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Prof. **LIU Cunming** is the Director of the Department of Anesthesiology at the First Affiliated Hospital of Nanjing Medical University and a PhD supervisor. He is also a visiting scholar at the University of Pittsburgh Medical Center, USA. With rich clinical experience, he specializes in anesthesia for liver transplantation and anesthetic management of critically ill patients. Professor Liu has led four national and provincial-level research projects. As the first author or corresponding author, he has published more than 50 papers in domestic and international journals and has contributed to over 10 academic books. Member of the Anesthesiology Branch of the Chinese Medical Association, a standing committee member of the Anesthesiology Branch of the Jiangsu Medical Association, the Vice Leader of the Anesthesia Collaboration Group of the Gastrointestinal Endoscopy Branch of the Chinese Medical Association, a member of the Anesthesiology Physician Branch of the Chinese Medical Doctor Association, and the Vice President of the Anesthesiology Physician Branch of the Jiangsu Medical Association. Prof. LIU serves as the Executive Editorial Board Member of *Journal of Clinical Anesthesiology* and is a member of the editorial boards of several academic journals, including *Chinese Journal of Anesthesiology*, *Chinese Journal of Oncology Surgery*, and *Jiangsu Medical Journal*.

Perioperative application of remimazolam in specific patients

LI Bowen, WANG Haoran, YANG Chun, LIU Cunming

Department of Anesthesia and Perioperative Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China

Corresponding author: LIU Cunming, E-mail: cunmingliu@njmu.edu.cn

Abstract: Remimazolam is a novel ultrashort-acting sedative-hypnotics of benzodiazepines, which metabolized by tissue non-specific cholinesterase. It has the character that hardly influence on hemodynamics and respiratory function. With rapid metabolism, it has a strong controllability and doesn't accumulation after long-time infusion. Moreover, it provides a rapid recovery after anesthesia that can be antagonized by flumazenil specifically. Nowadays, remimazolam is used in procedure sedation in numerous situations of anesthesia. This article focuses on elderly, hepatic and renal impairment, pediatrics, obesity, and obstetrics patients, aims at providing references in clinical applications.

Keywords: Remimazolam; Elderly; Hepatic impairment; Renal impairment; Children; Obesity; Obstetrics
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Remimazolam is an ultra-short-acting benzodiazepine drug that was launched in 2020, breaking the nearly 30-year hiatus in the development of innovative sedative drugs both domestically and internationally. It is used for anesthesia and sedation in various settings, producing dose-dependent sedative, hypnotic, and anxiolytic effects. It is characterized by hydrolysis by non-specific esterase in tissues, the lack of activity of its major metabolic products, and its ability to be antagonized by flumazenil [1]. Nowadays, remimazolam is widely used in perioperative procedural sedation. Compared to midazolam, remimazolam has a shorter duration of action and half-life with no tendency to accumulate. Compared to propofol, remimazolam provides equivalent sedative effects, better hemodynamic stability, less respiratory depression, and no injection pain concerns [2]. Studies have shown that remimazolam has similar safety and efficacy profiles in both high and low ASA grade patients [3]. After continuous infusion for 3 hours, the half-life of remimazolam is about one-fifth that of midazolam [4]. It causes much less postoperative nausea and vomiting than inhalational anesthetics and is expected to provide faster and better postoperative recovery than traditional propofol anesthesia [3]. In summary, the application of remimazolam in high-risk patients holds promising prospects. This article reviews the clinical use of remimazolam in special populations, including the

elderly, patients with liver and kidney dysfunction, children, obese patients, and obstetric patients, aiming to provide a reference for its rational clinical use in these special groups.

1 Pharmacological Effects and Pharmacokinetics

Like other benzodiazepines, remimazolam acts on γ-aminobutyric acid-A ($GABA_A$) receptors, altering the conformation of chloride ion channels, leading to their hyperpolarization and resulting in central nervous system inhibition [5]. Remimazolam is currently the benzodiazepine sedative with the least cardiopulmonary suppression. It is a metabolizable ester derivative that accelerates the metabolic rate while retaining the pharmacological properties of benzodiazepines, thus providing ultra-short sedative effects. In healthy subjects, remimazolam has a high clearance rate [(1.15±0.12) L/min], a small volume of steady-state distribution [(35.4±4.2) L], and a short half-life [(70±10) min]. Remimazolam is hydrolyzed by tissue carboxylesterases (mainly hepatic carboxylesterase) into the inactive metabolite CNS7054, which is then excreted via the kidneys [6]. Moreover, renal impairment does not affect the peak plasma concentration of remimazolam. When administered intravenously at 0.1 mg/kg, 99.7% of remimazolam is rapidly hydrolyzed to CNS7054, which accounts for 98.6% of the total metabolites identified in urine. The plasma clearance rate in subjects with renal impairment (including end-stage renal disease) is comparable to that in healthy subjects [7-8]. In patients with mild to moderate hepatic impairment, the plasma clearance rate is similar to that of healthy volunteers. However, in those with severe liver impairment (Child-Pugh score ≥10), plasma clearance is reduced by 38.1% compared to healthy volunteers. The time to regain consciousness in healthy individuals, those with moderate liver impairment, and severe liver impairment patients were 8 min, 12.1 min, and 16.7 min, respectively [8]. In pediatric patients, intravenous remimazolam administration at 5 mg/(kg·h) (5 min) and 1.5 mg/(kg·h) (55 min) resulted in a clearance rate of 15.9 (12.9, 18.2) mL/(kg·min), a central distribution volume of 0.11 (0.08, 0.14) L/kg, and a terminal half-life of 67 (49, 85) min. After continuous infusion for 4 hours, the dose-related half-life was 17 (12, 21) min. The pharmacokinetic characteristics in children are similar to those in adults, with high drug clearance and no accumulation after prolonged infusion [9]. Currently, there are insufficient pharmacokinetic data on remimazolam in pregnant and postpartum women, and further research is needed.

2 Clinical Application of Remimazolam in Special Populations

2.1 Elderly Patients

In elderly patients, an average intraoperative blood pressure < 55 mmHg is a risk factor for delirium, which is associated with decreased functional activity and increased postoperative mortality [10]. Several studies have shown that remimazolam results in a lower incidence of adverse effects such as hypotension, respiratory depression, and bradycardia compared to propofol in elderly patients undergoing gastroscopy [11-13]. In elderly frail and non-frail patients, the 95% effective dose for suppressing tracheal intubation response was 0.297 mg/kg (95%*CI*: 0.231–0.451 mg/kg) and 0.331 mg/kg (95%*CI*: 0.272–0.472 mg/kg), respectively [14]. Remimazolam may be particularly suitable for elderly hypertensive patients. Both lower doses (0.2 mg/kg) and higher doses (0.3 mg/kg) of remimazolam can be safely and effectively used in non-cardiac surgeries for elderly hypertensive patients [15]. In one study, remimazolam 0.2 mg/kg and propofol 1.5 mg/kg were used to induce anesthesia. During anesthesia induction, the remimazolam group had smaller hemodynamic fluctuations, stable circulation, fewer adverse reactions, and no injection pain, which improved patient comfort [16]. In elderly patients undergoing cardiovascular surgery, remimazolam also demonstrated safety and reliability. In 20 patients with a median age of 84 years and ASA IV aortic valve replacement, remimazolam at a dose of 6 mg/(kg·h) and remifentanil at 0.25 μg/(kg·min) were used to induce loss of consciousness. Intubation was completed with 1.5% sevoflurane and 0.6–0.9 mg/kg rocuronium, and no serious adverse events occurred during anesthesia induction [17]. However, whether remimazolam promotes better postoperative recovery in elderly patients remains a matter of debate [18-19] and requires further research.

2.2 Patients with Hepatic Insufficiency

In general, chronic liver damage patients should avoid the use of long-acting anesthetics and sedatives [20]. Due to its fast onset, short half-life, and independence from hepatic metabolism, remimazolam may be a suitable alternative as a routine sedative for these patients in surgical anesthesia.

In 2022, Onoda *et al.* [21] first reported the use of remimazolam for general anesthesia in a Child-Pugh B cirrhosis patient. Anesthesia was induced with 3 mg/(kg·h) remimazolam, 0.1 μg/kg/h remifentanil, 250 μg fentanyl, and 30 mg rocuronium. The maintenance dose of remimazolam was 0.5-0.8 mg/(kg·h). No vasopressors were used intraoperatively, and the bispectral index (BIS) remained stable around 45. The patient woke up well postoperatively without the use of antagonists, and liver function was not affected. Kawasaki *et al.* [22] found that in a Child-Pugh C liver

transplant patient, induction doses of 12 mg/(kg·h) and maintenance doses of 0.6-1.0 mg/(kg·h) of remimazolam were used. Despite liver being the primary organ for remimazolam metabolism, it can also be directly metabolized by non-specific esterase in tissues without relying on the liver. In postoperative recovery, remimazolam reduced recovery time, postoperative delirium, and ICU stay duration. For patients with liver insufficiency, it may be a safer and more effective alternative to propofol for general anesthesia [20, 23-25]. Zhuo *et al.* [23] compared remimazolam with propofol anesthesia in 60 patients undergoing liver resection surgery, and the results showed that the remimazolam group had significantly shorter recovery times, fewer adverse reactions, and no impact on postoperative cognitive function. Shi *et al.* [20] and Yuan *et al.* [24] compared remimazolam and propofol for ASA II or III cirrhotic patients undergoing endoscopic variceal ligation. In both studies, the remimazolam group showed significantly shorter recovery times, extubation times, and PACU stays, with lower incidences of intraoperative hypotension and postoperative hypoxia compared to the propofol group.

2.3 Patients with Renal Impairment

In general, renal impairment can affect the distribution, metabolism, elimination, and protein binding of drugs within the body. When using sedatives, careful consideration should be given to the type and dosage, otherwise there is concern about the accumulation of metabolites leading to respiratory arrest, delayed awakening, and other issues.

In a phase I clinical safety study conducted in 2021, no significant pharmacokinetic differences were observed between patients with renal impairment and healthy subjects. Although CNS7054, the metabolite of remimazolam, had reduced elimination due to decreased renal clearance, it has no pharmacological activity and does not exert a clinical effect. Thus, it is speculated that no dosage adjustment is necessary for renal impairment patients using remimazolam [8]. Nishioka *et al.* [26] reported an 82-year-old female patient with chronic heart failure undergoing hemodialysis. She underwent partial tongue resection for tongue cancer under general anesthesia with remimazolam and sufentanil. Remimazolam was administered intravenously at a dosage of 6 mg/(kg·h) for induction and 0.3-0.4 mg/(kg·h) for maintenance. Sufentanil was administered at 15 μg/(kg·h) for induction and 3-18 μg/(kg·h) for maintenance. During anesthesia, sedation was satisfactory, hemodynamics remained stable, and she woke up rapidly and completely without the need for antagonists. Multiple studies have since shown that remimazolam can be safely and effectively used in patients with renal failure for general anesthesia and neuroaxial anesthesia without affecting postoperative renal function, and it has better hemodynamic stability and postoperative recovery compared to propofol [27-28].

2.4 Pediatric Patients

The safety and efficacy of remimazolam in pediatric patients have also been confirmed, with advantages in hemodynamic stability and postoperative recovery compared to the commonly used propofol. Chu *et al.* [29] compared the efficacy and safety of remimazolam and propofol in pediatric gastrointestinal endoscopy. A total of 106 subjects were given remimazolam 0.3 mg/kg or propofol 3 mg/kg. Although induction time was longer in the remimazolam group, hemodynamic parameters were more stable, and no delayed awakening was observed in younger patients. Another study conducted in China evaluated the use of remimazolam combined with flumazenil in pediatric cardiac surgery. Induction with remimazolam 0.3 mg/kg and maintenance at 1 mg/(kg·h) was compared to propofol 3 mg/kg for induction and 8 mg/(kg·h) for maintenance. The remimazolam group showed smaller fluctuations in hemodynamics, earlier extubation after flumazenil antagonism, shorter hospital stays, and no increase in adverse events [30]. Yang *et al.* [31] found that remimazolam significantly reduced the likelihood of delirium after sevoflurane anesthesia (12% *vs.* 44%). Additionally, continuous infusion of remimazolam [1 mg/(kg·h)] and a single bolus (0.2 mg/kg) at the start of skin suturing were effective in reducing the occurrence of postoperative delirium in children, with no significant adverse effects [32].

2.5 Obese Patients

Obese patients have a higher incidence of airway obstruction and are at risk of drug accumulation, often with comorbidities such as hypertension and hyperglycemia, making it difficult to control the dosage of sedative medications during clinical anesthesia. The dosage of anesthetic drugs for obese patients is often adjusted based on their ideal body weight (ideal weight + 0.4 × [total weight - ideal weight]).

Compared to propofol, remimazolam 0.1 mg/kg combined with esketamine 0.5 mg/kg can reduce the incidence of severe hypoxemia during gastrointestinal endoscopy in obese patients, and remimazolam users have shorter PACU stay times [33]. Deng *et al.* [34] found that remimazolam is safe and effective for general anesthesia in obese patients with a body mass index (BMI) >28 kg/m² undergoing gastrointestinal surgery. Induction was performed with remimazolam 6 mg/(kg·h), and maintenance was at 0.2-1.0 mg/(kg·h). The incidence of cardiopulmonary suppression and adverse reactions was significantly lower than in the dexmedetomidine group. Specifically, in elderly obese

patients (BMI 30-40 kg/m²) undergoing gastrointestinal endoscopy, remimazolam 0.15 mg/kg showed shorter recovery times, lower incidence of adverse reactions, and significantly higher correct rate of memory test by neurobehavioral cognitive status examination (NCSE) and cognitive screening pass rates at 5 minutes post-awakening compared to propofol 1.5 mg/kg [35]. Obesity, gender (the elimination rate in male patients is 10%-20% lower than in females), and ASA score are the most significant factors affecting the pharmacokinetics of remimazolam [36]. A dosing study of remimazolam in obese patients [37] is ongoing and is expected to provide more reliable dosing recommendations in the near future.

2.6 Obstetric Patients

When administering anesthesia to pregnant women, both maternal and fetal considerations must be taken into account. Traditional propofol anesthesia may cause significant hemodynamic fluctuations, which could pose substantial risks to both the mother and the fetus.

A 34-year-old pregnant woman with infective endocarditis and heart failure underwent a cesarean section under general anesthesia with remimazolam. The patient, weighing 49 kg, was given 7.2 mg of remimazolam and fell asleep within 90 seconds. Anesthesia was maintained at a dosage of 1.2 mg/(kg·h). During the surgery, the mother's mean arterial pressure remained above 65 mmHg without the need for vasoactive drugs. The newborn had an Apgar score of 4 at 1 minute and 7 at 5 minutes [38]. remimazolam 0.1 mg/kg combined with esketamine 0.25 mg/kg for cesarean section can improve anesthesia effectiveness, reduce the incidence of intraoperative psychological symptoms, and help prevent postpartum depression [39]. Huai *et al.* [40] administered 5 mg of remimazolam as a loading dose after oxytocin injection to 80 patients with uterine atony undergoing cesarean section under spinal anesthesia, followed by 1 mg injections every minute (a total of 5 doses). This stabilized maternal vital sign, reduced adverse reactions, and did not increase the risk of uterine atony. Based on these results, remimazolam shows potential as an adjunctive sedative for cesarean sections, improving perioperative safety and patient satisfaction.

3 Summary and Outlook

Remimazolam, a novel sedative that retains the advantages of traditional sedatives like midazolam while addressing its shortcomings, has the potential to become a new option for anesthesia and sedation in special populations such as the elderly, patients with liver and kidney dysfunction, children, the obese, and obstetric patients. It offers high safety, no injection pain, minimal organ function dependence during metabolism, no accumulation, and is reversible. It can be applied in various anesthesia and sedation scenarios, demonstrating good performance in hemodynamic stability, reducing adverse reactions, and improving postoperative recovery. Remimazolam has the potential to become a major anesthetic sedative for these special populations in the future. However, most current research focuses on intraoperative and early postoperative clinical observations, and further studies are needed to evaluate its long-term effects on these special patients' outcomes. This will provide reliable evidence for the broader clinical application of remimazolam.

Conflicts of Interest None

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·学术前沿·

瑞马唑仑在特殊患者围术期应用的进展

李博文，　王浩然，　杨春，　刘存明
南京医科大学第一附属医院麻醉与围术期医学科，江苏 南京 210029

刘存明教授，南京医科大学第一附属医院麻醉科主任，博士研究生导师。美国匹兹堡大学医学中心访问学者。拥有丰富的临床经验，擅长肝移植麻醉和危重症患者的麻醉。主持国家级及省、市级项目共 4 项，以第一作者或通信作者在国内外期刊发表论文 50 余篇，参编专著 10 余部。担任中华医学会麻醉学分会委员，江苏省医学会麻醉学分会常委，中华医学会消化内镜分会麻醉协作组副组长，中国医师协会麻醉学医师分会委员，江苏省医师协会麻醉医师分会副会长。任《临床麻醉学杂志》常务编委，《中华麻醉学杂志》、《中国肿瘤外科杂志》、《江苏医药》等多家学术期刊编委。

摘要：瑞马唑仑是一种新型的超短效苯二氮䓬类镇静催眠药，主要经肝脏非特异性酯酶代谢，具有对血流动力学和呼吸功能影响小、可控性强、代谢迅速、长时间使用无药物蓄积、苏醒迅速等优点，且有特异性拮抗药氟马西尼，目前已被用于多种环境下的麻醉镇静。本文就瑞马唑仑在老年、肝肾功能不全、儿童、肥胖和产科患者麻醉中的应用进行综述，旨在为临床合理使用提供参考。

关键词：瑞马唑仑；老年；肝功能不全；肾功能不全；儿童；肥胖；产科
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Perioperative application of remimazolam in specific patients

LI Bowen, WANG Haoran, YANG Chun, LIU Cunming
Department of Anesthesia and Perioperative Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China
Corresponding author: LIU Cunming, E-mail: cunmingliu@njmu.edu.cn

Abstract: Remimazolam is a novel ultrashort-acting sedative-hypnotics of benzodiazepines, which metabolized by tissue non-specific cholinesterase. It has the character that hardly influence on hemodynamics and respiratory function. With rapid metabolism, it has a strong controllability and doesn't accumulation after long-time infusion. Moreover, it provides a rapid recovery after anesthesia that can be antagonized by flumazenil specifically. Nowadays, remimazolam is used in procedure sedation in numerous situations of anesthesia. This article focuses on elderly, hepatic and renal impairment, pediatrics, obesity, and obstetrics patients, aims at providing references in clinical applications.

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瑞马唑仑是 2020 年上市的超短效苯二氮䓬类药物，打破了国内外临床镇静药物领域近 30 年无创新

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通信作者：刘存明，E-mail：cunmingliu@njmu.edu.cn
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药上市的局面。它可用于多种环境下的麻醉镇静，产生剂量依赖性的镇静、催眠和抗焦虑作用，具有可经组织非特异性酯酶水解、主要代谢产物无活性、可被氟马西尼拮抗的特点[1]。如今瑞马唑仑已被广泛应用于围术期程序性镇静。与咪达唑仑相比，瑞马唑仑的作用时间和半衰期更短，没有蓄积倾向；与丙泊酚相比，瑞马唑仑有效果相当的镇静作用，且血流动力学稳定性好，呼吸抑制更小，没有注射痛的担忧[2]。研究表明，瑞马唑仑在高美国麻醉医师协会（American Society of Anesthesiologists，ASA）分级和低 ASA 分级患者中的安全性和有效性相当[3]。连续输注 3 小时后，瑞马唑仑的半衰期约为咪达唑仑的 1/5[4]，其引起的术后恶心和呕吐比吸入麻醉药要轻得多，有望提供比传统的丙泊酚麻醉更快更好的术后恢复[3]。瑞马唑仑在高危患者中的应用前景令人期待，本文就瑞马唑仑在老年、肝肾功能不全、儿童、肥胖、产科等特殊患者中的应用进行综述，旨在为瑞马唑仑在特殊患者中的临床合理使用提供参考。

1　药理作用与药代动力学

和其他苯二氮䓬类药物一样，瑞马唑仑也作用于 γ-氨基丁酸-A（γ-amino butyric acid A，$GABA_A$）受体，改变氯离子通道的构象，导致其超极化，产生对中枢神经系统的抑制[5]。瑞马唑仑为目前心肺抑制最小的苯二氮䓬类镇静药物与可代谢丙酸甲酯侧链的结合体，在保留苯二氮䓬类药理学特性的基础上加快了代谢速度，从而产生超短效镇静作用。在健康受试者体内，瑞马唑仑清除率高[（1.15±0.12）L/min]、稳态分布容积小[（35.4±4.2）L]，半衰期短[（70±10）min]。瑞马唑仑可在组织羧酸酯酶（主要是肝羧酸酯酶）的作用下转化为非活性代谢物 CNS7054，并经肾脏排泄[6]。此外，肾损害并不影响瑞马唑仑的血浆峰浓度，静脉注射 0.1 mg/kg 时，99.7%的瑞马唑仑被迅速水解成 CNS7054，占鉴定尿中代谢物总数的 98.6%，肾损害（包括终末期肾病）受试者的血浆清除率与健康受试者相当[7-8]；轻、中度肝损害患者的血浆清除率与健康志愿者无明显差异，仅在严重肝损害（Child-Pugh 评分≥10）的受试者中观察到比健康志愿者低 38.1%的血浆清除率，健康人、中度肝损害、重度肝损害患者从意识丧失中苏醒的时间分别为 8 min、12.1 min 和 16.7 min[8]。在儿童患者中，静脉输入瑞马唑仑 5 mg/（kg · h）（5 min）和 1.5 mg/（kg · h）（55 min）的清除率为 15.9（12.9，18.2）mL/（kg · min）、中心分布容积为 0.11（0.08，0.14）L/kg、终末半衰期为 67（49，85）min、连续输注 4 小时后时量相关半衰期为 17（12，21）min，标准化体重下的药代动力学特征与成人相似，药物清除率高，长时间输注后无蓄积[9]。目前尚缺少瑞马唑仑在孕产妇中的药代动力学报道，亟待更多的研究完善。

2　瑞马唑仑在特殊人群中的临床应用

2.1　*老年患者*　老年患者术中平均血压<55 mmHg 是谵妄的危险因素，与日常活动能力下降和术后死亡率增加相关[10]。研究表明瑞马唑仑在老年患者胃镜中的剂量相关低血压、呼吸抑制和心动过缓等不良反应发生率低于丙泊酚[11-13]。瑞马唑仑在老年衰弱患者和非衰弱患者中抑制气管插管反应 95%有效剂量分别为 0.297 mg/kg（95% *CI*：0.231～0.451 mg/kg）和 0.331 mg/kg（95% *CI*：0.272～0.472 mg/kg）[14]。瑞马唑仑可能更加适用于老年高血压患者，较低剂量（0.2 mg/kg）和较高剂量（0.3 mg/kg）均能安全有效地应用于老年高血压患者非心脏手术[15]，分别以瑞马唑仑 0.2 mg/kg 和丙泊酚 1.5 mg/kg 诱导麻醉，麻醉诱导期间瑞马唑仑组血流动力学波动小、循环稳定、不良反应少，且无注射痛，患者舒适度高[16]。在老年患者的心血管手术中，瑞马唑仑同样表现出安全而可靠的优势。对 20 例中位年龄 84 岁的 ASA Ⅳ级主动脉瓣置换患者使用瑞马唑仑 6 mg/（kg · h）和瑞芬太尼 0.25 μg/（kg · min）诱导意识丧失，随后在 1.5%七氟烷和 0.6～0.9 mg/kg 罗库溴铵的帮助下完成气管插管，在麻醉诱导期间未发生严重不良事件[17]。但瑞马唑仑是否更加有利于老年患者的术后恢复仍存在争议[18-19]，有待更多的研究讨论。

2.2　*肝功能不全患者*　一般情况下，慢性肝损伤患者应避免使用长效麻醉剂和镇静剂[20]，瑞马唑仑因其起效快、半衰期短、不依赖于肝脏代谢，可能成为这类患者手术麻醉中常规镇静剂的合适替代方案。

2022 年，Onoda 等[21]首次报道了瑞马唑仑应用于 Child-Pugh B 级肝硬化患者的全身麻醉，以 3 mg/（kg · h）瑞马唑仑、0.1 μg/（kg · h）瑞芬太尼、250 μg 芬太尼和 30 mg 罗库溴铵诱导麻醉，瑞马唑仑的维持剂量为 0.5～0.8 mg/（kg · h），术中没有使用血管活性药，脑电双频指数（bispectral index，BIS）值稳定在 45 左右，术后在未使用拮抗剂的情况下患者苏醒良好，肝功能未受影响。Kawasaki 等[22]则在 1 例 Child-Pugh C 级肝移植患者的手术麻醉中发现，选择 12 mg/（kg · h）诱导剂量，0.6～1.0 mg/（kg · h）维持剂量的瑞马唑仑，在不调整无肝期输注速率的情况

下,术中 BIS 值和患者状态指数均与无肝前期相当,即虽然肝脏是瑞马唑仑代谢的主要器官,它也可直接被组织非特异性酯酶代谢而不依赖于肝脏。在术后恢复方面,瑞马唑仑能缩短苏醒时间和减少术后谵妄等不良反应发生率,减少术后重症监护病房(intensive care unit, ICU)住院时间,对于肝功能不全患者而言可能是比丙泊酚更安全、更有效的全身麻醉方法[20, 23-25]。卓明等[23]对 60 例肝切除术患者应用瑞马唑仑和丙泊酚麻醉镇静进行了比较,结果表明瑞马唑仑组较丙泊酚组苏醒时间明显缩短、不良反应发生率更低,且不影响术后认知功能。Shi 等[20]和袁永瑾等[24]比较了瑞马唑仑和丙泊酚用于 ASA 分级Ⅱ级或Ⅲ级的肝硬化患者内镜下静脉曲张结扎术,两项研究均以瑞马唑仑 0.2 mg/kg 诱导,1.0~2.0 mg/(kg·h)的剂量维持,瑞马唑仑组苏醒时间、拔管时间、麻醉恢复室(postanesthesia care unit, PACU)停留时间均明显短于丙泊酚组,术中低血压和术后低血氧饱和度(saturation of peripheral oxygen, SpO_2)发生率也低于丙泊酚组。

2.3　肾功能不全患者　一般而言,肾功能不全可影响药物在体内的分布、代谢、消除和蛋白结合,使用镇静药物时应仔细斟酌种类和用量,否则有代谢物蓄积导致呼吸停止、苏醒延迟等情况的担忧。

在 2021 年进行的Ⅰ期药物临床安全性研究中,肾功能不全患者与正常受试者在药代动力学上未观察到显著性差异,虽然瑞马唑仑的代谢物 CNS7054 因肾清除率下降而消除减少,但其无药理学活性,不发挥临床作用,由此推测肾功能不全患者使用瑞马唑仑时无需进行剂量调整[8]。Nishioka 等[26]报道了一例 82 岁女性血液透析且患有慢性心力衰竭的患者,在瑞马唑仑和瑞芬太尼全麻下接受舌癌部分舌切除术,通过静脉输注瑞马唑仑 6 mg/(kg·h)和瑞芬太尼 15 μg/(kg·h)诱导麻醉,瑞马唑仑 0.3~0.4 mg/(kg·h)和瑞芬太尼 3~18 μg/(kg·h)维持麻醉,麻醉期间镇静满意、血流动力学稳定、术后无需拮抗剂即能迅速彻底地苏醒。随后有多项研究表明,瑞马唑仑能在不影响术后肾功能的情况下,安全有效地应用于肾衰竭患者的全身麻醉和神经阻滞麻醉,且在血流动力学稳定性和术后恢复等方面优于丙泊酚[27-28]。

2.4　儿童患者　瑞马唑仑在儿童患者中的安全性和有效性同样得到证实,且在血流动力学稳定性、术后恢复等方面一定程度上优于目前常用的丙泊酚。Chu 等[29]比较了瑞马唑仑与丙泊酚在儿童胃肠镜检查的有效性与安全性,共 106 名受试者分别采用瑞马唑仑 0.3 mg/kg 和丙泊酚 3 mg/kg,瑞马唑仑组虽然诱导时间更长,但血流动力学指标更加稳定,在低龄患者中也未观察到苏醒延迟的现象。另一项在我国进行的研究评估了瑞马唑仑联合氟马西尼在儿童心脏外科手术中的应用价值,采用瑞马唑仑 0.3 mg/kg 麻醉诱导,1 mg/(kg·h)维持;对比丙泊酚 3 mg/kg 麻醉诱导,8 mg/(kg·h)维持,瑞马唑仑组的血流动力学波动幅度更小、氟马西尼拮抗后拔管更早、住院时间更短,同时不增加不良反应的发生率[30]。Yang 等[31]发现使用瑞马唑仑显著降低七氟烷麻醉后出现谵妄的可能性(12%和 44%)。此外,瑞马唑仑连续输注[1 mg/(kg·h)]和缝皮开始时单次推注(0.2 mg/kg)均可有效减少儿童苏醒性谵妄的发生,且无明显不良反应[32]。

2.5　肥胖患者　肥胖患者呼吸道梗阻发生率高,且存在药物蓄积的风险,常伴随高血压、高血糖等合并症,临床麻醉时镇静药物剂量难以把控。肥胖患者的麻醉用药剂量常参考调整后的体重[理想体重+0.4×(总体重-理想体重)]。

与丙泊酚相比,瑞马唑仑 0.1 mg/kg 联合艾司氯胺酮 0.5 mg/kg 可降低肥胖患者胃肠镜检查时严重低氧血症的发生率,且使用瑞马唑仑的患者 PACU 停留时间更短[33]。Deng 等[34]发现瑞马唑仑用于体质量指数(body mass index, BMI)>28 kg/m^2 的肥胖患者胃肠道手术全身麻醉安全且有效,以瑞马唑仑 6 mg/(kg·h)进行麻醉诱导,0.2~1.0 mg/(kg·h)麻醉维持,心肺抑制和不良反应发生率均明显低于右美托咪定组。特别地,在老年肥胖患者(BMI 30~40 kg/m^2)的胃肠镜检查中,0.15 mg/kg 的瑞马唑仑与 1.5 mg/kg 丙泊酚相比恢复时间更短、不良反应发生率更低、清醒后 5 min 时神经行为认知状态检查(neurobehavioral cognitive status examination, NCSE)记忆力测试正确率和计算能力筛查通过率明显升高[35]。肥胖、性别(男性患者的消除率略低于女性 10%~20%)、ASA 评分是对瑞马唑仑药代动力学影响最大的因素[36]。一项瑞马唑仑用于肥胖患者的剂量研究[37]正在进行中,有望在不久的将来提供更加可靠的用药建议。

2.6　产科患者　孕产妇的麻醉在用药时要考虑母体与胎儿两个方面,传统丙泊酚麻醉过程中可能引起血流动力学的剧烈波动,可能对产妇和胎儿带来很大风险。

一例 34 岁感染性心内膜炎合并心力衰竭的孕妇使用瑞马唑仑全身麻醉下进行剖宫产术,产妇 49 kg

在 7.2 mg 瑞马唑仑给药 90 s 后入睡,以 1.2 mg/(kg·h)的剂量维持麻醉,手术期间母亲的平均动脉压维持在 65 mmHg 以上,无需血管活性药;1 min 新生儿 Apgar 评分为 4 分,5 min 为 7 分[38]。瑞马唑仑 0.1 mg/kg 联合艾司氯胺酮 0.25 mg/kg 用于剖宫产手术可提高麻醉效果、降低术中精神症状等不良反应发生率以及预防产后抑郁的发生[39]。怀其亮等[40]对 80 例椎管内麻醉下行剖宫产术的宫缩乏力患者给予缩宫素后注射 5 mg 负荷剂量的瑞马唑仑,随后每隔 1 min 以 1 mg 的单次剂量进行静脉推注(共计 5 次),稳定了产妇的生命体征、减少了不良反应,同时不增加产妇宫缩乏力的风险。基于以上结果,瑞马唑仑是有潜力应用于剖宫产手术辅助镇静的药物,能提高围术期安全性和患者满意度。

3　小结与展望

瑞马唑仑作为一种保留了传统镇静药咪达唑仑优点,并对其缺点进行改造的新型镇静药物,有潜力成为老年、肝肾功能损害、儿童、肥胖、产科等特殊患者麻醉镇静药物的新选择。其麻醉镇静作用安全性高、无注射痛、代谢过程对器官功能的依赖小、无蓄积、可逆转,可应用于多种场景下的麻醉镇静,在血流动力学稳定性,减少不良反应以及改善术后恢复中都有良好的表现。瑞马唑仑有潜力成为未来在这些特殊患者中麻醉镇静中的主要药物,但目前研究多集中在对术中和术后早期的临床观察,对这些特殊患者远期预后的影响还有待进一步的研究,从而为瑞马唑仑在临床的更广泛应用提供可靠的依据。

利益冲突　无

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