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全身給予利多卡因改善門診腹腔鏡手術術後蘇醒品質

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

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背景：圍術期靜脈注射利多卡因可以提高術後鎮痛效果。先前有一些關於門診病人應用利多卡因的研究，但並沒有對影響病人出院後的阿片用量方面的報導。更重要的事，靜脈注射利多卡因對於日間手術病人術後恢復品質是否更好也是不清楚的。我們此次研究正是想檢驗靜脈注射利多卡因對門診腹腔鏡手術患者的蘇醒品質的影響。

方法：試驗遵循隨機雙盲、安慰劑對照原則，健康女性被分成兩組，試驗組給予 1.5mg/kg 負荷劑量的利多卡因後，隨後以 2.0mg/kg/h 速率輸注至手術結束。對照組則給與生理鹽水。原始資料來自一份手術結束 24h 後關於復蘇品質的調查表 ，基於先前病人麻醉及手術後的復蘇品質 40 分區間排序，建立一個代表其臨床相關的 10 分區間排序，其他資料包括阿片消耗量，疼痛得分及出院時間，資料對照採用 t 檢驗及 Wilcoxon 檢驗，應用 Spearman ρ 系統分析評估阿片消耗量及蘇醒品質的相關性，當原始資料 $P < 0.01$ 時拒絕無效假設。

結果：研究中總共 70 個樣本，最後完成 63 份，在試驗兩組中樣本及手術方法均無差異，相比於生理鹽水組，利多卡因組具有更好的蘇醒品質，中位數的差值爲 16（99%可信區間爲 2–28), $P = 0.002$. 利多卡因組較生理鹽水組更快達到出院標準，中位數差值爲-26 分鐘 (95% 可信區間爲-6 to -46 分鐘) ($P = 0.03$).出院後，研究物件在利多卡因組較生理鹽水組需要更少的口服阿片類藥物，中位數差值爲-10 (95% 可信區間, 0 到−30)（或口服等效劑量的嗎啡）($P = 0.01$)。阿片類需要量與復蘇品質成反比($\rho = 0.64$, $P < 0.001$)。

結論：靜脈注射利多卡因可提高門診腹腔鏡手術患者術後蘇醒品質，並且需要更少的阿片消耗量。對於門診手術的復蘇品質方面，利多卡因是一種安全、經濟、有效的藥物。

（鄧利兵譯 薛張綱校）

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.

一項評估 Remimazolam (CNS 7056)的安全性，藥代動力學和藥效動力學，以安慰劑和咪達唑侖作對照組，單一劑量逐漸遞增的 I 期研究：第二部分，群體藥代動力學和藥效動力學的建模與模擬

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

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背景：一種新的苯二氮䓬類藥物，remimazolam，被組織酯酶迅速代謝成爲一種無活性的化合物，它起效快，鎮靜作用時間短且可預測持續時間，並且比現有的藥物恢復更快。爲今後的研究，我們就有關資料模型和給藥方案的模擬作以報告。

方法：以 I 期，單中心，雙盲試驗，安慰劑和陽性對照組，隨機化，單一劑量逐漸增加的方法來研究。54 名健康受試者分爲 9 組，分別接受單一劑量 1 分鐘靜脈注射 remimazolam (0.01–0.3 mg/kg)。18 名對照受試者使用咪達唑侖，9 名使用安慰劑。群體藥代動力學和藥效動力學的資料進行了建模，獲取的參數用於蒙特卡羅方法替代給藥方案。

結果：一個咪達唑侖 4 室哺乳動物的藥代動力學模型和一個 remimazolam 生理基礎的再迴圈模型與觀察到的血漿水準相適應。remimazolam 的再迴圈模型解釋了觀察到的在稍後的時間點靜脈比動脈有更高的濃度。這 2 個模型被用來類比鎮靜的藥效動力學模型所需的動脈濃度（改良警覺鎮靜評分[MOAA/S]）並提供了藥效動力學參數的總體平均值，如下：remimazolam 和咪達唑侖分別是腦電雙頻指數- 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。總數中獲得>70%的 MOAA/S 評分爲 2 至 4 分的模型可以進一步建立。這個標準在 remimazolam 6mg 的初始負荷劑量，>2 分鐘的時間間隔維持 3mg 的維持劑量得以達成（95%置信區間：67%-74%）。預計在 16 分鐘以內，89%被這個負荷/維持劑量方案處理人群的(95% 置信區間: 87%–91%)MOAA/S 評分會恢復到 5 分。

結論：remimazolam 和咪達唑侖建立的群體藥代動力學和藥效動力學模型觀察到的資料相吻合。基於這些模型的類比結果表明，remimazolam 產生極爲迅速的鎮靜，在治療開始的 3 分鐘內達到最大效果。這種性能將使維持劑量比慢反應藥物更加精准地使用。所觀察到的沒有臨床相關的協變數的影響，建議按體重注射劑量相比較在體重範圍研究(65–90 kg)內的一致性的 remimazolam 固定劑量可能不佔優勢。

（方昕譯 薛張綱校）

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).

技術交流：麻醉呼吸內迴圈:學步兒童與新生兒到達設定七氟烷濃度的時間：模擬肺測試

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

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我們應用 Primus (Drägerwerk, AG, Lübeck, Germany)麻醉機以及 Avance（ GE Datex-Ohmeda, Munich, Germany）麻醉機對於學步兒童和新生兒通氣設定測量了達到預計吸入麻醉濃度所花費的時間。七氟烷濃度從 o%至 6%的洗入時間和通過 1-2 倍於分鐘通氣的新鮮氣體將七氟烷濃度從 6%至 0%的洗脫時間之和測量得到七氟烷達到 95%目標吸入濃度的時間。在 1.5 升新鮮氣體流量，潮氣量 50ml，呼吸頻率 30 次/分標準下，Avance 麻醉機比 Primus 麻醉機快（Avance 65 秒[95%可信區間：55-78]，Primus 310 秒[95%可信區間：261-359]）。在更高的新鮮氣體流量和更大的分鐘通氣率條件下兩者時間縮短的程度相同。新鮮氣體流量加倍的效果變數大且低於預期。對於 Primus 麻醉機，新生兒比學步兒童達到設定濃度的時間要慢，Avance 麻醉機則兩組時間相同。我們的資料證實：呼吸機達到目標吸入麻醉藥物濃度的時間取決於呼吸迴圈容量、新鮮氣體流量以及分鐘通氣量。

（郭晨躍譯 薛張綱校）

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

比較在正常情況下的綿羊和膿毒血症高代謝狀態下的綿羊中，苯腎對全身和局部血液動力學的影響

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

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背景：苯腎在治療低血壓時可引起重要器官血流減少。因此，我們研究正常狀態和患膿毒血症的綿羊中，苯腎對全身和局部血流的影響。

方法：觀察清醒的綿羊和活體大腸桿菌所致的膿毒血症的綿羊組對苯腎的反應，及持續灌注 6 小時後的反應。利用流量探頭監測心輸出量和腸系膜、冠脈、腎血流情況。

結果：在對照組，苯腎降低心輸出量和心率，但增加每搏量和平均動脈壓(84 ± 6 到 108 ± 6 mm Hg，平均差別爲 19；95%置信區間爲 17-21)。一過性降低局部腸系膜血流，對冠脈血流無影響，腎血流增加。高代謝膿毒血症期，所有血管床血管擴張，血流增加，苯腎可恢復 MAP 和每搏量至正常範圍，但心率、心輸出量、總外周迴圈逐漸降低。苯腎降低腸系膜和冠脈傳導，血流減少不會持續存在，但腎傳導明顯降低，而總的腎血流明顯增加 (293 ± 22 vs 347 ± 100 mL/min; 平均差別爲 55 [18.8%]；95% CI 爲 47-65)。

結論：在早期高代謝膿毒血症的綿羊中，苯腎可以維持 MAP、增加心輸出量和腎血流，降低心率和冠脈血流，但不降低腸系膜動脈血流。在正常動物中苯腎也有相似的反應。

（韓旭譯 薛張綱校）

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.

評論文章：評論在小兒心臟外科手術中使用未被臨床實驗認可的重組活化Ⅶ因數。

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

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摘要：近年來未被臨床實驗認可的重組活化因數Ⅶ（rFVIIa）的使用顯著增加，尤其是在小兒心臟外科手術中的應用，而且醫生對該藥物的用法很不一樣。 在 2009 年，先天性心臟麻醉協會（CCAS）組成一個專案組審查有關 rFVIIa 在小兒心臟手術病例中的應用的文獻。 CCAS 工作小組的目標是評估當前的使用和有關 rFVIIa 治療的建議，以提高醫療品質，改善患者的預後，降低醫療成本，並制定未來的研究。 在這次審查中，我們總結了幾項有關目前 rFVIIa 在小兒心臟外科手術病人中使用的重要結論，包括適應症、療效、安全性、劑量及監測。該小組選擇和研究了 所有 2000 以來發表的有關 rFVIIa 在小兒及相關成人心臟手術中的應用的文獻。 在審查的 40 名兒科病例中，只有 1 個是一個前瞻性的隨機對照試驗，從而使藥效測定困難。沒有實質性的證據支持 rFVIIa 在小兒心臟手術作爲預防或常規治療的療效。rFVIIa 在搶救性治療中可能有用，因爲目前的觀察證據表明，rFVIIa 在小兒心臟外科手術中的應用的潛在利益可能大於其所帶來的風險。搶救性治療適用於大出血、潛在威脅生命和常規療法難治的情況。然而，當考慮對有血栓栓塞併發症的患者使用 fFVIIa 時必須警惕，因爲在這個時候臨床和亞臨床血栓形成繼發 rFVIIa 治療是未知的。本文用以幫助醫生在決定何時和如何在小兒心臟手術的病人使用 rFVIIa，它的目的不是確定標準的護理或執業準則。沒有足夠的資料支援以證據爲基礎的建議。 我們需要隨機對照試驗來評估 rFVIIa 作爲預防，常規，或搶救治療的療效，並確定藥物的安全性，特別是在血栓方面。 CCAS 評估 rFVIIa 的專責小組將繼續檢索文獻，收集資料，並更新更多有用的資訊。

（賀盼譯 薛張綱校）

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.

使用加巴噴丁和普瑞巴林預防術後慢性疼痛：系統回顧與薈萃分析

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

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背景：許多臨床試驗已經證實了加巴噴丁和普瑞巴林作爲輔助手段在減少術後急性疼痛方面的效果。然而，很少有實驗來研究二者用於減少術後慢性疼痛。我們系統的回顧了一些已發表的關於使用加巴噴丁和普瑞巴林預防術後慢性疼痛（大於術後 2 個月）文獻，並且依據大量的資料做了薈萃分析。資料檢索相關的英文實驗（Medline,Embase,Cochrane,IPA 和 CINAL）在 2011 年 6 月實行。

方法：進入當前系統回顧所要滿足的標準是：隨機，雙盲評估疼痛和鎮痛藥的使用；利用有效手段鎮痛的報告；鎮痛藥消耗的報告；不應該出現設計的不足，方法的問題或者致使結果模棱兩可的混淆因素。不符合預防性鎮痛定義的和評估不在術後 2 個月的慢性疼痛的實驗被排除在外。

結果：資料庫檢索產生 474 條引文。11 個研究符合納入標準。在這 11 個實驗中，8 個是研究加巴噴丁，其中 4 項發現圍術期使用加巴噴丁減少了術後 2 月慢性疼痛的發生。3 個關於普瑞巴林的研究闡述了其顯著降低術後慢性疼痛，3 個實驗中的 2 個還發現了其對病

人術後身體功能的改善。在一個薈萃分析中包含 8 項研究，加巴噴丁的 6 項實驗闡述中至重度的減輕術後慢性疼痛（聯合比率【OR】0.52；95%可信區間【CI】0.27—0.98；P=0.04），2 項普瑞巴林的實驗發現非常大程度的降低術後慢性疼痛（OR 0.09；95%可信區間 CI，0.02—0.79；P=0.007）。

結論：當前的審查支持這個觀點即加巴噴丁和普瑞巴林的圍術期使用在減輕術後慢性疼痛方面是有效的。爲了證實早期的發現，需要更好的設計和適當投入的臨床實驗。

（胡曉清譯 薛張綱校）

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.

氨甲環酸減少不停跳冠狀動脈手術後失血：一個前瞻性、隨機、雙盲、安慰劑對照研究

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

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背景：不停跳冠狀動脈旁路移植術（OPCAB）後出血和需要同種異體輸血的問題仍然存在。因此，我們評估了抗纖維蛋白溶解藥氨甲環酸對實施 OPCAB 手術的患者術後出血和輸血需要的影響。

方法：連續 231 名預定擇期行 OPCAB 的病人入組參加研究。使用一個雙盲方法將病人隨機分配到接受氨甲環酸（劃皮前推注 1g 隨後以 400mg/h 術中滴注；*n*=116）或安慰劑（注射同等容積的生理鹽水；*n*=115）。主要觀察結果是術後 24 小時胸管引流量。還記錄了同種異體輸血、死亡率、大併發症和資源利用。

結果：與安慰劑組相比，接受氨甲環酸的病人在 6 小時時（270± 118 mL vs 416 ± 179 mL, $P < 0.001$）和 24 小時時（654 ± 224 mL vs 891 ± 295 mL, $P < 0.001$）的胸管引流量顯著減少。同種異體紅細胞輸注（47 vs 31.9%, $P = 0.019$）和新鮮冰凍血漿輸注（29.6% vs 17.2%, $P = 0.027$）也顯著減少。在死亡率、併發症和資源利用方面兩組之間沒有差別。

結論：氨甲環酸減少不停跳冠狀動脈手術後胸管引流量和同種異體輸血的需要。

（唐瑩 譯　馬皓琳 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.

教會一個舊的 GABA 受體新的技能

Teaching an Old GABA Receptor New Tricks

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在這期雜誌發行的特別收錄的伴隨文章中描述了改善依託咪酯和苯二氮卓類的類似藥物藥物分佈動力學和降低副作用的嘗試。兩個種類的藥物在 γ-氨基丁酸 A 受體上都有其主要的作用位點，但是它們的結合位點有很大不同，而且作用機制也不一樣。在這裡，我們綜述了 γ-氨基丁酸 A 受體的結構，並描述了兩個可能的結合位點的部位。此外，我們描述了這些藥是如何在系統水準上與神經系統相互作用的。我們留給其他的研究者們去探討這些新藥能否提供真正的臨床療效改善。

（張怡 譯 馬皓琳 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-羧化依託咪酯在體和離體的藥理學研究

In Vivo and In Vitro Pharmacological Studies of Methoxycarbonyl-Carboetomidate

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背景：我們既往曾研發出依託咪酯的兩種同型物：甲酯基-依託咪酯和羧化依託咪酯，這兩種化合物既可保持依託咪酯血流動力學平穩的特性又可縮短其抗腎上腺皮質類作用的持續時間並減輕作用程度。甲酯基（MOC）-依託咪酯代謝迅速，作用時間超短，而(R)-乙基 1-(1-苯乙基)-1H-吡咯-2-羧化物（羧化依託咪酯）並不強烈抑制 11β-羥化酶。本研究假設 MOC-依託咪酯不穩定的酯基可合併到羧化依託咪酯，從而產生一種能同時具備兩種藥劑各自的優點的新藥，我們介紹了羧化依託咪酯的一個軟性類似物——MOC-右旋-乙基-1H-吡咯環-2-羧化物（MOC-羧化依託咪酯）的合成及藥理學特性。

方法：層析法測定 MOC-羧化依託咪酯的辛醇：水分配係數並與依託咪酯、羧化依託咪酯和 MOC-依託咪酯的辛醇：水分配係數進行比較。在蝌蚪及大鼠分別測定 MOC-羧化依託咪酯翻正反射消失（LORR）的半數有效藥物濃度(EC_{50})及半數有效劑量。採用雙微電極電壓膜片鉗電生理技術測定 MOC-羧化依託咪酯對 $GABA_A$ 受體功能的作用，並採集混合大鼠血液標本使用高效液相質譜法評價其代謝穩定性。同時測定 MOC-羧化依託咪酯的作用持續時間及對大鼠動脈血壓、腎上腺皮質功能的影響。

結果：MOC-羧化依託咪酯的辛醇：水分配係數爲 3300 ± 280，而依託咪酯、羧化依託咪酯和 MOC 依託咪酯的分別爲 800 ± 180、15,000 ± 3700 和 190 ± 25。MOC 羧化依託咪酯致蝌蚪 LORR 的 EC_{50} 爲 9 ± 1 μM，致大鼠 LORR 的 EC_{50} 爲 13 ± 5 mg/kg。13 μM 的 MOC-羧化依託咪酯可提高 $GABA_A$ 受體電流 400% ± 100%。MOC-羧化依託咪酯在混合大鼠血中的代謝半衰期爲 1.3 分鐘。大鼠 LORR 持續時間-催眠劑量對數值的曲線斜率，MOC-羧化依託咪酯顯著低於羧化依託咪酯(4 ± 1 比 vs 15 ± 3; $P = 0.0004123$)。催眠劑量時，MOC-羧化依託咪酯與單獨的溶劑相比較對動脈血壓和腎上腺皮質功能的影響均無顯著差異。

結論：MOC 羧化依託咪酯是一種 $GABA_A$ 受體的調節劑，催眠作用強，較羧化依託咪酯代謝更爲迅速，從腦中清除也較快，維持血流動力學穩態的特性與羧化依託咪酯相似且並不抑制腎上腺皮質的功能。

（邱鬱薇 譯 馬皓琳 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.

麻醉中鎮靜成分在監視器上的延遲：狀態熵和意識指數分析

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

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通過分析腦電圖（EEG）來評估麻醉中鎮靜成分的監護儀可以幫助降低術中知曉及回憶的發生率。爲了計算代表麻醉水準的指數，這些監護儀在獲得準確的資料顯示前有不同程度的時間延遲。之前的研究用術中記錄的真實和類比腦電圖信號以確定大腦狀態和麻醉趨勢以及雙頻指數的時間延遲。本研究中筆者測定了狀態熵和意識指數的時間延遲。爲此，本研究重播了記錄的代表不同麻醉水準的真實和模擬的腦電圖序列來測試監護儀。

用類比的和在圍術期真實記錄的提示"清醒"、"全麻"和"皮層抑制"的穩定狀態的腦電信號以評估時間延遲。在從一個狀態轉換到另一個狀態時測量時間延遲，時間延遲的定義爲顯示器達到穩定目標指數需要的時間間隔。使用模擬的和真實的腦電圖序列獲得了類似的結果。時間延遲並不恒定，範圍 18 秒~152 秒。數值增加和減少時時間延遲也不相同。時間延遲取決於起始的和目標指數值。指數計算的時間延遲可能會限制被研究的監護儀預防術中知曉及回憶的能力。如果監護儀用於藥效學研究，麻醉水準向深或淺轉換時不同的時間延遲可能是一個問題。

（許辛 譯 馬皓琳 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.

既往腰椎間盤切除術不會改變椎管內分娩鎮痛的效果

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

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背景：腰椎間盤切除術是一種常見的神經外科手術。由於手術疤痕和解剖學的改變，椎管內分娩鎮痛的效果可能對有椎間盤切除手術史的產婦較差。在這個前瞻性觀察病例對照研究中，我們通過每小時分娩鎮痛布比卡因的用量，作爲比較曾行椎間盤切除術的婦女和那些未行背部手術的婦女分娩鎮痛效果的間接方法。

方法：對在一個較大型的大學的附屬婦產科醫院中所有要求椎管內分娩鎮痛且曾行過椎間盤切除手術的婦女進行了研究。對照受試者與麻醉醫師的技術水準相匹配。主要結果是分娩鎮痛每小時布比卡因的用量。記錄硬膜外導管放置的特點，包括椎間隙的嘗試次數、放置的時間和因鎮痛不足重置硬膜外導管次數。使用 Wilcoxon 排名秩和或 Fisher 精確檢驗來分析受試者的特點、分娩結果和鎮痛的效果。採用 Wilcoxon 符號秩、配對資料率或符號檢驗來分析硬膜外導管的放置資料。

結果：對椎間盤切除術組中的 42 名婦女和對照組中 42 名婦女的資料進行了分析。分娩鎮痛每小時布比卡因的用量在兩組之間是沒有差別的（中位數[四分位距，IQR]：椎間盤切除術組 12.7 mg/ h[11.0 至 15.3]和對照組 13.2mg/ h [11.3 至 15.7]，中位數差異[95％的置信區間，CI]：-0.55mg/h[-1.33 至 1.39]；*P* = 0.43）。從椎管內鎮痛開始到分娩的時間間隔以及分娩方式在兩組之間沒有差別。放置硬膜外導管的時間中位數在椎間盤切除術和對照組受試者之間的差異（95％CI）是 0 分鐘（-1 至 2.5）；*P* = 0.38。椎間盤切除術組和對照組中分別有 17％和 2%嘗試穿刺超過一個椎間隙，差異（95％CI）是 15％（2-26）；*P* = 0.03。硬膜外穿刺技術和估計的導管放置水準沒有差異。此操作過程在椎間盤切除術組中有 3 例由高年資的麻醉醫生完成，在對照組中有 2 例（p = 1.0）。這兩組中都沒有硬膜外導管的重置。

結論：進行椎管內鎮痛分娩的曾行椎間盤切除術組產婦和對照組相比，布比卡因每小時用量沒有差異。硬膜外導管放置時間也沒有差別。但是在椎間盤切除術組，穿刺需要嘗試

更多的椎間隙。我們的研究結果表明，標準的臨床椎管內鎮痛方法對於曾行椎間盤切除手術的婦女有效。

（崔曉娜 譯 馬皓琳 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.

晝夜節律鐘基因 HPER3 與非心臟手術後的認知功能障礙沒有關聯

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

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背景：特殊的時鐘基因 PERIOD3 在有關晝夜節律、睡眠動態平衡以及認知功能方面是很重要的。而等位基因 $PER3^{5/5}$ 與睡眠剝奪引起的更差的認知表現有關。我們推測在 $PER3^{5/5}$ 基因型患者在非心臟手術後 1 周具有較高的術後認知功能障礙（POCD）風險。

方法：我們從一個已完成的多中心研究中選取發生了 POCD 患者 93 名以及未發生 POCD 患者 186 名的血樣進行分析。研究人群包括了 40 歲及以上年齡進行非心臟手術的患者，他們在術前及術後 1 周都進行了由 7 個分測試組成的成套的神經心理學測試。通過用聚合酶鏈反應分析血液樣本的 DNA 來測定 PER3 基因型(臨床試驗.gov 識別字 NCT01088100）。

結果：3 種基因型的概率分別爲 11.8%（32 例）$PER3^{5/5}$，41.7%（113 例）$PER3^{4/5}$，和 46.5%（126 例）$PER3^{4/4}$。在術後 1 周關於 POCD 的 3 個基因型的分佈無顯著差異（P= 0.68）。發生 POCD 的患者中 12%（6%至 21%）和無 POCD 的患者中 12%（7%至 17%）具有 $PER3^{5/5}$ 基因型。POCD/-POCD 的發生率差異在 $PER3^{5/5}$ 基因型中是 1% (−7%~10%)。在一項神經心理學測試中發現有 $PER3^{4/4}$ 的患者的 Z 評分顯著更高（概念轉換試驗的錯誤評分）(邦弗朗尼矯正，P =0.042)。

結論：時鐘基因 $PER3^{5/5}$ 基因型與非心臟手術後 1 周 POCD 的發生沒有顯著相關性。如果 $PER3^{5/5}$ 的確會使認知表現更差，那麼在患者中的發生率小於 10%。

（余亦南 譯 馬皓琳 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.

鹽酸曲馬多在大鼠術後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：曲馬多在治療急性痛和慢性痛中廣泛應用。該藥鎮痛作用機制有 2 個：啓動阿片類受體和增強去甲腎上腺素（NA）和血清素（5-HT）的傳遞。然而曲馬多對脊髓中 NA 和 5-HT 濃度的影響未被評估。在本研究中，我們研究曲馬多在大鼠術後疼痛模型中的抗超敏作用。我們也通過在體微透析法來評估了在注射曲馬多後脊髓中 NA 和 5-HT 水準的增加。

方法：我們在雄性 SD 大鼠上做後足切割來製作術後疼痛模型。足部切割後 24 小時在大鼠腹膜內注射和鞘內注射曲馬多。通過使用馮弗雷纖維方法測定回縮閾來衡量機械性超敏。對腰椎脊髓背角進行微透析研究以測量腹腔內注射曲馬多後 NA 和 5-HT 水準。我們也測量正常大鼠和行足部切割大鼠脊髓中的 NA 和 5-HT 的含量。

結果:腹膜內注射曲馬多(10、20 和 40 mg/kg)和鞘內注射曲馬多(125、250 和 500 μg) 產生了劑量依賴方式的抗痛覺過敏作用。曲馬多的抗超敏作用可被鞘內預先注射美西麥角（一種羥色胺受體拮抗劑）30 μg、咪唑克生（一種去甲腎上腺素受體拮抗劑）30 μg 和納洛酮（一種非選擇性阿片類受體拮抗劑）30 μg 消除。微透析法研究提示脊髓背角中 5-HT 和 NA 濃度增加，在腹膜內注射 20 mg/kg 曲馬多後 30 分鐘達到峰值濃度。而且，身體同側的腰椎脊髓背角中 5-HT 和 NA 含量在足部切割後第一天和第三天分別增加。

結論:這些結果提示曲馬多通過增加脊髓中 NA 和 5-HT 水準和啓動阿片類受體來抑制術後疼痛超敏。曲馬多可能在脊髓中 NA 和 5-HT 水準增高的術後早期抗超敏作用更有效。

（方斌 譯 馬皓琳 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.

頸橫動脈和肩胛背動脈在鎖骨上臂叢神經阻滯中常用的三個超聲探頭位置的出現情況

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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背景：在超聲引導下行鎖骨上臂叢神經阻滯時，有穿刺到血管的風險。在這項研究中，我們測定了在鎖骨上阻滯臂叢神經阻滯時，通過在 3 個探頭位置的超聲評價檢測到頸橫動脈（TCA）和肩胛背動脈（DSA）的頻率。

方法：對 53 個健康成人志願者超聲檢查鎖骨上區域。在 3 個探頭位置得到鎖骨上區域的超聲圖像：位置 A（都橫躺在第一肋骨上的臂叢神經和鎖骨下動脈）；位置 B（在第一肋骨上的臂叢神經；在胸膜上的動脈）；位置 C（在前斜角肌與中斜角肌之間的臂叢神經）。主要的結果參數是二維和彩色多普勒超聲在 3 個指定探頭位置檢測到 TCA 和 DSA 的頻率。

結果： 對 53 個受試者的 106 個鎖骨上區域進行了檢查。在所有的受試者都檢測到了鎖骨下動脈。TCA 比 DSA 檢測到的頻率更高，在 106 個掃描中，分別爲 94 個（88.7％，95％可信區間[CI] 80.7％～93.8％）和 36 個（34％，95％CI 25.3％-43.9％）（McNemar *P* <0.001）。在探頭位置 A、B 和 C 分別檢測到 TCA 2 個（1.9％，95％CI 爲 0.3％-7.3％）、31 個（29.2％，95％CI 20.9％-38.9％）和 61 個（57.5％，95％CI 47.5％-66.9％），而在探頭位置 A、B 和 C 分別檢測到 DSA：3 個（2.8％，95％CI 爲 0.7％-8.6％）、23 個（21.7％，95％CI14.5％-30.9％）和 10 個（9.4％，95％CI 爲 4.8％-17.0％）。因此，TCA 和 DSA 在探頭位置 A 出現的可能性較小（P <0.001）。

結論：在鎖骨上區域臂叢神經附近 TCA 比 DSA 檢測的頻率更高。 TCA 和 DSA 都在探頭位置 A 出現的可能最小。彩色多普勒，尤其在探頭位置 A，有助於減少超聲引導下鎖骨上臂叢神經阻滯過程中不慎穿刺到血管的風險。

（安光惠 譯 馬皓琳 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.

絲氨酸蛋白酶抑制劑 MDCO-2010 對健康人以及心臟手術患者的啓動凝血時間的影響

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：啓動凝血時間（ACT）已廣泛用於監測心臟手術中肝素的抗凝情況。使用抑肽酶會延長矽藻土啓動的 ACT 時間。MDCO-2010 是一種新型絲氨酸蛋白酶抑制劑，目前認爲可能作爲抑肽酶的替代品。因此，作者採用了 3 種不同的床邊自測 ACT 儀器（高嶺土或矽藻土啓動）來評估此藥對 ACT 的影響。

方法：研究分爲兩部分。第一部分：從 15 名健康志願者中收集血液樣本，樣本用移液槍吸入 Eppendorf 試管內，分別單獨加入兩種濃度的 MDCO-2010（終濃度爲 100 nM 以及 500nM）或同時加入肝素（1.2 U/ml 或 2.4U/ml）。採用 Helena（矽藻土），Hemochron（高嶺土）以及 Medtronic（高嶺土）三個儀器測定 ACT 值。第二部分：從 15 名接受體外迴圈的心臟手術患者術中 5 個時間點收集血液樣本。先測定 ACT 值，再加入終濃度爲 100 或 500nM 的 MDCO-2010。其他需測定凝血指標有：凝血酶原時間（PT），活化的部分凝血活酶時間（APTT），纖維蛋白原，抗凝血酶，凝血素以及抗 Xa 量。

結果：無論何種 ACT 啓動物或者採用何種設備測定，加入 MDCO-2010 的志願者和患者血樣本的 ACT 時間都呈濃度依賴性延長。加入 MDCO-2010 的志願者樣本（未加肝素）和患者樣本（基線以及 ICU）的 Helena 矽藻土啓動 ACT 的變化百分比較 Hemochron 或 Medtronic 高嶺土啓動的 ACT 平均要長 3.1 ± 1.8 倍（95%可信區間 2.6–3.6; $P < 0.001$）。

結論：MDCO-2010 延長的高嶺土啓動的全血凝固時間要短于延長矽藻土啓動的全血凝固時間。

（陸秉瑋 譯 陳傑 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.

以安慰劑和咪達唑侖爲對照組評價 Remimazolam（CNS 7056）藥物安全性、藥代動力學和藥效學的 I 期單遞增劑量研究：第一部分：安全性、有效性和基礎藥代動力學

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

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背景：Remimazolam 是一種新的苯二氮卓類藥物，由組織酯酶代謝成無活性的 CNS 7054，被證實和目前使用的苯二氮卓類藥物相比有起效快、鎮靜時間短以及恢復快的優點。本文作者報導了該藥物安全性和有效性的 I 期臨床研究結果。

方法：這是一項單中心、雙盲以及安慰劑和藥物對照的隨機單劑量遞增藥物 I 期臨床研究。總共有 10 組健康人接受單劑量 1min 內靜脈內注射 remimazolam、咪達唑侖或者安慰劑。在這 10 組人中，remimazolam 的劑量從 0.01mg/kg 至 0.35mg/kg。在組 1 至組 3，6 例注射 remimazolam，1 例注射安慰劑。從組 4 開始，每組中額外的 3 例注射咪達唑侖 0.075mg/kg。研究其藥物安全性、藥代動力學以及藥效學。以大於 50%的受試者中意識喪失超過 5min 作爲試驗終止的標準。

結果：至組 9（remimazolam 0.30mg/kg）試驗終止，共有 81 名受試者。Remimazolam 在所有劑量組中均能很好地耐受，且無嚴重的副作用。三名受試者出現輕微的低氧（Spo_2 85%–88%）（其中 remimazolam 組 2 人，咪達唑侖組 1 人），但之後均自行緩解。在最高劑量的 remimazolam 組中 1 名受試者中度低氧(Spo_2 75%)，通過抬下頜而緩解。均不需要額外的氧通氣和手動通氣。在整個過程中，生命體征平穩。除了在 remimazolam 組和咪達唑侖組藥物注射 2min 後出現心率的上升，無低血壓、高血壓發生。Remimazolam 的藥代動力學與咪達唑侖呈線性關係，系統清除率約是其 3 倍。藥物清除與體重無相關性。remimazolam 劑量超過 0.05mg/kg 藥物起效迅速且呈藥物劑量依賴性的鎮靜作用。Remimazolam（0.075mg—0.20mg/kg）達到的峰鎮靜水準相似于甚至高於咪達唑侖（0.075mg/kg）。有效劑量相當的 remimazolam（0.10mg/kg 和 0.15mg/kg）和咪達唑侖（0.075mg/kg）的恢復時間中位數是 10min 和 40min。

結論：Remimazolam 具有起效快、恢復快以及耐受好等特點。不需要額外的氧氣和通氣。基於上述研究資料，今後應進一步研究 remimazolam 的鎮靜/麻醉作用。

（俞芳 譯 陳傑 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.

簡報：甲氧羰基依託咪酯的羧酸代謝物的藥理學研究

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

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背景：甲氧羰基依託咪酯（MOC-依託咪酯）是一個快速代謝和超短效依託咪酯類似物，單次注射後，不會產生長期腎上腺皮質功能抑制。它的代謝產物（MOC-ECA）是一種羧酸，其藥理學尚未研究。作者推測， MOC-ECA 與 MOC-依託咪酯相比，藥理活性顯著降低，單次注射後，催眠作用持續時間非常短暫且不產生長期腎上腺皮質功能抑制。爲了驗證這一假設，作者在 3 個生物檢測中比較了 MOC-ECA 和 MOC-依託咪酯的效力。

方法：採用蝌蚪的翻正反射消失來評估 MOC-ECA 的催眠效力。通過測定所需直接啓動 α1（L264T）β2γ2L GABAA 受體的濃度，界定 MOC-ECA 的 γ-氨基丁酸 A（GABAA）調節效力並與 MOC-依託咪酯進行比較。通過測定抑制腎上腺皮質細胞體外生成皮質醇需要的濃度，比較 MOC-ECA 和 MOC-依託咪酯對腎上腺皮質的抑制能力。

結果：MOC-ECA 使蝌蚪的翻正反射消失的 50％有效濃度爲 2.8±0.64 mM，較以前報導的 MOC-依託咪酯的有效濃度（8±2μM）更爲精確。MOC-ECA 直接啓動 $GABA_A$ 受體的 50％有效濃度爲 3.5±0.63 mM 而 MOC-依託咪酯爲 10±2.5μM。MOC-ECA 抑制腎上腺皮質細胞在體外的皮質醇半最大抑制濃度爲 30±7μM ，而 MOC-依託咪酯爲 0.10±0.02μM。

結論：在所有的生物實驗中，MOC-ECA 的效力低於 MOC-依託咪酯約爲 300 倍。

（孫曉瓊 譯 陳傑 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.

美國 1998 – 2008 間住院關節置換術術後主要併發症發生率和死亡率的趨勢

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

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背景：關節置換術在世界範圍內的應用不斷增加。作者旨在闡明行全髖關節置換術(THA)或全膝關節置換術(TKA)的人口資料和圍手術期結果的最近趨勢。

方法：資料來自美國 1998 年至 2008 年之間 THA 和 TKA 樣本。對患者年齡、疾病負擔,住院時間，主要的圍手術期併發症的發生率、住院死亡率進行了分析。住院結果以每 1000 名住院病人住院天數作爲住院日變化來報告。Deyo 指數、出院狀態和相互影響等調整發病率趨勢分析。

結果：1998 年和 2008 年之間,接受 TKA 和 THA 患者的平均年齡下降了 2 到 3 歲($P < 0.001$)。平均住院時間下降了大約 1 天 ($P < 0.001$)。患者出院回家的百分比 TKA 的患者從 29.7%下降到 25.4%,THA 的患者從 29.3%到 24.2%,患者更喜歡到長期和短期保健單位($P <$

0.0001)。TKA 和 THA 的疾病負擔通過測量 Deyo 疾病指數分別增加了 35%和 30%(P < 0.0001)。TKA 術後,下列主要併發症發生率增加:肺栓塞(係數估計[CE]0.069;95%可信區間[CI]爲 0.059 -0.079;P < 0.0001),敗血症(CE 0.034;95% CI,0.014 -0.054;P = 0.001),非心源性梗塞心臟併發症(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 術後,下列主要併發症的發生率增加:肺栓塞(CE 0.031;95% CI,0.012 -0.049;P = 0.001),敗血症(CE 0.060;95% CI,0.039 -0.081;P<0.0001),非心肌梗塞性心臟併發症(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%可信區間,0.077 −0.040;P<0.0001)和 THA(CE−0.068;95%可信區間,0.086 到−0.051;P<0.0001)。

結論：1998 年和 2008 年之間,THA 和 TKA 的幾個主要的住院併發症趨勢顯示增加,包括肺栓塞,敗血症，非心肌梗塞性心臟併發症和肺炎。儘管此期間併發症增加，住院死亡率在下降。

（龔寅　譯　陳傑　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.

行雙側鼓膜切開及放置通氣管手術患兒，術中芬太尼滴鼻、肌肉或靜脈注射嗎啡對術後鎮痛療效及精神行爲的影響

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

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背景：雙側鼓膜切開及放置通氣管（BMT）在美國是常見的兒科手術。許多 BMT 術後患兒在麻醉後監護室（PACU）有不良精神行爲，並需鎮痛治療。術中經滴鼻、肌肉或靜脈給予阿片類藥物的患兒與安慰劑組相比發生率降低。但是，目前沒有資料表明哪種給藥途徑更好。本研究的目的是，比較全身麻醉下行 BMT 的患兒，術中三種給藥方式對術後鎮痛效果及患兒精神行爲的影響。

方法： 171 名 ASAI-II 接受 BMT 患兒隨機分成 3 組： 組 1：2 μg/kg 芬太尼滴鼻與安慰劑靜脈和肌肉注射；組 2： 0.1 mg/kg 嗎啡滴鼻與安慰劑肌注；組 3：0.1 mg/kg 嗎啡肌注與安慰劑靜脈及滴鼻。所有受試患兒均接受規範化的七氟醚-N2O-O2 的全身麻醉和術後護理。該研究試驗的主要研究終點爲在 PACU 面部，腿疼痛評分，活動度，是否哭鬧，可安慰評分（FLACC）等。

結果：3 組間 FLACC 疼痛評分峰值無顯著差異（三組平均值[95% CI]分別爲芬太尼滴鼻組 2.0[1.2–2.8]，靜脈嗎啡組爲 2.7[1.7–3.6]，肌注嗎啡組爲 2.9 [2.1–3.7] ）。 三組小兒麻醉後精神錯亂（PAED）評分，術後譫妄（PAED 評分≥12 分），嘔吐，圍手術期低氧血症，是否需要氣道管理及需要術後鎮痛的發生率無顯著差異。各組患兒 PACU 逗留時間或父母滿意度也無顯著差異。

討論：行 BMT 手術患兒，術中芬太尼滴鼻，肌肉和靜脈注射嗎啡對術後鎮痛療效及精神行爲影響無顯著差異。肌肉注射是最簡單的方式，可避免行靜脈注射時建立血管通路延誤可能，並避免滴鼻藥物通過鼻咽部，刺激聲帶引起喉痙攣的風險。

（陳毓雯 譯 陳傑 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.

腦脊液搏動的頻率和強度影響鞘內藥物分佈: 病人間個體差異的關鍵因數

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

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背景: 鞘內給藥是一種很有效的治療中樞神經系統疾病的給藥手段。然而，即使用同一藥物相同劑量和用法，體內藥物分佈的範圍也因人而異，且可控性差。病人間不同的腦脊液(CSF)搏動可以產生不同的藥物分佈。作者運用醫學影像學-計算流體動力學(miCFD)構建一個病人個體特異性的模型，來定量化 CSF 的生理學搏動作爲藥物轉運的功能。

方法: 磁共振(MRI)和磁共振電影（CINE MRI）可用來捕捉病人的中樞神經系統的解剖結構和 CSF 搏動流速。基於這兩者可以重建病人的 miCFD 模型，並且計算出病人的 CSF 流速。作者研究了在 L2 水準給予一次定量藥物注射對於 CSF 搏動(頻率和每搏輸出量)的影響。通過不同的心率：43，60 和 120 bpm，以及各自的 CSF 每搏輸出量：1，2 和 3 mL，計算出整個脊柱的藥物分佈剖面圖。爲了評估不同生理學差異的病人的中毒風險，常用麻醉藥的治療劑量和中毒劑量是通過實驗得出的。中毒風險分析則是由病人對於蛛網膜下腔麻醉表現出的不同心率和 CSF 每搏輸出量而得出。

結果: 病人的心率和 CSF 每搏輸出量都會極大地影響鞘內注射的藥物分佈。加倍的心率(60~120 bpm) 使得注射後 CSF 的最高濃度下降了 26.4%。而加倍的 CSF 每搏輸出量使得注射後 CSF 的最高濃度減小了 38.1%。計算顯示，由於注射導致的可能的中毒最高濃度，通過改變注射速度可以避免。慢注射可以避免 CSF 的中毒最高濃度，同時又維持在治療濃度之上。

結論: 作者的計算確定了病人之間的鞘內藥物分佈的關鍵變數。藥物轉運速度受 CSF 搏動的頻率和強度的極大影響。通過嚴格的 miCFD 模型，可以調整藥物注射的變數，以此降低藥物注射相關的中毒風險。

（俞勍晶 譯 陳傑 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.

新生鼠鞘內注射可樂定：劑量依賴鎮痛以及脊髓凋亡和毒性的評估

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

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背景：在兒童各年齡階段，軸索內使用可樂定用於圍手術期鎮痛。大鼠的臨床前試驗比較了在整個大鼠生長過程中脊髓鎮痛的相對毒性和安全性。

原理：出生後 3、7、21 天的幼鼠鞘內注射可樂定或者生理鹽水。每個年齡段，記錄最大的鎮痛劑量（下肢機械刺激縮足反應閾值）和抗痛覺過敏劑量。腰部脊髓部分需要評估組織病理學凋亡和細胞死亡以及神經膠質反應性。P3 組鞘內注射氯胺酮作爲陽性對照組。除了這些分組，測量 P35 熱刺激縮足反應潛伏期和機械刺激縮足反應閾值。

結果：大鼠鞘內注射可樂定有年齡和劑量依賴的鎮痛作用。最大劑量的可樂定也不會改變新生鼠脊髓的細胞凋亡的程度和分佈以及增加神經膠質細胞的反應性。各年齡段在注射後的 1 天和第 7 天都沒有見到脊髓的組織病理學改變。在 P35，鞘內注射可樂定也不產生對機械性和溫度刺激的永久性改變。

結論：大鼠鞘內注射可樂定並不產生脊髓毒性，即使在劑量遠大於鎮痛所需的量時。治療比率（最大耐受劑量/痛覺過敏劑量）在 P3 組>300，在 P7 組>30，在 P21 組>10。這些資料提供了脊髓鎮痛藥的額外資訊有助於動物幼齡期的臨床選擇。

（範逸臣　譯　陳傑　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.