Cardiovascular Anesthesiology

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

- Guyan Wang,
- Gaoqiang Xie,
- Tingting Jiang,
- Yuefu Wang,
- Weipeng Wang,
- Hongwen Ji,
- Mingzheng Liu,
- Lei Chen,
- and Lihuan Li


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

- Heezoo Kim,
- Fania Szlam,
- Kenichi A. Tanaka,
- Andreas van de Locht,
- Satoru Ogawa,
- and Jerrold H. Levy

Anesth Analg August 2012 115:244-252; published ahead of print May 14, 2012
Ambulatory Anesthesiology

全身给予利多卡因改善门诊腹腔镜手术术后苏醒质量
(邓利兵译 薛张纲校)
Systemic Lidocaine to Improve Postoperative Quality of Recovery After Ambulatory Laparoscopic Surgery
  o Gildasio S. De Oliveira, Jr.,
  o Paul Fitzgerald,
  o Lauren F. Streicher,
  o R-Jay Marcus,
  o and Robert J. McCarthy

Anesthetic Pharmacology

教会一个旧的GABA受体新的技能
(张怡 译 马皓琳 李士通校)
Special Article: Teaching an Old GABA Receptor New Tricks
  o James R. Trudell,
  o Edward Bertaccini,
  o and M. Bruce MacIver

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
(俞芳译 陈杰校)
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
  o Laurie J. Antonik,
  o D. Ronald Goldwater,
  o Gavin J. Kilpatrick,
  o Gary S. Tilbrook,
  o and Keith M. Borkett

- Hugh R. Wiltshire,
- Gavin J. Kilpatrick,
- Gary S. Tilbrook,
- and Keith M. Borkett


In Vivo and In Vitro Pharmacological Studies of Methoxycarbonyl-Carboetomidate

- Ervin Pejo,
- Joseph F. Cotten,
- Elizabeth W. Kelly,
- Ri Le Ge,
- Gregory D. Cuny,
- Joydev K. Laha,
- Jifeng Liu,
- Xiang Jie Lin,
- and Douglas E. Raines


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

- Ri Le Ge,
- Ervin Pejo,
- Marian Haburcak,
- S. Shaukat Husain,
- Stuart A. Forman,
- and Douglas E. Raines
Technology, Computing, and Simulation

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
(郭晨跃译 薛张纲校)

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

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


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
(许辛译 马皓琳 李世通校)

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

- Matthias Kreuzer,
- Robert Zanner,
- Stefanie Pilge,
- Sabine Paprotny,
- Eberhard F. Kochs,
- and Gerhard Schneider


Patient Safety

美国1998–2008年住院关节置换术后主要并发症发生率和死亡率的趋势
(龚寅译 陈杰校)

- Meghan Kirksey,
- Ya Lin Chiu,
- Yan Ma,
- Alejandro Gonzalez Della Valle,
- Lazaros Poultsides,
- Peter Gerner,
- and Stavros G. Memtsoudis


### Critical Care, Trauma, and Resuscitation

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

(韩旭译 薛张纲校)

**The Systemic and Regional Hemodynamic Effects of Phenylephrine in Sheep Under Normal Conditions and During Early Hyperdynamic Sepsis**

- Hiroshi Morimatsu,
- Ken Ishikawa,
- Clive N. May,
- Michael Bailey,
- and Rinaldo Bellomo


### Obstetric Anesthesiology

既往腰椎间盘切除术不会改变椎管内分娩镇痛的效果

(崔晓娜 译 马皓琳 李士通 校)

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

- Jeanette R. Bauchat,
- Robert J. McCarthy,
- Tyler R. Koski,
- Christopher R. Cambic,
Pediatric Anesthesiology

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
(陈毓雯译 陈杰校)
Postoperative Analgesic and Behavioral Effects of Intranasal Fentanyl, Intravenous Morphine, and Intramuscular Morphine in Pediatric Patients Undergoing Bilateral Myringotomy and Placement of Ventilating Tubes
  o  Helena K. Hippard,
  o  Kalyani Govindan,
  o  Ellen M. Friedman,
  o  Marcelle Sulek,
  o  Carla Giannoni,
  o  Deidre Larrier,
  o  Charles G. Minard,
  o  and Mehernoor F. Watcha

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。
(贺盼译 薛张纲校)
Review Article: Review of the Off-Label Use of Recombinant Activated Factor VII in Pediatric Cardiac Surgery Patients
  o  Nina A. Guzzetta,
  o  Isobel A. Russell,
  o  and Glyn D. Williams

Neuroscience in Anesthesiology and Perioperative Medicine

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
(余亦南译 马皓琳 李士通校)
There Is No Association Between the Circadian Clock Gene HPER3 and Cognitive Dysfunction After Noncardiac Surgery

- Melissa Voigt Hansen,
- Lars Simon Rasmussen,
- Cathrine Jespersgaard,
- Jacob Rosenberg,
- and Ismail Gogenur


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

- Ying Hsu,
- H. D. Madhawa Hettiarachchi,
- David C. Zhu,
- and Andreas A. Linninger


Analgesia

Pain Medicine

The Prevention of Chronic Postsurgical Pain Using Gabapentin and Pregabalin: A Combined Systematic Review and Meta-Analysis

- Hance Clarke,
- Robert P. Bonin,
- Beverley A. Orser,
- Marina Englesakis,
- Duminda N. Wijeysundera,
- and Joel Katz

Pain and Analgesic Mechanisms

盐酸曲马多在大鼠术后疼痛模型中的抗超敏效果
(方斌译 马皓琳 李士通校)

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

○ Masafumi Kimura,
○ Hideaki Obata,
○ and Shigeru Saito


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
(范逸臣译 陈杰校)

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

○ Suellen M. Walker,
○ Marjorie Grafe,
○ and Tony L. Yaksh


Regional Anesthesia

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
(安光惠译 马皓琳 李士通校)

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

○ Hiroaki Murata,
○ Akiko Sakai,
○ Admir Hadzic,
○ and Koji Sumikawa


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.
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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。更重要的是，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。对照组则给予生理盐水。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，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至−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%可信区间为0到−30)（或口服等效剂量的吗啡）(P = 0.01)。阿片类需要量与苏醒质量呈反比(ρ = 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
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 ($\rho = 0.64$, $P < 0.001$).

**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.

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**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
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Anesth Analg August 2012 115:310-314
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0%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、新气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.

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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：观察清醒的绵羊和大肠杆菌所致的脓毒血症的绵羊对苯肾的反应，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/mi; 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.


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Abstract: Over the past few years, recombinant activated factor VII (rFVIIa) has been used extensively in pediatric cardiac surgery, and the use of the drug by different practitioners has varied. In 2009, the Congenital Cardiac Anaesthesia Society (CCAS) tasked a working group to determine the use of rFVIIa in pediatric cardiac surgery patients, with the goal of assessing the current use and associated practices, and to improve the quality of care for these patients. This review summarizes the findings of the CCAS working group on the use of rFVIIa in pediatric cardiac surgery patients. In this review, the authors discuss the current evidence for the use of rFVIIa in pediatric cardiac surgery patients, with an emphasis on the evidence for the use of rFVIIa as a rescue agent. The authors also discuss the potential risks and benefits of using rFVIIa in pediatric cardiac surgery patients.

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.

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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
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—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—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

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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

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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-
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.

**In Vivo and In Vitro Pharmacological Studies of Methoxycarbonyl-Carboetomidate**

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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-吲哚-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，从而产生一种既能保持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-吲哚环-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-依托咪酯的辛醇:水分配系数分别为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。
**CONCLUSION:** MOC-carboetomidate is a GABA<sub>A</sub> 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.

**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<sub>50</sub>) for loss of righting reflexes (LORR) were measured in tadpoles and rats, respectively. Its effect on γ-aminobutyric acid A (GABA<sub>A</sub>) 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<sub>50</sub> for LORR in tadpoles was 9 ± 1 μM and its EC<sub>50</sub> for LORR in rats was 13 ± 5 mg/kg. At 13 μM, MOC-carboetomidate enhanced GABA<sub>A</sub> 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<sub>A</sub> 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.
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 孙皓琳 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 Narcotrend 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

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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]：椎间盘切除组中1.25mL[0.50mL, 2.00mL]，对照组中1.25mL[0.50mL, 2.00mL]])。
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.
There Is No Association Between the Circadian Clock Gene HPER3 and Cognitive Dysfunction After Noncardiac Surgery

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BACKGROUND: The specific clock gene PERIOD3 is important with regard to circadian rhythmicity, sleep homeostasis, and cognitive function. The allele PER3^{3/5} has been associated with worse cognitive performance in response to sleep deprivation. We hypothesized that patients with the PER3^{3/5} 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^{3/5}, 41.7% (113 patients) PER3^{4/4}, 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^{3/5} genotype. The difference of the incidence of POCD/POCD for the PER3^{3/5} 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^{3/5} genotype and POCD at 1 week after noncardiac surgery. If PER3^{3/5} 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

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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5-HT受体拮抗剂）30 μg、咪唑克生（一种NA受体拮抗剂）30 μg和纳洛酮（一种非选择性阿片受体拮抗剂）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.

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

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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 \( P < 0.001 \)). 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*

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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.
Remimazolam组中1名受试者中度低氧(Spo<sub>2</sub> 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）达到的镇静水平相当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。

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<sub>2</sub> 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<sub>2</sub> 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

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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 α_1(L264T)β2γ2L 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.

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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 Inpatient 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.
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, N₂O, and O₂ 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.
**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.

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

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**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.

**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.