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Hans汉斯

延长周围神经阻滞时间的研究进展

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摘　要

严重的术后疼痛会使患者感到焦虑紧张、睡眠不足甚至影响术后恢复。全身应用阿片类药物是当前的主要镇痛手段，但其副作用(如恶心、呕吐、便秘和呼吸抑制等)会增加患者的不适，延缓患者的恢复时间。相比之下，区域阻滞技术因其副作用少，镇痛效果显著，逐渐成为围术期疼痛管理的重要方法。然而，目前常用的长效局麻药物如罗哌卡因和布比卡因，单次注射的镇痛时间有限，难以满足术后镇痛的需求。为延长区域阻滞的作用时间，研究者提出了多种策略，包括使用连续外周神经阻滞；添加右美托咪定、地塞米松等佐剂；创新药物输送系统和应用纳米技术等为延长局麻药的镇痛时间提供了新方向。本文综述了这些前沿技术的最新研究进展，以期为临床应用提供参考。

关键词

术后镇痛，局部麻醉药，周围神经阻滞，镇痛时间

Research Progress on Prolonging the Duration of Peripheral Nerve Block

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Abstract

Severe postoperative pain can cause anxiety, sleep disturbances, and even affect postoperative recovery. Systemic opioid administration is the primary method for pain relief, but its side effects, such as nausea, vomiting, constipation, and respiratory depression, can increase patient discomfort and delay recovery. In contrast, regional block techniques, due to their fewer side effects and significant analgesic effects, have gradually become an important method for perioperative pain management. How-

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ever, commonly used long-acting local anesthetics, such as ropivacaine and bupivacaine, have limited analgesic duration with a single injection, making them insufficient to meet the needs for postoperative pain control. To extend the duration of regional block, various strategies have been proposed, including the use of continuous peripheral nerve blocks, the addition of adjuvants such as dexmedetomidine and dexamethasone, innovative drug delivery systems, and the application of nanotechnology. These approaches provide new directions for prolonging the analgesic effects of local anesthetics. This review summarizes the latest research advancements in these cutting-edge technologies to offer guidance for clinical applications.

Keywords

Postoperative Analgesia, Local Anesthetics, Peripheral Nerve Block, Analgesic Duration

1. 引言

随着舒适化医疗和加速康复外科(Enhanced recovery after surgery, ERAS)理念的推广，麻醉面临新的挑战：既要满足手术需求，又要尽量减少术后并发症。未能有效控制的术后疼痛可能导致伤口愈合延迟、深静脉血栓、肺炎等并发症，甚至引发心理问题和睡眠障碍，约 10%~50%的患者可能发展为慢性疼痛[1] [2]。阿片类药物长期以来在镇痛中占主导地位，但其副作用(如便秘、恶心、呕吐等)严重影响患者的舒适度和恢复。因此寻找新的术后疼痛管理策略非常重要。

随着医学的发展，周围神经阻滞技术逐渐广泛应用，该技术通过在特定的神经干、丛、节周围或者神经经过的筋膜平面注射局麻药，阻断感觉冲动传导。尽管常用的长效局麻药如布比卡因和罗哌卡因能够提供镇痛，但其单次注射的效果通常只能维持 7~16 h，无法满足术后 48~72 h 的镇痛需求[3]。因此，延长神经阻滞镇痛时间成为当前的研究重点。现有的方案包括连续外周神经阻滞、采用脂质体等药物递送系统和添加地塞米松等佐剂，旨在为患者提供更持久且安全的镇痛效果。本文将综述这些新兴技术的最新进展。

2. 连续外周神经阻滞

连续外周神经阻滞(Continuous peripheral nerve block, CPNB)是在外周神经阻滞区域放置导管，持续给予稀释的长效局麻药，通常应用于由少数神经支配的手术部位如肩部和足部等，能够提供数天至数月的镇痛效果[4] [5]，镇痛效果的持续时间主要取决于局麻药的剂量[6]。典型的给药方式使推注体积为 2~10 mL，基础给药速率为 4~10 mL/h，锁定时间为 20~60 min [7]。已有研究表明，在不出现中毒的情况下，0.2%的罗哌卡因以高达 14 mL/h 的输注可持续 27 天[8]。通常采用神经刺激、超声引导、感觉异常诱导、荧光透视成像和触觉感知等方法来定位[9]-[11]，可选择非刺激性硬膜外导管或能够传递电流的“刺激导管”。给药模式可为基础输液、单次重复给药或两者结合[12]。

除术后镇痛外，CPNB 还用于治疗顽固性呃逆、缓解血管痉挛[13]-[16]。尽管该技术能够显著延长神经阻滞时间且应用广泛，但仍存在一些并发症限制了其在临床上的广泛推广。这些并发症包括导管移位或误插、液体泄漏、输液泵故障等[17]-[19]。此外，发生皮肤过敏、肌肉坏死和局麻药中毒等严重并发症的报道也时有发生[20]-[23]。CPNB 还可能引发神经损伤和感觉丧失[24] [25]。因此，进行 CPNB 时，必

须综合评估患者状况，合理选择导管插入方法及局麻药剂量，并采取适当的预防措施，监测神经功能和感觉状态，确保镇痛效果的同时，降低并发症的风险，确保治疗的安全性和有效性。

3. 创新药物输送系统

药物输送系统(Drug delivery systems, DDS)旨在控制药物释放的时间、速度和位置，以最大化其疗效，降低副作用，并增强药物的安全性和患者的依从性。目前，局麻药的输送系统分为有机载体和无机载体两类。有机载体以天然或合成高分子材料为基础，具有优异的生物相容性和可降解性，成为局麻药输送的研究热点。常见载体包括纳米晶体、脂质体、微粒、微针、水凝胶、胶束及树突状聚合物等[26] [27]。无机载体是以无机化合物如二氧化硅、磁性颗粒和碳基纳米颗粒等为载体的药物输送系统[28]，具有较高的药物装载量和稳定性，可以显著提高药物释放的安全性，为术后镇痛提供了更优的解决方案。

3.1. 有机载体

纳米晶体具有较高的比表面积和溶解度，适用于药物吸附和载药。其小尺寸和表面可定制处理，有助于提高药物的稳定性和生物利用度。Peng 等通过静电作用将带负电荷的纳米纤维与利多卡因结合，形成的纳米晶体可提供 24 h 的镇痛效果[29]。此外，罗哌卡因与阿奇霉形成的复合纳米晶体，不仅提供 48 h 的镇痛，还能抑制肿瘤复发[30]，为肿瘤切除患者带来福音。

脂质体是首个应用于临床的纳米输送系统，拥有类似于细胞膜的结构，能够携带亲水和疏水药物[31]。较大的粒径和低扩散性有助于降低高血浆浓度带来的毒性和免疫风险，提高中枢和心脏的安全性[32]。一种载有利多卡因的超柔脂质体，可直接涂抹通过皮肤渗透，减少了注射的痛感[33]。布比卡因脂质体通过 DepoFoam 颗粒缓慢释放布比卡因，可提供长达 72 h 的镇痛，减少了术后阿片药物使用，缩短住院时间[32] [34] [35]。然而，脂质体也存在着一些缺点，如较大的粒径可能会影响穿透能力，且制备成本较高。

微粒直径在 1 um~2 mm 之间，内含药物核心，外包裹膜或外壳，主要分为微球和微胶囊两类。微球的药物均匀分布，利于均匀释放，微胶囊则通过外膜控制释放速率，减少药物早期释放[36]。Horie 等人在豚鼠中使用利多卡因加载的微粒，延长药效时间至 3 天[37]。然而，微粒存在药物释放不均匀、生产成本高、载药量有限、体内稳定性差、免疫反应等挑战。

微针是由微米级针组成的贴片，结合透皮贴和皮下注射的优势，能直接穿过角质层到达真皮层，避免重复给药并减少注射痛[38] [39]。Yang 等制造的利多卡因/透明质酸微针，在 15 s 内释放药物，实现快速镇痛[40]。此外，微针的安全性和可控制性仍有待进一步验证，尤其是其对皮肤的潜在损伤和药物过量释放的风险需要在临床应用中更加谨慎。

水凝胶是一种交联亲水聚合物网络，具有吸水性，因其对温度、pH 值等环境变化，延长局麻药的释放时间的同时减少药物对正常组织的损伤。Yin 等人研究的复合水凝胶－纳米颗粒系统在生理温度下凝胶化，实现利多卡因的持续释放，使镇痛时间从 110 分钟延长至 360 分钟[41]。Chen 等开发的水凝胶系统可将利多卡因的感觉阻滞时间由 2 h 延长至 8.5 h [42]。然而，水凝胶的缺点是其物理结构的脆弱性，有时可能会导致药物递送系统的失效。

胶束因其独特的核壳结构在局麻药物输送中表现出显著优势，亲脂核包裹疏水药物，亲水壳确保其稳定分散，提升药物溶解度与稳定性，延长药物在体内的循环时间[43] [44]。Zhang 等开发的可注射胶束系统可将布比卡因的镇痛时间从 2.25 h 延长至 24.25 h [45]。然而，胶束系统同样面临稳定性的问题，尤其是在水溶性药物的输送过程中，可能会因胶束破裂或药物过早释放而导致疗效下降。此外，胶束的药物释放速率较难调控，因此其在临床中的广泛应用需要克服其释放控制的精准性问题。

树突状聚合物的高度分支和丰富的活性位点能够封装或共价键整合药物分子，实现有效的药物释放

控制[46] [47]。Zhao 等利用树突状聚合物承载河豚毒素，实现 71.5 h 的神经阻滞效果，且未引起神经功能障碍[48]。这一结果为树突状聚合物在术后镇痛中的应用提供了积极的前景。然而，树突状聚合物的合成成本较高，且其大规模生产中的可控性仍然是一个难题。

3.2. 无机载体

无机材料因其独特的物理特性在药物输送方面备受青睐。二氧化硅材料因其均匀的尺寸、高比表面积和可调节孔径，具有较高的载药能力。Gao 等合成的生物可降解混合有机硅纳米粒子输送罗哌卡因，结合介孔和中空结构，通过超声刺激实现了长达 6 h 的按需镇痛[49]。磁性纳米粒子则适用于靶向药物输送，能够提高局麻效果并减少血浆中的药物浓度[50]。碳纳米管、石墨烯及其衍生物高比表面积、良好的化学与机械稳定性以及优异的生物相容性，广泛应用用于局麻药输送。Zhang 等开发的还原氧化石墨烯修饰布比卡因，显著延长了镇痛时间[51]。然而，这些无机载体的主要问题在于其潜在的生物积累性和难以预测的体内代谢途径。因此，尽管无机载体在药物输送中具有显著优势，如何安全有效地将其应用于临床仍是未来研究的重要方向。

综上所述，不同的药物载体系统在延长周围神经阻滞时间方面表现出不同的优缺点，选择合适的载体不仅需要考虑其药物释放的速度和稳定性，还需综合评估其生物相容性和临床适用性。尽管目前已有多种药物输送系统进入临床试验阶段，但仍需进一步优化各类载体的设计，以满足临床应用中对药效、耐受性及成本等方面的高标准要求。未来的研究可以聚焦于多载体协同的智能药物输送系统，以实现更加精准的镇痛效果。

4. 佐剂

在局麻药中添加一些药物作为佐剂，旨在增强镇痛效果、延长作用时间。一般有静脉给药和神经周围给药两种给药方式。目前常用佐剂包括右美托咪定、地塞米松、肾上腺素、硫酸镁、氯胺酮、阿片类药物等。这些佐剂的作用机制尚不完全明了，但已知其主要通过减少炎症反应、稳定细胞膜、减轻神经传导等多重途径延长局麻药的镇痛作用。然而，每种佐剂的疗效、安全性及最佳使用剂量存在差异，临床应用时需要综合考虑不同佐剂的特点和潜在副作用。

4.1. 右美托咪定

右美托咪定是一种 α_2 肾上腺素能受体激动剂，具有镇静、镇痛、抗焦虑等作用。最新的荟萃分析显示，右美托咪可延长感觉阻滞时间至 11.5 h，并将感觉阻滞起效时间缩短至 10.8 min [52]。其作用机制可能包括阻断 Ih 电流、激活外周的 α_2 受体引起血管收缩、减少脊髓和脑干的 α_2 受体结合减少兴奋性神经递质的释放和再摄取以及减少炎症因子的释放[53]-[58]。然而，右美托咪定的使用也存在一定副作用，如镇静作用、心动过缓及神经元结构损伤等。根据最新的研究，最大安全剂量为 2 μg/kg，1 μg/kg 的剂量提供较好的镇痛效果的同时，也在副作用(如神经元结构损伤和心动过缓)之间达到最佳平衡[59]。

4.2. 地塞米松

地塞米松是一种长效的糖皮质激素，作为佐剂可延长局麻药的感觉和运动阻滞时间，并减少术后恶心呕吐的发生[60]。延长局麻药作用时间的机制包括减少炎症介质的产生、增加抗炎物质、抑制无髓 c 纤维的传递及局部血管收缩[60]。镇痛延长效果取决于局麻药类型、剂量及给药途径，可延长中效局麻药的镇痛时间 2.8 h，混合中长效局麻药延长 8.6 h，长效局麻药延长 11.1 h。通过静脉注射地塞米松同样能够延长镇痛时间，其效果与局部神经用药相当，但效力略低。临床推荐剂量为静脉注射 8 mg、神经周围注射 4 mg [60] [61]。值得注意的是，单次使用地塞米松不增加感染风险，但可导致血糖短暂升高[62]-[64]。

神经周围给药是一种超说明书用药方式，有潜在的神经毒性和结晶的风险，注射时应缓慢且使用不含防腐剂的制剂[65]。

4.3. 肾上腺素

肾上腺素作为 α 和 β 受体激动剂，通过收缩局部血管延缓局麻药清除，从而延长局麻药的作用时间并减少全身毒性反应[66]。肾上腺素通过激活外周 α_2 受体减少脊髓背角神经递质释放并改变周围神经轴突中的钾离子通道，增强局麻药的镇痛效果[67]。肾上腺素的作用效果具有剂量依赖性，副作用主要包括局部缺血、心动过速、血压升高等，因此在临床使用时需要严格控制剂量，尤其是在老年患者或心血管疾病患者中，较高剂量可能引发缺血，最大推荐剂量为 5 μg/mL，需避光储存，防止氧化[68] [69]。

4.4. 阿片类镇痛药

阿片类药物是术后急性疼痛管理的主要手段，通常通过静脉输注，FDA 也批准了在神经周围应用阿片类药物，常用的药物包括丁丙诺啡、舒芬太尼、芬太尼和吗啡等。阿片类药物主要通过结合外周和中枢受体，调节炎症反应，从而延长局麻药的作用时间。Berh 等人的研究显示，0.5%左旋布比卡因联合 0.15 mg 丁丙诺啡可使布比卡因的镇痛时间延长约 1 倍[70]。然而，阿片类药物的使用也带来了不少副作用，主要包括瘙痒、恶心、呕吐及呼吸抑制等。临床应用时需要根据患者的耐受性和镇痛需求，权衡镇痛效果与副作用，合理使用。

4.5. NMDA 受体拮抗剂

硫酸镁作为 NMDA 受体拮抗剂，可显著延长局麻药的感觉阻滞时间，减少术后恶心呕吐，并改善术后恢复质量[71]。其作用机制包括中和神经膜上的负电荷、调节钙离子内流及增加神经递质的释放[72] [73]。此外，硫酸镁在局麻药中易溶解，性质稳定，便于储存且经济实惠，但其最佳剂量尚需进一步研究[74]。氯胺酮作为另一种 NMDA 受体拮抗剂，也能有效减轻术后疼痛，延长首次请求镇痛药物的时间，延长感觉阻滞时间而不影响运动阻滞时间[75] [76]。然而，氯胺酮的副作用包括可能引发幻觉和精神症状，因此在应用时需特别注意剂量控制[77]。

4.6. 碳酸氢钠

碳酸氢钠通过增加局麻药的 pH 值，使其更容易以非电离的形式穿过神经脂质膜，从而加速起效时间并增强效果[78] [79]。研究表明，碳酸氢钠可缩短氯普鲁卡因起效时间，并减少阻滞作用的持续时间[80]。在某些局麻药中，如布比卡因和利多卡因，碳酸氢钠的加入能够显著缩短起效时间[81]。尽管这些变化通常只有 1-2 分钟，但在需要快速起效的临床情况下，碳酸氢钠仍具有重要的应用价值[81]-[83]。不过，碳酸氢钠的效果因局麻药种类的不同而有所差异，且其临床效用和安全性仍需更多高质量的试验验证。

5. 总结与展望

综上所述，连续周围神经阻滞技术、脂质体等药物输送系统，以及右美托咪定、地塞米松等佐剂的协同使用可以延长区域阻滞作用时间。然而，尽管这些方法展现了显著的优势，但在临床实践中的应用仍需要更多高质量的研究支持，以明确最佳剂量、安全性和长期效果。未来的研究应继续探索这些领域的创新，以期为患者提供更加安全、有效的疼痛管理方案。

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