reversed by flumazenil, the antagonist of benzodiazepine [4]. Considering these characteristics, remimazolam could be more appropriate as a sedative/hypnotic in elderly patients with critical illness, especially with impaired cardiac function [5].

Because remimazolam has recently been approved for general anesthesia, there are few case reports. Here, we present a case of anesthetic management using remimazolam-remifentanil for femur fracture surgery in an elderly patient with severely impaired cardiac function.

CASE REPORT

A written informed consent was obtained from the patient for the publication of this case report. An 85-year-old male patient (height 163 cm, weight 64.2 kg, body mass index 24.16 kg/m^2) was scheduled to undergo closed reduction and internal fixation for intertrochanteric fracture of left femur. He had underlying diseases including hypertension, chronic heart failure with aortic stenosis (AS), type 2 diabetes mellitus, stage 4 chronic kidney disease (CKD), cerebral aneurysm, and a history of multiple cerebral infarctions (20, 15, 3 years ago).

One week before the surgery, he was admitted to intensive care unit for the treatment of heart failure

accompanied by pulmonary edema and dyspnea. Transthoracic echocardiogram (TTE) showed enlarged left atrium and left ventricle (LV), apical akinesia and hypokinesia of LV, severe reduction of LV systolic function (ejection fraction 16%), significant degenerative aortic stenosis (valve area 0.95 cm^2), mild mitral regurgitation, and moderate pulmonary hypertension. After 3 days of intensive care with oxygen therapy, dobutamine and diuretics, he was transferred to general ward.

On preoperative laboratory tests, BUN was 70, serum creatinine level was 2.51 mg/dL (estimated glomerular filtration rate, 22.46 mL/min/1.73 m^2), Hb A1C was 9.5% and plasma albumin concentration was 3.3 g/dl. Brain magnetic resonance angiography showed left distal internal carotid artery (ICA) aneurysm, multiple stenosis in both distal ICA, focal severe stenosis in proximal basilar artery, diffuse luminal narrowing of left vertebral artery. American Society of Anesthesiologists (ASA) physical status classification was assessed to be 4.

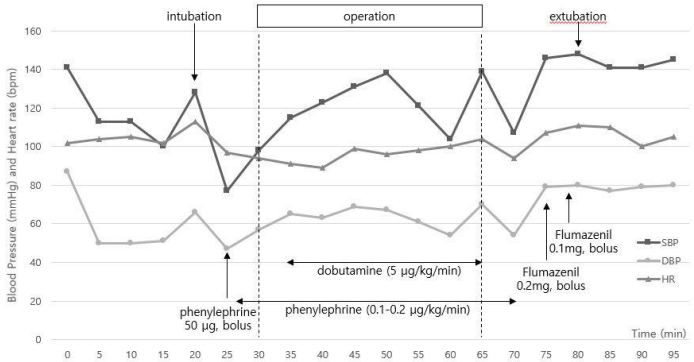
On arrival at the operating room, blood pressure, heart rate and room air oxygen saturation were measured as 141/87 mmHg, 102 beats per minute, and 90%, respectively. After local anesthetic infiltration, an arterial cannula was placed in the right radial artery for continuous blood pressure monitoring. Hemodynamic values including cardiac output (CO), cardiac index (CI) and stroke volume variation (SVV) were monitored with a Flotrac/Vigileo system (Edwards Lifesciences, USA). In addition to the standard monitoring, bispectral index (BIS) and cerebral regional oxygen saturation (rSO2) by O3 regional oximetry (Root®, Masimo Corp., USA) were used.

After denitrogenation, general anesthesia was induced by intravenous administration of remimazolam and remifentanil at the rate of 6 mg/kg/hr and 0.2 μg/kg/min, respectively. After loss of consciousness, the infusion rate of remimazolam was reduced to 1 mg/kg/hr for maintenance of anesthesia. Rocuronium 0.8 mg/kg was administered intravenously.

After intubation, the patient's mean blood pressure (MBP) decreased from 105 to 57 mmHg, and 50 μg of phenylephrine was administered to maintain MBP over 65 mmHg. To avoid vasodilation, phenylephrine was infused intravenously at the rate of 0.1 - 0.2 μg/kg/min. Dobutamine infusion at the rate of 5 μg/kg/min was initiated as mild reduction of CO (3.9 to 3.3 L/min) and cardiac index (CI, 2.3 to 1.9 L/min/m^2) was noticed. Hemodynamic changes during anesthesia are shown in Fig. 1. The maintenance dose of remimazolam was adjusted to maintain BIS value between 40 and 60, and it was decreased to 0.8 mg/kg/hr during anesthesia. The values of rSO2 were well preserved.

When the main procedure of the surgery was over and the skin suture began, administration of remimazolam was discontinued because mean time to recovery for awareness is reported to about 8.6-9.6 (±7.8-8.6) min [6]. After 30 min of discontinuation of remimazolam, the consciousness did not return. Flumazenil 0.2 mg was administered intravenously to reverse the effect of remimazolam. Because there was no response to verbal stimuli, additional 0.1 mg of flumazenil was administered. The patient gained consciousness with orientation 5 min after initial administration of flumazenil. We extubated endotracheal tube after confirming the patient's spontaneous breathing. After extubation, the blood pressure and heart rate increased to 148/80 mmHg and 111 beats per minute, respectively, and 10 mg of esmolol was administered intravenously.

The duration of anesthesia and operation was 90 min and 35 min, respectively. The patient was transferred to the ICU. After two days, he was transferred to general ward without any events.



	0	20	35	50	65	80	95 (min)
MBP (mmHg)	105	87	82	91	93	103	102
CO (L/min)	-	3.9	3.3	3.6	3.9	-	-
CI (L/min/m^2)	-	2.3	1.9	2.1	2.3	-	-
BIS	97	52	50	42	50	95	96

Fig 1: Anesthesia record. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heat rate; MBP: mean blood pressure; CO: cardiac output; CI: cardiac index; BIS: bispectral index

DISCUSSION

Benzodiazepine has less cardio-depressive effect than other anesthetics [7]. In a pre-clinical study, it was reported that remimazolam did not decrease cardiac index, although it dose-dependently reduced blood pressure [8]. Therefore, hypotensive events observed when using remimazolam can be result of decrease in peripheral vascular resistance. For this reason, phenylephrine was administered to our patent as well. Previous case reports using remimazolam have shown safe use in super-elderly (aged ≥ 95 years) patient and chronic heart failure (ejection fraction, 33%) patient without any hemodynamic event [5, 9].

Mild decrease in cardiac output, observed in this case, was presumed to be due to the sympatholytic effect of remifentanil [10]. To support cardiac function, dobutamine was infused in our patient. In patients with impaired cardiac function, hemodynamic instability can occur frequently and even cause critical circulatory disruptions during general anesthesia. Although propofol is one of the most widely used intravenous anesthetics, it can cause significant hemodynamic instability [11]. In a study by Doi *et al*., [7], remimazolam led to less hypotensive events compared with propofol.

Ketamine and etomidate were considered relatively safe in patients with cardiac dysfunction [12]. However, for these cardiac patients undergoing medication, there is not enough evidence about safety. In addition, ketamine is known for psychomimetic effect such as nightmares, hallucination, and postoperative delirium, especially in elderly patients [13]. It was reported that etomidate causes hypotensive events twice as less likely than propofol in patients with severe AS. However, etomidate reduced the cardiac index as much as propofol [14]. And etomidate is associated with adrenal cortical suppression. Taken together, remimazolam may be the most appropriate intravenous anesthetic for the patients with significant cardiac impairment who are prone to hemodynamic instability.

For induction of anesthesia, it is generally recommended to infuse remimazolam at the rate of 12 mg/kg/hr until loss of consciousness. However, in critically ill patients, 6 mg/kg/hr of remimazolam was reported to induce anesthesia successfully [6]. Considering the patient's old age and low cardiac function, we adopted 6 mg/kg/hr for induction dose.

It was reported that recovery time of awakening was significantly shorter among patients group using propofol than group using remimazolam [7]. In this case, the patient did not awake more than 30 min after stopping remimazolam infusion. Delayed awakening, defined as failure to open their eyes after 30 min after discontinuation of remimazolam, occurs in about 8-9 % of patients [7]. Shimamoto *et al*., [15] reported that high body mass index (BMI > 22.0 kg/m^2), old age (> 79.0 years) and low plasma albumin concentration (< 3.60 g/dl) were significantly related to delayed awakening. Because the patient, in this case, had all 3 factors, he would have more the tendency of delayed awakening. Therefore, to avoid delayed awakening, tapering remimazolam dose may be helpful in the patients with these risk factors. Flumazenil can reverse the effect of remimazolam very quickly. However, it could rapidly increase systemic vascular resistance and myocardial oxygen consumption by increasing sympathetic nervous tone [4]. Therefore, flumazenil should be used carefully in patients with impaired cardiac function.

In conclusion, remimazolam has prospects for maintaining hemodynamic stability during general anesthesia in patients with severe cardiac dysfunction. As recovery of consciousness is often delayed without flumazenil administration, it is required to decrease remimazolam dose in advance before the end of surgery.

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