

瑞马唑仑在老年患者全麻中应用的研究进展

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收稿日期: 2023年10月23日; 录用日期: 2023年11月16日; 发布日期: 2023年11月23日

摘要

当今社会老龄化进程加速, 老年人口数量剧增。由于老年患者重要器官、系统的功能衰竭, 此类患者的麻醉风险远大于其他年龄层的患者。合理地选择老年患者的麻醉用药是提高医疗安全的必要措施。瑞马唑仑是一种新型短效的苯二氮卓类镇静药, 清除度高、稳态分布体积小、消除半衰期短、起效快、组织蓄积小、镇静作用可被拮抗。临床研究证明瑞马唑仑已成功用于全麻诱导和维持时, 血流动力学更稳定; 呼吸、循环抑制作用更轻; 麻醉复苏快且复苏质量高; 并发症相对更少。本文结合老年患者的病理及生理改变和瑞马唑仑的药理学特点, 论述瑞马唑仑用于老年患者麻醉全身麻醉的现状和未来的发展趋势。

关键词

老年患者, 瑞马唑仑, 麻醉, 丙泊酚

Research Progress of Remazolam for General Anesthesia in Elderly Patients

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Received: Oct. 23rd, 2023; accepted: Nov. 16th, 2023; published: Nov. 23rd, 2023

Abstract

The aging process of today's society is accelerating, and the number of old people is soaring. Due to the failure of vital organs and systems in elderly patients, the risk of anesthesia in such patients is much greater than that in patients of other ages. Reasonable selection of anesthetic drugs for

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aged patients is a necessary measure to improve medical safety. Remazolam is a new short-acting benzodiazepine sedative with high clearance, small steady-state distribution volume, short elimination half-life, quick onset, small tissue accumulation and antagonistic sedation. Clinical studies have proved that Remazolam has been successfully used for induction and maintenance of general anesthesia, and hemodynamics is more stable. Respiratory and circulatory inhibition effect is lighter; Anesthetic resuscitation is fast and high quality; there are relatively few complications. Based on the pathological and physiological changes of elderly patients and the pharmacological characteristics of remazolam, the present situation and future development trend of remazolam for general anesthesia in elderly patients were discussed.

Keywords

Elderly Patient, Remimazolam, Anesthesia, Propofol

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1. 现状分析

当今各国均已逐渐步入老龄化社会,以我国为例,根据第七次人口普查数据显示中国的老年(>60岁)人数占比18.7%,约2.64亿人[1][2]。相较于其他年龄层的患者而言,老年人群重要器官和系统功能衰退,实施麻醉和手术发生不良反应的风险更高[3]。在一项包含6644例大于60岁的老年患者的研究中发现,老年患者接受深度全身麻醉时3级不良反应发生率约29%,4级不良反应发生率约为8%,远大于其他年龄层的患者[4][5]。这一现象归因于老年患者特殊的病理、生理改变。第一,老年人群循环系统比较脆弱,心脏收缩及舒张功能障碍、心泵功能减弱、血管弹性下降。第二,老年患者慢阻肺、肺气肿、慢性支气管炎等慢性呼吸系统疾病发病率高、肺功能差。第三,由于老年患者肝、肾功能衰退,故依赖肝、肾代谢的药物作用时间延长。第四,老年患者脑血流量及脑血管自我调节能力下降、血脑屏障通透性增加、神经系统退行性变等。由于这些特殊的改变,老年患者围手术期易出现剧烈的循环波动、低氧血症和呼吸衰竭、苏醒延迟、心脑血管意外事件等并发症,严重威胁到了老年患者的医疗安全。如何为老年患者制定一个安全、有效的麻醉方案将面临着极大的挑战,而选择合适的麻醉药是其中关键的一环。

目前老年患者全麻用药大致分为两类,分别是以丙泊酚为代表的静脉麻醉药和以七氟烷为代表的吸入麻醉药。丙泊酚由于其短效、快速的镇静作用而被广泛用于临床麻醉以及重症患者的镇静,也是插管全麻和非插管全麻的首选麻醉药。丙泊酚呈剂量依赖性的抑制循环和呼吸功能,有研究表明丙泊酚和瑞马唑仑分别用于胃镜检查镇静时,丙泊酚组出现镇静性低血压的比例(41.11%)明显高于瑞马唑仑组(1.20%),且丙泊酚组呼吸抑制发生率(17.78%)明显高于瑞马唑仑组(0例)[6]。也有研究表明丙泊酚用于全麻诱导时,出现低血压(平均压 < 55 mmHg)的概率高达22.6%,且发生低血压的概率与丙泊酚的使用剂量成正相关性[7]。而吸入麻醉药用于老年患者亦非最佳选择,研究表明吸入麻醉药与患者发生术后认知功能障碍相关,这一现象在老年患者中更为突出[8]。其机制可能与七氟烷激活PI3K/AKT通路调节海马神经元的凋亡以及诱导神经元炎症相关[9][10]。也有学者认为是由氟烷通过诱导脑内铁过载从而引发线粒体功能障碍引起的[11]。还有研究报道了地氟烷和七氟烷与患者术后呼吸道并发症高度相关,且并发症的发生随年龄增加而增加[12]。此外,最近的一项研究还发现,以七氟烷为主的吸入麻醉药导致患者肾排泄量减少以及血浆肾素升高[13]。由此可见,为进一步优化老年患者的舒适化就医体验和保障患者安全,

有必要研究新的麻醉用药。瑞马唑仑是一种新型的、短效的苯二氮卓类药物, 其镇静作用强、起效快、消除快、无呼吸及循环抑制作用、耐受性好, 在老年患者全麻中应用的有效性和安全性已得到初步验证[14]。

2. 瑞马唑仑的药理学及药代学特征

苯磺酸瑞马唑仑是一种新型的苯二氮卓类受体激动剂, 可以被非特异性组织酯酶迅速降解为无活性的水溶性羧酸代谢物[15] [16]。其代谢产物主要经肾脏排泄, 其中 80%为一级代谢产物, 原型不足 1% [17]。瑞马唑仑可增强 GABA_A 受体活性, 介导神经元细胞膜上氯离子内流引起超极化从而抑制神经活动, 可用于镇静及全身麻醉的诱导和维持。瑞马唑仑的药学特点是清除度高、稳态分布体积小、消除半衰期短、起效快、组织蓄积小、镇静作用可被拮抗(特效拮抗剂为氟马西尼); 研究证明, 瑞马唑仑具有更高的安全性, 对呼吸、循环的抑制轻, 注射疼痛的低易感性[18] [19] [20]。尽管瑞马唑仑的代谢途经肝、肾等重要器官, 但仍可用于肝、肾功能受损患者的麻醉。肝功能受损患者静脉注射瑞马唑仑后, 在不使用拮抗剂的情况下, 除了苏醒时间略延长外未见其他不良反应; 而肾功能受损患者与健康志愿者注射瑞马唑仑后相比无差异, 患者使用瑞马唑仑后未显示肝、肾损害进一步加重[21]。结合瑞马唑仑的药效学、药动学特点与老年患者的生理、病理改变, 研究瑞马唑仑用于老年患者全身麻醉具有广阔的前景。

3. 瑞马唑仑相关的器官、系统功能的影响

3.1. 瑞马唑仑对老年患者循环系统的影响

自瑞马唑仑面世以来, 经过多中心研究已经证明了其用于衰弱患者(ASA III 级)的全麻诱导和维持的有效性和安全性, 且麻醉相关的不良反应发生率明显低于丙泊酚[14] [22] [23] [24]。有研究证明, 瑞马唑仑被用于老年患者心脏瓣膜置换手术的麻醉诱导时, 诱导前后的血压变化、需要血管活性药物的剂量和给药次数均小于丙泊酚[25] [26] [27]。可见瑞马唑仑用于心功能减退的患者行术时, 对循环的抑制作用也较轻。这一现象可能与瑞马唑仑维持交感、副交感神经活动的平衡有关[28]。此外, 也有报道提示瑞马唑仑有助于维持心律失常患者麻醉时的循环稳定, 但缺乏更多的临床实验证明该结论[29]。也有报道称, 超高龄患者(年龄分别为 95 岁和 103 岁)以瑞马唑仑行全麻诱导和维持, 联合芬太尼和瑞芬太尼镇痛, 术中仅需小剂量升压药维持即可获得平稳的血流动力学, 术后苏醒完全、平稳且无并发症; 该报道认为瑞马唑仑可用于全身麻醉, 尤其适用于高龄患者, 但应根据镇静指数和生命体征仔细地调整麻醉诱导和维持的剂量[30]。与吸入麻醉药相比, 瑞马唑仑同样具有更好的血流动力学稳定性[31] [32]。由此可见, 以瑞马唑仑为主的静脉麻醉, 对循环系统的抑制轻, 有利于保护老年患者脆弱的循环系统, 从而降低围手术期不良事件的发生率。同时, 稳定的循环保证了重要器官的血供, 对保护重要器官功能有至关重要的作用, 也为高质量的麻醉苏醒奠定了良好的基础。

3.2. 瑞马唑仑对老年患者肝、肾功能的影响

老年患者肝、肾功能较为脆弱, 术中用药极有可能加重其负担从而诱发术后肝、肾功能衰竭。在一项包含肝损伤、肾损伤各 11 例及健康志愿者 21 例的研究中发现, 在不使用拮抗剂的前提下, 应用瑞马唑仑后肝损伤患者较健康志愿者仅仅苏醒时间随肝损伤程度增加而轻微延长, 而肾损伤患者则无任何影响, 且未见肝肾功能损伤进一步加重[21]。目前, 已有瑞马唑仑用于肝硬化患者全麻下行内镜静脉曲张结扎术的先例[33]。研究证明, 以瑞马唑仑和丙泊酚为接受内镜下食管静脉曲张的肝硬化患者提供麻醉时, 两组患者均能获得满意的麻醉效果, 且瑞马唑仑组的患者在以氟马西尼拮抗后显示出更快的苏醒时间和拔管时间、复苏室停留时间, 低血压和术中、术后低氧血症发生率也低于丙泊酚组[34]。近期, 一例病例

报道了关于瑞马唑仑用于 Child-Pugh B 型肝硬化患者在腹腔镜胆囊切除术, 也证实了瑞马唑仑在严重的肝功能受损患者中应用的安全性[35]。显而易见的是, 尽管瑞马唑仑代谢需要肝脏羧酸酯酶, 但并不会对肝功能造成损伤, 甚至在肝功能障碍的患者中应用的安全性也得到了初步验证, 但仍需要更多的临床实验和数据支持该观点。此外, 体外肝细胞培养实验也证明, 暴露于瑞马唑仑溶液中对肝细胞的完整性和代谢活性没有损害, 且瑞马唑仑在肝细胞中的代谢很稳定[36]。动物实验还发现瑞马唑仑可减弱脓毒症导致的急性肝损伤, 其机制可能与瑞马唑仑抑制巨噬细胞 p38 磷酸化有关[37]。可见瑞马唑仑在肝功能障碍的患者中应用也是安全的、有效的。但目前类似研究的对象尚缺乏老年患者, 需要更多临床实验予以证实这些观点。但可以遇见得到瑞马唑仑不损伤肝肾功, 且镇静作用可被氟马西尼特异性拮抗, 可以保证肝肾功能衰退的老年患者术后苏醒快速、完全, 有效减少围手术期并发症, 保证老年患者医疗安全。

4. 瑞马唑仑用于老年患者插管全麻的效果观察

插管全麻是指需要建立人工气道用于通气的一种麻醉方式, 通常用于手术室内实施手术时的镇静。此类麻醉往往时间较长, 麻醉药物用量大、易蓄积, 手术创伤大, 对患者生理功能影响大。老年患者接受插管全麻时, 围手术期并发症往往高于其他年龄层的患者, 例如术中知晓、拔管后呼吸抑制、顽固性低血压、苏醒延迟、术后躁动、术后认知功能障碍、恶心、呕吐等, 这些并发症严重威胁着老年患者的医疗安全。研究表明, 使用瑞马唑仑行全麻诱导和维持可以获得更好的苏醒质量, 且围手术期循环稳定性、入复苏室时的安静程度、术后镇痛药的需求量等指标均优于丙泊酚[38]。瑞马唑仑和丙泊酚在老年髋关节置换术中的效果观察还发现, 当两组患者镇静效果和镇痛强度相当时, 瑞马唑仑对呼吸及循环抑制、认知功能恢复更好、安全性更好[39]。不仅如此, 该实验还发现瑞马唑仑对于创伤应激反应有抑制作用。与此类似的是, 瑞马唑仑用于心脏手术的麻醉也可以更好的抑制全身炎症反应和应激反应, 其机制可能与瑞马唑仑激活肾上腺素受体和抑制细胞核因子 B 有关; 同时该研究还发现瑞马唑仑组患者术后苏醒时间和带管时间均短于丙泊酚组, 这归功于瑞马唑仑可被氟马西尼拮抗的特点, 也得益于瑞马唑仑维持了良好的循环, 从而保证了重要器官的氧供需平衡[40]。在动物实验中还发现, 瑞马唑仑对老年小鼠的认知功能没有造成长期损害, 甚至在一定程度上延缓了记忆功能的衰退[41]。这种神经保护机制能否预防老年患者术后认知功能障碍, 尚需要进一步的实验证明该观点。在吸入麻醉与瑞马唑仑麻醉进行对比时发现类似的结果, 瑞马唑仑用于全麻下行腹腔镜手术的患者中, 瑞马唑仑组的苏醒评分显著高于地氟醚组, 且瑞马唑仑组的术后恶心呕吐发生率更低[32][42]。这可能归因于瑞马唑仑用于老年患者全麻时保证了重要脏器的血液和氧供应, 对保护心、脑等重要器官的功能至关重要。老年患者的全麻苏醒质量与体温也有紧密关系, 术中低体温会导致术后苏醒延迟、凝血功能障碍、出血、诱发心律失常等麻醉相关并发症[43]。研究表明, 瑞马唑仑可以更好地控制体温, 其原因可能是瑞马唑仑降低了血管收缩的阈值, 血管收缩的时间提前, 从而更好的调节体温[44]。这些研究结果证明了瑞马唑仑用于老年患者的插管全麻时, 表现出更短的苏醒时间、更好的苏醒质量, 更稳定的循环、更合适的体温等, 有效减少老年患者围手术期并发症的发生率, 充分保障了老年患者的医疗安全。

5. 瑞马唑仑用于老年患者非插管全麻的效果观察

非插管全麻是指保留自主呼吸与部分保护性反射的全身麻醉。临床麻醉工作中, 实施不插管全麻的操作或手术主要包括胃肠镜检查、支气管镜检查、宫腔镜检查及人流手术、肿瘤射频消融术、不配合的无创检查(如 CT、MRI、眼科检查等)、短小的有创检查或操作等。非插管全麻的难点在于麻醉深度的掌握, 如何让患者感到舒适且配合术者需要又不至于影响患者医疗安全。老年患者往往合并严重的心、肺疾病, 器官功能衰退, 麻醉药对老年患者循环和呼吸的影响相较于其他年龄层的患者更为明显且难以纠

正。目前常用于非插管全麻的药物主要有丙泊酚、咪达唑仑、右美托咪定等, 不同的药物各有利弊。瑞马唑仑最早是作为胃、肠镜患者的全麻用药的选择之一。美国一项包含 461 位患者的多中心研究显示, 分别以瑞马唑仑、安慰剂、咪唑安定静脉注射并复合芬太尼后行结肠镜检查, 检查完成率分别是 91.3%、1.7%和 25.2%, 其中瑞马唑仑组患者苏醒更快、低血压发生率较低、无严重不良反应; 相比于安慰剂组, 瑞马唑仑和咪唑安定组低氧血症发生率仅约 1% [45]。可见瑞马唑仑与咪唑安定相比, 具有相同的有效性, 但瑞马唑仑代谢更快、更完全、镇静效果更好。也有一项包含 346 例老年患者的研究表明, 以瑞马唑仑为接受胃镜检查术的老年患者提供麻醉时发现, 与异丙酚组相比, 瑞马唑仑组呼吸抑制发生率显著降低, 但需要稍长一点的起效时间; 而异丙酚组低血压发生率、注射疼痛的发生率和严重程度高于瑞马唑仑组; 两组在镇静成功率、准备出院时间、内窥镜医师和麻醉师满意度及其他镇静相关不良事件方面无统计学差异[46]。瑞马唑仑也成功用于纤维支气管镜检查术的麻醉。行纤维支气管镜检查术的患者通常合并肺部感染、肺气肿、肺不张、气道狭窄、支气管扩张、肿瘤、结核等疾病, 老年患者尤甚。且术者与麻醉医生共用气道, 术中呼吸管理难度更大。目前常用于此类患者的麻醉药有丙泊酚、咪唑安定、右美托咪定等。相比丙泊酚、咪唑安定、右美托咪定等, 瑞马唑仑成功率高, 且起效快、苏醒快、苏醒质量高血流动力学稳定性更好, 呼吸抑制更轻; 而患者的配合程度、低氧血症发生率、咳嗽、患者满意度等无统计学差异[47] [48]。由此可见, 瑞马唑仑用于老年患者的非插管全麻是有效的、可靠的、安全的。瑞马唑仑相关的血流动力学稳定性、苏醒时间、复苏室停留时间、呼吸抑制发生率等优于传统麻醉用药。因此, 瑞马唑仑适合用于老年患者非插管全麻。但仍需注意的是, 尽管瑞马唑仑呼吸抑制不明显, 但镇静相关的睡眠呼吸暂停依旧威胁着患者的医疗安全[49]。目前针对老年患者这个特殊群体的类似的临床研究较少, 需要更多研究测算出最佳的用药剂量并观察临床效果及不良反应发生情况和应对措施。

6. 总结与展望

老年患者由于其特殊的生理、病理改变, 在全麻中需要保证更高质量的麻醉。瑞马唑仑用于老年患者的插管和非插管全麻其有效性和安全性已被证实, 麻醉质量更高, 主要体现在以下几个方面。第一, 瑞马唑仑用于老年患者全麻时, 可以为这类患者提供足够的镇静深度, 目前尚未见到与瑞马唑仑相关的术中知晓报道, 这归功于大部分研究都使用了 BIS 监测以确保患者处于足够的麻醉深度, 其次可能与苯二氮卓类镇静药通常具有顺行性遗忘作用有关, 但缺乏针对性研究予以证实。第二, 瑞马唑仑用于老年患者全身麻醉的诱导和维持, 血流动力学更稳定, 这得益于瑞马唑仑平衡交感神经和副交感神经的作用, 可以更好地保障老年患者围手术期的循环稳定和重要器官的血供和氧供, 为更好的苏醒质量奠定基础。第三, 尽管瑞马唑仑的代谢依靠肝、肾等重要脏器, 但不损害其功能; 此外, 瑞马唑仑持续输注无蓄积、苏醒快、苏醒质量更高、抑制应激反应等, 即使在肝、肾功能受损患者中应用也未见不良反应, 对预防老年患者围手术期的麻醉相关并发症和保护重要脏器功能具有积极作用。第四, 从现有研究不难看出瑞马唑仑用于老年患者的全麻时, 有效降低了围手术期并发症发生率, 有效减少了术后并发症, 诸如术后认知功能障碍、恶心、呕吐等。第五, 瑞马唑仑用于老年患者的胃镜、肠镜、支气管镜、宫腔镜等检查时的非插管全麻, 其血流动力学稳定性、苏醒时间、离院时间均有优势; 其次, 瑞马唑仑镇静作用可被氟马西尼拮抗, 可控性更好, 在契合了门诊检查短、频、快特点的前提下, 也有效地保证了老年患者的医疗安全。

尽管从现有研究来看, 瑞马唑仑用于老年患者的全麻是安全有效的, 但实际应用中仍旧观察到一些不良事件需要高度警惕, 诸如过敏、沉淀等[50] [51]。有病例报道瑞马唑仑诱导期间出现严重过敏反应, 主要表现为严重低血压、低血氧、心脏骤停[50] [52] [53] [54]。因此有学者针对瑞马唑仑在老年患者中的应用启动了更多的临床实验, 试图观察瑞马唑仑的最佳剂量和不良反应发生情况并制定相应对策, 更好

地保障老年患者医疗安全[55] [56]。其次, 瑞马唑仑除了用于全麻以外, 也可用于区域神经阻滞中辅助镇静。接受神经阻滞麻醉的患者意识清醒, 考虑到患者对陌生环境及手术恐惧, 因此麻醉医生通常会辅助镇静。瑞马唑仑具有镇静、抗焦虑、顺行性遗忘作用, 可作为辅助镇静药用于此类患者。目前已有研究证明, 接受了蛛网膜下腔神经阻滞的老年患者使用瑞马唑仑辅助镇静时, 循环、呼吸不被抑制, 苏醒快速, 无不良反应发生[57]。也有研究证明了瑞马唑仑用于重症监护室内长期带管的患者镇静效果与丙泊酚相当, 带管天数、住院时间、死亡率没有统计学差异, 显示了瑞马唑仑在重症患者镇静中应用的可能, 但该研究样本量较小, 需要扩大样本量进一步研究证实[58]。总体来讲, 从目前研究可以看出, 瑞马唑仑用于全麻或是辅助镇静, 都具有广阔的前景, 尤其针对老年患者这一特殊群体, 但需要更多的实验观察该药物实际临床效果和不良反应, 以及制定相应的应对策略, 以提高老年患者的舒适化就医体验和医疗安全。

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