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行双侧鼓膜切开及放置通气管手术患儿，术中芬太尼滴鼻、肌肉或静脉注射吗啡对术后镇痛疗效及精神行为的影响

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全身给予利多卡因改善门诊腹腔镜手术术后苏醒质量

Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery.

.Gildasio S. De Oliveira Jr., MD, MSCI*, Paul Fitzgerald, MS RN*, Lauren F. Streicher, MD†, R-Jay Marcus, MD* and Robert J. McCarthy, PharmD*

From the Departments of *Anesthesiology and †Obstetrics and Gynecology, Northwestern University, Chicago, Illinois.

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背景：围术期静脉注射利多卡因可以提高术后镇痛效果。先前有一些关于门诊病人应用利多卡因的研究，但并没有对影响病人出院后的阿片用量方面的报道。更重要的事，静脉注射利多卡因对于日间手术病人术后恢复质量是否更好也是不清楚的。我们此次研究正是想检验静脉注射利多卡因对门诊腹腔镜手术患者的苏醒质量的影响。

方法：试验遵循随机双盲、安慰剂对照原则，健康女性被分成两组，试验组给予1.5mg/kg负荷剂量的利多卡因后，随后以2.0mg/kg/h速率输注至手术结束。对照组则给与生理盐水。原始数据来自一份手术结束24h后关于复苏质量的调查表
，基于先前病人麻醉及手术后的复苏质量40分区间排序，建立一个代表其临床相关的10分区间排序，其他数据包括阿片消耗量，疼痛得分及出院时间，数据对照采用t检验及Wilcoxon 检验，应用Spearman ρ系统分析评估阿片消耗量及苏醒质量的相关性，当原始数据$P < 0.01$时拒绝无效假设。

结果：研究中总共70个样本，最后完成63份，在试验两组中样本及手术方法均无差异，相比于生理盐水组，利多卡因组具有更好的苏醒质量，中位数的差值为16（99%可信区间为 2–28), $P = 0.002$. 利多卡因组较生理盐水组更快达到出院标准，中位数差值为-26分钟(95% 可信区间为-6 to -46 分钟) ($P = 0.03$).出院后，研究对象在利多卡因组较生理盐水组需要更少的口服阿片类药物，中位数差值为-10 (95% 可信区间, 0 到−30)（或口服等效剂量的吗啡）($P = 0.01$)。阿片类需要量与复苏质量成反比($\rho = 0.64$, $P < 0.001$)。

结论：静脉注射利多卡因可提高门诊腹腔镜手术患者术后苏醒质量，并且需要更少的阿片消耗量。对于门诊手术的复苏质量方面，利多卡因是一种安全、经济、有效的药物。

（邓利兵译 薛张纲校）

BACKGROUND: Perioperative systemic lidocaine has been shown to have beneficial postoperative analgesic effects. The only previous study examining the use of lidocaine in the outpatient setting did not detect an opioid-sparing effect after hospital discharge. More importantly, it is unknown whether systemic lidocaine provides a better postoperative quality of recovery to patients undergoing ambulatory surgery. Our objective in the current study was to examine the effect of systemic lidocaine on postoperative quality of recovery in patients undergoing outpatient laparoscopic surgery.

METHODS: The study was a prospective, randomized, double-blind, placebo-controlled clinical trial. Healthy female subjects were randomized to receive lidocaine (1.5 mg/kg bolus followed by a 2 mg/kg/h infusion until the end of the surgical procedure) or the same volume of saline. The primary outcome was the Quality of Recovery-40 questionnaire at 24 hours after surgery.A 10-point difference represents a clinically relevant improvement in quality of recovery based on previously reported values on the mean and range of the Quality of Recovery-40 score in patients after anesthesia and surgery. Other data collected included opioid consumption, pain scores, and time to meet hospital discharge. Data were compared using group t tests and the Wilcoxon exact test.The association between opioid consumption and quality of recovery was evaluated using Spearman ρ. $P < 0.01$ was used to reject the null hypothesis for the primary outcome.

RESULTS: Seventy subjects were recruited and 63 completed the study. There were no baseline differences regarding subject and surgical characteristics between the study groups.Patients in the lidocaine group had better global quality of recovery scores compared with the saline group,median difference of 16 (99% confidence interval [CI], 2–28), $P = 0.002$. Patients in the lidocaine group met hospital discharge criteria faster than the saline group, mean difference of −26 minutes (95% CI, −6 to −46 minutes) ($P = 0.03$). After hospital discharge, subjects in the

lidocaine group required less oral opioids, median difference of −10 (95% CI, 0 to −30) (oral milligrams morphine equivalents), median difference of −10 (95% CI, 0 to −30)than the saline group (P = 0.01). There was an inverse association between postoperative opioid consumption and quality of recovery (ρ = 0.64, P < 0.001).

CONCLUSIONS: Systemic lidocaine improves postoperative quality of recovery in patients undergoing outpatient laparoscopy. Patients who received lidocaine had less opioid consumption, which translated to a better quality of recovery. Lidocaine is a safe, inexpensive, effective strategy to improve quality of recovery after ambulatory surgery.

一项评估Remimazolam (CNS 7056)的安全性，药代动力学和药效动力学，以安慰剂和咪达唑仑作对照组，单一剂量逐渐递增的I期研究：第二部分，群体药代动力学和药效动力学的建模与仿真

A Placebo- and Midazolam-Controlled, Phase I, Single Ascending-Dose Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of Remimazolam (CNS 7056): Part II. Population Pharmacokinetic and Pharmacodynamic Modeling and Simulation

Hugh R. Wiltshire, PhD*, Gavin J. Kilpatrick, PhD†, Gary S. Tilbrook, PhD† and Keith M. Borkett, BSc†

*Independent Consultant, Welwyn, Hertfordshire; and †PAION UK Ltd., Compass House, Vision Park, Histon, Cambridge, United Kingdom.

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背景：一种新的苯二氮䓬类药物，remimazolam，被组织酯酶迅速代谢成为一种无活性的化合物，它起效快，镇静作用时间短且可预测持续时间，并且比现有的药物恢复更快。为今后的研究，我们就有关数据模型和给药方案的模拟作以报告。

方法：以I期，单中心，双盲试验，安慰剂和阳性对照组，随机化，单一剂量逐渐增加的方法来研究。54名健康受试者分为9组，分别接受单一剂量1分钟静脉注射remimazolam (0.01–0.3 mg/kg)。18名对照受试者使用咪达唑仑，9名使用安慰剂。群体药代动力学和药效动力学的数据进行了建模，获取的参数用于蒙特卡罗方法替代给药方案。

结果：一个咪达唑仑4室哺乳动物的药代动力学模型和一个remimazolam生理基础的再循环模型与观察到的血浆水平相适应。remimazolam的再循环模型解释了观察到的在稍后的时间点静脉比动脉有更高的浓度。这2个模型被用来模拟镇静的药效动力学模型所需的动脉浓度（改良警觉镇静评分[MOAA/S]）并提供了药效动力学参数的总体平均值，如下：remimazolam和咪达唑仑分别是脑电双频指数- IC50: 0.26, 0.07 μg/mL; γ: 1.6, 8.6; ke0: 0.14, 0.053 min−1; IMAX: 39, 19, MOAA/S–IC50: 0.4, 0.08 μg/mL; γ: 1.4, 3.4; ke0: 0.25, 0.050 min−1。总数中获得>70%的MOAA/S评分为2至4分的模型可以进一步建立。这个标准在remimazolam 6mg的初始负荷剂量，>2分钟的时间间隔维持3mg的维持剂量得以达成（95%置信区间：67%-74%）。预计在16分钟以内，89%被这个负荷/维持剂量方案处理人群的(95% 置信区间: 87%–91%)MOAA/S评分会恢复到5分。

结论：remimazolam和咪达唑仑建立的群体药代动力学和药效动力学模型观察到的数据相吻合。基于这些模型的模拟结果表明，remimazolam产生极为迅速的镇静，在治疗开始的3分钟内达到最大效果。这种性能将使维持剂量比慢反应药物更加精准地使用。所观察到的没有临床相关的协变量的影响，建议按体重注射剂量相比较在体重范围研究(65–90 kg)内的一致性的remimazolam固定剂量可能不占优势。

（方昕译 薛张纲校）

BACKGROUND: A new benzodiazepine, remimazolam, which is rapidly metabolized by tissue esterases to an inactive metabolite, has been developed to permit a fast onset, a short, predictable

duration of sedative action, and a more rapid recovery profile than currently available drugs. We report on modeling of the data and simulations of dosage regimens for future study.

METHODS: A phase I, single-center, double-blind, placebo and active controlled, randomized, single-dose escalation study was conducted. Fifty-four healthy subjects in 9 groups received a single 1-minute IV infusion of remimazolam (0.01–0.3 mg/kg). There were 18 control subjects taking midazolam and 9 placebos. Population pharmacokinetic and pharmacodynamic modeling of the data was undertaken and the parameters obtained were used for Monte-Carlo simulations of alternative dosing regimens.

RESULTS: A 4-compartment mammillary pharmacokinetic model of midazolam and a physiologically based recirculation model of remimazolam were fitted to the observed plasma levels. The recirculation model of remimazolam explained the observed high venous, compared with arterial, concentrations at later time points. The 2 models were used to simulate the arterial concentrations required for the pharmacodynamic models of sedation (Bispectral Index and Modified Observer's Assessment of Alertness/Sedation [MOAA/S]) and gave population mean pharmacodynamic parameters as follows: Bispectral Index–IC50: 0.26, 0.07 μg/mL; γ: 1.6, 8.6; ke0: 0.14, 0.053 min−1; IMAX: 39, 19, and MOAA/S–IC50: 0.4, 0.08 μg/mL; γ: 1.4, 3.4; ke0: 0.25, 0.050 min−1 for remimazolam and midazolam, respectively. Simulations to obtain >70% of the population with MOAA/S scores of 2 to 4 were developed. This criterion was achieved (95% confidence intervals: 67%–74%) with a 6-mg initial loading dose of remimazolam followed by 3-mg maintenance doses at >2-minute intervals. Recovery to a MOAA/S score of 5 is predicted to be within 16 minutes for 89% (95% confidence intervals: 87%–91%) of the treated population after this loading/maintenance dose regimen.

CONCLUSIONS: Population pharmacokinetic and pharmacodynamic models developed for remimazolam and midazolam fitted the observed data well. Simulations based on these models show that remimazolam delivers extremely rapid sedation, with maximal effect being reached within 3 minutes of the start of treatment. This property will enable maintenance doses to be given more accurately than with slower-acting drugs. No covariate effects considered to be clinically relevant were observed, suggesting that dosing by body weight may offer no advantage over fixed doses in terms of consistency of exposure to remimazolam within the weight range studied (65–90 kg).

技术交流：麻醉呼吸内循环:学步儿童与新生儿到达设定七氟烷浓度的时间：模拟肺测试

Technical Communications: Inside Anesthesia Breathing Circuits: Time to Reach a Set Sevoflurane Concentration in Toddlers and Newborns: Simulation Using a Test Lung

Delphine Kern, MD, PhD, Claire Larcher, MD, Bertrand Basset, MD, Xavier Alacoque, MD, Rose Fesseau, MD, Kamran Samii, MD, Vincent Minville, MD, PhD and Olivier Fourcade, MD, PhD

From the Department of Anesthesiology and Intensive Care, University Hospital of Toulouse, Toulouse, France.

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我们应用Primus (Drägerwerk, AG, Lübeck, Germany)麻醉机以及Avance（ GE Datex-Ohmeda, Munich,
Germany）麻醉机对于学步儿童和新生儿通气设定测量了达到预计吸入麻醉浓度所花费的时间。七氟烷浓度从o%至6%的洗入时间和通过1-
2倍于分钟通气的新鲜气体将七氟烷浓度从6%至0%的洗脱时间之和测量得到七氟烷达到95%目标吸入浓度的时间。在1.5升新鲜气体流量，潮气量50ml，呼吸频率30次/分标准下，Avance麻醉机比Primus麻醉机快（Avance 65秒[95%可信区间：55-78]，Primus
310秒[95%可信区间：261-
359]）。在更高的新鲜气体流量和更大的分钟通气率条件下两者时间缩短的程度相同。新

鲜气体流量加倍的效果变量大且低于预期。对于Primus麻醉机，新生儿比学步儿童达到设定浓度的时间要慢，Avance麻醉机则两组时间相同。我们的数据证实：呼吸机达到目标吸入麻醉药物浓度的时间取决于呼吸循环容量、新鲜气体流量以及分钟通气量。

（郭晨跃译 薛张纲校）

We measured the time it takes to reach the desired inspired anesthetic concentration using the Primus (Drägerwerk, AG, Lübeck, Germany) and the Avance (GE Datex-Ohmeda, Munich, Germany) anesthesia machines with toddler and newborn ventilation settings. The time to reach 95% of inspired target sevoflurane concentration was measured during wash-in from 0 to 6 vol% sevoflurane and during wash-out from 6 to 0 vol% with fresh gas flows equal to 1 and 2 times the minute ventilation. The Avance was faster than the Primus (65 seconds [95% confidence interval (CI): 55 to 78] vs 310 seconds [95% CI: 261 to 359]) at 1.5 L/min fresh gas flow, tidal volume of 50 mL, and 30 breaths/min. Times were shorter by the same magnitude at higher fresh gas flows and higher minute ventilation rates. The effect of doubling fresh gas flow was variable and less than expected. The Primus is slower during newborn than toddler ventilation, whereas the Avance's response time was the same for newborn and toddler ventilation. Our data confirm that the time to reach the target-inspired anesthetic concentration depends on breathing circuit volume, fresh gas flow, and minute ventilation

比较在正常情况下的绵羊和脓毒血症高代谢状态下的绵羊中，苯肾对全身和局部血液动力学的影响

The systemic and regional hemodynamic effects of phenylephrine in sheep under normal conditions and during early hyperdynamic sepsis.

Hiroshi Morimatsu, MD*, Ken Ishikawa, MD†, Clive N. May, PhD†, Michael Bailey, PhD‡ and Rinaldo Bellomo, MD*

From the *Department of Intensive Care and Department of Medicine, Austin Health, Melbourne, Victoria, Australia; †Howard Florey Institute, University of Melbourne, Parkville, Victoria, Australia; and ‡Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.

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背景：苯肾在治疗低血压时可引起重要器官血流减少。因此，我们研究正常状态和患脓毒血症的绵羊中，苯肾对全身和局部血流的影响。

方法：观察清醒的绵羊和活体大肠杆菌所致的脓毒血症的绵羊组对苯肾的反应，及持续灌注6小时后的反应。利用流量探头监测心输出量和肠系膜、冠脉、肾血流情况。

结果：在对照组，苯肾降低心输出量和心率，但增加每搏量和平均动脉压(84 ± 6 到108 ± 6 mm Hg，平均差别为19；95%置信区间为17-21)。一过性降低局部肠系膜血流，对冠脉血流无影响，肾血流增加。高代谢脓毒血症期，所有血管床血管扩张，血流增加，苯肾可恢复MAP和每搏量至正常范围，但心率、心输出量、总外周循环逐渐降低。苯肾降低肠系膜和冠脉传导，血流减少不会持续存在，但肾传导明显降低，而总的肾血流明显增加(293 ± 22 vs 347 ± 100 mL/min; 平均差别为55 [18.8%]；95% CI为47-65)。

结论：在早期高代谢脓毒血症的绵羊中，苯肾可以维持MAP、增加心输出量和肾血流，降低心率和冠脉血流，但不降低肠系膜动脉血流。在正常动物中苯肾也有相似的反应。

（韩旭译 薛张纲校）

BACKGROUND: Phenylephrine treatment of hypotension in sepsis raises concern because it may decrease vital organ bloodflow. Accordingly, we investigated the effects of phenylephrine on systemic and regional bloodflow in normal and septic sheep.

METHODS: Responses to phenylephrine or vehicle infusion for 6 hours were determined in conscious normal sheep and sheep with early sepsis induced by administration of live Escherichia coli. Cardiac output and coronary, mesenteric, and renal bloodflow were measured with implanted flow probes.

RESULTS: In normal sheep, phenylephrine decreased cardiac output and heart rate (HR) but increased stroke volume and mean arterial blood pressure (MAP) (84 ± 6 to 108 ± 6 mm Hg, magnitude of mean difference [diff.] 19 [22.6%]; 95% confidence intervals [CI], 17-21). There were significant decreases in regional conductance values with a transient decrease in mesenteric bloodflow, no change in coronary bloodflow, and increased renal bloodflow (222 ± 53 to 271 ± 55 mL/min; diff. 31 [13.9%]; 95% CI, 26-36). During hyperdynamic sepsis, vasodilatation and increased bloodflow occurred in all vascular beds. Phenylephrine restored MAP and stroke volume to baseline values, but HR, cardiac output, and total peripheral conductance progressively decreased. Phenylephrine decreased mesenteric and coronary conductance, with no sustained reduction in flows, but renal conductance was significantly decreased and overall renal bloodflow increased (293 ± 22 vs 347 ± 100 mL/min; diff. 55 [18.8%]; 95% CI, 47-65).

CONCLUSIONS: In sheep with early hyperdynamic sepsis, phenylephrine, at a dose that restored MAP, increased stroke volume and renal bloodflow while decreasing HR and coronary bloodflow but not mesenteric bloodflow. Similar responses were seen in normal animals.

评论文章：评论在小儿心脏外科手术中使用未被临床实验认可的重组活化Ⅶ因子。

Review Article: Review of the Off-Label Use of Recombinant Activated Factor VII in PediatricCardiac Surgery Patients.

Nina A. Guzzetta, MD, FAAP*, Isobel A. Russell, MD, PhD, FACC† and Glyn D. Williams, MBChB, FFA‡

From the *Department of Anesthesiology, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA; †Department of Anesthesiology, University of California School of Medicine, San Francisco, Moffitt Long Hospitals, San Francisco, CA; ‡Department of Anesthsiology, Stanford University School of Medicine, Lucile Packard Children's Hospital, Palo Alto, CA.

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摘要：近年来未被临床实验认可的重组活化因子Ⅶ（rFVIIa）的使用显著增加，尤其是在小儿心脏外科手术中的应用，而且医生对该药物的用法很不一样。 在2009年，先天性心脏麻醉协会（CCAS）组成一个专案组审查有关rFVIIa在小儿心脏手术病例中的应用的文献。 CCAS工作小组的目标是评估当前的使用和有关rFVIIa治疗的建议，以提高医疗质量，改善患者的预后，降低医疗成本，并制定未来的研究。 在这次审查中，我们总结了几项有关目前rFVIIa在小儿心脏外科手术病人中使用的重要结论，包括适应症、疗效、安全性、剂量及监测。该小组选择和研究了 所有2000以来发表的有关rFVIIa在小儿及相关成人心脏手术中的应用的文献。 在审查的40名儿科病例中，只有1个是一个前瞻性的随机对照试验，从而使药效测定困难。没有实质性的证据支持rFVIIa在小儿心脏手术作为预防或常规治疗的疗效。rFVIIa在抢救性治疗中可能有用，因为目前的观察证据表明，rFVIIa在小儿心脏外科手术中的应用的潜在利益可能大于其所带来的风险。抢救性治疗适用于大出血、潜在威胁生命和常规疗法难治的情况。然而，当考虑对有血栓栓塞并发症的患者使用fFVIIa时必须警惕，因为在这个时候临床和亚临床血栓形成继发rFVIIa治疗是未知的。本文用以帮助医生在决定何时和如何在小儿心脏手术的病人使用rFVIIa，它的目的不是确定标准的护理或执业准则。没有足够的数据支持以证据为基础的建议。 我们需要随机对照试验来评估rFVIIa作为预防，常规，或抢救治疗的疗效，并确定药物的安全性，特别是在血栓方面。 CCAS评估rFVIIa的专责小组将继续检索文献，收集数据，并更新更多有用的信息。

（贺盼译 薛张纲校）

Abstract：In recent years the off-label use of recombinant activated factor VII (rFVIIa) has markedly increased, particularly in pediatric cardiac surgery patients, and practitioners differ widely in their usage of the drug. In 2009, the Congenital Cardiac Anesthesia Society (CCAS) assembled a task force to review the literature on rFVIIa administration to pediatric cardiac surgery patients. The goal of the CCAS Task Force was to assess current practices and make recommendations about rFVIIa therapy to enhance quality of care, improve patient outcomes, reduce costs, and develop future research. In this review we summarized the important topics on current administration of rFVIIa to pediatric cardiac surgery patients including indications for use, efficacy, safety, dosing, and monitoring. All pediatric and pertinent adult literature regarding the administration of rFVIIa to cardiac surgical patients and published since 2000 were selected and studied. Of the 40 pediatric publications reviewed for this report, only 1 was a prospective randomized controlled trial thus making determinations of efficacy difficult. There is no substantive evidence to support the efficacy of rFVIIa as prophylactic or routine therapy during pediatric cardiac surgery. It may prove reasonable as rescue therapy because current observational evidence suggests that potential benefits of rFVIIa for this indication might outweigh the risks. Rescue therapy is appropriate for bleeding that is massive, potentially life-threatening, and refractory to conventional therapy. Nevertheless, extreme caution is advised when considering the administration of rFVIIa to patients who are at risk for thromboembolic complications because rates for clinical and subclinical thrombosis secondary to rFVIIa therapy are unknown at this time. This review is designed to aid practitioners in deciding when and how to administer rFVIIa to pediatric cardiac surgery patients; it is not intended to determine standard-of-care or practice guidelines. There are insufficient data to make evidence-based recommendations. Randomized controlled trials are needed to assess the efficacy of rFVIIa as prophylactic, routine, or rescue therapy and to determine the drug's safety profile particularly with regard to thrombosis. The CCAS rFVIIa Task Force will continue to monitor the literature, gather data, and make updates as more information becomes available.

使用加巴喷丁和普瑞巴林预防术后慢性疼痛：系统回顾与荟萃分析

The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis.

Hance Clarke, MSc, MD, FRCPC*†‡, Robert P. Bonin, PhD§, Beverley A. Orser, MD, PhD, FRCPC†‡, Marina Englesakis, BA MLIS‖, Duminda N. Wijeysundera, MD, PhD, FRCPC*‡¶# and Joel Katz, PhD**

From the *Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Ontario, Canada; †Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; ‡Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada; §Centre de Recherche Universite′ Laval Robert-Giffard, Universite′ Laval, Que′bec, Canada; ‖Library and Information Services, University Health Network, Toronto, Ontario, Canada; ¶Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada; #Institute of Health Policy Management and Evaluation, University of Toronto; **Department of Psychology and School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada.

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背景：许多临床试验已经证实了加巴喷丁和普瑞巴林作为辅助手段在减少术后急性疼痛方面的效果。然而，很少有实验来研究二者用于减少术后慢性疼痛。我们系统的回顾了一些已发表的关于使用加巴喷丁和普瑞巴林预防术后慢性疼痛（大于术后2个月）文献，并且依据大量的数据做了荟萃分析。数据检索相关的英文实验（Medline,Embase,Cochrane,IPA和CINAL）在2011年6月实行。

方法：进入当前系统回顾所要满足的标准是：随机，双盲评估疼痛和镇痛药的使用；利用有效手段镇痛的报告；镇痛药消耗的报告；不应该出现设计的不足，方法的问题或者致

使结果模棱两可的混淆因素。不符合预防性镇痛定义的和评估不在术后2个月的慢性疼痛的实验被排除在外。

结果：数据库检索产生474条引文。11个研究符合纳入标准。在这11个实验中，8个是研究加巴喷丁，其中4项发现围术期使用加巴喷丁减少了术后2月慢性疼痛的发生。3个关于普瑞巴林的研究阐述了其显著降低术后慢性疼痛，3个实验中的2个还发现了其对病人术后身体功能的改善。在一个荟萃分析中包含8项研究，加巴喷丁的6项实验阐述中至重度的减轻术后慢性疼痛（联合比率【OR】0.52；95%可信区间【CI】0.27—0.98；P=0.04），2项普瑞巴林的实验发现非常大程度的降低术后慢性疼痛（OR 0.09；95%可信区间 CI，0.02—0.79；P=0.007）。

结论：当前的审查支持这个观点即加巴喷丁和普瑞巴林的围术期使用在减轻术后慢性疼痛方面是有效的。为了证实早期的发现，需要更好的设计和适当投入的临床实验。

（胡晓清译 薛张纲校）

BACKGROUND: Many clinical trials have demonstrated the effectiveness of gabapentin and pregabalin administration in the perioperative period as an adjunct to reduce acute postoperative pain. However, very few clinical trials have examined the use of gabapentin and pregabalin for the prevention of chronic postsurgical pain (CPSP). We (1) systematically reviewed the published literature pertaining to the prevention of CPSP (≥2 months after surgery) after perioperative administration of gabapentin and pregabalin and (2) performed a meta-analysis using studies that report sufficient data. A search of electronic databases (Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, IPA, and CINAHL) for relevant English-language trials to June 2011 was conducted.

METHODS: The following inclusion criteria for identified clinical trials were used for entry into the present systematic review: randomization; double-blind assessments of pain and analgesic use; report of pain using a reliable and valid measure; report of analgesic consumption; and an absence of design flaws, methodological problems or confounders that render interpretation of the results ambiguous. Trials that did not fit the definition of preventive analgesia and did not assess chronic pain at 2 or more months after surgery were excluded.

RESULTS: The database search yielded 474 citations. Eleven studies met the inclusion criteria. Of the 11 trials, 8 studied gabapentin, 4 of which (i.e., 50%) found that perioperative administration of gabapentin decreased the incidence of chronic pain more than 2 months after surgery. The 3 trials that used pregabalin demonstrated a significant reduction in the incidence of CPSP, and 2 of the 3 trials also found an improvement in postsurgical patient function. Eight studies were included in a meta-analysis, 6 of the gabapentin trials demonstrated a moderate-to-large reduction in the development of CPSP (pooled odds ratio [OR] 0.52; 95% confidence interval [CI], 0.27 to 0.98; P = 0.04), and the 2 pregabalin trials found a very large reduction in the development of CPSP (pooled OR 0.09; 95% CI, 0.02 to 0.79; P = 0.007).

CONCLUSIONS: The present review supports the view that perioperative administration of gabapentin and pregabalin are effective in reducing the incidence of CPSP. Better-designed and appropriately powered clinical trials are needed to confirm these early findings.

氨甲环酸减少不停跳冠状动脉手术后失血：一个前瞻性、随机、双盲、安慰剂对照研究

Tranexamic Acid Reduces Blood Loss After Off-Pump Coronary Surgery: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

Guyan Wang, MD, PhD*, Gaoqiang Xie, PhD†, Tingting Jiang, MD‡, Yuefu Wang, MD, PhD*, Weipeng Wang, MD, PhD*, Hongwen Ji, MD, PhD*, Mingzheng Liu, MD*, Lei Chen, MD, PhD* and Lihuan Li, MD, PhD*

From the *Department of Anesthesiology, Fuwai Hospital and Cardiovascular Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; †Department of

Data Management, Peking University Clinical Research Institute, Beijing, China; ‡Department of Anesthesiology, 3201 Hospital, Shanxi province, China.

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背景：不停跳冠状动脉旁路移植术（OPCAB）后出血和需要同种异体输血的问题仍然存在。因此，我们评估了抗纤维蛋白溶解药氨甲环酸对实施OPCAB手术的患者术后出血和输血需要的影响。

方法：连续231名预定择期行OPCAB的病人入组参加研究。使用一个双盲方法将病人随机分配到接受氨甲环酸（划皮前推注1g随后以400mg/h术中滴注；*n*=116）或安慰剂（注射同等容积的生理盐水；*n*=115）。主要观察结果是术后24小时胸管引流量。还记录了同种异体输血、死亡率、大并发症和资源利用。

结果：与安慰剂组相比，接受氨甲环酸的病人在6小时时（270± 118 mL vs 416 ± 179 mL, $P < 0.001$）和24小时时（654 ± 224 mL vs 891 ± 295 mL, $P < 0.001$）的胸管引流量显著减少。同种异体红细胞输注（47 vs 31.9%, $P = 0.019$）和新鲜冰冻血浆输注（29.6% vs 17.2%, $P = 0.027$）也显著减少。在死亡率、并发症和资源利用方面两组之间没有差别。

结论：氨甲环酸减少不停跳冠状动脉手术后胸管引流量和同种异体输血的需要。

（唐莹 译 马皓琳 李士通 校）

BACKGROUND: Bleeding and the need for allogeneic transfusions are still problems after off-pump coronary artery bypass grafting (OPCAB) surgery. We therefore evaluated the effects of an antifibrinolytic, tranexamic acid, on postoperative bleeding and transfusion requirements in patients undergoing OPCAB surgery.

METHODS: Two hundred thirty-one consecutive patients scheduled for elective OPCAB were enrolled in the study. Using a double-blind method, the patients were randomly assigned to receive either tranexamic acid (bolus 1 g before surgical incision followed by an infusion of 400 mg/h during surgery; $n = 116$) or a placebo (infusion equivalent volume of saline solution; $n = 115$). The primary outcome was 24-hour postoperative chest tube drainage. Allogeneic transfusion, mortality, major morbidities, and resource utilization were also recorded.

RESULTS: In comparison with the placebo group, the patients receiving tranexamic acid had a significant reduction in chest tube drainage at 6 hours (270 ± 118 mL vs 416 ± 179 mL, $P < 0.001$) and 24 hours (654 ± 224 mL vs 891 ± 295 mL, $P < 0.001$). There was also a significant reduction in allogeneic red blood cell transfusions (47 vs 31.9%, $P = 0.019$) and fresh frozen plasma (29.6% vs 17.2%, $P = 0.027$) transfusions. There were no differences in mortality, morbidity, and resource utilization between the 2 groups.

CONCLUSIONS: Tranexamic acid reduces postoperative chest tube drainage and the requirement for allogeneic transfusion in off-pump coronary surgery.

教会一个旧的GABA受体新的技能

Teaching an Old GABA Receptor New Tricks

James R. Trudell, PhD, Edward Bertaccini, MD and M. Bruce MacIver, PhD

From the Department of Anesthesia, Stanford School of Medicine, Stanford, California.

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在这期杂志发行的特别收录的伴随文章中描述了改善依托咪酯和苯二氮卓类的类似药物药物分布动力学和降低副作用的尝试。两个种类的药物在γ-氨基丁酸A受体上都有其主要的作用位点，但是它们的结合位点有很大不同，而且作用机制也不一样。在这里，我们综述了γ-

氨基丁酸A受体的结构，并描述了两个可能的结合位点的部位。此外，我们描述了这些药是如何在系统水平上与神经系统相互作用的。我们留给其他的研究者们去探讨这些新药能否提供真正的临床疗效改善。

（张怡 译 马皓琳 李士通校）

The accompanying articles in this issue of the journal's special collection describe attempts to improve on the dynamics of distribution and reduce side effects of analogs of etomidate and benzodiazepines. Both classes of drugs have their principal sites of action on γ-aminobutyric acid type A receptors, although at very different binding sites and by different mechanisms of action. Herein, we review the structure of γ-aminobutyric acid type A receptors and describe the location of the 2 likely binding sites. In addition, we describe how these drugs can interact with the nervous system at a systems level. We leave it to other reviewers to discuss whether these new drugs offer true clinical improvements.

甲酯基-羧化依托咪酯在体和离体的药理学研究

In Vivo and In Vitro Pharmacological Studies of Methoxycarbonyl-Carboetomidate

Ervin Pejo, BS*, Joseph F. Cotten, MD, PhD*, Elizabeth W. Kelly, BA*, Ri Le Ge, MD, PhD*, Gregory D. Cuny, PhD†, Joydev K. Laha, PhD†, Jifeng Liu, PhD‡, Xiang Jie Lin, MSc‡ and Douglas E. Raines, MD*

From the *Massachusetts General Hospital, Boston, MA; †Brigham and Women's Hospital, Boston, MA; ‡Aberjona Laboratories, Inc, Beverly, MA.

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背景：我们既往曾研发出依托咪酯的两种同型物：甲酯基-依托咪酯和羧化依托咪酯，这两种化合物既可保持依托咪酯血流动力学平稳的特性又可缩短其抗肾上腺皮质类作用的持续时间并减轻作用程度。甲酯基（MOC）-依托咪酯代谢迅速，作用时间超短，而(R)-乙基 1-(1-苯乙基)-1H-吡咯-2-羧化物（羧化依托咪酯）并不强烈抑制11β-羟化酶。本研究假设MOC-依托咪酯不稳定的酯基可合并到羧化依托咪酯，从而产生一种能同时具备两种药剂各自的优点的新药，我们介绍了羧化依托咪酯的一个软性类似物——MOC-右旋-乙基-1H-吡咯环-2-羧化物（MOC-羧化依托咪酯）的合成及药理学特性。

方法：层析法测定MOC-羧化依托咪酯的辛醇：水分配系数并与依托咪酯、羧化依托咪酯和MOC-依托咪酯的辛醇：水分配系数进行比较。在蝌蚪及大鼠分别测定MOC-羧化依托咪酯翻正反射消失（LORR）的半数有效药物浓度(EC_{50})及半数有效剂量。采用双微电极电压膜片钳电生理技术测定MOC-羧化依托咪酯对$GABA_A$受体功能的作用，并采集混合大鼠血液标本使用高效液相质谱法评价其代谢稳定性。同时测定MOC-羧化依托咪酯的作用持续时间及对大鼠动脉血压、肾上腺皮质功能的影响。

结果：MOC-羧化依托咪酯的辛醇：水分配系数为3300 ± 280，而依托咪酯、羧化依托咪酯和MOC依托咪酯的分别为800 ± 180、15,000 ± 3700和190 ± 25。MOC羧化依托咪酯致蝌蚪LORR的EC_{50}为9 ± 1 μM，致大鼠LORR的EC_{50}为13 ± 5 mg/kg。13 μM的MOC-羧化依托咪酯可提高$GABA_A$受体电流400% ± 100%。MOC-羧化依托咪酯在混合大鼠血中的代谢半衰期为1.3分钟。大鼠LORR持续时间-催眠剂量对数值的曲线斜率，MOC-羧化依托咪酯显著低于羧化依托咪酯(4 ± 1比 vs 15 ± 3; $P = 0.0004123$)。催眠剂量时，MOC-羧化依托咪酯与单独的溶剂相比较对动脉血压和肾上腺皮质功能的影响均无显著差异。

结论：MOC羧化依托咪酯是一种$GABA_A$受体的调节剂，催眠作用强，较羧化依托咪酯代谢更为迅速，从脑中清除也较快，维持血流动力学稳态的特性与羧化依托咪酯相似且并不抑制肾上腺皮质的功能。

（邱郁薇 译 马皓琳 李士通 校）

BACKGROUND: We previously developed 2 etomidate analogs that retain etomidate's favorable hemodynamic properties but whose adrenocortical effects are reduced in duration or magnitude. Methoxycarbonyl (MOC)-etomidate is rapidly metabolized and ultrashort acting whereas (R)-ethyl 1-(1-phenylethyl)-1H-pyrrole-2-carboxylate (carboetomidate) does not potently inhibit 11β-hydroxylase. We hypothesized that MOC-etomidate's labile ester could be incorporated into carboetomidate to produce a new agent that possesses favorable properties individually found in each agent. We describe the synthesis and pharmacology of MOC-(R)-ethyl 1-(1-phenylethyl)-1H-pyrrole-2-carboxylate (MOC-carboetomidate), a "soft" analog of carboetomidate.

METHODS: MOC-carboetomidate's octanol:water partition coefficient was determined chromatographically and compared with those of etomidate, carboetomidate, and MOC-etomidate. MOC-carboetomidate's 50% effective concentration (EC_{50}) and 50% effective dose for loss of righting reflexes (LORR) were measured in tadpoles and rats, respectively. Its effect on γ-aminobutyric acid A ($GABA_A$) receptor function was assessed using 2-microelectrode voltage clamp electrophysiological techniques and its metabolic stability was determined in pooled rat blood using high performance liquid chromatography. Its duration of action and effects on arterial blood pressure and adrenocortical function were assessed in rats.

RESULTS: MOC-carboetomidate's octanol:water partition coefficient was 3300 ± 280, whereas those for etomidate, carboetomidate, and MOC-etomidate were 800 ± 180, 15,000 ± 3700, and 190 ± 25, respectively. MOC-carboetomidate's EC_{50} for LORR in tadpoles was 9 ± 1 μM and its EC_{50} for LORR in rats was 13 ± 5 mg/kg. At 13 μM, MOC-carboetomidate enhanced $GABA_A$ receptor currents by 400% ± 100%. Its metabolic half-life in pooled rat blood was 1.3 min. The slope of a plot of the duration of LORR in rats versus the logarithm of the hypnotic dose was significantly shallower for MOC-carboetomidate than for carboetomidate (4 ± 1 vs 15 ± 3, respectively; $P = 0.0004123$). At hypnotic doses, the effects of MOC-carboetomidate on arterial blood pressure and adrenocortical function were not significantly different from those of vehicle alone.

CONCLUSIONS: MOC-carboetomidate is a $GABA_A$ receptor modulator with potent hypnotic activity that is more rapidly metabolized and cleared from the brain than carboetomidate, maintains hemodynamic stability similar to carboetomidate, and does not suppress adrenocortical function.

麻醉中镇静成分在监视器上的延迟：状态熵和意识指数分析

Time Delay of Monitors of the Hypnotic Component of Anesthesia: Analysis of State Entropy and Index of Consciousness

Matthias Kreuzer, MSc*, Robert Zanner, MD†, Stefanie Pilge, MD†, Sabine Paprotny, MD*, Eberhard F. Kochs, MD* and Gerhard Schneider, MD†

From the *Department of Anesthesiology, Technische Universität München, Munich, Germany; †Department of Anesthesiology, Witten/Herdecke University, HELIOS Clinic, Wuppertal, Germany.

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通过分析脑电图（EEG）来评估麻醉中镇静成分的监护仪可以帮助降低术中知晓及回忆的发生率。为了计算代表麻醉水平的指数，这些监护仪在获得准确的数据显示前有不同程度的时间延迟。之前的研究用术中记录的真实和模拟脑电图信号以确定大脑状态和麻醉趋势

以及双频指数的时间延迟。本研究中笔者测定了状态熵和意识指数的时间延迟。为此，本研究回放了记录的代表不同麻醉水平的真实和模拟的脑电图序列来测试监护仪。

用模拟的和在围术期真实记录的提示“清醒”、“全麻”和“皮层抑制”的稳定状态的脑电信号以评估时间延迟。在从一个状态转换到另一个状态时测量时间延迟，时间延迟的定义为显示器达到稳定目标指数需要的时间间隔。使用模拟的和真实的脑电图序列获得了类似的结果。时间延迟并不恒定，范围18秒~152秒。数值增加和减少时时间延迟也不相同。时间延迟取决于起始的和目标指数值。指数计算的时间延迟可能会限制被研究的监护仪预防术中知晓及回忆的能力。如果监护仪用于药效学研究，麻醉水平向深或浅转换时不同的时间延迟可能是一个问题。

（许辛 译 马皓琳 李世通 校）

Monitors evaluating the hypnotic component of anesthesia by analyzing the electroencephalogram (EEG) may help to decrease the incidence of intraoperative awareness with recall. To calculate an index representing the anesthetic level, these monitors have different time delays until the correct index is displayed. In previous studies, intraoperatively recorded real and simulated EEG signals were used to determine time delays of cerebral state and Narco trend and Bispectral indices. In the present study, we determined time delays of state entropy and index of consciousness. For this purpose, recorded real and simulated EEG sequences representing different anesthetic levels were played back to the tested monitors.

Simulated and real perioperatively recorded EEG signals indicating stable states “awake,” “general anesthesia,” and “cortical suppression” were used to evaluate the time delays. Time delays were measured when switching from one state to another and were defined as the required time span of the monitor to reach the stable target index. Comparable results were obtained using simulated and real EEG sequences. Time delays were not constant and ranged from 18 to 152 seconds. They were also different for increasing and decreasing values. Time delays were dependent on starting and target index values. Time delays of index calculation may limit the investigated monitor's ability to prevent interoperative awareness with recall. Different time delays for increasing and decreasing transitions could be a problem if the monitors are used for pharmacodynamic studies.

既往腰椎间盘切除术不会改变椎管内分娩镇痛的效果

Prior Lumbar Discectomy Surgery Does Not Alter the Efficacy of Neuraxial Labor Analgesia

Jeanette R. Bauchat, MD, Robert J. McCarthy, PharmD, Tyler R. Koski, MD, Christopher R. Cambic, MD, Amy I. Lee, MD and Cynthia A. Wong, MD

From the Department of Anesthesiology, Northwestern University, Chicago, IL.

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背景：腰椎间盘切除术是一种常见的神经外科手术。由于手术疤痕和解剖学的改变，椎管内分娩镇痛的效果可能对有椎间盘切除手术史的产妇较差。在这个前瞻性观察病例对照研究中，我们通过每小时分娩镇痛布比卡因的用量，作为比较曾行椎间盘切除术的妇女和那些未行背部手术的妇女分娩镇痛效果的间接方法。

方法：对在一个较大型的大学的附属妇产科医院中所有要求椎管内分娩镇痛且曾行过椎间盘切除手术的妇女进行了研究。对照受试者与麻醉医师的技术水平相匹配。主要结果是分娩镇痛每小时布比卡因的用量。记录硬膜外导管放置的特点，包括椎间隙的尝试次数、放置的时间和因镇痛不足重置硬膜外导管次数。使用Wilcoxon排名秩和或Fisher精确检验来分析受试者的特点、分娩结果和镇痛的效果。采用Wilcoxon符号秩、配对资料率或符号检验来分析硬膜外导管的放置数据。

结果：对椎间盘切除术组中的42名妇女和对照组中42名妇女的数据进行了分析。分娩镇痛每小时布比卡因的用量在两组之间是没有差别的（中位数[四分位距，IQR]：椎间盘切

除术组12.7 mg/ h[11.0至15.3]和对照组13.2mg/ h
[11.3至15.7]，中位数差异[95%的置信区间，CI]：-0.55mg/h[-1.33至1.39]；*P* =
0.43）。从椎管内镇痛开始到分娩的时间间隔以及分娩方式在两组之间没有差别。放置硬膜外导管的时间中位数在椎间盘切除术和对照组受试者之间的差异（95%CI）是0分钟（-1至2.5）；*P* =
0.38。椎间盘切除术组和对照组中分别有17%和2%尝试穿刺超过一个椎间隙，差异（95%CI）是15%（2-26）；*P* =
0.03。硬膜外穿刺技术和估计的导管放置水平没有差异。此操作过程在椎间盘切除术组中有3例由高年资的麻醉医生完成，在对照组中有2例（p =
1.0）。这两组中都没有硬膜外导管的重置。

结论：进行椎管内镇痛分娩的曾行椎间盘切除术组产妇和对照组相比，布比卡因每小时用量没有差异。硬膜外导管放置时间也没有差别。但是在椎间盘切除术组，穿刺需要尝试更多的椎间隙。我们的研究结果表明，标准的临床椎管内镇痛方法对于曾行椎间盘切除手术的妇女有效。

（崔晓娜 译 马皓琳 李士通 校）

BACKGROUND: Lumbar discectomy surgery is a common neurosurgical procedure. Neuraxial labor analgesia may be less effective in parturients with a history of discectomy surgery because of postsurgical scarring and anatomical distortion. In this prospective observational case-controlled study, we compared bupivacaine consumption per hour of labor analgesia as an indirect measure of labor analgesic effectiveness between women with prior discectomy surgery and those who did not have back surgery.

METHODS: All women with prior discectomy surgery who requested neuraxial labor analgesia at a high-volume, single university-affiliated women's hospital during the study period were approached. Control subjects were matched for anesthesiologist skill level. The primary outcome was bupivacaine consumption per hour of labor analgesia. Characteristics associated with the epidural catheter placement including the number of interspaces attempted, time to placement, and number of epidural catheters replaced for inadequate analgesia were recorded. Subject characteristics, labor outcomes, and analgesia outcomes were analyzed using the Wilcoxon ranked sum or Fisher exact test. Epidural placement data were analyzed using the Wilcoxon signed rank, McNemar's, or sign test.

RESULTS: Data were analyzed for 42 women in the discectomy group and 42 women in the control group. Bupivacaine consumption per hour of labor analgesia was not different between groups (median [interquartile range, IQR]: discectomy 12.7 mg/h [11.0 to 15.3] and control 13.2 mg/h [11.3 to 15.7]; difference in medians [95% confidence interval, CI]: −0.55 mg/h [−1.33 to 1.39]; *P* = 0.43). The interval from initiation of neuraxial analgesia and delivery and mode of delivery did not differ between groups. The median difference (95% CI) in the time to place the epidural catheter between the discectomy and control subjects was 0 minute (−1 to 2.5); *P* = 0.38. More than 1 interspace was attempted in 17% discectomy in comparison with 2% of the control subjects—difference (95% CI) 15% (2–26); *P* = 0.03. The neuraxial technique and estimated level of catheter placement did not differ. Completion of the procedure by a more senior anesthesiologist occurred in 3 discectomy subjects and 2 control subjects (*P* = 1.0). No epidural catheters were replaced.

CONCLUSIONS: There was no difference in hourly bupivacaine consumption in parturients with prior lumbar discectomy surgery undergoing neuraxial labor analgesia in comparison with controls. Time to placement of the epidural catheter was not different either, but more interspaces were attempted in the discectomy group. Our findings suggest that standard clinical neuraxial analgesic methods are effective in women with discectomy surgery.

昼夜节律钟基因HPER3与非心脏手术后的认知功能障碍没有关联

There Is No Association Between the Circadian Clock Gene HPER3 and Cognitive Dysfunction After Noncardiac Surgery

Melissa Voigt Hansen, MD*, Lars Simon Rasmussen, DSc, MD†, Cathrine Jespersgaard, PhD‡, Jacob Rosenberg, DSc, MD* and Ismail Gogenur, DSc, MD*

From the *Department of Gastroenterology, Surgical Section, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; †Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ‡Department of Clinical Biochemistry and Immunology, Statens Serum Institut, Copenhagen, Denmark.

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背景：特殊的时钟基因PERIOD3在有关昼夜节律、睡眠动态平衡以及认知功能方面是很重要的。而等位基因PER3$^{5/5}$与睡眠剥夺引起的更差的认知表现有关。我们推测在PER3$^{5/5}$基因型患者在非心脏手术后1周具有较高的术后认知功能障碍（POCD）风险。

方法：我们从一个已完成的多中心研究中选取发生了POCD患者93名以及未发生POCD患者186名的血样进行分析。研究人群包括了40岁及以上年龄进行非心脏手术的患者，他们在术前及术后1周都进行了由7个分测试组成的成套的神经心理学测试。通过用聚合酶链反应分析血液样本的DNA来测定PER3基因型(临床试验.gov标识符NCT01088100）。

结果：3种基因型的概率分别为11.8%（32例）PER3$^{5/5}$，41.7%（113例）PER3$^{4/5}$，和46.5%（126例）PER3$^{4/4}$。在术后1周关于POCD的3个基因型的分布无显著差异（P= 0.68）。发生POCD的患者中12%（6%至21%）和无POCD的患者中12%（7%至17%）具有PER3$^{5/5}$基因型。POCD/-POCD的发生率差异在PER3$^{5/5}$基因型中是1% (−7%~10%)。在一项神经心理学测试中发现有PER3$^{4/4}$的患者的Z评分显著更高（概念转换试验的错误评分）(邦弗朗尼矫正，P =0.042)。

结论：时钟基因PER3$^{5/5}$基因型与非心脏手术后1周POCD的发生没有显著相关性。如果PER3$^{5/5}$的确会使认知表现更差，那么在患者中的发生率小于10%。

（余亦南 译 马皓琳 李士通 校）

BACKGROUND: The specific clock-gene PERIOD3 is important with regard to circadian rhythmicity, sleep homeostasis, and cognitive function. The allele PER3$^{5/5}$ has been associated with worse cognitive performance in response to sleep deprivation. We hypothesized that patients with the PER3$^{5/5}$ genotype would have an increased risk of postoperative cognitive dysfunction (POCD) 1 week after noncardiac surgery.

METHODS: Blood samples were analyzed from 93 patients with POCD and 186 patients without POCD from a completed multicenter study. The study population comprised patients ages 40 years and older undergoing noncardiac surgery who were tested preoperatively and 1 week after surgery with a neuropsychological test battery comprising 7 subtests. PER3 genotypes were determined by polymerase chain reaction analysis of DNA from blood samples (Clinicaltrials.gov identifier NCT01088100).

RESULTS: The frequencies of the 3 genotypes were 11.8% (32 patients) PER3$^{5/5}$, 41.7% (113 patients) PER3$^{4/5}$, and 46.5% (126 patients) PER3$^{4/4}$. No significant difference was found in the distribution of the 3 genotypes according to POCD at 1 week (P = 0.68). Twelve percent (6% to 21%) of the patients with POCD and 12% (7% to 17%) of the patients without POCD had the PER3$^{5/5}$ genotype. The difference of the incidence of POCD/−POCD for the PER3$^{5/5}$ genotype was 1% (−7% to 10%). A significantly higher Z score was found in patients having the PER3$^{4/4}$ in 1 of the neuropsychological tests (error score of the Concept Shifting Test) (Bonferroni corrected P = 0.042).

CONCLUSION: No significant association was found between the clock-gene PER3$^{5/5}$ genotype and POCD at 1 week after noncardiac surgery. If PER3$^{5/5}$ does worsen cognitive performance, the incidence is <10% of patients.

盐酸曲马多在大鼠术后疼痛模型中的抗超敏效果

Antihypersensitivity Effects of Tramadol Hydrochloride in a Rat Model of Postoperative Pain

Masafumi Kimura, MD, Hideaki Obata, MD, PhD and Shigeru Saito, MD, PhD

From the Department of Anesthesiology, Gunma University Graduate School of Medicine, Gunma, Japan.

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背景：曲马多在治疗急性痛和慢性痛中广泛应用。该药镇痛作用机制有2个：激活阿片类受体和增强去甲肾上腺素（NA）和血清素（5-HT）的传递。然而曲马多对脊髓中NA和5-HT浓度的影响未被评估。在本研究中，我们研究曲马多在大鼠术后疼痛模型中的抗超敏作用。我们也通过在体微透析法来评估了在注射曲马多后脊髓中NA和5-HT水平的增加。

方法：我们在雄性SD大鼠上做后足切割来制作术后疼痛模型。足部切割后24小时在大鼠腹膜内注射和鞘内注射曲马多。通过使用冯弗雷纤维方法测定回缩阈来衡量机械性超敏。对腰椎脊髓背角进行微透析研究以测量腹腔内注射曲马多后NA和5-HT水平。我们也测量正常大鼠和行足部切割大鼠脊髓中的NA和5-HT的含量。

结果:腹膜内注射曲马多(10、20和40 mg/kg)和鞘内注射曲马多(125、250和500 μg)产生了剂量依赖方式的抗痛觉过敏作用。曲马多的抗超敏作用可被鞘内预先注射美西麦角（一种羟色胺受体拮抗剂）30 μg、咪唑克生（一种去甲肾上腺素受体拮抗剂）30 μg和纳洛酮（一种非选择性阿片类受体拮抗剂）30 μg消除。微透析法研究提示脊髓背角中5-HT和NA浓度增加，在腹膜内注射20 mg/kg曲马多后30分钟达到峰值浓度。而且，身体同侧的腰椎脊髓背角中5-HT和NA含量在足部切割后第一天和第三天分别增加。

结论:这些结果提示曲马多通过增加脊髓中NA和5-HT水平和激活阿片类受体来抑制术后疼痛超敏。曲马多可能在脊髓中NA和5-HT水平增高的术后早期抗超敏作用更有效。

（方斌 译 马皓琳 李士通 校）

BACKGROUND: Tramadol is used to treat a wide range of acute and chronic pain. This drug induces analgesia by 2 mechanisms of action: opioid receptor activation and enhancement of noradrenaline (NA) and serotonin (5-HT) transmission. The effect of tramadol on NA and 5-HT concentrations in the spinal cord, however, have not been assessed. In the present study, we investigated the antihypersensitivity effect of tramadol using a rat model of postoperative pain. We also evaluated the increase in NA and 5-HT levels in the spinal cord after tramadol injection using in vivo microdialysis.

METHODS: We made a hindpaw incision in male Sprague-Dawley rats (postoperative pain model). Tramadol was administered intraperitoneally and intrathecally 24 hours after paw incision. Mechanical hypersensitivity was measured by determining the withdrawal threshold using von Frey filaments. Microdialysis studies from the dorsal horn of the lumbar spinal cord were performed to measure NA and 5-HT levels after intraperitoneal injection of tramadol. We also measured the NA and 5-HT content in the spinal cord in normal rats and rats with paw incision.

RESULTS: Intraperitoneal (10, 20, and 40 mg/kg) and intrathecal (125, 250, and 500 μg) injection of tramadol produced an antihyperalgesic effect in a dose-dependent manner. The antihypersensitivity effect of tramadol was prevented by intrathecal pretreatment with methysergide (30 μg), a serotonin receptor antagonist; idazoxane (30 μg), a noradrenaline receptor antagonist; and naloxone (30 μg), a nonselective opioid receptor antagonist. Microdialysis study revealed that 5-HT and NA concentrations at the spinal dorsal horn were

increased, peaking at 30 minutes after intraperitoneal injection of 20 mg/kg tramadol. Furthermore, the NA and 5-HT content in the ipsilateral dorsal half of the lumbar spinal cord was increased 1 day and 3 days after paw incision, respectively.

CONCLUSIONS: These findings indicate that tramadol inhibits postoperative hypersensitivity by increasing NA and 5-HT levels in the spinal cord and activating opioid receptors. Tramadol might be more effective in the early postoperative period when spinal NA and 5-HT levels are increased.

颈横动脉和肩胛背动脉在锁骨上臂丛神经阻滞中常用的三个超声探头位置的出现情况

The Presence of Transverse Cervical and Dorsal Scapular Arteries at Three Ultrasound Probe Positions Commonly Used in Supraclavicular Brachial Plexus Blockade

Hiroaki Murata, MD, PhD*, Akiko Sakai, MD*, Admir Hadzic, MD, PhD† and Koji Sumikawa, MD, PhD*

From the *Department of Anesthesiology, Nagasaki University School of Medicine, Nagasaki, Japan; and †Department of Anesthesiology, St. Luke's and Roosevelt Hospitals, College of Physicians and Surgeons, Columbia University, New York, New York.

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背景：在超声引导下行锁骨上臂丛神经阻滞时，有穿刺到血管的风险。在这项研究中，我们测定了在锁骨上阻滞臂丛神经阻滞时，通过在3个探头位置的超声评价检测到颈横动脉（TCA）和肩胛背动脉（DSA）的频率。

方法：对53个健康成人志愿者超声检查锁骨上区域。在3个探头位置得到锁骨上区域的超声图像：位置A（都横躺在第一肋骨上的臂丛神经和锁骨下动脉）；位置B（在第一肋骨上的臂丛神经；在胸膜上的动脉）；位置C（在前斜角肌与中斜角肌之间的臂丛神经）。主要的结果参数是二维和彩色多普勒超声在3个指定探头位置检测到TCA和DSA的频率。

结果：
对53个受试者的106个锁骨上区域进行了检查。在所有的受试者都检测到了锁骨下动脉。TCA比
DSA检测到的频率更高，在106个扫描中，分别为94个（88.7％，95％可信区间[CI] 80.7％～93.8％）和36个（34％，95％CI 25.3％-43.9％）（McNemar *P* <0.001）。在探头位置A、B和C分别检测到TCA 2个（1.9％，95％CI为0.3％-7.3％）、31个（29.2％，95％CI 20.9％-38.9％）和61个（57.5％，95％CI 47.5％-66.9％），而在探头位置A、B和C分别检测到DSA：3个（2.8％，95％CI为0.7％-8.6％）、23个（21.7％，95％CI14.5％-30.9％）和10个（9.4％，95％CI为4.8％-17.0％）。因此，TCA和DSA在探头位置A出现的可能性较小（P <0.001）。

结论：在锁骨上区域臂丛神经附近TCA比DSA检测的频率更高。
TCA和DSA都在探头位置A出现的可能最小。彩色多普勒，尤其在探头位置A，有助于减少超声引导下锁骨上臂丛神经阻滞过程中不慎穿刺到血管的风险。

（安光惠 译 马皓琳 李士通 校）

BACKGROUND: Ultrasound-guided supraclavicular brachial plexus block carries a risk for puncture of vascular structures. In this study, we determined the frequency with which the transverse cervical artery (TCA) and the dorsal scapular artery (DSA) are detected by ultrasound evaluation at 3 probe positions during supraclavicular block.

METHODS: Ultrasound examinations of the supraclavicular region were performed in 53 healthy adult volunteers. Ultrasound images of the supraclavicular region were acquired at 3 probe positions: *position A* (the brachial plexus and the subclavian artery both lying on the first rib); *position B* (the brachial plexus on the first rib; the artery on the pleura); and *position C* (the brachial plexus between the anterior and middle scalene muscles). The primary outcome

variables were the frequencies with which TCA and DSA were detected by 2-dimensional and color Doppler imaging at 3 specified probe positions.

RESULTS: One hundred six supraclavicular regions were examined in 53 subjects. The subclavian artery was detected in all subjects. TCA was more often detected than DSA, 94 (88.7%, 95% confidence interval [CI] 80.7%–93.8%) and 36 (34%, 95% CI 25.3%–43.9%) of 106 scans, respectively (McNemar *P* value <0.001). TCA was detected in 2 (1.9%, 95% CI 0.3%–7.3%), 31 (29.2%, 95% CI 20.9%–38.9%), and 61 (57.5%, 95% CI 47.5%–66.9%) of scans at probe positions A, B, and C, respectively, whereas DSA was detected in 3 (2.8%, 95% CI 0.7%–8.6%), 23 (21.7%, 95% CI 14.5%–30.9%), and 10 (9.4%, 95% CI 4.8%–17.0%) of scans at probe positions A, B, and C, respectively. Thus, the TCA and DSA were less likely to be present with probe position A (all $P < 0.001$).

CONCLUSION: TCA was more often detected than DSA in the vicinity of the brachial plexus in the supraclavicular region. Both TCA and DSA were least likely to be present in probe position A. Color Doppler, particularly for probe position A, may help to reduce the risk for inadvertent vascular puncture during ultrasound-guided supraclavicular block.

丝氨酸蛋白酶抑制剂MDCO-2010对健康人以及心脏手术患者的激活凝血时间的影响

The Effects of MDCO-2010, a Serine Protease Inhibitor, on Activated Clotting Time in Blood Obtained from Volunteers and Cardiac Surgical Patients

Heezoo Kim, MD*, Fania Szlam, MMSc*, Kenichi A. Tanaka, MD, MSc*, Andreas van de Locht, PhD†, Satoru Ogawa, MD* and Jerrold H. Levy, MD, FAHA*

From the *Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; and †The Medicines Company GmbH, Leipzig, Germany.

Heezoo Kim, MD, is currently affiliated with the Department of Anesthesiology, Korea University Guro Hospital, Seoul, Korea.

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背景：激活凝血时间（ACT）已广泛用于监测心脏手术中肝素的抗凝情况。使用抑肽酶会延长硅藻土激活的ACT时间。MDCO-2010是一种新型丝氨酸蛋白酶抑制剂，目前认为可能作为抑肽酶的替代品。因此，作者采用了3种不同的床边自测ACT仪器（高岭土或硅藻土激活）来评估此药对ACT的影响。

方法：研究分为两部分。第一部分：从15名健康志愿者中收集血液样本，样本用移液枪吸入Eppendorf试管内，分别单独加入两种浓度的MDCO-2010（终浓度为100 nM以及500nM）或同时加入肝素（1.2 U/ml或2.4U/ml）。采用Helena（硅藻土），Hemochron（高岭土）以及Medtronic（高岭土）三个仪器测定ACT值。第二部分：从15名接受体外循环的心脏手术患者术中5个时间点收集血液样本。先测定ACT值，再加入终浓度为100或500nM的MDCO-2010。其他需测定凝血指标有：凝血酶原时间（PT），活化的部分凝血活酶时间（APTT），纤维蛋白原，抗凝血酶，凝血素以及抗Xa量。

结果：无论何种ACT激活物或者采用何种设备测定，加入MDCO-2010的志愿者和患者血样本的ACT时间都呈浓度依赖性延长。加入MDCO-2010的志愿者样本（未加肝素）和患者样本（基线以及ICU）的Helena硅藻土激活ACT的变化百分比较Hemochron或Medtronic高岭土激活的ACT平均要长3.1 ± 1.8倍（95%可信区间2.6–3.6; $P < 0.001$）。

结论：MDCO-2010延长的高岭土激活的全血凝固时间要短于延长硅藻土激活的全血凝固时间。

（陆秉玮 译 陈杰 校）

BACKGROUND: The activated clotting time (ACT) is widely used for monitoring heparin anticoagulation during cardiac surgery. Celite-based ACT values are prolonged when aprotinin is administered. MDCO-2010, a novel serine protease inhibitor, is currently being evaluated as a possible alternative to aprotinin. Therefore, we evaluated the in vitro effects of this novel agent on ACT values using 3 different point-of-care instruments with kaolin or celite as an activator.

METHODS: The study was performed in 2 parts. In the first part, blood samples were obtained from 15 healthy volunteers. Samples were pipetted into small Eppendorf tubes and 2 concentrations of the MDCO-2010 (100 and 500 nM, final concentration) alone or with heparin (1.2 or 2.4 U/mL) were added. ACTs were measured using Helena (celite), Hemochron (kaolin), and Medtronic (kaolin) devices. In the second part of the study, blood samples were obtained intraoperatively, at 5 time points, from 15 patients undergoing cardiopulmonary bypass. MDCO-2010 at a final concentration of 100 or 500 nM was added and ACT testing was performed as before. Additional coagulation tests included prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin, prothrombin, and anti-Xa levels.

RESULTS: Addition of MDCO-2010 concentration-dependently prolonged ACTs in volunteers' and patients' blood samples regardless of the ACT activator or device used. In volunteer samples (no heparin) and in patient samples (baseline and intensive care unit) percent changes in ACTs due to MDCO-2010 were on average 3.1 ± 1.8 times higher (95% confidence interval 2.6–3.6; $P < 0.001$) for the celite-based Helena device compared with either Hemochron or Medtronic devices.

CONCLUSION: MDCO-2010 causes less ACT prolongation with kaolin than with celite activation.

以安慰剂和咪达唑仑为对照组评价Remimazolam（CNS 7056）药物安全性、药代动力学和药效学的I期单递增剂量研究：第一部分：安全性、有效性和基础药代动力学

A Placebo- and Midazolam-Controlled Phase I Single Ascending-Dose Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of Remimazolam (CNS 7056): Part I. Safety, Efficacy, and Basic Pharmacokinetics

Laurie J. Antonik, MD*, D. Ronald Goldwater, MD†, Gavin J. Kilpatrick, PhD‡, Gary S. Tilbrook, PhD‡ and Keith M. Borkett, BSc‡

From the *Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; †PAREXEL International, Early Phase Clinical Unit, Harbor Hospital, Baltimore, Maryland; ‡PAION UK Ltd., Cambridge, United Kingdom.

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背景：Remimazolam是一种新的苯二氮卓类药物，由组织酯酶代谢成无活性的CNS 7054，被证实和目前使用的苯二氮卓类药物相比有起效快、镇静时间短以及恢复快的优点。本文作者报道了该药物安全性和有效性的I期临床研究结果。

方法：这是一项单中心、双盲以及安慰剂和药物对照的随机单剂量递增药物I期临床研究。总共有10组健康人接受单剂量1min内静脉内注射remimazolam、咪达唑仑或者安慰剂。在这10组人中，remimazolam的剂量从0.01mg/kg至0.35mg/kg。在组1至组3，6例注射remimazolam，1例注射安慰剂。从组4开始，每组中额外的3例注射咪达唑仑0.075mg/kg。研究其药物安全性、药代动力学以及药效学。以大于50%的受试者中意识丧失超过5min作为试验终止的标准。

结果：至组9（remimazolam 0.30mg/kg）试验终止，共有81名受试者。Remimazolam在所有剂量组中均能很好地耐受，且无严重的副作用。三名受试者出现轻微的低氧（Spo_2 85%–88%）（其中remimazolam组2人，咪达唑仑组1人），但之后均自行缓解。在最高剂量的r

emimazolam组中1名受试者中度低氧(Spo_2 75%)，通过抬下颌而缓解。均不需要额外的氧通气和手动通气。在整个过程中，生命体征平稳。除了在remimazolam组和咪达唑仑组药物注射2min后出现心率的上升，无低血压、高血压发生。Remimazolam的药代动力学与咪达唑仑呈线性关系，系统清除率约是其3倍。药物清除与体重无相关性。remimazolam剂量超过0.05mg/kg药物起效迅速且呈药物剂量依赖性的镇静作用。Remimazolam（0.075 mg—0.20mg/kg）达到的峰镇静水平相似于甚至高于咪达唑仑（0.075mg/kg）。有效剂量相当的remimazolam（0.10mg/kg和0.15mg/kg）和咪达唑仑（0.075mg/kg）的恢复时间中位数是10min和40min。

结论：Remimazolam具有起效快、恢复快以及耐受好等特点。不需要额外的氧气和通气。基于上述研究数据，今后应进一步研究remimazolam的镇静/麻醉作用。

（俞芳 译 陈杰 校）

BACKGROUND: A new benzodiazepine, remimazolam, metabolized by tissue esterases to an inactive compound, CNS 7054, has been developed to permit a fast onset, a short and more predictable duration of sedative action, and a more rapid recovery profile than with currently available benzodiazepines. We report on the safety and efficacy of the first human study.

METHODS: A phase I, single-center, double-blind, placebo- and active-controlled, randomized, single-dose escalation study was conducted. Up to 10 cohorts of healthy subjects were scheduled to receive a single 1-minute IV infusion of remimazolam, midazolam, or placebo. In the 10 possible cohorts, remimazolam doses were from 0.01 to 0.35 mg/kg. In cohorts 1 to 3, 6 subjects received remimazolam and 1 placebo. From cohort 4 onward, an additional 3 subjects in each cohort received midazolam (0.075 mg/kg). Safety, pharmacokinetics, and pharmacodynamics were measured. A stop criterion of loss of consciousness for >5 minutes in >50% of subjects was predefined.

RESULTS: The stop criterion was reached in cohort 9 (0.30 mg/kg remimazolam) so that 81 subjects were enrolled. Remimazolam was well tolerated in all dose cohorts, and no serious adverse events (AEs) were reported. Three AEs of mild (Spo_2 85%–88%) hemoglobin desaturation (2 in the remimazolam groups and 1 in the midazolam group) resolved spontaneously, and 1 AE of moderate hemoglobin desaturation (Spo_2 75%) resolved with a chin lift in the highest remimazolam dose group. No supplemental oxygen or manual ventilation was required. Vital signs remained stable throughout, although there was an increase in heart rate 2 minutes postdose for both remimazolam and midazolam. There were no reports of hypo- or hypertension. The pharmacokinetic behavior of remimazolam was linear and its systemic clearance approximately 3 times that of midazolam. Clearance was essentially independent of body weight. A rapid onset and dose-dependent sedation was observed after administration of remimazolam at 0.05 mg/kg and higher. Remimazolam (0.075 to 0.20 mg/kg) induced peak sedation levels similar to or higher than those achieved with midazolam (0.075 mg/kg). Median recovery times after approximately equieffective doses of remimazolam (0.10 and 0.15 mg/kg) and midazolam (0.075 mg/kg) were 10 and 40 minutes, respectively.

CONCLUSIONS: Remimazolam provided sedation with rapid onset and offset, and was well tolerated. There was no supplemental oxygen or ventilation required. On the basis of these data, further studies on the potential utility of remimazolam for sedation/anesthesia are warranted.

简报：甲氧羰基依托咪酯的羧酸代谢物的药理学研究

Brief Report: Pharmacological Studies of Methoxycarbonyl Etomidate's Carboxylic Acid Metabolite

Ri Le Ge, MD, PhD, Ervin Pejo, BS, Marian Haburcak, PhD, S. Shaukat Husain, DPhil, Stuart A. Forman, MD, PhD and Douglas E. Raines, MD

From the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

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背景：甲氧羰基依托咪酯（MOC-依托咪酯）是一个快速代谢和超短效依托咪酯类似物，单次注射后，不会产生长期肾上腺皮质功能抑制。它的代谢产物（MOC-ECA）是一种羧酸，其药理学尚未研究。作者推测， MOC-ECA 与MOC-依托咪酯相比，药理活性显著降低，单次注射后，催眠作用持续时间非常短暂且不产生长期肾上腺皮质功能抑制。为了验证这一假设，作者在3个生物检测中比较了MOC-ECA和MOC-依托咪酯的效力。

方法：采用蝌蚪的翻正反射消失来评估MOC-ECA的催眠效力。通过测定所需直接激活α1（L264T）β2γ2L GABAA受体的浓度，界定MOC-ECA的γ-氨基丁酸A（GABAA）调节效力并与MOC-依托咪酯进行比较。通过测定抑制肾上腺皮质细胞体外生成皮质醇需要的浓度，比较MOC-ECA和MOC-依托咪酯对肾上腺皮质的抑制能力。

结果：MOC-ECA使蝌蚪的翻正反射消失的50％有效浓度为2.8±0.64 mM，较以前报道的MOC-依托咪酯的有效浓度（8±2μM）更为精确。MOC-ECA直接激活$GABA_A$受体的50％有效浓度为3.5±0.63 mM而MOC-依托咪酯为10±2.5μM。MOC-ECA抑制肾上腺皮质细胞在体外的皮质醇半最大抑制浓度为30±7μM ，而MOC-依托咪酯为0.10±0.02μM。

结论：在所有的生物实验中，MOC-ECA的效力低于MOC-依托咪酯约为300倍。

（孙晓琼 译 陈杰 校）

BACKGROUND: Methoxycarbonyl etomidate (MOC-etomidate) is a rapidly metabolized and ultrashort-acting etomidate analog that does not produce prolonged adrenocortical suppression after bolus administration. Its metabolite (MOC-ECA) is a carboxylic acid whose pharmacology is undefined. We hypothesized that MOC-ECA possesses significantly lower pharmacological activity than MOC-etomidate, accounting for the latter's very brief duration of hypnotic action and inability to produce prolonged adrenocortical suppression after bolus administration. To test this hypothesis, we compared the potencies of MOC-ECA and MOC-etomidate in 3 biological assays.

METHODS: The hypnotic potency of MOC-ECA was assessed in tadpoles using a loss-of-righting reflexes assay. The γ-aminobutyric acid type A ($GABA_A$) receptor modulatory potencies of MOC-ECA and MOC-etomidate were compared by defining the concentrations of each required to directly activate $\alpha_1(L264T)\beta_2\gamma_{2L}$ $GABA_A$ receptors. The adrenocortical inhibitory potencies of MOC-ECA and MOC-etomidate were compared by defining the concentrations of each required to inhibit in vitro cortisol production by adrenocortical cells.

RESULTS: MOC-ECA's 50% effective concentration for loss-of-righting reflexes in tadpoles was 2.8 ± 0.64 mM as compared with a previously reported value of 8 ± 2 μM for MOC-etomidate. The 50% effective concentrations for direct activation of $GABA_A$ receptors were 3.5 ± 0.63 mM for MOC-ECA versus 10 ± 2.5 μM for MOC-etomidate. The half-maximal inhibitory concentration for inhibiting in vitro cortisol production by adrenocortical cells was 30 ± 7 μM for MOC-ECA versus 0.10 ± 0.02 μM for MOC-etomidate.

CONCLUSIONS: In all 3 biological assays, MOC-ECA's potency was approximately 300-fold lower than that of MOC-etomidate.

美国1998 – 2008间住院关节置换术术后主要并发症发生率和死亡率的趋势

Trends in In-Hospital Major Morbidity and Mortality After Total Joint Arthroplasty: United States 1998–2008

Meghan Kirksey, MD, PhD*, Ya Lin Chiu, MS†, Yan Ma, PhD‡, Alejandro Gonzalez Della Valle, MD§, Lazaros Poultsides, MD, MS, PhD§, Peter Gerner, MD‖ and Stavros G. Memtsoudis, MD, PhD¶

From the *Department of Anesthesiology, New York Presbyterian Hospital-Weill Cornell, New York, NY; †Department of Public Health and Biostatistics, Weill Medical College of Cornell University, New York, NY; ‡Department of Public Health, Hospital of Special Surgery, Weill Medical College of Cornell University, New York; §Department of Orthopedics, Hospital for Special Surgery, New York; ‖Department of Anesthesiology, Paracelsus University Salzburg, Salzburg, Austria; ¶Department of Anesthesiology, Hospital for Special Surgery, New York.

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背景：关节置换术在世界范围内的应用不断增加。作者旨在阐明行全髋关节置换术(THA)或全膝关节置换术(TKA)的人口数据和围手术期结果的最近趋势。

方法：数据来自美国1998年至2008年之间THA和TKA样本。对患者年龄、疾病负担,住院时间，主要的围手术期并发症的发生率、住院死亡率进行了分析。住院结果以每1000名住院病人住院天数作为住院日变化来报告。Deyo指数、出院状态和相互影响等调整发病率趋势分析。

结果：1998年和2008年之间,接受TKA和THA患者的平均年龄下降了2到3岁(P < 0.001)。平均住院时间下降了大约1天 (P < 0.001)。患者出院回家的百分比TKA的患者从29.7%下降到25.4%,THA的患者从29.3%到24.2%,患者更喜欢到长期和短期保健单位(P < 0.0001)。TKA和THA的疾病负担通过测量Deyo疾病指数分别增加了35%和30%(P < 0.0001)。TKA术后,下列主要并发症发生率增加:肺栓塞(系数估计[CE]0.069;95%可信区间[CI]为0.059 -0.079;P < 0.0001),败血症(CE 0.034;95% CI,0.014 -0.054;P = 0.001),非心源性梗塞心脏并发症(CE 0.038;95% CI,0.035 -0.041;P < 0.0001),肺炎(CE 0.039;95% CI,0.031 -0.047;P < 0.0001)。THA术后,下列主要并发症的发生率增加:肺栓塞(CE 0.031;95% CI,0.012 -0.049;P = 0.001),败血症(CE 0.060;95% CI,0.039 -0.081;P<0.0001),非心肌梗塞性心脏并发症(CE 0.040;95% CI,0.036 -0.043;P<0.0001),肺炎(CE 0.039;95% CI,0.029 -0.048)。住院死亡率在下降(TKA CE −0.059;95%可信区间,0.077 −0.040;P<0.0001)和THA(CE−0.068;95%可信区间,0.086到−0.051;P<0.0001)。

结论：1998年和2008年之间,THA和TKA的几个主要的住院并发症趋势显示增加,包括肺栓塞,败血症，非心肌梗塞性心脏并发症和肺炎。尽管此期间并发症增加，住院死亡率在下降。

（龚寅　译　陈杰　校）

BACKGROUND: The use of total joint arthroplasties is increasing worldwide. In this work we aim to elucidate recent trends in demographics and perioperative outcomes of patients undergoing total hip (THA) or total knee arthroplasty (TKA).

METHODS: Data from the US Nationwide Impatient Sample between 1998 and 2008 were gathered for primary THAs and TKAs. Trends in patient age, comorbidity burden, length of hospitalization, frequency of major perioperative complications, and in-hospital mortality were analyzed. In-hospital outcomes were reported as events per 1000 inpatient days to account for changes in length of hospitalization over time. Deyo index, discharge status, and the interaction effect of time and discharge status were included in the adjusted trend analysis for morbidity.

RESULTS: Between 1998 and 2008, the average age of patients undergoing TKA and THA decreased by 2 to 3 years ($P < 0.001$). The average length of stay decreased by approximately 1 day over the time interval studied ($P < 0.001$). The percentage of patients being discharged home

declined from 29.7% to 25.4% after TKA and from 29.3% to 24.2% after THA, in favor of dispositions to long- and short-term care facilities ($P < 0.0001$). Comorbidity burden as measured by the Deyo comorbidity index increased by 35% and 30% for TKA and THA patients, respectively ($P < 0.0001$). After TKA, there was an increase in the incidence of the following major complications: pulmonary embolism (coefficient estimate [CE] 0.069; 95% confidence interval [CI], 0.059–0.079; $P < 0.0001$), sepsis (CE 0.034; 95% CI, 0.014–0.054; $P = 0.001$), nonmyocardial infarction cardiac complications (CE 0.038; 95% CI, 0.035–0.041; $P < 0.0001$), and pneumonia (CE 0.039; 95% CI, 0.031–0.047; $P < 0.0001$). After THA, there was an increase in the incidence of the following major complications: pulmonary embolism (CE 0.031; 95% CI, 0.012–0.049; $P = 0.001$), sepsis (CE 0.060; 95% CI, 0.039–0.081; $P < 0.0001$), nonmyocardial infarction cardiac complications (CE 0.040; 95% CI, 0.036–0.043; $P < 0.0001$), and pneumonia (CE 0.039; 95% CI, 0.029–0.048). In-hospital mortality declined after both TKA (CE −0.059; 95% CI, −0.077 to −0.040; $P < 0.0001$) and THA (CE −0.068; 95% CI, −0.086 to −0.051; $P < 0.0001$).

CONCLUSION: Between 1998 and 2008, trends show increases in several major in-hospital complications after THA and TKA, including pulmonary embolism, sepsis, nonmyocardial infarction cardiac complications, and pneumonia. Despite the increase in complications, declining in-hospital mortality was noted over this period.

行双侧鼓膜切开及放置通气管手术患儿，术中芬太尼滴鼻、肌肉或静脉注射吗啡对术后镇痛疗效及精神行为的影响

Postoperative Analgesic and Behavioral Effects of Intranasal Fentanyl, Intravenous Morphine, and Intramuscular Morphine in Pediatric Patients Undergoing Bilateral Myringotomy and Placement of Ventilating Tubes

Helena K. Hippard, MD*, Kalyani Govindan, MD*, Ellen M. Friedman, MD†, Marcelle Sulek, MD†, Carla Giannoni, MD†, Deidre Larrier, MD†, Charles G. Minard, PhD‡ and Mehernoor F. Watcha, MD*

From the *Department of Anesthesiology & Pediatrics, †The Bobby R. Alford, Department of Otolaryngology-Head and Neck Surgery, and ‡Dan L. Duncan Institute for Clinical and Translational Research, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas.

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背景：双侧鼓膜切开及放置通气管（BMT）在美国是常见的儿科手术。许多BMT术后患儿在麻醉后监护室（PACU）有不良精神行为，并需镇痛治疗。术中经滴鼻、肌肉或静脉给予阿片类药物的患儿与安慰剂组相比发生率降低。但是，目前没有数据表明哪种给药途径更好。本研究的目的是，比较全身麻醉下行BMT的患儿，术中三种给药方式对术后镇痛效果及患儿精神行为的影响。

方法： 171名 ASAI-II接受BMT患儿随机分成3组： 组1：2 μg/kg 芬太尼滴鼻与安慰剂静脉和肌肉注射；组2： 0.1 mg/kg 吗啡滴鼻与安慰剂肌注；组3：0.1 mg/kg 吗啡肌注与安慰剂静脉及滴鼻。所有受试患儿均接受规范化的七氟醚-N2O-O2的全身麻醉和术后护理。该研究试验的主要研究终点为在PACU面部，腿疼痛评分，活动度，是否哭闹，可安慰评分（FLACC）等。

结果：3组间FLACC疼痛评分峰值无显著差异（三组平均值[95% CI]分别为芬太尼滴鼻组2.0[1.2–2.8]，静脉吗啡组为2.7[1.7–3.6]，肌注吗啡组为2.9 [2.1–3.7] ）。
三组小儿麻醉后精神错乱（PAED）评分，术后谵妄（PAED评分≥12分），呕吐，围手术期低氧血症，是否需要气道管理及需要术后镇痛的发生率无显著差异。各组患儿PACU逗留时间或父母满意度也无显著差异。

讨论：行BMT手术患儿，术中芬太尼滴鼻，肌肉和静脉注射吗啡对术后镇痛疗效及精神行为影响无显著差异。肌肉注射是最简单的方式，可避免行静脉注射时建立血管通路延误可能，并避免滴鼻药物通过鼻咽部，刺激声带引起喉痉挛的风险。

（陈毓雯 译 陈杰 校）

BACKGROUND: Bilateral myringotomy and placement of ventilating tubes (BMT) is one of the most common pediatric surgical procedures in the United States. Many children who undergo BMT develop behavioral changes in the postanesthesia care unit (PACU) and require rescue pain medication. The incidence of these changes is lower in children receiving intraoperative opioids by the nasal, IM, or IV route compared with placebo. However, there are no data to indicate which route of administration is better. Our study was designed to compare the immediate postoperative analgesic and behavioral effects of 3 frequently used intraoperative techniques of postoperative pain control for patients undergoing BMT under general anesthesia.

METHODS: One hundred seventy-one ASA physical status I and II children scheduled for BMT were randomized into 1 of 3 groups: group 1—nasal fentanyl 2 μg/kg with IV and IM saline placebo; group 2—IV morphine 0.1 mg/kg with nasal and IM placebo; or group 3—IM morphine 0.1 mg/kg with nasal and IV placebo. All subjects received a standardized general anesthetic with sevoflurane, N_2O, and O_2 and similar postoperative care. The primary end point of the study was the pain scores measured by the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale in the PACU.

RESULTS: There were no significant differences in peak FLACC pain among the 3 groups (mean [95% CI] 2.0 [1.2–2.8] for intranasal fentanyl, 2.7 [1.7–3.6] for IV morphine, and 2.9 [2.1–3.7] for IM morphine, respectively). There were no differences in the scores on the Pediatric Anesthesia Emergence Delirium (PAED) scale, incidence of postoperative emergence delirium (PAED score ≥12), emesis, perioperative hypoxemia, or need for airway intervention, and postoperative rescue analgesia. There were also no differences in the duration of PACU stay or parental satisfaction among the groups.

CONCLUSION: In this double-blind, double-dummy study, there was no difference in the efficacy of intranasal fentanyl, IM and IV morphine in controlling postoperative pain and emergence delirium in children undergoing BMT placement. The IM route is the simplest and avoids the potential for delays to establish vascular access for IV therapy and the risks of laryngospasm if intranasal drugs pass through the posterior nasopharynx and irritate the vocal cords.

脑脊液搏动的频率和强度影响鞘内药物分布: 病人间个体差异的关键因子

The Frequency and Magnitude of Cerebrospinal Fluid Pulsations Influence Intrathecal Drug Distribution: Key Factors for Interpatient Variability

Ying Hsu, BS*, H. D. Madhawa Hettiarachchi, PhD*, David C. Zhu, PhD†‡§ and Andreas A. Linninger, PhD*

From the *Department of Bioengineering, University of Illinois at Chicago, Chicago, Illinois; and Departments of †Psychology, ‡Radiology, and §Electrical and Computer Engineering, Michigan State University, East Lansing, Michigan.

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背景:
鞘内给药是一种很有效的治疗中枢神经系统疾病的给药手段。然而，即使用同一药物相同剂量和用法，体内药物分布的范围也因人而异，且可控性差。病人间不同的脑脊液(CSF)搏动可以产生不同的药物分布。作者运用医学影像学-
计算流体动力学(miCFD)构建一个病人个体特异性的模型，来定量化CSF的生理学搏动作为药物转运的功能。

方法: 磁共振(MRI)和磁共振电影（CINE MRI）可用来捕捉病人的中枢神经系统的解剖结构和CSF搏动流速。基于这两者可以重建病人的miCFD模型，并且计算出病人的CSF流速。作者研究了在L2水平给予一次定量药物注射对于CSF搏动(频率和每搏输出量)的影响。通过不同的心率：43，60和120 bpm，以及各自的CSF 每搏输出量：1，2和3 mL，计算出整个脊柱的药物分布剖面图。为了评估不同生理学差异的病人的中毒风险，常用麻醉药的治疗剂量和中毒剂量是通过实验得出的。中毒风险分析则是由病人对于蛛网膜下腔麻醉表现出的不同心率和CSF每搏输出量而得出。

结果:
病人的心率和CSF每搏输出量都会极大地影响鞘内注射的药物分布。加倍的心率(60~120 bpm)使得注射后CSF的最高浓度下降了26.4%。而加倍的CSF每搏输出量使得注射后CSF的最高浓度减小了38.1%。计算显示，由于注射导致的可能的中毒最高浓度，通过改变注射速度可以避免。慢注射可以避免CSF的中毒最高浓度，同时又维持在治疗浓度之上。

结论:
作者的计算确定了病人之间的鞘内药物分布的关键变量。药物转运速度受CSF搏动的频率和强度的极大影响。通过严格的miCFD模型，可以调整药物注射的变量，以此降低药物注射相关的中毒风险。

（俞劼晶 译 陈杰 校）

BACKGROUND: Intrathecal drug delivery is an efficient method to administer therapeutic molecules to the central nervous system. However, even with identical drug dosage and administration mode, the extent of drug distribution in vivo is highly variable and difficult to control. Different cerebrospinal fluid (CSF) pulsatility from patient to patient may lead to different drug distribution. Medical image–based computational fluid dynamics (miCFD) is used to construct a patient-specific model to quantify drug transport as a function of a spectrum of physiological CSF pulsations.

METHODS: Magnetic resonance imaging (MRI) and CINE MRI were performed to capture the patient's central nervous system anatomy and CSF pulsatile flow velocities. An miCFD model was reconstructed from these MRIs and the patient's CSF flow velocities were computed. The effect of CSF pulsatility (frequency and stroke volume) was investigated for a bolus injection of a model drug at the L2 vertebral level. Drug distribution profiles along the entire spine were computed for different heart rates: 43, 60, and 120 bpm, and varied CSF stroke volumes: 1, 2, and 3 mL. To assess toxicity risk for patients with different physiological variables, therapeutic and toxic concentration thresholds for a common anesthetic were derived from experimental studies. Toxicity risk analysis was performed for an injection of a spinal anesthetic for patients with different heart rates and CSF stroke volumes.

RESULTS: Both heart rate and CSF stroke volume of the patient strongly influence drug distribution administered intrathecally. Doubling the heart rate (from 60 to 120 bpm) caused a 26.4% decrease in peak concentration in CSF after injection. Doubling the CSF stroke volume diminished the peak concentration after injection by 38.1%. Computations show that potentially toxic peak concentrations due to injection can be avoided by changing the infusion rate. Using slower infusion rates could avoid high peak concentrations in CSF while maintaining drug concentrations above the therapeutic threshold.

CONCLUSIONS: Our computations identify key variables for patient to patient variability in drug distribution in the spine observed clinically. The speed of drug transport is strongly affected by the frequency and magnitude of CSF pulsations. Toxicity risks associated with an injection can be reduced for a particular patient by adjusting the infusion variables with our rigorous miCFD model.

新生鼠鞘内注射可乐定：剂量依赖镇痛以及脊髓凋亡和毒性的评估

Intrathecal Clonidine in the Neonatal Rat: Dose-Dependent Analgesia and Evaluation of Spinal Apoptosis and Toxicity

Suellen M. Walker, MBBS, PhD, FANZCA, FFPMANZCA*, Marjorie Grafe, MD, PhD† and Tony L. Yaksh, PhD‡

From the *Portex Unit: Pain Research, UCL Institute of Child Health and Great Ormond Street Hospital NHS Trust, London, United Kingdom; †Department of Pathology, Oregon Health and Science University, Portland, Oregon; and ‡Department of Anesthesiology, University of California San Diego, La Jolla, California.

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背景：在儿童各年龄阶段，轴索内使用可乐定用于围手术期镇痛。大鼠的临床前试验比较了在整个大鼠生长过程中脊髓镇痛的相对毒性和安全性。

原理：出生后3、7、21天的幼鼠鞘内注射可乐定或者生理盐水。每个年龄段，记录最大的镇痛剂量（下肢机械刺激缩足反应阈值）和抗痛觉过敏剂量。腰部脊髓部分需要评估组织病理学凋亡和细胞死亡以及神经胶质反应性。P3组鞘内注射氯胺酮作为阳性对照组。除了这些分组，测量P35热刺激缩足反应潜伏期和机械刺激缩足反应阈值。

结果：大鼠鞘内注射可乐定有年龄和剂量依赖的镇痛作用。最大剂量的可乐定也不会改变新生鼠脊髓的细胞凋亡的程度和分布以及增加神经胶质细胞的反应性。各年龄段在注射后的1天和第7天都没有见到脊髓的组织病理学改变。在P35，鞘内注射可乐定也不产生对机械性和温度刺激的永久性改变。

结论：大鼠鞘内注射可乐定并不产生脊髓毒性，即使在剂量远大于镇痛所需的量时。治疗比率（最大耐受剂量/痛觉过敏剂量）在P3组>300，在P7组>30，在P21组>10。这些数据提供了脊髓镇痛药的额外信息有助于动物幼龄期的临床选择。

（范逸臣　译　陈杰　校）

BACKGROUND: Neuraxial clonidine is used for perioperative analgesia in children of all ages. Preclinical studies in the postnatal rat allow comparison of the relative toxicity and safety of spinal analgesics throughout postnatal development.

METHODS: Rat pups aged 3, 7, or 21 postnatal (P) days were briefly anesthetized for intrathecal injections of saline or clonidine. At each age, the maximum tolerated, antinociceptive (increased hindlimb mechanical withdrawal threshold) and antihyperalgesic (hindpaw carrageenan inflammation) doses were determined. Lumbar spinal cord sections were assessed for apoptosis and cell death (histology, activated caspase-3 immunohistochemistry, Fluoro-Jade C staining), histopathology (hematoxylin and eosin staining), and increased glial reactivity (microglial and astrocytic markers). P3 intrathecal ketamine sections served as positive controls. In additional groups, thermal latency and mechanical withdrawal threshold were measured at P35.

RESULTS: Intrathecal clonidine produces age- and dose-dependent analgesia in rat pups. Maximal doses of clonidine did not alter the degree or distribution of apoptosis or increase glial reactivity in the neonatal spinal cord. No spinal histopathology was seen 1 or 7 days after injection at any age. Intrathecal clonidine did not produce persistent changes in reflex sensitivity to mechanical or thermal stimuli at P35.

CONCLUSIONS: Intrathecal clonidine in the postnatal rat did not produce signs of spinal cord toxicity, even at doses much larger than required for analgesia. The therapeutic ratio (maximum tolerated dose/antihyperalgesic dose) was >300 at P3, >30 at P7, and >10 at P21. These data provide additional information to inform the clinical choice of spinal analgesic drug in early life.