

瑞马唑仑预防蛛网膜下腔麻醉下剖宫产术围术期恶心呕吐的研究进展

马巧睿, 张茂荷*, 杨羽彤, 杨艳芳, 罗荣新, 施飞云, 陈建芹

大理大学第一附属医院麻醉科, 云南 大理

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摘要

临床上, 剖宫产手术恶心呕吐的发生率高, 而蛛网膜下腔麻醉下剖宫产患者恶心呕吐的发生率更高, 给手术安全性和病人的舒适度造成不小的影响, 严重的呕吐误吸甚至会危及生命。因此, 预防蛛网膜下腔麻醉下剖宫产患者围术期恶心呕吐对产妇的安全至关重要。很多研究表明咪达唑仑可以预防剖宫产患者术中的恶心呕吐, 瑞马唑仑作为新型超短效苯二氮卓类药物, 不仅具有了咪达唑仑所具有的镇静、催眠、抗焦虑等作用, 还弥补了咪达唑仑在起效时间、消除速率和药物蓄积上的不足。在预防剖宫产患者恶心呕吐方面, 瑞马唑仑可能是一个更优的选择。产妇恶心呕吐的影响因素较多, 本文探讨了剖宫产患者恶心呕吐的影响因素、苯二氮卓类药物的作用机制及瑞马唑仑的镇静优势, 为预防剖宫产患者恶心呕吐的治疗方面提供新的选择。

关键词

瑞马唑仑, 剖宫产, 恶心呕吐, 苯二氮卓类药物

Research Progress on Remimazolam for Preventing Perioperative Nausea and Vomiting in Cesarean Section under Spinal Anesthesia

Qiaorui Ma, Maohe Zhang*, Yutong Yang, Yanfang Yang, Rongxin Luo, Yunfei Shi, Jianqin Chen

Department of Anesthesiology, The First Affiliated Hospital of Dali University, Dali Yunnan

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*通讯作者。

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Abstract

Clinically, nausea and vomiting are common during cesarean section, and the incidence is even higher in patients undergoing cesarean section under spinal anesthesia. This significantly impacts surgical safety and patient comfort, and severe vomiting and aspiration can even be life-threatening. Effective prevention of perioperative nausea and vomiting in this patient population is paramount for maternal safety. Numerous studies have demonstrated the efficacy of midazolam in mitigating these symptoms during cesarean sections. Remimazolam, as a novel ultra-short-acting benzodiazepine, not only possesses the sedative, hypnotic, and anxiolytic effects of midazolam, but also overcomes the shortcomings of midazolam in terms of onset time, elimination rate, and drug accumulation. Consequently, remimazolam presents a promising alternative for preventing nausea and vomiting in cesarean section patients. This review explores the factors influencing nausea and vomiting in postpartum women undergoing cesarean sections, elucidates the mechanisms of benzodiazepines, highlights the sedative benefits of remimazolam, and proposes it as a novel strategy for managing these symptoms in this patient population.

Keywords

Remimazolam, Cesarean Section, Nausea and Vomiting, Benzodiazepines

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1. 背景

剖宫产(Cesarean section)是指通过一个开放的腹部切口和子宫切口娩出胎儿的外科手术方式。通常适用于自然分娩(顺产)有一定风险的产妇。剖宫产手术的顺利进行依赖于成熟的外科手术技术和安全的麻醉方式。而剖宫产手术麻醉方式的选择需要考虑兼顾孕妇和胎儿两者的安全,区域神经阻滞麻醉是首选的麻醉方法。椎管内麻醉是剖宫产术常用的快速、简单和安全的麻醉方法[1],该方法是通过向椎管内注入药物,达到暂时阻断神经传导作用的麻醉方式。根据注入药物的位置不同,它包含了蛛网膜下腔神经阻滞(腰麻或脊麻)、硬膜外腔神经阻滞和蛛网膜下腔-硬膜外联合神经阻滞。其中腰麻是首选麻醉方式[2]。尽管腰麻技术不断进步,但仍有相当数量的患者存在术中恶心和呕吐(Intraoperative Nausea and Vomiting, IONV)。这些症状可能会让患者感到痛苦和不舒服,并可能对他们的整体分娩体验产生负面影响[3]。由于使用的麻醉方式(腰麻、硬膜外麻醉或腰硬联合麻醉)以及采取的预防和治疗措施的差异,还有产妇术前情况的不同,椎管内麻醉下的剖宫产术中恶心呕吐(IONV)的总体发生率差异很大,最高可达 80% [3]。

2. 恶心呕吐机制及影响因素

2.1. 恶心呕吐中枢机制

恶心和呕吐的中枢神经调节属于髓质中的两个独立单位,化学感受器触发区(Chemoreceptor Trigger Zone, CTZ)和呕吐中枢[4] [5]。CTZ 位于第四脑室底部的最后区,是血脑屏障发育不良的高度血管化区域。呕吐中枢位于延髓的外侧网状结构中,在此整合了呕吐反应。呕吐中枢从胃肠道中接收了许多富含多巴胺能、毒蕈碱、色胺能、组胺和阿片受体的兴奋传入信号后,传递出信号到腹部肌肉的迷走神经、膈神经和脊神经,从而引起呕吐的机械作用。止吐药的作用机制就是阻断这些兴奋传入信号的特异性受

体[4]。

2.2. 剖宫产术恶心呕吐的影响因素

腰麻下行剖宫产术的患者发生恶心呕吐的风险较高,影响因素有多种。可以分为麻醉与非麻醉的因素。麻醉的因素包括低血压、迷走神经活动增加和神经轴或胃肠外阿片类药物给药。其中腰麻诱导后产妇低血压可引起相对脑干低氧血症,可直接触发呕吐中枢引起呕吐症状。非麻醉因素包括手术刺激、手术出血、药物(如子宫收缩剂和抗生素)以及手术结束时对病人的搬动[3][6]。除此之外还有患者自身因素,如术前饱胃、情绪过度紧张、晕动症、有术后恶心呕吐病史、不吸烟和使用阿片类药物等[7]。这些因素都可能单独或联合作用导致恶心呕吐的发生。

当剖宫产术中出现恶心呕吐时,会干扰患者、加重其紧张情绪、并给手术增加难度[8]。若术中出现恶心呕吐并持续到整个恢复期时,会降低患者的舒适度,加重紧张焦虑,延长住院时间并增加住院费用[9]。如果出现持续多次恶心呕吐,则会造成脱水、电解质紊乱、肌肉无力、心律失常等,并且会影响伤口愈合出血、增加感染风险。还有可能阻塞气道、引起窒息和吸入性肺炎甚至食管破裂的风险[10]。因此为预防剖宫产围术期出现严重的恶心呕吐,医生可以对相关危险因素进行适当的管理,同时采用止吐药物进行额外的预防[3]。

3. 苯二氮卓类药物的止吐作用

Maher [11]在 1981 年就发表文章提出了静脉注射劳拉西泮可以有效减少与化疗相关的呕吐和痛苦。Bowcock 等[12]研究表明,在预防止吐的效果上劳拉西泮和高剂量甲氧氯普胺(经典止吐药)之间无显著统计学差异,说明了劳拉西泮的止吐效果与经典止吐药的止吐效果相似。Olynyk 等[13]提出咪达唑仑已作为化疗患者有效的止吐药,这说明咪达唑仑也同样具有止吐作用。劳拉西泮与咪达唑仑同属于苯二氮卓类药物。Grunberg [14]在 1989 年提出苯二氮卓类药物在治疗与化疗相关的恶心呕吐方面无论是联合辅助用药还是单一用药都有极好的疗效。以上研究表明苯二氮卓类药物除了具有镇静催眠、抗焦虑、抗惊厥等作用外,还具有止吐作用,尤其是对于化疗患者来说。大多数研究[15]-[18]认为苯二氮卓类药物止吐的作用机制是与 γ -氨基丁酸 A 型(GABA_A)受体结合,在化学感受器触发区抑制了多巴胺的合成、释放和突触后作用,同时阻断腺苷的再摄取,导致腺苷介导的多巴胺释放减少。多巴胺是引起呕吐反应的兴奋传入信号,减少多巴胺的释放就能减少呕吐反应的发生[4]。由于担心可能发生的不良反应,包括谵妄和过度镇静导致的住院时间延长,苯二氮卓类药物尚未纳入术后恶心呕吐(postoperative nausea and vomiting, PONV)预防指南。

苯二氮卓类药物尤其是咪达唑仑,不仅可以作为化疗患者的有效止吐药,也可以对其他手术患者术中恶心呕吐(IONV)和术后恶心呕吐(PONV)有一定的作用。Rodolà [18]研究表明,咪达唑仑已经在成人和儿童中被用作止吐剂,既可以作为预防药物,也可以作为抢救药物。Unlugenc 等[19]认为咪达唑仑与和传统止吐药(昂丹司琼)相比,对 PONV 的有效作用至少是相同的,且没有不良的镇静或心血管作用。还有研究表明在预防 PONV 方面,心脏手术后持续输注咪达唑仑比静脉注射昂丹司琼更有效[20]。更重要的是,咪达唑仑还可以用作腰麻下剖宫产术中的止吐药。在术中静脉输注小剂量咪达唑仑($1\text{ mg}\cdot\text{h}^{-1}$)不仅能提供可接受的镇静和抗焦虑作用,还可以有效预防腰麻期间剖宫产产妇术中的恶心呕吐,并且静脉单次输注咪达唑仑(2 mg)比甲氧氯普胺(10 mg)更加有效[21]-[23]。小剂量静脉输注咪达唑仑既能提供止吐、抗焦虑、轻微镇静作用,又无明显的血流动力学影响和呼吸抑制,这对剖宫产手术来说不仅提高了手术的安全性,而且很大程度上提高了腰麻下剖宫产产妇的术中舒适度和满意度。然而,长期输注咪达唑仑会导致呼吸抑制,并增加术后恢复时间[24]。那么是否有一种药物,作用效果与咪达唑仑相似、满足镇静要

求的同时副作用和风险最小, 目前的研究发现新型超短效苯二氮卓类药物瑞马唑仑具有这一特性。

4. 瑞马唑仑的产生和优势

4.1. 瑞马唑仑的产生

瑞马唑仑(Remimazolam)也叫作 CNS 7056, 是近年来新研制的一种新型超短效苯二氮卓类药物。它结合了咪达唑仑和瑞芬太尼两种独特的麻醉药物的特性(图 1)。它像咪达唑仑一样选择性作用于 $GABA_A$ 受体, 又像瑞芬太尼一样超短效且具有非器官依赖性的代谢方式, 可以说它是结合了瑞芬太尼药代动力学特性的咪达唑仑[25]。瑞马唑仑在体内主要通过非器官依赖性的羧酸酯酶水解, 其水解产物 CNS 7054 与苯二氮卓类结合位点的亲和力比瑞马唑仑弱 300~400 倍, 基本无药理活性, 且能通过尿液排出体外[26] (图 2)。因此瑞马唑仑具有起效快、持续时间短、恢复快、无蓄积且肝肾功能不全者安全性高等优点。麻醉医生在使用瑞马唑仑时可以很快地调节麻醉深度和持续时间, 从而减少麻醉的恢复时间以及术后可能的不良反应。瑞马唑仑在程序性镇静、全身麻醉的诱导和维持以及 ICU 患者的镇静中具有广阔的应用前景[27]。

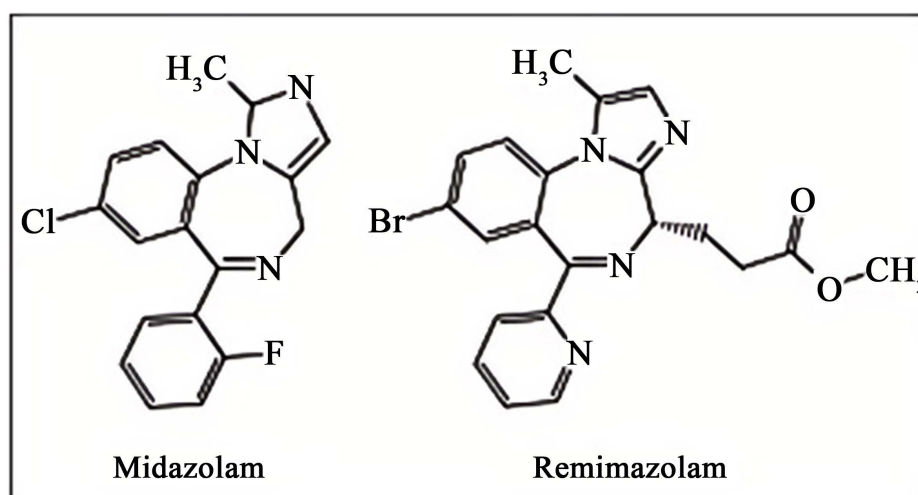


Figure 1. Structural formulas of Midazolam and Remimazolam

图 1. 咪达唑仑与瑞马唑仑的结构式

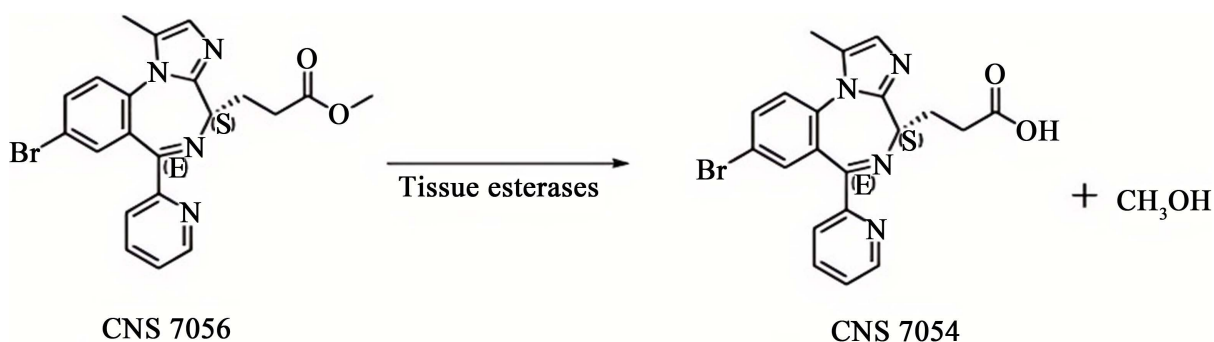


Figure 2. Remimazolam and its metabolites

图 2. 瑞马唑仑及其代谢产物

一项静脉推注瑞马唑仑的药效学分析表明, 静脉推注瑞马唑仑有明确的剂量-反应关系, 静脉给药要

达到意识丧失和呼吸抑制之间有足够的范围[28]。这就说明我们在静脉使用瑞马唑仑时,可以方便地达到所需的无意识水平,并且最大限度地减少过度镇静的风险。

4.2. 瑞马唑仑的优势

瑞马唑仑与其他常用的镇静药物相比,也有其独特的优势存在。丙泊酚作为目前使用最广泛的静脉镇静药物,一直以来都以起效快、作用持续时间短,停药后苏醒迅速,均优于其他麻醉诱导药物。而瑞马唑仑在诱导和麻醉恢复方面(拔管时间、睁眼时间和 PONV 风险)与丙泊酚相似,同时瑞马唑仑诱导后出现低血压的风险较丙泊酚低,注射痛的发生率较丙泊酚低[29],对呼吸和循环的抑制作用也较丙泊酚低[30]。瑞马唑仑因其特殊的代谢方式在体内蓄积少,还有特异性拮抗药物氟马西尼可快速逆转其作用,缩短麻醉恢复和苏醒时间,这些都是瑞马唑仑优于丙泊酚的方面。

咪达唑仑作为瑞马唑仑的前身,很多作用与瑞马唑仑相似。二者都具有镇静、催眠、抗焦虑等作用,并且对呼吸和循环的影响都比丙泊酚低。然而,咪达唑仑若持续输注或频繁推注,会在外周组织中发生蓄积,延长作用时间。有研究表明咪达唑仑的作用持续时间随患者年龄增长和肝肾功能不全而增加[31]。咪达唑仑主要通过肝脏代谢,初步代谢产物依然具有药理活性,其药理作用与咪达唑仑相似,进一步代谢后为无活性的水溶性代谢产物,从肾脏中排出。因此咪达唑仑的作用持续时间长也与其代谢方式和代谢产物在体内重新分布有关。Bauer 等[32]研究报道,即使使用了氟马西尼去拮抗咪达唑仑,咪达唑仑仍可能引起过度镇静,这是因为咪达唑仑在体内蓄积并重新分布,其代谢产物也具有相似的药理学活性,而氟马西尼的半衰期是有限的,氟马西尼药效消失后可能会出现镇静反弹。瑞马唑仑通过一级药代动力学消除,体重和消除清除率之间没有明确的关系,长期输注或大剂量输注几乎不会导致蓄积和延长效应[24](图 3)。瑞马唑仑与咪达唑仑相比,虽同为苯二氮卓类药物,但瑞马唑仑因其独特的代谢方式和具有极低药理活性的代谢产物,不仅起效和恢复时间快,长期输注无蓄积,而且在氟马西尼拮抗后,瑞马唑仑不会出现像咪达唑仑类似的镇静反跳的风险[24]。从药物代谢和麻醉恢复方面看,瑞马唑仑是优于咪达唑仑的。

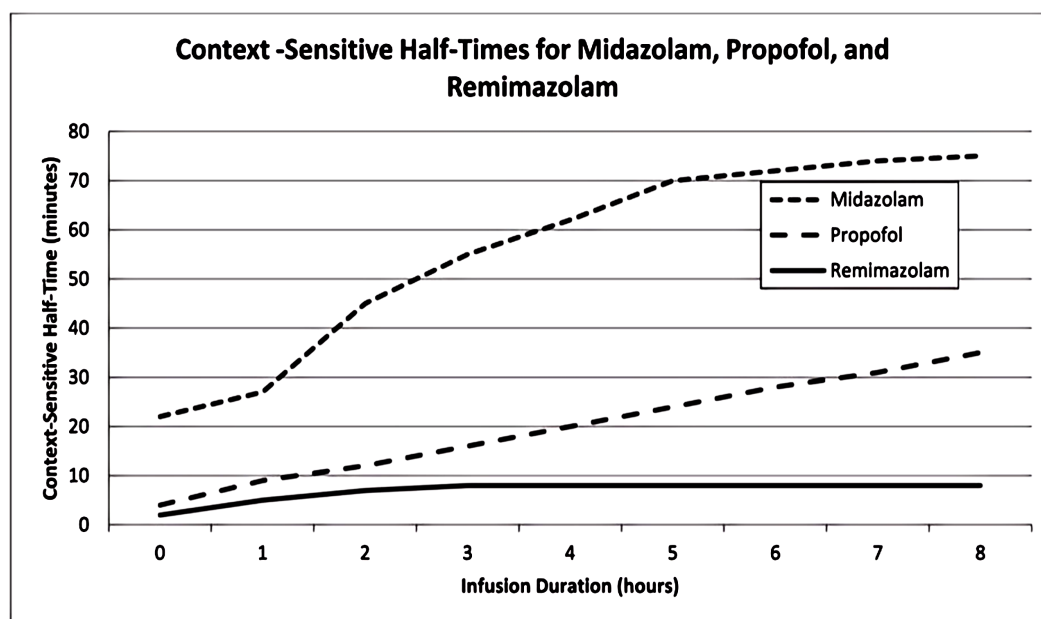


Figure 3. Comparison of the half-lives of Propofol, Midazolam and Remimazolam

图 3. 丙泊酚、咪达唑仑、瑞马唑仑半衰期对比

5. 瑞马唑仑的止吐作用

因为咪达唑仑已被证实有明确的止吐作用,那么作为咪达唑仑的衍生物,瑞马唑仑可能也具有类似的止吐效果。Hari 等人[33]对比了地氟烷和瑞马唑仑在妇科手术全身麻醉中的应用,发现使用瑞马唑仑可降低腹腔镜下妇科手术后早期 PONV 的发生率,并且瑞马唑仑组在术后早期急救止吐药的使用和恶性呕吐的评分也比地氟烷组低。但是该研究对象均为女性病人,研究结果有一定的局限性。Yoo 等人[34]将七氟烷与瑞马唑仑在腹腔镜下胆囊切除术或半结肠切除术中进行实验比较,受试者年龄横跨 20~80 岁,性别不限,结果显示,与七氟烷相比,使用瑞马唑仑进行全身麻醉维持可能会降低术后恶心呕吐的发生率,并减少腹腔镜手术后 24 小时内止吐药的使用。除此之外,还有其他研究也证实了瑞马唑仑可以降低多种手术中恶心呕吐的发生率[35][36]。虽然这些研究的目标并非以恶心呕吐为主,但在他们的观察指标中都体现出了瑞马唑仑可以降低术中恶心呕吐的发生率。说明瑞马唑仑与咪达唑仑一样具有止吐作用。

咪达唑仑可以有效预防腰麻期间剖宫产产妇术中的恶心呕吐并且止吐效果优于传统止吐药甲氧氯普胺,那么瑞马唑仑因其较小的血流动力学影响力、无器官依赖性的代谢方式以及麻醉恢复迅速的优势可能优于咪达唑仑。Lee 等人[37]研究对比了腰麻下的剖宫产患者在术中分别接受静脉注射咪达唑仑 2 mg 和瑞马唑仑 5 mg 后 IONV 的发生率,结果显示与咪达唑仑相比,瑞马唑仑显著降低了新发 IONV 的发生率和严重程度。瑞马唑仑还可以有效降低因子宫收缩剂卡前列素氨丁三醇导致的不良反应,从而降低产妇潜在的风险[38]。这不仅提高了手术的安全性与患者的舒适性,还可以帮助患者最大限度地减少额外的医疗费用。这些研究结果都证实了瑞马唑仑可以用于腰麻期间的剖宫产产妇,并且可以提供适当的镇静和有效的止吐作用。然而,目前关于瑞马唑仑对恶心呕吐的影响方面的研究有限,它是否适用于所有剖宫产患者以及用药的最佳剂量和最佳输注方式仍然不确定,瑞马唑仑在剖宫产术中的给药时机也不明确,未来仍需要更多的研究去探究瑞马唑仑在临床应用中的安全性和有效性,探索它对剖宫产患者围术期甚至更长时间的影响。

6. 瑞马唑仑在产科手术中应用的潜在风险

首先是胎盘透过性与代谢特点,瑞马唑仑可通过胎盘屏障,但因其代谢迅速,在人体内可被非器官依赖性的羧酸酯酶水解,其水解产物 CNS 7054 基本无药理活性[26],时量相关半衰期仅 7~8 分钟,在胎儿体内的药物蓄积风险较低。其次是对产妇血流动力学的影响,瑞马唑仑是苯二氮卓类药物,对循环系统有抑制作用,若产妇术中发生严重低血压,可能会间接导致胎盘灌注不足,增加胎儿缺血缺氧风险。因此,瑞马唑仑的给药剂量应尽可能小或给药时机安排在胎儿取出后。

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