Journal of Anesthesia (2023) 37:825–827
https://doi.org/10.1007/s00540-023-03242-z

EDITORIAL

Remimazolam for cardiovascular anesthesia

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Received: 4 August 2023 / Accepted: 4 August 2023 / Published online: 16 August 2023

Keywords Remimazolam · Postoperative delirium · Cardioprotective effects

Remimazolam, a novel benzodiazepine, has been widely used for general anesthesia in Japan since 2020. Initial clinical trials for general anesthesia showed that remimazolam has less cardiodepressant effects than those of propofol [1] and that remimazolam is safe for patients with cardiovascular complications, who are vulnerable to unstable hemodynamics after general anesthesia [2]. Although the clinical trials on remimazolam for general anesthesia did not include cardiovascular surgical cases [1, 2], recent studies have shown the efficacy of remimazolam for cardiovascular surgery. In this Editorial, the advantages and limitations of remimazolam for cardiovascular anesthesia are summarized.

Remimazolam for postoperative delirium after cardiac surgery

Postoperative delirium (POD) and cognitive dysfunction (POCD) are major complications after cardiac surgery [3–5]. The incidence of postoperative delirium (POD) after cardiac surgery is estimated to be 26–52% [3], which is higher than that after non-cardiac surgery. POD is characterized by a reversible state of impaired cognition, inattention, altered level of consciousness, and disturbances of memory, orientation, and perception. POD is associated with poorer functional recovery, longer length of hospital stay, and long-term cognitive decline [4]. Risk factors of POD include history of delirium, frailty, cognitive impairment, renal insufficiency, advanced age, impairment of activity of daily life, and psychotropic medication use [6]. Benzodiazepine is included in psychotropic medications, and anesthesiologists may thus have concerns about POD after general anesthesia using remimazolam.

In a recent prospective observational study [7], the association between remimazolam and POD in older adults undergoing elective cardiovascular surgery was investigated. In that study, the incidences of POD within 5 days after surgery were compared in patients undergoing general anesthesia using remimazolam ($n=78$) and patients undergoing general anesthesia with anesthetics other than remimazolam (control group, $n=122$). The study showed that the incidence of POD in the remimazolam group (30.3%) was comparable to that in the control group (26.6%, risk difference, 3.8%; 95% confidence interval, -11.5% to 19.1%; $P=0.63$). They concluded that remimazolam was not significantly associated with POD when compared with other anesthetic agents.

Kaneko and colleagues [8] retrospectively studied the effects of remimazolam on the incidence of POD after transcatheter aortic valve implantation (TAVI) under general anesthesia. They investigated the incidences of POD within 3 days after TAVI in patients who underwent general anesthesia using remimazolam (remimazolam group, $n=40$) and patients who underwent general anesthesia using propofol (propofol group $n=58$). In both groups, remifentanil (0.5–1.0 μg/kg/min for induction and 0.3–0.4 μg/kg/min for maintenance) was administered as an analgesic agent. Of note, all of the patients in the remimazolam group received 0.2 mg flumazenil after surgery. If patients in the remimazolam group did not awaken within 4 min after the first dose of flumazenil, an additional 0.1–0.2 mg of flumazenil was administered. The authors found that the incidence of POD in the remimazolam group (8%) was significantly lower than that in the propofol group (26%, $P=0.032$). In addition, multiple logistic regression analysis revealed that remimazolam was independently associated with POD (odds ratio: 0.17, 95% confidence interval: 0.04–0.08, $P=0.024$).

In cardiac surgery with cardiopulmonary bypass, most patients are under sedation after surgery until hemodynamics

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and respiratory conditions become stable. Therefore, the clinical significance of earlier recovery using antagonization of sedatives may be controversial in cardiovascular surgery with cardiopulmonary bypass. However, in less-invasive cardiovascular surgery including TAVI and MitraClip for mitral valve regurgitation, early recovery and neurological assessment are required, because structural heart diseases including advanced aortic stenosis and mitral valve regurgitation are prevalent in the elderly patients who are vulnerable to neurocognitive decline. Remimazolam and antagonization with flumazenil may be a strategy for preventing POD after TAVI and MitraClip in elderly patients.

Less cardiodepressant effects of remimazolam in cardiovascular anesthesia

Less cardiodepressant effects of remimazolam have been demonstrated in the previous studies [1, 2]. In cardiovascular anesthesia, similar effects have been reported.

Liu and colleagues [9] investigated differential effects of remimazolam (0.3 mg/kg, $n=30$) and propofol (1.8 mg/kg, $n=30$) on hemodynamic changes during anesthesia induction in patients undergoing cardiac surgery with cardiopulmonary bypass. They found that the difference between maximum or minimum mean arterial pressure and baseline arterial pressure (ΔMAP) was significantly lower in the remimazolam group (19.5 ± 7.5 mmHg) than in the propofol group (26.7 ± 9.1 mmHg, $P=0.0016$). The incidence of hypotension (MAP < 60 mmHg) and the cumulative norepinephrine dose used per patient (remimazolam group: 8.3 ± 18.9 μg, propofol group: 33.33 ± 42.2 μg, $P=0.012$) during induction were significantly lower in the remimazolam group.

Nam and colleagues [10] investigated the differential effects of remimazolam and desflurane on hemodynamic changes and doses of vasoactive agents during cardiac ablation for atrial fibrillation under general anesthesia. In the remimazolam group ($n=78$), anesthesia was induced with 6 mg/kg/h remimazolam and maintained with 1–2 mg/kg/h. In the desflurane group ($n=78$ after propensity score matching), anesthesia was induced with 1–2 mg/kg propofol and maintained with 6–10% desflurane. They found that the overall incidence of vasoactive agent use was significantly lower in the remimazolam group (41%) than in the desflurane group (73%, $P<0.001$). The incidence rate, duration, and maximum dose of continuous vasopressor infusion were also significantly lower in the remimazolam group ($P<0.001$). While that retrospective study had the limitations of no definitions of intraoperative hypotension and protocol for hemodynamic changes during surgery, the results suggested that the effects of remimazolam on hemodynamic changes might be less than the effects of volatile anesthetics.

Clinical researches and case reports have shown less cardiodepressant effects of remimazolam in cardiovascular surgery and the clinical significance of remimazolam [9–12]. However, the optimal dose and methods of administration (bolus or continuous administration) of remimazolam during anesthesia induction varied in those studies. In addition, the doses of opioids administered with remimazolam can affect the hemodynamic changes. Further studies may be required to elucidate the optimal administration of remimazolam in cardiac surgery.

Limitations and prospects of remimazolam in cardiovascular anesthesia

It has been well documented that volatile anesthetics have cardioprotective effects in cardiac surgery [13, 14]. A recent meta-analysis of randomized trials demonstrated that volatile anesthesia can reduce mortality and preserve cardiac function after cardiac surgery [15]. However, intravenous anesthesia might not have cardioprotective effects [13–15] and co-administration of intravenous anesthetics with volatile anesthetics might counteract the cardioprotective effects of volatile anesthetics [16, 17]. To maximize the cardioprotective effects of volatile anesthetics in cardiac surgery, administration of volatile anesthetics during cardiopulmonary bypass would be desirable [18]. However, the use of volatile anesthetics during cardiopulmonary bypass may be limited by several issues, including intraoperative awareness, air pollution, and damage to the oxygenator caused by volatile anesthetics.

Further studies are needed to determine which is better for outcomes after cardiac surgery: volatile anesthesia with cardioprotective effects or remimazolam anesthesia with less cardiodepressant effects intraoperatively followed by less POD occurrence via antagonization with flumazenil.

Declarations

Conflict of interest There are no conflicts of interest regarding the publication of this paper.

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