

• 综述 •

布比卡因脂质体在心胸外科围术期镇痛中的应用进展

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[摘要] 心胸外科手术创伤较大, 术后疼痛管理是围术期治疗的重要环节。传统区域阻滞技术因单次给药时效较短或硬膜外置管相关并发症, 难以有效覆盖术后24~72 h的重度疼痛高峰期。布比卡因脂质体(liposomal bupivacaine, LB)采用多囊脂质体缓释技术, 可将单次给药的镇痛效果延长至72 h, 为减少导管相关并发症、优化区域镇痛方案提供了新的技术选择。文章系统综述了LB在心胸外科领域的药理机制及临床应用进展。分析表明, LB的核心临床价值在于通过单次给药实现长效镇痛, 替代连续导管技术以减少置管相关并发症, 并作为多模式镇痛的重要组成部分发挥阿片节俭效应。同时, 探讨其在复杂手术中绝对镇痛强度可能不足的争议、物理弥散局限及卫生经济学挑战, 以期临床合理应用提供参考。

[关键词] 布比卡因脂质体; 心胸外科; 多模式镇痛; 区域阻滞

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Advances in the application of liposomal bupivacaine in perioperative analgesia for cardiothoracic surgery

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[Abstract] Cardiothoracic surgery is associated with significant trauma, making effective postoperative pain management critical for enhanced recovery. Traditional regional analgesia is often limited by the short duration of single-dose local anesthetics or complications associated with continuous catheter techniques, which can hinder effective pain control during the intense 24-72 h postoperative period. Liposomal bupivacaine (LB), a multivesicular liposome formulation of bupivacaine, provides a single-dose analgesic effect lasting up to 72 h. This extended-release profile offers a novel, catheter-free approach to regional analgesia, with the potential to reduce catheter-related complications and serve as a key component of multimodal analgesia. This review systematically summarizes the pharmacological mechanisms and clinical applications of LB in cardiothoracic surgery. The evidence indicates that LB enables prolonged analgesia with a single dose, replacing continuous catheter techniques to mitigate catheter-associated complications, and exerting an opioid-sparing effect as a key component of multimodal analgesia. Meanwhile, this paper discusses ongoing controversies, including its comparative analgesic efficacy against established techniques like thoracic epidural analgesia, limitations due to its physical properties affecting tissue spread, and challenges related to its cost-effectiveness in different healthcare systems, so as to provide evidence-based references for rational clinical utilization.

[Key words] liposomal bupivacaine; cardiothoracic surgery; multimodal analgesia; regional block

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心胸外科手术创伤较大, 术后疼痛管理直接关系到患者的早期康复及并发症发生率。术后急性疼痛机制复杂, 除皮肤及肌肉组织切口痛外, 还包括肋间神经受压、胸膜牵拉、纵隔分离及胸腔闭式

引流管对胸膜的持续刺激^[1]。术后镇痛不全可引发一系列病理生理改变:疼痛限制患者有效咳嗽与深呼吸,增加肺不张、低氧血症及肺部感染风险;同时,交感神经过度兴奋易诱发心动过速与高血压,增加围术期心肌缺血及心律失常发生率^[2]。此外,30%~50%的心胸外科患者可由急性疼痛进展为慢性术后疼痛,影响远期生活质量^[3]。

加速康复外科(enhanced recovery after surgery, ERAS)理念强调通过多模式干预减少手术应激、加速术后康复^[4]。其中,有效的区域阻滞是多模式镇痛的基础,但传统技术存在单次给药时效短、连续置管并发症多等局限,难以有效覆盖术后疼痛高峰期^[5],急性疼痛控制不佳不仅影响患者早期恢复,还可能进展为慢性术后疼痛(chronic postsurgical pain, CPSP)。研究显示,开胸术后CPSP发生率高达30%~50%,心脏术后为20%~30%^[3]。CPSP不仅影响患者生活质量,还带来持续的医疗负担,其发生与急性疼痛控制不佳密切相关^[6]。现阶段,多模式镇痛虽已作为心胸外科的标准镇痛策略,但具体干预手段仍面临临床挑战^[7]。阿片类药物伴发剂量依赖性的呼吸抑制、术后恶心呕吐及肠麻痹等不良反应,影响患者恢复进程^[8-9]。胸段硬膜外镇痛(thoracic epidural analgesia, TEA)或胸椎旁阻滞(thoracic paravertebral block, TPVB)虽可提供有效的区域镇痛,但单次给药时效受限,连续置管技术则因导管相关并发症及围术期抗凝禁忌,难以常规用于术后疼痛高峰期^[10]。

布比卡因脂质体(liposomal bupivacaine, LB)是一种基于多囊脂质体缓释技术的新型长效局麻药,可将单次给药镇痛效果延长至72 h,为实现“无导管化”连续区域镇痛提供了可能^[11-12]。2022年底, LB

(国内商品名:艾恒平®)在我国获批上市,成为首个超长效局麻药^[13]。该药物的引入为我国心胸外科围术期镇痛提供了新的选择,但临床应用中仍存在诸多争议,亟需系统梳理现有证据。文章对LB的药理机制及其在心胸外科围术期镇痛中的临床应用进展进行系统综述,以期优化多模式镇痛方案提供参考。

1 LB概述

1.1 药理机制与药代动力学

LB采用DepoFoam™多囊脂质体技术,由多个非同心的脂质腔室构成。多囊脂质体与传统的单层或多层脂质体不同,其内部由多个非同心的小囊泡组成,呈“蜂窝状”排列。每个小囊泡包裹布比卡因水溶液,囊泡之间由脂质双分子层分隔(图1)。这种独特结构使药物释放呈现“逐级塌陷”模式:当最外层的囊泡破裂后,药物释放;随后内层囊泡依次塌陷,形成持续释放的瀑布效应。每个囊泡的破裂是随机事件,因此在群体水平上表现为平稳的零级释放动力学^[14]。给药后,布比卡因通过脂质膜的逐步侵蚀和腔室塌陷缓慢释放,镇痛效应可持续72 h,避免了传统局麻药释放过快所致的镇痛时间短暂^[15]。

药代动力学研究显示, LB呈现“双峰”释放特征:首个血药浓度峰值出现于给药后0.5~2.0 h,由制剂中约3%的游离布比卡因迅速吸收入血所致,提供初期镇痛;第2个峰值出现于12~24 h,为脂质体持续释放所致^[16]。Hu等^[16]对LB的药代动力学进行了系统研究,纳入4项临床试验共214例受试者。结果显示, LB单次给药后血药浓度在0.5~2.0 h出现第1个峰值(C_{max} 200~400 ng/mL),随后下降;12~24 h出现第2个峰值(C_{max} 300~500 ng/mL),为第1个峰值的1.2~1.5倍;表观分布容积(V_d)为100~

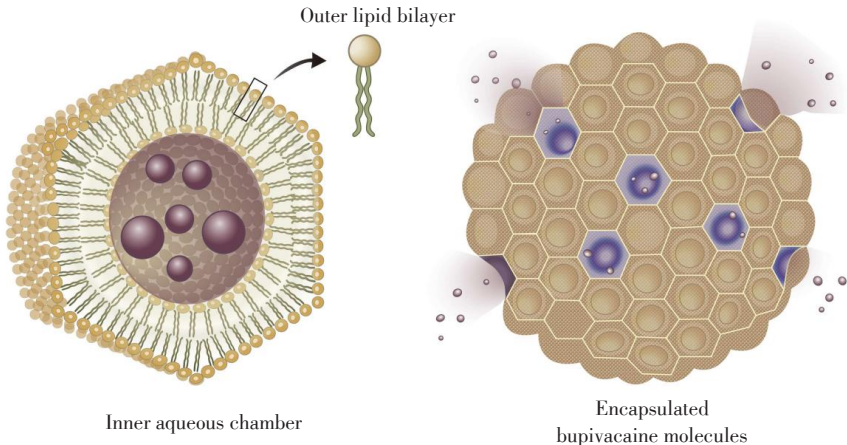


图1 布比卡因脂质体的多囊脂质体结构示意图

Figure 1 Schematic diagram of the multivesicular liposome structure of liposomal bupivacaine

150 L,提示药物广泛分布于组织中;清除半衰期($t_{1/2}$)为12~18 h,显著长于普通布比卡因的2~4 h^[16]。LB颗粒直径较大(10~30 μm),难以穿透毛细血管壁进入血液循环,从空间位阻上降低了药物的系统性吸收,从而降低心脏和神经毒性风险^[17]。Joshi等^[17]的动物研究表明,LB经局部给药后,血药浓度仅为同等剂量普通布比卡因的1/3~1/2,且达峰时间延迟。

多囊脂质体的结构完整性对外界理化环境高度敏感。临床应用中需特别注意配伍禁忌:LB禁忌与利多卡因等其他非布比卡因类局麻药混合;若与普通盐酸布比卡因联合使用,普通布比卡因剂量不得超过LB剂量的50%,且不宜在注射器内长时间混合^[18]。配伍禁忌的机制:利多卡因等非布比卡因类局麻药具有较高的脂溶性,可插入脂质双分子层,改变膜流动性,导致囊泡破裂。普通布比卡因虽为同类药物,但高浓度混合时仍可因渗透压变化破坏囊泡结构^[19]。药液稀释仅能使用不含防腐剂的0.9%氯化钠注射液,禁用注射用水等低渗溶液或任何高渗溶液,以免脂质体破裂导致“剂量倾泻”^[20]。LB的临床使用涉及剂量、浓度和容积3个变量的平衡。单次最大推荐剂量为266 mg(20 mL, 1.33%)。临床可根据阻滞范围和手术需求进行稀释:稀释至30 mL时浓度约为8.9 mg/mL,稀释至40 mL时浓度约为6.7 mg/mL。但需注意,过度稀释会导致单位体积内脂质体数量减少,可能影响阻滞致密性。目前推荐维持浓度不低于1.3 mg/mL(即20 mL原液稀释至40 mL以内)^[20]。

1.2 安全性

LB基于其多囊脂质体结构与缓释机制,在心胸外科围术期镇痛中表现出良好的安全性。局麻药全身毒性(local anesthetic systemic toxicity, LAST)是区域阻滞的严重并发症。传统布比卡因的心脏毒性阈值约为2 000 ng/mL,超过此浓度可致心律失常、心搏骤停^[21]。LB的血药峰浓度通常在500~600 ng/mL,远低于毒性阈值。文献报道的LB相关LAST极为罕见,且多与误入血管、超剂量使用或配伍不当有关^[22]。

药代动力学研究显示,LB在健康中国志愿者中的血药峰浓度低于毒性阈值,未观察到严重不良事件^[23]。Cheung等^[23]的I期临床试验纳入24例健康受试者,分别接受LB 106 mg、266 mg和532 mg局部浸润,结果显示所有剂量组血药峰浓度均低于1 600 ng/mL,未出现心电图异常或神经系统症状。在心脏外科手术中,LB较大的颗粒尺寸及缓慢释放特性降低了药物误入血管后引发急性心脏毒性的可能性^[24]。相关临床研究显示,LB给药后血浆浓度

低于已知毒性阈值,未观察到明显的心电图改变或严重心脏不良事件^[25-27]。Bergese等^[25]对LB的心脏安全性进行了系统评估,纳入300余例患者的心电图监测数据,结果显示LB组QTc间期变化与安慰剂组差异无统计学意义。在神经毒性方面,动物实验显示盐酸布比卡因处理后周围神经组织出现结构改变,而LB干预组未见类似异常^[28]。Markova等^[27]的动物研究比较了LB与普通布比卡因对坐骨神经的影响,结果显示普通布比卡因组出现明显的轴突变性、髓鞘水肿,而LB组神经组织结构基本正常。现有临床研究较少观察到LB引发明显神经毒性反应^[29]。Tirota等^[24]开展的PLAY研究纳入102例6~17岁手术患者,评估LB在不同给药方式下的安全性。结果显示,所有患儿血药峰浓度均低于1 000 ng/mL,未观察到LAST相关表现。在老年患者中,张春燕等^[30]的研究纳入80例65岁以上心脏手术患者,LB组术后血药峰浓度为(412±156)ng/mL,未出现心脏或神经系统不良事件。上述研究提示LB在特殊人群中具有良好的安全性。

在特殊人群中需关注用药安全。布比卡因主要依赖肝脏细胞色素P450酶系代谢^[21],心胸外科患者常伴有高龄及肾功能减退。对于此类患者,LB的体内清除半衰期可能延长,尽管其缓释特性降低了血药浓度峰值,但仍需注意药物蓄积风险,应酌情调整剂量并加强监测。

2 临床应用

2.1 肋间神经阻滞(intercostal nerve block, ICNB)

ICNB是胸外科手术镇痛的常用技术,可直接作用于手术切口及引流管所在的皮节区域^[31]。LB的应用将ICNB的镇痛时限从传统局麻药的数小时延长至术后72 h,其临床有效性和安全性已获多项研究证实。

在胸腔镜手术中,多项研究一致显示LB用于ICNB可显著改善术后镇痛质量。刘世娅等^[32]通过胸腔镜引导下ICNB观察到,LB应用于胸腔镜肺叶切除术后,患者术后12~72 h静息及活动时NRS评分均显著低于罗哌卡因组($P < 0.05$),术后舒芬太尼总消耗量减少,PCIA首次按压时间延长,首次下床时间缩短。卢建国等^[33]在单孔胸腔镜肺部手术中的前瞻性研究($n=228$)显示,LB组术后4~72 h视觉模拟评分(visual analogue scale, VAS)评分均低于盐酸布比卡因组($P < 0.05$),术后48 h内活动总次数显著增加,提示LB有助于促进患者术后早期活动。郑

国长^[34]的回顾性研究($n=100$)同样证实, LB组术后12~72 h VAS评分低于对照组, 镇痛泵首次按压时间延迟, 术后72 h舒芬太尼用量减少, 且术后1、3 d恢复质量评分(QoR-15)显著提高($P < 0.05$)。

操作技术优化可进一步提升LB-ICNB效果。Li等^[31]研究显示, 超声引导下ICNB组术后0~48 h VAS评分均显著低于对照组($P < 0.05$), 术后48 h内补救镇痛需求率降低(9.83% vs. 31.03%, $P=0.004$), 胸管留置时间缩短[(4.69±2.14)d vs. (5.67±2.86)d, $P=0.036$], 提示超声引导可改善早期镇痛效果并促进恢复。Xiao等^[29]的随机对照试验($n=50$)比较了预防性ICNB与术毕阻滞的效果, 结果显示: 预防性给药组术后6、12 h静息VAS评分及Prince Henry疼痛量表评分均显著低于术毕给药组($P < 0.05$), 但24 h后两组无显著差异($P > 0.05$), 提示预防性ICNB的优势主要体现于术后早期(12 h内)。针对多孔胸腔镜手术, 多节段注射是确保镇痛范围的关键, 卢建国等^[33]在单孔胸腔镜手术中采用第2~9肋间共8个肋间、各注射LB 5 mL的方案, 获得了确切的镇痛效果。

在复杂胸外科手术中, Sun等^[35]对173例胸腔镜手术患者的前瞻性随机对照研究显示, 单纯ICNB组、ICNB联合TPVB组及竖脊肌平面阻滞组术后48 h内静息VAS评分差异无统计学意义($P > 0.05$), 3组间舒芬太尼用量、补救镇痛需求及住院时间差异亦无统计学意义, 提示在静息镇痛方面, ICNB单独应用可获得与其他联合阻滞方案相当的临床效果。安全性方面, Manson等^[36]对15例开胸手术患者的前瞻性观察研究显示, 外科医生实施的多节段ICNB中, LB的血药峰浓度中位浓度为0.6 $\mu\text{g/mL}$ (范围0.3~1.2 $\mu\text{g/mL}$), 远低于2 $\mu\text{g/mL}$ 的毒性阈值; 达峰时间中位时间为24 h(范围15 min~48 h)。所有患者在96 h内均未发生局麻药毒性反应, 提示LB用于ICNB具有良好的全身安全性。

2.2 TPVB

TPVB通过将局麻药注射于胸椎旁间隙, 阻滞同侧脊神经根及交感干, 可同时覆盖躯体痛与内脏痛, 是目前镇痛效能最接近TEA的区域阻滞技术, 在复杂开胸手术及食管癌根治术等创伤较大的手术中具有重要价值。目前尚无直接评价LB用于TPVB的临床研究发表, 因此本节主要基于两类证据进行间接分析: ①传统局麻药用于TPVB的成熟研究, 用以说明TPVB技术本身的镇痛价值; ②LB的药代动力学特性及其在其他区域阻滞技术中的应

用数据, 为LB用于椎旁间隙提供理论可行性参考。

从技术本身的角度, TPVB的临床价值已得到充分验证。徐建国等^[37]明确指出, TPVB可作为胸科手术术后镇痛的有效选择, 为TPVB的临床应用提供了规范指导。在此共识基础上, 多项高质量研究进一步证实了其效能。Ren等^[38]Meta分析显示, 全身麻醉联合TPVB可显著降低术后24 h疼痛评分、减少阿片用量, 并缩短住院时间。与TEA相比, Davies等^[39]的系统评价(基于传统局麻药)亦证实, TPVB在术后镇痛效果方面与TEA差异无统计学意义, 且尿潴留、低血压和恶心呕吐等并发症发生率更低, 显示出更好的安全性。

从LB应用于椎旁间隙的可行性角度, 其药代动力学特性提供了理论依据。尽管肋间与椎旁间隙的解剖和血供存在差异, 但Manson等^[36]在肋间神经阻滞中的药代动力学研究显示, LB的血药峰浓度远低于2 000 ng/mL的毒性阈值, 提示即使在血供较丰富的区域阻滞中, LB的全身安全性依然良好, 为将其拓展至椎旁间隙应用提供了初步的安全性参考。此外, Sun等^[35]的前瞻性随机对照研究虽未直接使用LB, 但其结果显示, 在胸腔镜手术中, TPVB联合ICNB组的术后24、48 h VAS评分与竖脊肌平面阻滞组差异无统计学意义, 这一结果间接提示TPVB在胸腔镜手术中具有稳定且确切的镇痛效能。

然而, 上述可行性推论尚未得到临床研究的直接验证。目前国内外均缺乏LB-TPVB的高质量研究报告, 造成这一研究空白的可能原因包括: ①解剖位置深, 椎旁间隙毗邻胸膜、椎体及节段血管, 穿刺技术要求较高, 药物误入血管或胸膜腔的风险相对较大, 研究者对超长效制剂的安全边界尚缺乏充分信心; ②LB的多囊脂质体颗粒直径较大, 其在椎旁间隙致密疏松结缔组织中的扩散特性尚不明确, 是否存在局部聚集或分布不均等问题有待验证; ③与ICNB或筋膜平面阻滞相比, TPVB的操作难度和潜在风险更高, 开展探索性临床研究面临更严格的伦理审查和更高的受试者入组门槛。

综上所述, TPVB作为胸科手术区域镇痛的核心技术, 其临床价值已获广泛验证。然而, LB在该领域的应用仍处于探索阶段, 现有证据主要源于间接推论。鉴于TPVB在胸外科镇痛中的不可替代性, 开展LB-TPVB的高质量随机对照试验是明确其临床效能与安全性的必要前提。

2.3 筋膜平面阻滞

筋膜平面阻滞因其操作便捷、远离重要血管和

胸膜,已成为心胸外科加速康复外科路径中广泛应用的区域镇痛技术,主要包括竖脊肌平面阻滞(erector spinae plane block, ESPB)和前锯肌平面阻滞(serratus anterior plane block, SAPB)。

ESPB穿刺位点位于竖脊肌深面,药液可沿筋膜面头尾侧扩散,实现同侧多节段躯体神经阻滞。Forero等^[40]于2016年首次描述该技术。Malan等^[41]纳入202例成人漏斗胸矫正术患者的回顾性研究显示,接受双侧LB-ESPB的患者术中阿片用量(以吗啡当量计)低于历史对照组[(36.7±17.1)mg vs. (41.8±17.0)mg, $P=0.05$],且术后7 d内急诊就诊率显著降低(0 vs. 4.8%, $P=0.05$)。两组在围术期总阿片用量、麻醉后监测治疗室(PACU)重度疼痛发生率、PACU停留时间等方面差异无统计学意义,且未观察到与ESPB相关的不良事件。在胸腔镜手术中,Sun等^[35]研究显示,ESPB联合ICNB组与TPVB联合ICNB组在术后24、48 h的静息及咳嗽状态下VAS评分差异均无统计学意义($P>0.05$),提示ESPB可作为TPVB的有效替代方案。

SAPB因操作简单、不干扰交感神经且不受围术期抗凝状态限制,已成为侧胸壁及引流管区域镇痛的常用入路。吴春培等^[42]于2013年首次描述该技术。在胸腔镜手术中,Zhang等^[43]的随机对照试验($n=64$)比较了LB与罗哌卡因用于SAPB的镇痛效果。结果显示,LB组术后12~72 h静息及活动时疼痛评分均显著低于罗哌卡因组($P<0.05$),围术期舒芬太尼及术后氟比洛芬酯用量显著减少($P<0.05$);首次排气时间、首次下床活动时间、导尿管拔除时间均提前,ICU停留时间缩短,术后恶心呕吐发生率降低,住院费用减少,且术后3 d内QoR-15显著提高(均 $P<0.05$)。两组在拔管时间、术中瑞芬太尼用量及总住院时间方面差异无统计学意义,多因素回归分析显示LB是镇痛质量的独立预测因子(OR=2.34, 95% CI: 1.45~3.78)。在心脏手术中,Bailey等^[44]的可行性研究($n=20$)采用连续SAPB方案(单次LB负荷剂量联合术后48 h罗哌卡因持续输注),结果显示患者术后48 h内静息VAS评分中位数均 ≤ 3 分,无导管相关并发症。Alfirevic等^[45]的随机对照试验($n=80$)显示,在机器人辅助二尖瓣修复术中,SAPB联合胸肌平面阻滞可使术后24 h内阿片用量减少45%($P<0.01$),术后恶心呕吐发生率降低28%($P<0.05$)。

需要关注的是,上述联合阻滞方案的安全性尚需审慎评估。Alfirevic等^[46]的药代动力学亚组研

究显示,采用普通布比卡因联合LB行胸-前锯肌平面阻滞,动脉血药峰浓度几何均数为1 492 ng/mL,中位达峰时间30 min;31%的患者血药浓度超过2 000 ng/mL的毒性阈值。血药浓度呈双峰曲线,第2个峰值出现在注射后约32 h。虽未观察到临床局麻药全身毒性表现,但研究者明确指出,常规联合应用普通布比卡因与LB行胸部筋膜平面阻滞并非安全,需警惕血药浓度过高的风险。

此外,操作层面需注意LB作为悬浊液的特性,其镇痛效能与给药容积和浓度平衡密切相关。过度稀释可增加药液扩散范围,但可能导致单位面积内LB分布密度下降,引发“斑片状”阻滞不全。临床实践中建议采用“有限稀释”原则,在保证容积足以覆盖手术野(通常20~30 mL)的前提下,控制LB浓度不低于1.3 mg/mL^[20],超声引导下应确认针尖位置正确、药液在筋膜平面内均匀扩散。

2.4 胸骨旁阻滞(parasternal block, PIB)与切口浸润(local infiltration analgesia, LIA)

在心脏外科正中胸骨切开后镇痛中,PIB和LIA是两类重要的区域镇痛技术。两者均可在围术期高度抗凝背景下规避深部神经轴索阻滞的出血风险,契合早期拔管临床路径要求。

PIB通过将局麻药注射于胸骨旁肋间内肌与胸横肌之间的筋膜平面(胸横肌平面),阻滞肋间神经前皮支,实现双侧多节段胸骨区域镇痛。该平面位于胸骨旁2~3 cm处,深度1~2 cm,超声下可清晰显示胸横肌及胸廓内血管。Hunter等^[47]研究证实,双侧深部PIB可为正中胸骨切开术提供有效镇痛,平均血药峰浓度为0.60 $\mu\text{g/mL}$,低于2.0 $\mu\text{g/mL}$ 的毒性阈值。

值得注意的是,LB用于PIB的临床研究结果并不一致。Lee等^[48]随机对照试验($n=79$)比较了LB与生理盐水安慰剂用于PIB的效果,结果显示,虽各时间点术后疼痛评分无显著差异,但LB组整体疼痛水平略低($P=0.04$);两组术后72 h内阿片用量、ICU停留时间、住院时间、拔管时间、肠功能恢复时间等次要结局均无显著差异。研究者认为,LB无阿片节约效应,仅与术后疼痛水平边际性降低相关。Subramaniam等^[49]的随机对照试验($n=60$)比较了LB联合普通布比卡因(LB+PB组)与单纯普通布比卡因(PB组)用于胸骨LIA的效果,同样未观察到显著优势:两组术后4~72 h各时间点疼痛评分无显著差异,72 h内阿片用量亦无显著差异(139 mg vs. 105 mg, $P=0.29$);虽混合模型回归显示LB+PB组活动时疼痛趋势略低($P=0.01$),但恢复特征和不良事件

发生率组间可比。上述研究提示,在心脏手术PIB和LIA中,LB的附加价值可能有限。

LIA由外科医师在关胸前沿胸骨切口全程分层注射,将局麻药直接浸润于皮下组织、肌肉层及胸骨骨膜表面,操作简便但镇痛范围局限于切口局部。与上述阴性结果不同,部分研究在特定人群中观察到LB的临床获益。张春燕等^[30]纳入106例老年胸骨正中切口心脏手术患者的研究显示,与盐酸布比卡因相比,切口局部注射LB联合患者自控静脉镇痛可显著降低术后24、48、72 h静息及活动状态下VAS评分($P < 0.05$),降低血清疼痛介质(5-羟色胺、P物质、前列腺素E2)及应激激素(皮质醇、去甲肾上腺素)水平,提高 β -内啡肽水平($P < 0.05$);LB组术后首次使用镇痛药物时间延长,术后72 h内阿片类药总用量减少($P < 0.05$)。两组住院时间及不良反应发生率差异无统计学意义。Tirotta等^[50]回顾性队列研究纳入小儿心脏手术患者222例,比较胸骨正中切口皮下注射LB(4 mg/kg LB混合0.25%布比卡因)与ON-Q镇痛泵(0.25%布比卡因持续输注)

的效果,结果显示LB组手术室拔管率显著高于ON-Q组($P < 0.05$),ON-Q组阿片(吗啡)使用率更高(100.0% vs. 95.5%, $P < 0.05$);虽LB组术后24 h内疼痛评分中位数略高(27.0 vs. 17.0, $P < 0.05$),但综合指标显示LB用于小儿胸骨正中切口术后镇痛的效果至少与ON-Q泵相当。

从药代动力学角度而言,LB局部给药后呈现“双峰”释放曲线,第2个血药浓度峰值出现于给药后12~24 h,与心脏手术后炎性疼痛高峰期重合,有利于提供针对性镇痛^[16]。然而,上述临床研究结果的不一致性提示,LB在PIB和LIA中的应用效果可能受患者人群、手术类型、给药方案及联合用药等多种因素影响,需在临床应用中个体化选择。

综上所述,LB在心胸外科围术期的区域阻滞中展现出多维度的应用潜力。不同的阻滞技术在解剖靶点、操作难度及抗凝背景下的安全性方面各有侧重。为更直观地展示各类阻滞技术的临床特征与现有循证医学证据,文章对其进行了系统梳理与横向对比(表1、2)。在实际临床干预中,麻醉医师

表1 心胸外科常用区域阻滞技术特征比较
Table 1 Comparison of characteristics of commonly used regional block techniques in cardiothoracic surgery

Block technique	Anatomical plane	Target	Coverage	Technical difficulty	Safety under anticoagulation	Main indications
Intercostal nerve block (ICNB)	Between internal and external intercostal muscles	Intercostal nerves	Unilateral, single or multiple intercostal spaces (T2-T9)	Low	Relatively safe	VATS, thoracotomy, rib fracture surgery
Thoracic paravertebral block (TPVB)	Paravertebral space	Spinal nerve roots, sympathetic trunk	Unilateral multiple dermatomes (somatic and visceral pain)	High	Caution required*	Complex thoracotomy, radical esophagectomy
Erector spinae plane block (ESPB)	Deep fascia of the erector spinae muscle	Dorsal/ventral rami of spinal nerves	Ipsilateral multi-segmental somatic nerves	Moderate	Safe	Pectus excavatum repair, chest wall surgery, VATS
Serratus anterior plane block (SAPB)	Superficial/deep to the serratus anterior muscle	Lateral cutaneous branches of intercostal nerves	Lateral chest wall, multiple dermatomes (T2-T9)	Low	Safe	VATS, chest drain analgesia, robotic cardiac surgery
Parasternal intercostal block (PIB)	Transversus thoracis plane/internal intercostal muscle	Anterior cutaneous branches of intercostal nerves	Bilateral parasternal multiple intercostal spaces	Moderate	Safe	Median sternotomy cardiac surgery
Local infiltration analgesia (LIA)	Subcutaneous, muscular, perosteal layers	Free nerve endings	Incisional site	Low	Safe	Cardiac surgery in the elderly/children, surgical incision analgesia for various procedures

Note: VATS: video-assisted thoroscopic surgery; RATS: robot-assisted thoroscopic surgery; TEA: thoracic epidural analgesia. Technical difficulty is graded based on the learning curve and dependence on ultrasound guidance. “Caution required” indicates that, owing to the deep anatomical location and elevated risk of hematoma, a comprehensive assessment of the patient’s anticoagulation status is necessary.

表2 各类阻滞技术的临床证据总结

Table 2 Summary of clinical evidence for various block techniques

Block technique	Included literature	Key findings	Level of evidence
Intercostal nerve block(ICNB)	7 articles (including 3 RCTs)	① Analgesia extended to 72 h with significantly reduced opioid consumption; ②Ultrasound guidance reduces the need for rescue analgesia; ③Peak plasma concentration far below the toxicity threshold, indicating good safety.	High
Thoracic paravertebral block (TPVB)	Indirect evidence and 2 meta-analyses	①Analgesic efficacy approaching TEA but with lower complication rates; ② Currently no high-quality studies directly using LB in TPVB; ③Meta-analyses show reduced pain scores and opioid consumption.	Very low (for LB)
Erector spinae plane block (ESP)	2 articles (including 1 retrospective study)	①Reduced opioid consumption in pectus excavatum surgery; ② In VATS, analgesic effect comparable to TPVB combined with ICNB.	Low
Serratus anterior plane block (SAPB)	5 articles (including 3 RCTs)	①Significant pain reduction and improved quality of recovery after VATS; ②Reduced opioid consumption after cardiac surgery; ③ Caution required for high plasma concentration when combined with other agents.	High
Parasternal intercostal block(PIB)	2 articles (including 1 RCT)	① Plasma concentration below the toxicity threshold; ②Both RCTs showed that LB did not significantly improve opioid consumption or primary analgesic outcomes.	Moderate (predominantly negative results)
Local infiltration analgesia(LIA)	3 articles	①Reduced pain scores and opioid consumption in elderly patients; ②Analgesic effect in pediatric patients non-inferior to continuous infusion pump; ③Plasma concentration shows a double-peak curve, coinciding with postoperative pain peaks.	Moderate

The level of evidence was comprehensively assessed based on the number of included studies, study design (RCT as the gold standard), sample size, and consistency of conclusions, and is classified into four grades: high, moderate, low, and very low. “For LB” specifically refers to direct evidence concerning the use of liposomal bupivacaine in a particular technique.

需结合患者的具体术式、创伤范围及围术期凝血功能状态,为其制定个体化的区域镇痛方案。

3 局限性

3.1 镇痛效能争议

尽管LB在延长镇痛时效方面具有优势,但其在复杂心胸手术中的绝对镇痛强度仍存争议。目前TEA及连续TPVB仍被视为心胸外科术后重度疼痛管理的金标准。多项系统评价指出,在术后早期(24 h内),单次注射LB的动态疼痛评分及阿片节俭效应与普通局麻药相比未显示优效性,多数研究仅证实其非劣效性或差异无统计学意义^[51-53]。Ji等^[51]的系统评价纳入23项RCT共1 845例患者,结果显示在术后24 h疼痛评分方面,LB与安慰剂或其他活性药物相比差异无统计学意义(SMD=-0.12, 95% CI: -0.28~0.04),但在术后48~72 h LB组疼痛评分更低(SMD=-0.31, 95% CI: -0.52~-0.10)。与连续局麻药泵注方案相比,LB的即刻镇痛效能可能不具优势,但目前缺乏直接对比的高质量证据。

3.2 药理特性与弥散局限

LB的理化特性限制了其在特定解剖间隙内的物理弥散能力。由于LB多囊脂质体颗粒直径(10~30 μm)显著大于普通盐酸布比卡因分子(<0.1 μm)^[54],其在致密筋膜或血供相对匮乏组织中的穿透与扩散程度受限。从药代动力学角度推测,高体重指数(body mass index, BMI)患者的镇痛持续时间可能受到影响^[54-55]。Salehi等^[54]对多囊脂质体递送系统的综述指出,脂质体药物的释放特性受局部组织微环境影响;NYSORA指南^[55]提示,LB在肥胖患者中的临床效果可能存在个体差异,并建议,LB稀释后浓度不应低于1.3 mg/mL,单点注射容积不宜超过30 mL,以避免因药液分布不均导致的“斑片状”阻滞不全。

3.3 经济成本考量

高昂的制剂成本是制约LB广泛普及的因素之一,尤其在我国医保支付改革背景下更为突出。部分成本效果分析显示,LB可通过减少阿片相关不良反应及缩短住院时间,使整体住院成本接近成本中

性。Noviasky 等^[56]的综述指出, LB 的药品成本虽高,但若考虑到导管相关并发症的减少和住院时间的缩短,其总体医疗成本可能与传统方案相当。近年发表的 Meta 分析也提示 LB 在减少术后阿片用量方面具有潜在优势,但其成本效益结论仍存在异质性。然而,上述成本效益结论主要基于国外医疗体系的数据。在我国以按疾病诊断相关分组和按病种分值付费为主导的医保支付背景下,高值药品的引入需以改善核心预后指标为前提。现有临床试验在多模式镇痛方案标准化、手术微创化程度等方面存在异质性, LB 在降低总体医疗成本、提升卫生经济学获益方面,尚缺乏高质量本土循证医学证据。

4 总结与展望

LB 依托多囊脂质体缓释技术,可将外周神经及筋膜平面阻滞的镇痛时效延长至 72 h。将其纳入心胸外科围术期多模式镇痛方案,有助于减少术后阿片用量,规避硬膜外置管相关并发症,促进患者早期康复。

然而, LB 在心胸外科的推广应用仍面临以下挑战:①与 TEA 相比的镇痛效能争议;②药理弥散受限;③经济成本较高。针对上述局限,未来研究应从以下方向突破:①深化镇痛效能验证,明确 LB 在不同手术类型中的临床定位,探索 LB 联合其他镇痛干预的优化方案;②优化给药策略,探索不同区域阻滞路径的最佳容量与浓度配比,为高 BMI 等特殊群体建立个体化剂量方案;③关注特殊人群的药代动力学与用药安全;④开展基于医保支付体系的本土化卫生经济学评价。⑤针对 PIB 等 LB 优势不明确的解剖区域,需进一步探索优化给药策略,并明确 LB 在不同疼痛来源(皮肤/肌肉/骨骼)中的效能差异,以指导精准选择适用解剖靶点。

综上所述, LB 为心胸外科围术期镇痛提供了新的选择,其临床应用仍需在效能验证、技术优化和经济学评估等方面持续深入。随着本土研究的不断积累和给药方案的日趋完善, LB 有望在我国心胸外科加速康复路径中发挥更为重要的作用。

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LI Bingqian was responsible for drafting the manuscript, LI Bingqian and GAO Yuxin jointly conducted the literature review. CHEN Yu provided academic supervision, manuscript review, and funding acquisition for the study.

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