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舒芬太尼靶控输注的临床应用进展

丁慧萍，宦烨，王雯 综述 蔡宏伟 审校

(中南大学湘雅医院麻醉科，长沙 410000)

[摘 要] 靶控输注(target-controlled Infusion，TCI)是在输注静脉麻醉药物时应用药代动力学和药效动力学原理，通过调节目标(血浆或效应室)的药物浓度来控制或维持麻醉深度。舒芬太尼TCI广泛应用于不同手术的麻醉，本文将主要介绍舒芬太尼TCI在全麻的诱导和气管插管、心脏手术、需要术中唤醒手术、病态肥胖患者手术以及术后镇痛中的应用，旨在为今后的临床应用和基础研究提供理论参考。

[关键词] 舒芬太尼；靶控输注；麻醉

Clinical application progress of sufentanil target-controlled infusion

DING Huiping, HUAN Ye, WANG Wen, CAI Hongwei

(Department of Anesthesiology, Xiangya Hospital, Central South University, Changsha 410000, China)

Abstract Target-controlled Infusion (TCI) is the application of pharmacokinetics and pharmacodynamic principles when intravenous anesthetics are infused, and the depth of anesthesia is controlled or maintained by adjusting the drug concentration of the target (plasma or effect chamber). Sufentanil TCI is widely used in anesthesia for different operations. This article summarizes domestic and foreign literature, to give an introduction of sufentanil TCI in induction of general anesthesia and tracheal intubation, cardiac surgery, surgery that requires intraoperative wake-up, surgery for morbidly obese patients and the application of postoperative analgesia, with an aim to provide theoretical references for future clinical applications and basic research.

Keywords sufentanil; target-controlled infusion; anesthesia

舒芬太尼是迄今为止发现的最有效的长效阿片类受体激动剂，它对μ1受体的选择性高，但对δ受体的亲和力低[1]，具有镇痛作用强、血流动力学稳定的优点。靶控输注(target-controlled Infusion，TCI)是输注静脉麻醉药物时应用药代动力学和药效动力学原理，通过调节目标(血浆或效应室)的药物浓度来控制或维持麻醉深度，它具有快速输送药物和操作简单的优点[2]，使静脉麻醉更加精确、简

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通信作者 (Corresponding author)：蔡宏伟，Email: chw2005@163.com
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便、可控，大大提高了临床麻醉的可控性和安全性。舒芬太尼的药物代谢半衰期较长，TCI可防止出现药物的蓄积，且有利于患者术后快速苏醒[3]。舒芬太尼TCI的应用范围目前已扩大到全身麻醉的诱导和气管插管、心脏手术的麻醉、需要术中唤醒手术的麻醉、病态肥胖患者手术的麻醉，术后镇痛等各个领域，也得到了普遍认可。本文对靶控输注舒芬太尼的药代动力学模型和临床应用进行总结。

1 舒芬太尼的药代动力学模型

舒芬太尼的血浆蛋白结合率为92.5%，起效快、脂溶性高、镇痛时间长、对呼吸抑制作用弱，同时还具有对循环影响小、可降低创伤引起的全身应激反应以及稳定血流动力学等特点。舒芬太尼的代谢特点常使用“三室模型”来描述[4]，适用于TCI，且靶控的(血浆或效应室)浓度稳定[5]。舒芬太尼TCI包括启动剂量、逐渐降低的输注速率和恒定的维持速率。

目前舒芬太尼TCI的药代动力学有Gepts、Hudson、Scott、Bovill等模型[6]。其中临床上舒芬太尼TCI常用的药代动力学模型为Gepts模型，该模型用于接受普外科手术的患者[7]。国内有研究[8]将体重(M)和中央室容积(V1)进行线性回归分析，修正了药代动力学模型，结果表明修正参数后的模型舒芬太尼TCI的准确性提高，更适用于中国患者。Hudson、Scott模型来自需要接受体外循环(cardiopulmonary bypass，CPB)的心脏手术患者，Hudson模型用于需要CPB的心脏手术中准确性良好[9-11]。Bovill模型分为高浓度和中等浓度舒芬太尼TCI，高浓度舒芬太尼TCI用于中国人时，TCI期间的准确性较高，而在停止TCI后预计的血药浓度与实际测量的血药浓度差异较大[5]；中等浓度舒芬太尼TCI用于中国人时，模型所预计的舒芬太尼血药浓度与实际测量的血药浓度的偏差在临床可接受的范围内，可安全有效地用于成人全身麻醉手术[12]。

2 舒芬太尼 TCI 的临床应用

2.1 全身麻醉的诱导和气管插管

舒芬太尼是目前镇痛作用最强的阿片类药物，具有使用后心血管功能稳定等特点[13-14]，并且临床研究证实舒芬太尼很少导致患者术后急性疼痛和痛觉过敏的发生[15]。TCI技术使静脉麻醉更精确、平稳和可控。因此，舒芬太尼TCI经常用于全身麻醉的诱导和气管插管。在诱导阶段，舒芬太尼TCI能有效抑制气管插管的心血管反应，靶控输注给药可以调整舒芬太尼的输注速度，以保持所需的目标靶控浓度[12]。钱晓岚等[16]发现：在靶控输注丙泊酚浓度为3.0 μg/mL进行麻醉诱导时，舒芬太尼抑制普通喉镜和视频喉镜气管插管反应的半数有效浓度(the half-effective target effect-site concentration，Ce_{50})为0.32 ng/mL。也有文献[17]报道舒芬太尼抑制帝视内窥镜气管插管反应的Ce_{50}为0.29 ng/mL。这提示帝视内窥镜的刺激强度低于普通喉镜或视频喉镜。因此在选择不同的喉镜插管时，可选用合适的舒芬太尼TCI的靶控浓度，使患者安全平稳地度过全身麻醉诱导期。

2.2 心脏手术的麻醉

在心脏手术麻醉期间，通常通过持续输注阿片类药物来实现镇痛作用。相比于短效阿片类药物瑞芬太尼，在心脏手术中使用舒芬太尼不仅可改善血液动力学的稳定性、提高脑组织氧合水平[18]，还会降低患者术后疼痛和痛觉过敏的发生率，减少术后吗啡的消耗量[19]。TCI不仅可以改善患者术中血流动力学的稳定性，而且可以降低术中阿片类药物的用量[20]。通常在心脏手术的麻醉期间使用舒芬太尼TCI，并且已经开发了几种药代动力学模型。Hudson等[9,11,21]和Scott等[10]等的模型用于需要CPB的心脏手术过程中准确性良好。但是也有不同观点表示与CPB相关的病理生理变化可能会极大地影响舒芬太尼的药代动力学。Gepts模型用于心脏手术麻醉时，在CPB之前准确性良好，而在CPB期间，舒芬太尼TCI实际测量与模型预测的舒芬太尼药物浓度之间存在重大误差[22]。在冠状动脉搭桥手术中使用Gepts模型进行舒芬太尼TCI，结果表明：CPB之前、期间和之后实际测量与模型预测的舒芬太尼药物浓度之间存在重大误差[7]。因此可以得出结论，尽管目前Gepts模型是舒芬太尼TCI泵中唯一可用的模型，但该模型源自进行非心脏手术的患者，它不适用于使用CPB的心脏手术的麻醉。

2.3 需要术中唤醒手术的麻醉

在斜视手术和特发性脊柱侧弯等手术过程中，常常需要在术中唤醒患者来配合外科医生。术中唤醒要求患者术中从麻醉状态快速恢复意识，可能会伴有多种不良现象，包括咳嗽、躁动、高血压和心动过速等[23]。因此，在需要术中唤醒的外科手术中，麻醉医生必须平衡镇静和镇痛，使患者对

于术中唤醒有积极的回忆，并且有足够的意识来响应医生的指令[24]。最近的报道[25-26]表明：与麻醉期间使用的短效阿片类药物瑞芬太尼相比，舒芬太尼TCI对实现术中镇痛和预防咳嗽和躁动更有用。通常联合使用舒芬太尼TCI和七氟醚或丙泊酚来实现平衡麻醉[27]。Zhang等[28]选择60例需要接受术中唤醒的青少年特发性脊柱侧弯的患者作为研究对象，采用Gepts模型的舒芬太尼TCI联合七氟醚静吸复合麻醉，在术中唤醒期间停止七氟醚，接受低浓度舒芬太尼TCI，结果表明舒芬太尼TCI作为术中唤醒期间的目标靶控效应室浓度中位数(median effective effect-site concentration，EC_{50})和95%可信区间(confidence interval，CI)分别为0.1682 ng/mL和0.1641~0.1724 ng/mL。在唤醒期间靶控低浓度舒芬太尼可提高唤醒的质量[29]，减少术后并发症的可能性[30]，且七氟醚和舒芬太尼TCI联合麻醉诱导可提高术中唤醒测试的成功率。舒芬太尼TCI可作为需要术中唤醒的患者首选的阿片类药物，提高术中唤醒测试的成功率，改善术中唤醒质量[28,31]。

2.4 病态肥胖患者手术的麻醉

病态肥胖与麻醉相关的病死率和发病率增加有关[32]。病态肥胖患者($BMI>35\ kg/m^2$)在麻醉期间呼吸受损，这增加了术后低氧血症和高碳酸血症的发生率[33]。合理选择药物对于病态肥胖患者手术后的苏醒质量和恢复至关重要。阿片类药物的选择及其给药方式可能会影响肥胖患者的术后疼痛、吗啡消耗、血液动力学和呼吸的平稳[34]。对于病态肥胖患者，术中使用舒芬太尼TCI较瑞芬太尼TCI拥有更好的术后苏醒质量以及术后镇痛效果[35]，并且舒芬太尼TCI可更好地控制出现药物蓄积、术后苏醒延迟和呼吸抑制等不良反应[36]。Slepchenko等[37]研究表明来自正常体重人群的药代动力学参数集可准确预测病态肥胖患者的血浆舒芬太尼浓度。当在病态肥胖患者中使用舒芬太尼TCI时，建议将起始诱导的目标靶控效应室浓度设为0.4 ng/mL，在0.3~0.65 ng/mL的靶控效应室浓度范围间调控维持术中麻醉[36]。手术结束前30 min，应降低舒芬太尼TCI的目标效应室浓度，以实现术后自主呼吸的良好恢复和令人满意的镇痛效果。自发通气期间测得的舒芬太尼血浆浓度为(0.13±0.03) ng/mL[38]。

2.5 术后镇痛

许多患者术后均出现急性疼痛，在一项全国性调查[39]中，大约80%的患者术后经历了急性疼痛，在这些患者中，有86%的患者疼痛中度、重度或极重度。急性疼痛会影响患者术后的生活质量、功能恢复，增加术后并发症和慢性疼痛的发生风险[40]。舒芬太尼是镇痛作用很强的阿片类药物之一，已广泛用于控制术后疼痛。舒芬太尼TCI可防止长时间输注引起的药物蓄积，并且可设定不抑制患者自主呼吸的目标靶控血浆药物浓度。在进行大腹部手术后，与瑞芬太尼TCI 1 ng/mL合用术毕前30 min给予0.15 mg/kg吗啡相比，术后使用舒芬太尼TCI 0.25 ng/mL维持镇痛可以更有效地治疗术后疼痛，并且不引起呼吸抑制、不影响患者的拔管时间和术后苏醒时间[41]。但使用舒芬太尼TCI用于术后镇痛时，减轻疼痛缓解而不引起呼吸抑制所需的目标血浆浓度尚未明确定义。多项研究确定了获得令患者满意的止痛效果的舒芬太尼有效血浆药物浓度范围为0.08~0.15 ng/mL[42]，预防呼吸抑制的血浆浓度为0.25 ng/mL以下[43]。

3 结语

舒芬太尼TCI的临床应用范围逐渐扩大，选择合适的药代动力学模型，合理的调控舒芬太尼的目标靶控浓度，不仅能很好地配合外科手术的需求，而且可保证患者术中血流动力学平稳和术后良好的苏醒质量及镇痛效果。目前，舒芬太尼TCI尚未普及使用，是由于目前临床没有疼痛程度监测的金标准及成熟的闭环靶控输注设备，我们期望日后可以研究出关于疼痛程度监测的最佳指标，将其联合运用在TCI输注泵，可根据患者疼痛程度，自动调整镇痛药物的输注速度，并将镇痛水平维持在设定的目标范围内。避免单纯TCI技术中群体药物代谢动力学的限制，日后可以做到镇痛药物使用的个性化和精细化，有效避免由于个体差异以及手术刺激的疼痛强度改变导致的镇痛水平过深或过浅。日后TCI也可能运用到慢性癌性疼痛的全身治疗、重症患者[44]等中。在不抑制患者呼吸及循环系统的情况下、有效解决患者疼痛。我们希望未来研究出各种镇痛药物的闭环靶控输注泵，将人工智能引入控制算法中将会有效地鉴别临床有效数据和噪声干扰，使镇痛效果可视、可控，做到更精准化管理。同时引入反馈信息更快、受干扰程度更小的镇痛监测指标，进一步提高闭环系统的稳定性。从而为临床合理应用镇痛药物、解决世界疼痛难题做出贡献，更好地服务于患者。

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