中国临床研究 Chin J Clin Res, March 2026, Vol.39, No.3
Cite as: Wang CH, Guan YC, Yu SY. Application of remimazolam in monitored anesthesia care [J]. Chin J Clin Res, 2026, 39(3):333-336, 346.
DOI: 10.13429/j.cnki.cjcr.2026.03.002

Application of remimazolam in monitored anesthesia care

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Abstract: Monitored anesthesia care (MAC) is a technique in which anesthesiologists use analgesic or sedative drugs while closely monitoring the vital signs of patients undergoing anesthesia without intubation and with spontaneous breathing. Its advantages include maintaining patient's spontaneous breathing, avoiding lung injury caused by mechanical ventilation, and shortening the postoperative recovery time. Currently, the drug regimens for MAC mainly consist of anesthetic sedatives combined with analgesics. Common sedative drugs include propofol and midazolam. However, they have inhibitory effects on the respiratory and circulatory systems, which limits their application in clinical practice. In recent years, a newly discovered anesthetic, remimazolam, is a short-acting intravenous anesthetic developed from midazolam by adding a methyl propionate side chain. Reminazolam has a minor effect on respiration and circulation, a low incidence of injection pain, rapid onset, and inactive metabolites, presenting certain advantages in terms of anesthetic safety. Existing research has found that remimazolam can stabilize circulation, reduce respiratory depression, and lower the incidence of adverse reactions such as nausea and vomiting when used in MAC, with broad application prospects. However, the safety and efficacy of remimazolam in general anesthesia still need to be confirmed. This article will review the pharmacological characteristics of remimazolam, its perioperative application advantages, and the problems that need to be solved, providing a reference for the majority of clinical practitioners.

Keywords: Remimazolam; Monitored anesthesia care; Comfortable diagnosis and treatment; Outpatient surgery; Sedative drug
Fund program: Youth General Program of Shandong Provincial Natural Science Foundation (ZR2024QH295)

Monitored anesthesia care (MAC) is a safe and effective anesthesia technique that ensures patient comfort during surgery through moderate sedation and analgesia, providing conditions for rapid postoperative recovery [1]. Currently, MAC is applicable to a variety of outpatient and minor surgeries, as well as patients with poor preoperative pulmonary function who are expected to have difficulty weaning from mechanical ventilation after surgery. It can reduce anesthetic medication, maintain the physiological state of the patient's nervous, muscular, cardiopulmonary systems, preserve spontaneous breathing and protective reflexes, and achieve the goal of enhanced recovery after surgery (ERAS) [1]. Currently, commonly used sedative drugs in clinical anesthesia include benzodiazepines, propofol, etomidate, and dexmedetomidine. However, studies have found that these drugs carry risks such as central respiratory and circulatory depression and transient upper airway obstruction [2]. Remimazolam, a new type of benzodiazepine, has the advantages of rapid onset, short duration of sedative effect, fast recovery, and no accumulation after long-term infusion [2], making it a potential option for the safe implementation of MAC. This article reviews the pharmacological mechanism of remimazolam and its application in MAC.

1 Pharmacological Mechanism of Remimazolam

Remimazolam is a novel lipophilic benzodiazepine sedative that enhances the activity of gamma-aminobutyric acid subtype A (GABAA) receptors, induces cell membrane hyperpolarization, increases chloride ion influx, and inhibits neural activity, playing a critical role in regulating neuronal excitability [3]. Pharmacodynamic analyses of the sedative effect of remimazolam based on the electroencephalogram β ratio, bispectral index (BIS), Narcotrend index, and Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) show that remimazolam has a rapid onset of sedation, and its sedation depth and duration are dose-dependent [4]. In addition, remimazolam contains metabolically unstable ester groups, which can be rapidly metabolized by tissue esterase (carboxylesterase-1) into the inactive compound CNS7054. The pharmacokinetics of remimazolam are linear, and compared with midazolam, its pharmacokinetic half-life is relatively short, at 7-8 minutes [5], giving it an ultra-short-acting effect. Animal experimental studies have confirmed that in mice, sleep-inducing doses of remimazolam and midazolam can cause loss of righting reflex within a few minutes and nearly one hour, respectively [6]. Furthermore, remimazolam is mainly excreted through urine, and its clearance rate is essentially independent of body weight. After 24 hours of injection (0.20 / 0.30 mg/kg), more than 80% of the dose is detected in urine as metabolites, and less than 1% of the original dose is detected as unchanged drug, with a systemic clearance rate approximately 3 times that of midazolam [3]. Studies have shown that remimazolam at doses of 0.05 mg/kg and higher has a rapid onset of sedative effect in a dose-dependent manner [7]. From the perspective of pharmacokinetics and pharmacodynamics, remimazolam has a small steady-state distribution volume, rapid onset, and fast metabolism [5]. According to existing clinical trial results, remimazolam is not metabolized by the liver during *in vivo* metabolism. It is mainly rapidly decomposed by

non-specific plasma esterases and does not accumulate in the body. It takes approximately 1 minute to reach the maximum blood concentration, and its mean residence time is also short [8]. Therefore, remimazolam maintains long-term metabolic stability in human hepatocytes and has no adverse effects on the metabolic activity and integrity of hepatocytes. However, adverse reactions associated with remimazolam during procedural sedation and anesthesia have been documented in detail in various clinical studies. The more common ones include changes in blood pressure and heart rate, nausea and vomiting, and other adverse events include headache, drowsiness, and hypoxia [2]. Clinical studies have confirmed that remimazolam has good tolerance, can be used for procedural sedation as well as induction and maintenance of general anesthesia, has relatively high safety, reduces cardiopulmonary depression and injection pain, and can be one of the sedative drug options for MAC [2,5]. Research on the clinical application of remimazolam in MAC anesthesia is of great significance. However, to date, the clinical application of remimazolam has been limited to a small number of volunteers and a limited number of clinical investigations [5,8].

2 Application of Remimazolam in Clinical Diagnosis and Treatment

At present, remimazolam-based MAC management protocols are gradually being implemented and demonstrating advantages in examinations and treatments such as bronchoscopy, painless gastroenteroscopy, and hysteroscopy. The following section discusses the application progress of remimazolam-based MAC protocols in the management of partial clinical diagnosis and treatment processes.

2.1 Application of Remimazolam in Bronchoscopy

Bronchoscopy plays an increasingly important role in the examination, diagnosis, and treatment of airway and pulmonary diseases [9]. In 2011, the American College of Chest Physicians published a consensus statement recommending that all patients undergoing bronchoscopy receive local anesthesia, analgesia, and sedation in the absence of contraindications to improve patient tolerance and satisfaction. Meanwhile, the guideline points out that there is no single perfect sedative for bronchoscopy currently, and the combination of remimazolam and opioids is an anesthetic regimen recommended by the guideline [9].

Remimazolam can be safely and effectively used in bronchoscopy. Studies have confirmed that compared with midazolam, remimazolam is safe and effective during bronchoscopy. Remimazolam can meet the needs of surgical sedation, has a rapid onset, enables faster recovery of neuropsychiatric function in patients, and allows for rapid recovery of postoperative cognitive function [10]. A study by Zhou *et al.,* [11] found that compared with dexmedetomidine, remimazolam reduces the incidence of oxygen desaturation during bronchoscopy and can provide better MAC. During the surgical procedure, patients receiving remimazolam have more stable hemodynamics and reduced requirement for airway assistance, which improves the safety of the procedure and patient compliance. Therefore, remimazolam can serve as a new option in sedation regimens during bronchoscopy.

2.2 Application of Remimazolam in Painless Gastroenterostomy

Digestive endoscopy is an important and commonly used endoscopic method for the diagnosis and treatment of gastrointestinal and colorectal diseases. Prolonged operation by the practitioner may cause visceral pain, spasm, and even complications such as cardiovascular and cerebrovascular accidents in patients [12]. With the development and improvement of diagnostic and therapeutic technologies, an increasing number of patients choose to undergo painless gastroenteroscopy. The application of painless protocols for gastroenteroscopy can not only effectively eliminate patients' nervousness and anxiety, but also inhibit upper respiratory tract reflexes during gastroscopy, alleviate patients' discomfort and pain, and improve the comfort of diagnosis and treatment [12]. During painless gastroscopy, since anesthesiologists and operators need to share the airway, intraoperative airway management, ensuring the safety of the anesthesia process, and selecting effective anesthetic drugs with minimal adverse effects are particularly important, which are the focus of anesthesia attention [12].

Commonly used sedative drugs for painless gastroenteroscopy include propofol, etomidate, and remimazolam, among others. However, in painless gastroscopy, the incidence of hypoxemia in patients using propofol is 8.40%, while remimazolam exerts a milder inhibitory effect on the circulatory and respiratory systems, reducing the incidence of adverse reactions such as severe hemodynamic fluctuations after induction, excessive sedation, and injection pain [13]. The guidance on clinical application of remimazolam besylate in 2023 recommends that for sedation during diagnostic gastroenteroscopy or simple therapeutic procedures, remimazolam can be used alone or in combination with opioids in adults to improve the comfort of diagnosis and treatment [14]. Nevertheless, clinical practice has found that the sedation depth of remimazolam when used alone cannot meet the requirements of gastroscopy, and patients may experience reactions such as cough, hiccups, and body movement. Although increasing the dose of remimazolam can improve sedation depth and inhibit stress responses, it exerts a significant inhibitory effect on the patient's circulatory system and prolongs the patient's awakening time and discharge time [15]. Therefore, the combination of remimazolam with other drugs may be more acceptable than single-administration regimens in painless gastroscopy.

2.3 Application of Remimazolam in Hysteroscopic Examination

With the increasing awareness of endometrial lesions among women and the continuous advancement of hysteroscopic technology, the application of hysteroscopic examination in clinical practice has become increasingly prevalent [16]. General anesthesia, paracervical block, and

local anesthesia are all applicable for hysteroscopic procedures [17]. Although general anesthesia can meet the requirements of hysteroscopic surgery and has become the preferred anesthesia method, it is associated with large drug dosage, frequent adverse reactions, and high anesthesia costs. For hysteroscopic procedures characterized by short duration and simple operation, MAC is recommended in expert consensus guidelines [17].

The most commonly used anesthesia regimen in MAC is the combination of propofol and opioids. However, these conventional anesthetics may cause severe respiratory and hemodynamic depression, with potential side effects such as nausea and vomiting, and occasionally require laryngeal mask airway or endotracheal intubation for respiratory support [7]. Yang *et al.* [18] found that compared with target-controlled infusion of propofol, target-controlled infusion of remimazolam has significant advantages in improving postoperative recovery of patients, maintaining perioperative heart rate, mean arterial pressure, respiratory rate, and blood oxygen saturation, as well as enhancing anesthesia efficiency. Additionally, the incidences of injection pain and hypotension after induction are reduced. Meanwhile, according to the study by Zhang *et al.* [19], remimazolam can also be combined with low-dose propofol. This drug combination can improve the safety of hysteroscopic examination with minor effects on cardiovascular and respiratory depression, thus the sedation method of remimazolam combined with propofol is more optimal. Furthermore, the sedation depth of remimazolam in MAC for hysteroscopic procedures has been recognized. Bispectral index (BIS) data records show that after anesthesia induction, the electroencephalogram BIS value produced by remimazolam is significantly higher than that of propofol [20]. In addition to comparison with propofol, studies have also found that compared with esketamine, remimazolam can effectively reduce psychiatric adverse reactions in hysteroscopic surgery [21]. Moreover, a prospective randomized study revealed that remimazolam combined with alfentanil has the advantages of good analgesic effect, rapid onset, fast consciousness recovery, and short awakening time in painless colonoscopy surgery [22].

2.4 Application of Remimazolam in Pain-Induced Abortion

Compared with traditional abortion surgery, pain-induced abortion significantly reduces the incidence of perioperative adverse events, alleviates pain and discomfort caused by the surgery, relieves patients' fear and tension, and improves patient satisfaction, thus it is increasingly applied in clinical practice [23].

Currently, the commonly used intravenous anesthesia regimen in pain-induced abortion is the combination of propofol and opioids [24]. Propofol has a rapid onset and short half-life, but it is associated with a high incidence of adverse reactions such as respiratory depression, hypoxia, hypotension, and injection pain during administration [24-25], so caution must be exercised when using propofol. Yue *et al.* [26] found that both remimazolam and propofol can provide the required anesthesia depth and duration for abortion surgery, but the minimum effective dose of remimazolam can not only achieve sufficient anesthesia in pain-induced abortion, but also reduce drug dosage and the occurrence of adverse events. Meanwhile, it reduces the frequency and intensity of propofol-induced injection pain during abortion, which has been widely recognized by patients. Furthermore, pre-treatment with remimazolam reduces the incidence and intensity of injection pain in abortion patients, with an effect equivalent to that of lidocaine, and no serious adverse reactions occur [25]. Similarly, remimazolam can also be combined with other drugs for use in pain-induced abortion. The combined administration of remimazolam and esketamine has a shorter duration of action, faster metabolism, and lower risk of serious adverse events (such as hypotension and respiratory depression) [26]. Combination with flumazenil can accelerate postoperative recovery of consciousness and reduce the occurrence of adverse reactions, which has potential advantages in pain-induced abortion surgery [27].

2.5 Application of Remimazolam in Interventional Therapy

Intracranial aneurysm is a common cerebrovascular disease that affects the quality of life of approximately 1%-2% of the global population [28]. Rupture of cerebral aneurysms can lead to subarachnoid hemorrhage, imposing a heavy medical burden on patients. Since some minimally invasive interventional procedures require precise manipulation, anesthesia management is necessary for patients who are unable to cooperate [28]. The *Expert Consensus on Anesthesia Management for Interventional Therapy of Craniocerebral Diseases in China* [29] clearly states that the core of anesthesia management for intracranial aneurysms, arteriovenous malformations, and acute ischemic stroke is strict perioperative blood pressure control. Propofol is a commonly used sedative for general anesthesia in cerebrovascular interventional surgery at present, but it can cause numerous adverse reactions, among which the most prominent is circulatory function depression, manifested as an increased risk of cardio-cerebrovascular events and damage to other vital organs [7].

Zhang *et al.* [30] conducted a randomized controlled trial comparing the vital sign fluctuations between remimazolam and propofol in patients undergoing endovascular cerebral surgery under general anesthesia. This is also the first study investigating the application of remimazolam in patients receiving coil embolization for cerebral aneurysms. The results showed that the use of remimazolam can prevent hypotension. Meanwhile, Lee *et al.* [20] also demonstrated that during interventional neuroradiology procedures, patients anesthetized with remimazolam have more stable hemodynamics compared with those receiving propofol anesthesia. However, most existing studies focus on the application of remimazolam in intubated patients under the administration of muscle relaxants [31], while research on remimazolam applied in interventional surgery under MAC is relatively less.

2.6 Application of Remimazolam in Combination with Other Anesthesia Methods

2.6.1 Remimazolam Combined with Nerve Block

For some pediatric and orthopedic surgeries, as well as uncooperative patients, nerve block is usually performed under sedation to alleviate pain and prevent new injuries caused by body movement during manipulation [32]. Appropriate sedation depth can reduce preoperative stress, maintain stable vital signs, and allow rapid recovery of consciousness after block to evaluate the efficacy of the block [32]. The ideal sedation effect is characterized by rapid onset, fast recovery, and minimal residual effect. Remimazolam has an amnesic effect, which can eliminate patients' memory of the painful process of nerve block, thereby achieving the goal of comfortable medical care [2].

Midazolam, a commonly used benzodiazepine sedative at present, has disadvantages such as long sedation duration, incomplete consciousness recovery, and interference with the judgment of sedation effect [7]. As a novel benzodiazepine drug, remimazolam has the advantages of rapid onset, fast recovery, no residual effect, no dependence on liver and kidney function for metabolism, and mild and few side effects [4]. Therefore, remimazolam combined with nerve block yields better efficacy than nerve block alone, with higher satisfaction among patients and surgeons [32]. Studies have shown that administration of remimazolam prior to nerve block can eliminate patients' nervousness and anxiety, as well as blood pressure elevation caused by pain stimulation. After sedation, patients have a short consciousness recovery time, better stability of blood pressure and heart rate than midazolam, milder respiratory depression, and favorable safety profile [33]. Meanwhile, Liu *et al.* [34] found that remimazolam combined with sufentanil for sedation and analgesia under nerve block can provide patients with safe, painless, and fear-free "comfortable medical care" services without increasing the risk of nerve injury and local anesthetic poisoning.

2.6.2 Remimazolam Combined with Neuraxial Anesthesia

Cesarean section causes negative psychological states such as tension and fear in most parturients, and perioperative pain stimulation is more likely to induce postpartum depression (PPD) [35]. Currently, most anesthesia regimens administer certain sedative and analgesic drugs after fetal delivery to relieve maternal pain and eliminate the psychology of tension and fear [35]. Studies have shown that remimazolam combined with esketamine for cesarean section can improve intraoperative anesthesia effect, reduce the incidence of adverse reactions such as perioperative psychiatric symptoms, lower the Edinburgh Postnatal Depression Scale score, and ameliorate PPD [36].

However, the incidence of postoperative nausea and vomiting (PONV) after cesarean section is very high, reaching up to 80% in cesarean section performed under neuraxial anesthesia [37]. Studies have shown that compared with midazolam, remimazolam significantly reduces the incidence of PONV and severe adverse reactions during sedation, and has the minimal impact on hemodynamics. These advantages make it a useful sedative for cesarean section under neuraxial anesthesia and knee arthroplasty under combined spinal-epidural anesthesia [38].

For patients undergoing neuraxial anesthesia for lower limb surgery, remimazolam and dexmedetomidine were combined for adjuvant sedation, and the sedative effects of the two drugs after administration were observed and compared. The results showed that both remimazolam and dexmedetomidine have significant sedative effects in adjuvant sedation for lower limb surgery, but compared with dexmedetomidine, remimazolam has a faster onset and its sedative effect is dose-dependent [39].

2.6.3 Remimazolam Combined with Local Anesthesia

Some outpatient tooth extraction surgeries, otorhinolaryngologic surgeries under local anesthesia, and breast minimally invasive biopsy only require simple local anesthesia. However, after local anesthesia, patients remain awake, which may cause tension and anxiety, and even lead to hyperalgesia. Therefore, in some local anesthesia procedures, additional sedative anesthetics can be administered to induce sleep, alleviate tension and anxiety, and achieve the goal of comfortable diagnosis and treatment [4]. Studies have shown that sedation with remimazolam concurrent with local anesthesia can be safely applied for comfortable tooth extraction in elderly outpatient patients with periodontal disease. During the surgery, patients' blood pressure and heart rate are stable, and adverse reactions are fewer than those with midazolam [40]. Yang *et al.* [41] confirmed that remimazolam combined with sufentanil in endoscopic sinus surgery for sinusitis can ensure more stable perioperative hemodynamics by virtue of its advantages of reducing heart rate and blood pressure, increasing oxygenation state, slowing respiratory rate, and alleviating pain perception, making it a favorable anesthesia method for endoscopic sinus surgery. In breast minimally invasive biopsy surgery, both remimazolam and propofol can provide effective sedation depth, but remimazolam has higher safety than propofol. Remimazolam can reduce the occurrence of adverse reactions such as transient respiratory depression, hypotension, and bradycardia, and can effectively avoid injection pain, resulting in higher patient comfort [42].

3 Conclusion and Prospect

The pharmacological characteristics of remimazolam can reduce the risk of severe hemodynamic instability during anesthesia. Its controllable sedation level and minimal impact on blood pressure and heart rate are favorable properties contributing to patient safety. The application of remimazolam in MAC can achieve satisfactory anesthetic sedation and analgesia effects. More importantly, it can reduce the respiratory depression caused by other potent analgesic and sedative agents, and also shorten the anesthesia recovery time. Although numerous studies have confirmed the advantage of remimazolam in

exerting minimal effects on respiratory and circulatory functions, there are relatively few studies on the application of remimazolam combined with other anesthesia methods, and the research populations for remimazolam are not yet extensive. Studies on remimazolam in obese patients are relatively scarce, and its application in MAC for interventional procedures is also insufficient. Existing relevant studies almost exclusively focus on the use of remimazolam in interventional surgeries requiring intraoperative endotracheal intubation. Therefore, whether remimazolam combined with other anesthesia methods in MAC, as well as its application in populations such as obese patients, can achieve effective anesthetic effects while reducing complications caused by anesthetics remains to be investigated. Currently, studies on the perioperative application of remimazolam are limited, and the evidence-based basis is still insufficient. More clinical studies are needed in the future to explore its application effects, optimal doses, and applicable scopes in different surgeries and different populations, so as to provide a strong basis for individualized anesthetic medication.

Conflict of Interest None

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Submission Received 2025-06-06/**Revised** 2025-08-02

·临床麻醉专题·研究进展·

瑞马唑仑在麻醉监测管理中的应用

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摘要：麻醉监测管理(MAC)是麻醉医生利用镇痛或镇静药物的同时密切监测未插管且保留自主呼吸的麻醉患者生命体征的一种技术手段，具有保留自主呼吸、避免机械通气造成的肺损伤、缩短术后恢复时间的优势。目前MAC方案主要为麻醉性镇静药联合镇痛药，常用的镇静药物有丙泊酚和咪达唑仑等，但是对呼吸循环有抑制作用，限制了其在临床中的开展。近年来新上市的苯二氮䓬类镇静药物瑞马唑仑，是在咪达唑仑的基础上加入丙酸甲酯侧链，使其成为一种超短效静脉麻醉药。临床实践证明瑞马唑仑具有对呼吸和循环影响轻微、注射痛发生率低、起效快且代谢产物无活性等优点，在麻醉安全方面具有一定的优势。目前研究发现瑞马唑仑应用于MAC中能够起到稳定循环、减轻呼吸抑制、降低恶心呕吐等不良反应的作用，应用前景广阔，但在全身麻醉中的安全性和有效性仍需进一步探讨。本文将从瑞马唑仑的药理特点、围手术期应用优势以及尚需解决的问题等方面进行综述，为广大临床工作者提供参考。

关键词：瑞马唑仑；麻醉监测管理；舒适化医疗；门诊手术；镇静药物

中图分类号：R614 **文献标识码：**A **文章编号：**1674-8182(2026)03-0333-05

Application of remimazolam in monitored anesthesia care

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Abstract: Monitored anesthesia care (MAC) is a technique in which anesthesiologists use analgesic or sedative drugs while closely monitoring the vital signs of patients undergoing anesthesia without intubation and with spontaneous breathing. Its advantages include maintaining patient's spontaneous breathing, avoiding lung injury caused by mechanical ventilation, and shortening the postoperative recovery time. Currently, the drug regimens for MAC mainly consist of anesthetic sedatives combined with analgesics. Common sedative drugs include propofol and midazolam. However, they have inhibitory effects on the respiratory and circulatory systems, which limits their application in clinical practice. In recent years, a newly discovered anesthetic, remimazolam, is a short-acting intravenous anesthetic developed from midazolam by adding a methyl propionate side chain. Remimazolam has a minor effect on respiration and circulation, a low incidence of injection pain, rapid onset, and inactive metabolites, presenting certain advantages in terms of anesthetic safety. Existing research has found that remimazolam can stabilize circulation, reduce respiratory depression, and lower the incidence of adverse reactions such as nausea and vomiting when used in MAC, with broad application prospects. However, the safety and efficacy of remimazolam in general anesthesia still need to be confirmed. This article will review the pharmacological characteristics of remimazolam, its perioperative application advantages, and the problems that need to be solved, providing a reference for the majority of clinical practitioners.

Keywords: Remimazolam; Monitored anesthesia care; Comfortable diagnosis and treatment; Outpatient surgery; Sedative drug

Fund program: Youth General Program of Shandong Provincial Natural Science Foundation (ZR2024QH295)

麻醉监测管理(monitored anesthesia care，MAC)是一种安全有效的麻醉技术，通过适度的镇静和镇痛确保患者在手术过程中保持舒适，为患者术后快速恢复提供条件[1]。目前MAC适用于多种门诊和小型手术以及术前肺功能较差、预计术后脱机困难的患者，可以减少麻醉用药，确保患者的神经、肌肉和心肺处于生理状态，保留患者的自主呼吸和保护性反射，达到术后快速康复(enhanced recovery after surgery，ERAS)的目的[1]。目前临床麻醉中常用的镇静药物有苯二氮䓬类药

DOI:10.13429/j.cnki.cjcr.2026.03.002

基金项目：山东省自然科学基金青年面上专项类别(ZR2024QH295)

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出版日期：2026-03-20

QR code for English version

物、异丙酚、依托咪酯和右美托咪定等，但是研究发现上述药物有中枢呼吸循环抑制和短暂性上呼吸道阻塞等风险[2]。新型苯二氮䓬类药物瑞马唑仑具有起效快、镇静作用持续时间短、恢复快、长期输注后不会导致蓄积的优势[2]，使之成为安全实施 MAC 的可能选择。本文就瑞马唑仑的药理机制及其在 MAC 中的应用进行综述。

1　瑞马唑仑的药理机制

瑞马唑仑是一种新型的亲脂类苯二氮䓬类镇静药，可增强γ-氨基丁酸 A 型（gamma-aminobutyric acid subtype A，$GABA_A$）受体活性，诱导细胞膜超极化，增加氯化物内流，抑制神经活性，在调节神经元兴奋性方面起着重要作用[3]。基于脑电图β比值、双频指数（bispectral index，BIS）、Narcotrend 指数和改良观察者警觉性/镇静评估（Modified Observer's Assessment of Alertness/Sedation Scale，MOAA/S）对瑞马唑仑镇静作用进行药效学分析显示，瑞马唑仑镇静起效快，其镇静深度和持续时间与剂量相关[4]。此外，瑞马唑仑含有代谢不稳定的酯基团，可以被组织酯酶（羧酸酯酶-1）快速代谢为无活性化合物 CNS7054，且瑞马唑仑的药代动力学呈线性，与咪达唑仑相比，其药代动力学半衰期相对较短，为 7~8 min[5]，使其具有超短效作用。动物实验研究证实，对于小鼠而言，达到睡眠剂量的瑞马唑仑和咪达唑仑，分别可在数分钟及近一小时内导致其扶正反射丧失[6]。此外，瑞马唑仑主要通过尿液排泄，且清除率基本上与体质量无关，注射 24 小时后（0.20 或 0.30 mg/kg），尿液中检测到超过 80%的剂量为代谢物，不到原始剂量的 1% 被检测为未改变的药物，其全身清除率约为咪达唑仑的 3 倍[3]。有研究表明 0.05 mg/kg 及更高剂量的瑞马唑仑给药后镇静作用起效迅速且呈剂量依赖性[7]。从药代动力学和药效学上看，瑞马唑仑稳态分布容积小、起效快，代谢快[5]。根据已有的临床试验结果发现，瑞马唑仑在体内代谢过程中不经过肝脏，主要通过非特异性的血浆酯酶快速分解，不会在体内积累，达到血液中的最高浓度大约需要 1 min，并且其平均停留时间也较短[8]，所以瑞马唑仑在人肝细胞中代谢长期稳定，对肝细胞的代谢活性和完整性没有有害影响。但是在各种临床研究中，瑞马唑仑在程序镇静和麻醉期间相关的不良反应都有详细记录，较常见的是血压和心率的变化、恶心和呕吐，其他不良事件包括头痛、嗜睡和缺氧等[2]。临床研究证实了瑞马唑仑耐受性良好，可用于程序性镇静以及全身麻醉的诱导和维持，具有相对较高的安全性，减少心肺抑制并降低注射痛，可以成为 MAC 的镇静药物选择之一[2,5]。研究瑞马唑仑在 MAC 麻醉中的临床应用具有重大意义。然而，迄今为止，瑞马唑仑的临床应用仅限于少数志愿者和有限数量的临床调查[5,8]。

2　瑞马唑仑在诊疗中的应用

目前以瑞马唑仑为基础的 MAC 管理方案在支气管镜、无痛胃肠镜、宫腔镜等检查和治疗中逐渐开展并显露优势，下文将探讨以瑞马唑仑为基础的 MAC 方案在部分临床诊疗过程中管理的应用进展。

2.1　瑞马唑仑在支气管镜检查中的应用

支气管镜检查在气道和肺部疾病的检查、诊断及治疗中发挥着日益重要作用[9]。2011 年美国胸科医师学会发表了共识声明，即在没有禁忌证的情况下，建议所有接受支气管镜检查的患者进行局部麻醉、镇痛和镇静来增加患者的耐受性和满意度，同时指南指出，目前不存在用于支气管镜检查的单一的完美镇静剂，瑞马唑仑联合阿片类药物为指南推荐的麻醉方案[9]。

瑞马唑仑可以安全有效地用于支气管镜检查，有研究证实与咪达唑仑相比，瑞马唑仑在支气管镜检查期间安全有效，可以满足手术镇静的需求，起效快，患者神经精神功能恢复更快，术后认知功能可以得到快速恢复[10]。Zhou 等[11]研究发现与右美托咪定相比，瑞马唑仑在支气管镜检查中氧饱和度下降的发生率降低，可以提供更好的 MAC，在手术过程中，使用瑞马唑仑的患者血流动力学更稳定，气道辅助需求减少，提高了手术的安全性和患者的依从性。因此，瑞马唑仑可成为支气管镜检查期间的镇静方案中新的选择。

2.2　瑞马唑仑在无痛胃肠镜检查中的应用

消化内镜检查是诊断和治疗胃肠道和结直肠疾病的重要和常用的内窥镜方法，如若术者操作时间过长会引起患者内脏痛，出现痉挛，甚至心脑血管意外等并发症[12]。随着诊疗技术的发展和改进，越来越多患者选择进行无痛胃肠镜检查，胃肠镜采取无痛方案，不仅可以有效消除患者紧张焦虑的心情，而且可以抑制胃镜检查过程中的上呼吸道反射，减轻患者的不适和痛苦，提高诊疗舒适度[12]。在无痛胃镜检查过程中，由于麻醉医生与术者需共用气道，因此术中的气道管理，保证麻醉过程的安全以及选择有效且不良反应小的麻醉药物格外重要，是麻醉关注的重点[12]。

无痛胃肠镜常用的镇静药物有丙泊酚、依托咪酯和瑞马唑仑等，但在无痛胃镜检查中，使用丙泊酚的患者低氧血症的发生率为 8.40%，而瑞马唑仑却对循环和呼吸系统的抑制作用较轻，降低了诱导后出现的血流动力学剧烈波动、过度镇静和注射疼痛等不良反应的发生率[13]。2023 年《苯磺酸瑞马唑仑临床应用指导意见》中建议胃肠镜诊断性检查或简单治疗镇静时，成年人可单独应用瑞马唑仑或联合阿片类药物以提高诊疗舒适度[14]。但在临床实践中发现，单独使用瑞马唑仑时的镇静深度无法满足胃镜检查的条件，患者可能会出现咳嗽、打嗝、身体运动等反应，虽然增加瑞马唑仑的剂量可以提高镇静深度，抑制应激反应，但对患者的循环系统有明显的抑制作用，延长患者苏醒时间和出院时间[15]。因此，在无痛胃镜中，瑞马唑仑联合其他药物可能比单一给药方案更可取。

2.3　瑞马唑仑在宫腔镜检查中的应用

随着女性对子宫内膜病变的认识不断提高和宫腔镜技术的不断进步，宫腔镜检查在临床实践中的应用变得越来越普遍[16]。全身麻醉、宫颈旁阻滞和局部麻醉都可用于宫腔镜检查[17]。全身麻醉可以满足宫腔镜手术的需要，成为首选的麻醉方式，但全身麻醉用药量大、不良反应多且麻醉费用高，对于宫腔镜这种时间短、操作简单的手术，专家共识推荐了 MAC[17]。

在 MAC 中最常用的麻醉方式为丙泊酚与阿片类药物联

合使用，但这些常用的麻醉药物会导致严重的呼吸和血流动力学抑制，存在恶心和呕吐等潜在的副作用，甚至有时需要使用喉罩或插管来辅助呼吸[7]。杨广标等[18]发现与靶向输注丙泊酚相比，靶向输注瑞马唑仑在改善患者术后苏醒和维护围手术期心率、平均动脉压、呼吸频率、血氧饱和度以及提高麻醉效率等方面具有明显优势，而且诱导后注射痛和血压降低的发生率减少。与此同时，根据Zhang等[19]的研究发现瑞马唑仑还可以联合低剂量丙泊酚，这种联合用药可改善宫腔镜检查的安全性，对心血管和呼吸抑制的影响较小，因此瑞马唑仑联合丙泊酚使用镇静方法更为理想。并且瑞马唑仑在MAC宫腔镜中的镇静程度也得到了认可，BIS数据记录显示，麻醉诱导后，瑞马唑仑产生的脑电图BIS值明显高于丙泊酚[20]。除了和丙泊酚相比，还有研究发现与艾司氯胺酮相比，在宫腔镜手术中瑞马唑仑可有效减少精神方面的不良反应[21]。另外，一项前瞻性随机研究发现瑞马唑仑联合阿芬太尼在无痛结肠镜手术中具有镇痛效果好、起效快、意识恢复快、清醒时间短等优点[22]。

2.4 瑞马唑仑在无痛人工流产中的应用 与传统人工流产手术相比，无痛人工流产显著降低了围手术期不良事件的发生率，缓解手术引起的疼痛和不适，减轻了患者的恐惧和紧张，并提高了患者的满意度，因此越来越多地用于临床实践[23]。

目前，无痛人工流产中常用的静脉麻醉方法是丙泊酚和阿片类药物组合应用[24]。丙泊酚起效快且半衰期短但使用时患者出现呼吸抑制、缺氧、低血压、注射痛等不良反应发生较多[24-25]，所以使用丙泊酚时必须谨慎。Yue等[26]研究发现，瑞马唑仑和丙泊酚都可以为流产手术提供必要的麻醉深度和持续时间，但是瑞马唑仑最小有效剂量不仅在无痛人工流产中可以实现充分的麻醉，而且减少了药物剂量和不良事件的发生，同时也降低了流产中丙泊酚引起的注射痛的频率和强度，获得了患者的广泛认可。不仅如此，用瑞马唑仑预处理降低了流产患者注射痛的发生率和强度，与利多卡因的效果相当，并且没有严重的不良反应发生[25]。同样，瑞马唑仑也可以联合其他药物用于无痛人工流产中。瑞马唑仑与艾司氯胺酮联合给药具有更短的作用持续时间、更快的新陈代谢和较低的严重不良事件（如低血压和呼吸抑制）发生的风险[26]，与氟马西尼联合使用会加快患者术后意识恢复和减少不良反应发生，在无痛流产手术中具有潜在的优势[27]。

2.5 瑞马唑仑在介入治疗中的应用 颅内动脉瘤是一种常见的脑血管疾病，给全球约1%~2%人口的生活带来影响[28]。脑动脉瘤破裂会导致蛛网膜下腔出血，从而给患者造成巨大的医疗负担，然而一些介入微创手术需要细微的操作，因此对于一些不能配合的患者需要进行麻醉处理[28]。《中国颅脑疾病介入治疗麻醉管理专家共识》[29]中明确对于颅内动脉瘤、动静脉畸形、急性缺血性脑卒中的麻醉管理核心均是围手术期严格的血压管理。丙泊酚是目前脑血管介入手术全身麻醉常用的镇静药物，然而其可引起许多不良反应，其中最突出的就是循环功能抑制，表现为增加了一些心脑血管事件及其它重要脏器损害的风险[7]。

Zhang等[30]进行了一项随机对照试验，比较瑞马唑仑与丙泊酚在全身麻醉下接受脑血管内手术患者的生命体征波动情况，这也是首次对接受线圈栓塞治疗脑动脉瘤的患者应用瑞马唑仑进行研究，结果发现瑞马唑仑的使用可以预防低血压。同时，Lee等[20]也证明在介入性神经放射学过程中，与丙泊酚麻醉相比，用瑞马唑仑麻醉患者的血流动力学更稳定。但大部分研究都是关于给予肌松药下行插管应用瑞马唑仑[31]，而针对瑞马唑仑应用于MAC下的介入手术研究相对较少。

2.6 瑞马唑仑在联合其他麻醉方式中的应用

2.6.1 瑞马唑仑联合神经阻滞 对于一些儿科、骨科手术和无法配合的患者，通常在镇静下完成神经阻滞，以减轻痛苦和操作时的体动造成新的损伤[32]。而适当的镇静深度可减少术前应激，维持生命体征稳定，且阻滞后能尽快恢复患者意识，以评估阻滞的效果[32]。理想的镇静效果是起效快、恢复快及残留少。瑞马唑仑有遗忘的作用，可以使患者对神经阻滞的痛苦过程无记忆，从而达到舒适化医疗的目的[2]。

目前常用的苯二氮䓬类镇静药咪达唑仑存在镇静时间长、意识恢复不全、影响镇静效果判断等缺点[7]。瑞马唑仑作为一种新型苯二氮䓬类药物，具有起效快、恢复快、无残留、不依赖肝肾功能代谢、副作用轻且少的优点[4]。因此，瑞马唑仑联合神经阻滞比单独应用神经阻滞效果更好，患者和术者的满意度更高[32]。研究表明给予瑞马唑仑后行神经阻滞可以消除患者的紧张焦虑及疼痛刺激引起的血压升高，镇静后患者意识恢复时间短且比咪达唑仑具有更好的血压及心率稳定性，呼吸抑制更轻微，安全性好[33]。同时刘小红等[34]研究发现，瑞马唑仑复合舒芬太尼用于神经阻滞下的镇静镇痛，可为患者提供安全、无痛、无恐惧的“舒适化医疗”服务，且不增加神经损伤及局麻药中毒风险。

2.6.2 瑞马唑仑联合椎管内麻醉 剖宫产手术对大部分产妇会造成紧张、恐惧的负面心理，围手术期的疼痛刺激更易诱发产后抑郁（post partum depression，PPD）[35]。目前多数麻醉选择胎儿娩出后给予一定的镇静镇痛药，从而减轻产妇疼痛并且消除紧张恐惧的心理[35]。研究表明瑞马唑仑联合艾司氯胺酮用于剖宫产手术可提高术中麻醉效果，降低围手术期精神症状等不良反应发生率，降低爱丁堡产后抑郁量表评分，改善PPD[36]。

然而，剖宫产术后恶心呕吐（postoperative nausea and vomiting，PONV）的发生率很高，椎管内麻醉后行剖宫产时，PONV发生率高达80%[37]。有研究表明，与咪达唑仑相比，瑞马唑仑显著降低了PONV的发生率以及镇静过程中的严重不良反应，并且对血流动力学的影响最小，这些优点使它成为椎管内麻醉下剖宫产术、腰硬联合麻醉膝关节置换术中有用的镇静药[38]。

在下肢手术中行椎管内麻醉的患者，联合使用瑞马唑仑与右美托咪定进行辅助镇静，观察并比较两种药物在给药后的镇静效果，结果表明瑞马唑仑和右美托咪定在下肢手术辅助镇静中都具有显著的镇静效果，但较右美托咪定相比，瑞马唑仑起效更快且瑞马唑仑的镇静效果与剂量相关[39]。

2.6.3 瑞马唑仑联合局部麻醉 一些门诊拔牙手术、耳鼻喉局麻手术、乳腺旋切术仅仅需要单纯的局部麻醉，但是由于局

部麻醉后，患者仍处于清醒状态，会产生紧张焦虑的心情，甚至可能会产生痛觉超敏化，因此在一些局部麻醉中，额外给予一些镇静麻醉药，可以使患者入睡，减轻紧张焦虑心情，达成舒适化诊疗的目标[4]。有研究表明，在局部麻醉的同时使用瑞马唑仑镇静，可安全应用于门诊老年牙周病患者舒适化拔牙，术中患者血压、心率平稳，不良反应较咪达唑仑少[40]。杨燕等[41]研究证实，瑞马唑仑联合舒芬太尼在鼻内镜治疗鼻窦炎手术中，利用其降低心率、血压，增加氧合状态，减慢呼吸频率以及减轻疼痛感受等优势，保障患者围手术期血流动力学更为稳定，成为鼻内镜治疗鼻窦炎手术中一种很好的麻醉方法。在乳腺微创旋切手术中瑞马唑仑和丙泊酚均可以提供有效的镇静深度，但瑞马唑仑相较于丙泊酚安全性更高，瑞马唑仑可以减少一过性呼吸抑制、低血压、心动过缓等不良反应的发生，且可以有效避免注射痛，患者舒适度更高[42]。

3　总结与展望

瑞马唑仑的药理学特征可降低麻醉期间血流动力学严重不稳定的风险，其可控的镇静水平和对血压心率影响小是有助于患者安全的有利特性。MAC 中应用瑞马唑仑可达到满意的麻醉镇静镇痛效果，更重要的是能够减少其他强效镇痛镇静药带来的呼吸抑制反应，而且还能缩短麻醉恢复时间。即便很多研究证实了瑞马唑仑对于呼吸循环影响小的优点，但是瑞马唑仑联合其他麻醉方式的应用研究相对较少，而且对于瑞马唑仑的研究人群也并不广泛，瑞马唑仑用于肥胖患者的研究相对较少，瑞马唑仑在介入手术中的 MAC 应用也相对较少，基本上都是研究瑞马唑仑在术中行气管插管的介入术中的应用，因此在 MAC 中应用瑞马唑仑联合其他麻醉方式、应用于肥胖患者等，是否能达到有效麻醉效果的同时还能减少麻醉药带来的并发症有待研究。目前对瑞马唑仑应用于围手术期的研究有限，循证依据尚不充分，后续还需要更多的临床研究来探究其在不同手术不同人群中的应用效果、最佳剂量以及适用范围，为个体化麻醉用药提供有力的依据。

利益冲突　所有作者均声明不存在利益冲突

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收稿日期:2025-04-29 **修回日期**:2025-07-10 **编辑**:许煜晗

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收稿日期:2025-06-06 **修回日期**:2025-08-02 **编辑**:许煜晗