

右美托咪啶用于老年患者全身麻醉中的研究进展

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收稿日期: 2024年2月18日; 录用日期: 2024年3月12日; 发布日期: 2024年3月18日

摘 要

右美托咪啶是一种高选择性 α_2 肾上腺素能受体激动剂, 具有镇静、抗焦虑和抗交感神经以及稳定血流动力学的作用, 并且不会对患者呼吸造成明显的影响而广泛用于围麻醉期的各个阶段。老年手术患者, 因其年龄大、自主神经系统发生退行性改变, 且有较多合并症, 给予右美托咪啶麻醉时可有效减缓肠蠕动, 并对各种术后症状进行预防, 较好地保护了患者的心脑血管, 降低了心脑血管不良事件发生率, 稳定了患者的血流动力学。与传统阿片类药物相比, 右美托咪啶的安全性和有效性更高, 本研究就右美托咪啶在老年患者麻醉中的优势和具体内容进行综述。

关键词

右美托咪啶, 老年患者, 全身麻醉, 研究进展

Research Progress in the Use of Dexmedetomidine for General Anesthesia in Elderly Patients

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Received: Feb. 18th, 2024; accepted: Mar. 12th, 2024; published: Mar. 18th, 2024

Abstract

Dexmedetomidine is a highly selective α_2 -adrenergic agonist with sedative, anxiolytic, and anti-sympathetic properties as well as hemodynamic stabilization, and is widely used in all phases of

the perianesthesia period without significant effects on patient respiration. In elderly surgical patients, because of their age, degenerative changes in the autonomic nervous system and more comorbidities, dexmedetomidine anesthesia can effectively slow down intestinal motility and prevent various postoperative symptoms, better protect patients' cardiovascular and cerebrovascular, reduce the incidence of cardiovascular and cerebrovascular adverse events, and stabilize patients' hemodynamics. Compared with traditional opioids, dexmedetomidine is safer and more effective. This study reviews the advantages and specifics of dexmedetomidine in the anesthesia of elderly patients.

Keywords

Dexmedetomidine, Elderly Patients, General Anesthesia, Research Progress

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1. 引言

随着我国老年人口的迅速增长, 需要进行手术的高龄患者的比例也不断增高。老年人的自主神经系统发生退行性改变, 对靶器官的调节能力下降, 且有较多合并症, 老年人生理储备下降或多种功能异常致使机体易损性增加、抗应激能力减退, 并对手术治疗科学性和有效性提出了更高且严苛的要求。右美托咪定是一种高选择性的 α_2 -肾上腺素能受体激动剂, 具有镇静、镇痛、交感神经溶解和抗焦虑的特性[1]。它被广泛用作围手术期的麻醉辅助剂和重症监护室的镇静剂。以前的研究报告称, 与其他镇静剂相比, 右美托咪定可能与术后谵妄的发生率较低有关[2], 防止在重症监护室出现谵妄[3], 减弱术中应激反应[4], 并降低术后死亡率达 1 年之久[5], 右美托咪定具有独特的作用机制, 具有镇静、缓解焦虑和止痛作用, 而不会导致呼吸抑制, 此外, 右美托咪定改善危重患者的睡眠质量, 主要类似于非快速眼动睡眠模式。作为一种 α_2 肾上腺素能受体激动剂, 它也被证明具有显著的阿片类药物非依赖性作用。此外, 右美托咪定缺乏临床上显著的抗胆碱能作用, 已被证明可以减轻 CP1B 的炎症反应。所有这些独特的特性的结合可能有助于减少 POD 的发生率和持续时间。因此, 在心脏手术后围手术期应用右美托咪定也与降低死亡率有关, 这并不令人惊讶。近年来, 越来越多的相关医学研究报道显示, 盐酸右美托咪定能够对交感神经兴奋性进行抑制, 促进迷走神经兴奋性的增强, 其药理特性包括促进心率减慢、血压及心肌氧耗降低、镇静镇痛等, 故对患者的自主呼吸具有较轻的影响。本研究通过收集、整理相关文献, 就右美托咪定用于老年患者麻醉的研究进展进行了总结和归纳, 现报告如下。

2. 右美托咪定药理特性及进展

右美托咪定是一种 α_2 -肾上腺素受体激动剂, 具有镇静、抗焦虑、交感神经溶解和镇痛的作用, 对呼吸功能的抑制最小。它对 α_2 受体具有强效和高度选择性, $\alpha_2:\alpha_1$ 的比例为 1620:1。血液动力学效应包括短暂的高血压、心动过缓和低血压, 是由于该药的外周血管收缩和交感神经溶解特性所致。右美托咪定通过激活脑室中枢突触前和突触后的 α_2 受体来发挥其催眠作用, 从而诱发一种类似于自然睡眠的无意识状态, 产生自然的、“可唤醒”的睡眠[6] [7] [8] [9] [10], 其独特之处在于病人仍然容易振作和合作。右美托咪定分布迅速, 主要通过葡萄糖醛酸化和羟化作用被肝脏代谢为非活性代谢物。现有证据表明, 围手术期应用右美托咪定可以抑制应激反应, 降低各种应激调节剂, 即儿茶酚胺和皮质醇的浓度, 从而在

手术或麻醉诱导等应激事件期间产生更稳定的血流动力学曲线[11][12][13]。它以剂量依赖的方式减少中枢神经系统(CNS)的交感神经外流,其镇痛效果被描述为节省阿片类药物。越来越多的证据表明,它对缺血和缺氧损伤具有器官保护作用,包括心脏保护、神经保护和肾脏保护[14]。

3. 右美托咪啶应用于麻醉

3.1. 右美托咪啶给药方式和剂量问题

右美托咪啶可以通过静脉、肌肉、皮下、鼻、颊、直肠和口腔等途径给药[15],右美托咪啶口服时生物利用度较差(约 15%),鼻内血管丰富,药物通透性好,其简单方便、非侵入性、可降低首过效应。由于它是一种镇静剂、抗焦虑剂、镇痛剂、交感神经溶解剂,并且具有稳定的血流动力学,右美托咪啶被用于预处理。它可以减少术中(达 8%)和术后(达 17%)的氧气消耗[16]。术前剂量为 0.33~0.67 微克/公斤静脉注射或 2.5 微克/公斤肌肉注射,在术前 15 分钟给予。当术中使用较低的浓度时,对其他麻醉剂的需求就会减少。治疗心动过速所需的干预措施较少。心肌缺血的发生率也会减少。然而,像低血压和心动过缓的副作用可能会发生,需要干预。在年龄超过 65 岁的病人中,观察到在服用右美托咪啶后,心动过缓和低血压的发生率较高。因此需要减少剂量,并应监测肾功能。

3.2. 右美托咪啶在老年手术患者区域麻醉中的应用

右美托咪啶具有高度的亲脂性,因此在神经组织中迅速分布,在神经轴上使用,通过与脊髓背角的 α -2 受体结合而产生抗痛作用[17]。硬膜外右美托咪啶作为局麻药的辅助剂,延长了感觉和运动阻滞的时间,运动阻滞更强烈,术后镇痛效果好[18]。硬膜外右美托咪啶作为局麻药的辅助药与全身麻醉一起使用,显示出降低术中麻醉需求,改善氧合和延长术后镇痛[19]。在硬膜外麻醉中,右美托咪啶作为罗哌卡因的辅助药物,与氯尼丁和芬太尼相比,效果更好[20][21]。在局麻药中加入右美托咪啶,可以增强感觉阻滞,产生更强烈的运动阻滞,延长术后镇痛时间,因此可以减少局麻药的使用剂量。在外周神经阻滞中,右美托咪啶与局麻药一起使用时,也显示出其延长感觉阻滞时间和延长术后镇痛的功效。动物研究已经验证了直接应用于神经模型时没有神经毒性[22][23]。此外,在锁骨上臂丛神经阻滞等外周神经阻滞中,右美托咪啶作为局麻药的辅助剂与氯尼丁进行了比较,发现右美托咪啶可以延长感觉和运动阻滞的时间,并延长了对解救镇痛剂的需求[24]。在静脉区域阻滞中,将右美托咪啶添加到利多卡因中,已被证明可以提高阻滞质量,减少止血带疼痛,并延长术后镇痛时间,且副作用最小[25][26]。

3.3. 右美托咪啶在老年手术患者全麻中的应用

由于右美托咪啶具有抗焦虑、镇痛、交感神经溶解和镇静的作用,它已被发现应用于预处理、预防喉镜检查的应激反应和预防出现谵妄的情况。右美托咪啶对血压的影响是双相的,由于刺激血管平滑肌中的 α -2B 亚型受体,最初会出现短暂的血压上升和心率反射性下降。随后血压和心率下降,这是由于抑制了中枢交感神经的流出,刺激突触前的 α -2 受体导致去甲肾上腺素的释放减少,从而导致血压进一步下降。[27][28]然而,这些血流动力学效应在有固定卒中量的病人、使用降速药物如 β 受体阻滞剂、洋地黄等的病人以及低血容量的病人中可能是有害的。右美托咪啶会导致脑血流和脑氧代谢需求的减少,同时颅内压也略有下降。它通过减少循环和大脑中的儿茶酚胺而具有神经保护作用;因此,减少了兴奋性,改善了缺血脑组织的血液供应。它还能降低谷氨酸的水平,而谷氨酸被发现能增强细胞的脑损伤,特别是在蛛网膜下腔出血中[29]。右美托咪啶对呼吸功能没有任何抑制作用,即使在较高的剂量下也不会损害通气或气体交换;但可能产生轻度高碳酸血症。

3.4. 右美托咪定在老龄手术患者麻醉期间的应用

机体在围麻醉期的应激反应强烈, 发生这一现象的原因为留置气管导管、疼痛等, 导致患者具有较快的心率、较高的血压计不平衡的心肌氧供需。一方面促进了高血压高龄患者心血管意外等并发症发生的显著增加, 如心律失常、心肌缺血等; 另一方面也进一步提升了没有基础疾病的高龄患者心血管意外等并发症的发生风险。右美托咪定由于其交感神经的作用, 可以减弱对喉镜检查和高动力反应, 并保持稳定的血液动力学状态[30] [31]。它还被发现能增强所有麻醉剂(即静脉注射和吸入)的作用, 并具有阿片类药物的节约作用, 从而减少所需的剂量[32] [33] [34] [35], 它还能帮助减少身体的氧气需求, 并有助于预防术中心肌缺血[36] [37]。据报道, 右美托咪定可以减少七氟醚麻醉中对罗库仑的需求, 这种效果可能是由于右美托咪定改变了罗库仑的药代动力学[38]。最近, 右美托咪定被用于帮助因上呼吸道解剖扭曲和感染而导致气道受损的病人进行清醒的光纤插管。它提供了良好的镇静和镇痛效果, 几乎没有呼吸抑制, 也不影响气道反射, 使病人保持平静, 并将吸入的机会降到最低[39] [40] [41]。最近, 它被用于清醒光纤插管, 没有对上呼吸道进行局部麻醉, 作为唯一的镇静剂, 用于记录对局部麻醉剂过敏的病人[42]。右美托咪定既有交感神经的作用, 又有麻醉剂的作用, 这使它成为诱导和维持各种手术中可控低血压的理想工具, 可以最大限度地减少失血, 并为脊柱融合手术、鼻内窥镜手术、鼻窦手术和颌面手术提供最佳条件[43] [44]。

3.5. 右美托咪啉用于困难气道

众所周知, 对气道困难的病人进行清醒的光纤插管会引起不适。这个问题是有问题的, 因为麻醉师希望通过自发的通气来维持一个通畅的气道, 以避免呼吸抑制和肺部吸入的并发症。然而, 病人在手术过程中必须有足够的舒适感。许多药物已被描述为促进这一过程, 包括苯二氮卓类药物、局部麻醉剂输注和阿片类激动剂。右美托咪啉为这个问题提供了一个理想的解决方案, 除了为麻醉师创造一个干燥的场地, 因为它是一种抗异物癖。在最近对 7 名使用右美托咪啉和口咽局部麻醉剂进行静脉镇静的病人的调查中[45], 没有病人出现饱和度变化, 所有病人都成功进行了光纤插管, 没有病人出现任何呼吸抑制的潮末二氧化碳证据[46]。

3.6. 右美托咪啉对老年患者术后谵妄与认知功能障碍的影响

麻醉后认知功能障碍是术后精神障碍的常见临床表现, 目前已逐渐成为人们关注的焦点[47] [48]。这通常发生在心脏手术、髋关节置换术、下颌骨骨折和其他主要手术之后[49]。表现为记忆障碍、抽象思维和麻醉后的迷失方向, 同时伴有社交活动减少(即性格、社交技能、认知能力和技能的变化)。据报道, 术前应用右美托咪啉镇静可降低术后急性谵妄的发生率。右美托咪啉以剂量依赖的方式减少脑血流量。然而, CO_2 反应性和脑血管的自动调节保持不变。动物实验表明右美托咪啉对大脑有保护作用。它作用于 $\alpha_2\text{A}$ 受体, 减少围手术期兴奋性毒素引起的灰质和白质损伤面积。对于缺乏 $\alpha_2\text{A}$ 受体的大鼠, 右美托咪啉不能保护白质免受损伤。此外, 白质病变相对严重。就局部效应而言, 在全脑缺血和缺血/再灌注后, 右美托咪啉可以提高神经细胞的存活率。脑保护作用的机制可以概括为: 脑组织中去甲肾上腺素释放的减少, 凋亡蛋白和抗凋亡蛋白的平衡的调节, 脑中兴奋性神经递质释放的减少、热休克蛋白 27 的磷酸化和脑组织中 caspase-3 表达的减少, 细胞外信号调节蛋白激酶 1/2 的激活产生神经保护作用。此外, 据报道, 术前使用右美托咪啉镇静也可降低术后急性谵妄的发生率[50]。然而, 目前尚无关于右美托咪啉对老年患者术后认知功能影响的研究报道。

4. 结论

右美托咪啉是一种强效、高选择性的 α_2 肾上腺素能受体激动剂, 具有镇静、镇痛、抗焦虑、抗交

感神经和阿片类药物的特性。它提供了一种独特的镇静类型, 即“清醒镇静”, 患者看起来很困, 但在受到刺激时很容易被唤醒、合作和交流。它起效快, 起效时间相对短, 其特点使右美托咪定适合重症监护室、术后心脏病和非心脏病患者以及侵入性和非侵入性手术, 因为它可以很容易地滴定。一些研究表明, 短期镇静是安全的, 尽管低血压和心动过缓是最显著的副作用。此外, 它似乎具有最小的呼吸抑制, 因此, 它可以安全地用于机械通气和自然呼吸患者。这些特性使右美托咪定成为当前早期拔管和术后心脏病患者快速追踪的有效药物。总的来说, 右美托咪定具有独特的性质, 使其成为麻醉医生和重症监护医生的理想药物。它是一种优秀的镇静和镇痛剂, 具有阿片类药物的保留特性和最小的呼吸抑制; 不会降低肠动力; 防止术后恶心、呕吐和颤抖; 同时, 对神经保护、心脏保护和肾脏保护具有潜在的益处。如上所述, 它可以被广泛使用, 同时需要在使用过程中保持警惕。可考虑使用术中右美托咪定作为老年手术后增强恢复的总体策略的一部分是有必要的。

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