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**吸入一氧化碳對豬肺體外迴圈的後處理作用**

**Postconditioning of the Lungs with Inhaled Carbon Monoxide After Cardiopulmonary Bypass in Pigs**

Ulrich Goebel, MD, Matthias Siepe, MD, Christian I. Schwer, MD, David Schibilsky, MD, Kerstin Brehm, MD, Hans-Joachim Priebe, MD, Christian Schlensak, MD and Torsten Loop, MD

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**背景：**動物模型中已經證實，在器官缺血損傷前吸入一氧化碳對器官有保護作用。但是尚未證實缺血損傷發生後吸入一氧化碳是否同樣有效。本試驗的目的是研究在豬模型中，體外迴圈後吸入一氧化碳是否會減少肺損傷。

**方法：**所有動物被隨機分到假手術組 (n=5), 假手術+吸入一氧化碳組 (n=5), 標準 CPB 組 (n=10), CPB+吸入一氧化碳組 (n=10)。在 CPB 結束後給予 1 小時的一氧化碳 (250ppm)。CPB 開始前，CPB 結束即刻，CPB 結束後 5 小時分別進行肺組織活檢，檢測肺熱休克蛋白 70 和 90 的表達，細胞因數，肺泡巨噬細胞滲透以及 caspase-3 的活性。

**結果：**CPB 結束後 5 小時，給予吸入一氧化碳明顯減少炎性細胞因數腫瘤壞死因數 (CPB+CO  $521 \pm 77$  vs CPB  $821 \pm 97$  pg/ml,  $P < 0.001$ ) 和白細胞介素-6 的表達 ( $304 \pm 81$  vs  $860 \pm 153$  pg/ml,  $P < 0.001$ )，增加了熱休克蛋白 70 (CPB+CO  $79 \pm 14$  vs CPB  $36 \pm 9$  ng/ml,  $P < 0.001$ ) 和抗炎因數白介素-10 的表達 (CPB+CO  $278 \pm 40$  vs CPB  $63 \pm 20$  pg/ml,  $P < 0.001$ )，同時減弱了肺凋亡蛋白 caspase-3 的活性 (CPB + CO  $0.73 \pm 0.11$  vs CPB  $0.99 \pm 0.1$  RFU,  $P < 0.05$ )。給予一氧化碳可以減少肺組織損傷和肺泡巨噬細胞滲透 ( $78 \pm 39$  vs  $145 \pm 34$  counts per field of vision,  $P < 0.001$ )。

**結論：**本試驗證實在 CPB 後給予低濃度的一氧化碳有減少 CPB 相關肺損傷的作用。

(張婷 譯 陳傑 校)

**BACKGROUND:** Administration of inhaled carbon monoxide before organ ischemic injury exerts protective effects in animal models. Because there are no data showing that this also works after an ischemic insult, our objective in this study was to investigate whether inhaled carbon monoxide attenuates cardiopulmonary bypass (CPB)-induced lung injury in a pig model.

**METHODS:** Animals were randomized to a SHAM group ( $n = 5$ ), a SHAM group plus inhaled carbon monoxide ( $n = 5$ ), standard CPB ( $n = 10$ ), and to CPB plus inhaled carbon monoxide ( $n = 10$ ). Carbon monoxide (250 ppm) was given for 1 hour after termination of CPB. Lung biopsies were obtained before CPB, immediately after separation from CPB, and for 5 hours after termination of CPB to determine expression of pulmonary heat shock proteins 70 and 90, cytokines, alveolar macrophage infiltration, and fluorogenic caspase-3 activity.

**RESULTS:** At 5 hours after CPB, administration of inhaled carbon monoxide was associated with reduced pulmonary expression of the inflammatory cytokines tumor necrosis factor (CPB + CO  $521 \pm 77$  vs CPB  $821 \pm 97$  pg  $\cdot$  mL<sup>-1</sup>,  $P < 0.001$ ) and interleukin-6 ( $304 \pm 81$  vs  $860 \pm 153$  pg  $\cdot$  mL<sup>-1</sup>,  $P < 0.001$ ), increased pulmonary expression of the cytoprotective heat shock protein 70 (CPB + CO  $79 \pm 14$  vs CPB  $36 \pm 9$  ng  $\cdot$  mL<sup>-1</sup>,  $P < 0.001$ ) and the antiinflammatory cytokine interleukin-10 (CPB + CO  $278 \pm 40$  vs CPB  $63 \pm 20$  pg  $\cdot$  mL<sup>-1</sup>,  $P < 0.001$ ), and with reduced pulmonary apoptotic protein caspase-3 activity (CPB + CO  $0.73 \pm 0.11$  vs CPB  $0.99 \pm 0.1$  RFU,  $P < 0.05$ ). Carbon monoxide administration was associated with reduced histological evidence of lung injury and alveolar macrophage infiltration ( $78 \pm 39$  vs  $145 \pm 34$  counts per field of vision,  $P < 0.001$ ).

**CONCLUSIONS:** These results suggest that administration of low concentrations of carbon monoxide after CPB (“postconditioning”) protects the lung from CPB-related lung injury.

使用自適應神經模糊推理系統 (ANFIS) 建立內鏡檢查時具有鎮靜-鎮痛效果的異丙酚、瑞芬太尼組合模型

### Modeling the Effect of Propofol and Remifentanil Combinations for Sedation-Analgesia in Endoscopic Procedures Using an Adaptive Neuro Fuzzy Inference System (ANFIS)

P. L. Gambús, MD, E. W. Jensen, MSc, PhD, M. Jospin, MSc, X. Borrat, MD, G. Martínez Pallí, MD, J. Fernández-Candil, MD, J. F. Valencia, MSc, X. Barba, CRNA, P. Caminal, MSc, PhD and I. F. Trocóniz, PhD

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**背景：**消化道內鏡檢查的需求日益增加，但目前沒有提供並控制患者的鎮靜和鎮痛效果方案。這項研究中，作者通過靶控輸注系統評估不同組合的異丙酚和瑞芬太尼，得出提供接受超聲內鏡患者的鎮痛效果的誘導藥物組合的最佳濃度。

**方法：**120 例接受超聲內鏡檢查患者，隨機分配至異丙酚或瑞芬太尼的 8 種不同濃度組合靶控輸注系統，固定異丙酚或瑞芬太尼的某一濃度，允許調整另一種藥物的濃度。預測異丙酚 ( $C_{e\text{pro}}$ ) 和瑞芬太尼 ( $C_{e\text{remi}}$ ) 效應室濃度，收集、記錄，並通過自適應神經模糊推理系統分析聽覺誘發電位參數，聽覺誘發電位指數 (AAI/2) 和腦電圖信號 (雙頻指數[BIS]和意識指數[IoC])，以及明確有或無疼痛刺激的情況下 (Ramsay 鎮靜評分[RSS]分數)。這個模型通過使用執行誤差絕對值中位數(MDAPE)、平均均方根誤差 (MDRMSE) 和執行誤差中位數 (MDPE) 的模糊理論描述了  $C_{e\text{pro}}$  及  $C_{e\text{remi}}$  相對 AAI/2, BIS 及 IoC 之間的關係。68 名患者運用此模型接受異丙酚和瑞芬太尼不同組合進行前瞻性的驗證。就預測峰值 ( $P_k$ ) AAI/2, BIS 及 IoC 鎮靜水準, RSS 評分進行了探討。

**結果：**對 110 例患者資料進行了分組分析。由此產生模型的 MDAPE 為 32.87, 12.89 及 8.77; MDRMSE 為 17.01, 12.81 及 9.40; AAI/2, BIS 及 IoC 的 MDPE 分別為 -1.86, 3.97 及 2.21。在無刺激和相似刺激下 AAI/2, BIS, 及 IoC, 的  $P_k$  值分別為 0.82, 0.81 和 0.85。用該模型預測的 MDAPE 34.81, 14.78 及 10.25; MDRMSE 為 16.81, 15.91 和 11.81; MDPE 為 -8.37, 5.65 及 -1.43 和 AAI/2, BIS 及 IoC  $P_k$  值分別 0.81, 0.8, 及 0.8。

**結論：**本文制定並前瞻性驗證  $C_{e\text{pro}}$  and  $C_{e\text{remi}}$  的 AAI/2, BIS 及 IoC 的模型。根據模型，符合 RSS 評分為 4 分的 ( $C_{e\text{pro}}$  and  $C_{e\text{remi}}$ ) 濃度組合範圍從 ( $1.8 \mu\text{g}\cdot\text{mL}^{-1}$ ,  $1.5 \text{ ng}\cdot\text{mL}^{-1}$ ) 至 ( $2.7 \mu\text{g}\cdot\text{mL}^{-1}$ ,  $0 \text{ ng}\cdot\text{mL}^{-1}$ )。這些濃度對應的 AAI/2 為 25 至 30, BIS 71 至 75, IoC 為 72 至 76。當有疼痛刺激時，如達到相同程度的鎮靜作用需增加  $C_{e\text{pro}}$  和  $C_{e\text{remi}}$ 。

(陳毓雯 譯 陳傑 校)

**BACKGROUND:** The increasing demand for anesthetic procedures in the gastrointestinal endoscopy area has not been followed by a similar increase in the methods to provide and control sedation and analgesia for these patients. In this study, we evaluated different combinations of propofol and remifentanyl, administered through a target-controlled infusion system, to estimate the optimal concentrations as well as the best way to control the sedative effects induced by the combinations of drugs in patients undergoing ultrasonographic endoscopy.

**METHODS:** One hundred twenty patients undergoing ultrasonographic endoscopy were randomized to receive, by means of a target-controlled infusion system, a fixed effect-site concentration of either propofol or remifentanyl of 8 different possible concentrations, allowing adjustment of the concentrations of the other drug. Predicted effect-site propofol ( $C_{e\text{pro}}$ ) and remifentanyl ( $C_{e\text{remi}}$ ) concentrations, parameters derived from auditory

evoked potential, autoregressive auditory evoked potential index (AAI/2) and electroencephalogram (bispectral index [BIS] and index of consciousness [IoC]) signals, as well as categorical scores of sedation (Ramsay Sedation Scale [RSS] score) in the presence or absence of nociceptive stimulation, were collected, recorded, and analyzed using an Adaptive Neuro Fuzzy Inference System. The models described for the relationship between  $C_{e\text{pro}}$  and  $C_{e\text{remi}}$  versus AAI/2, BIS, and IoC were diagnosed for inaccuracy using median absolute performance error (MDAPE) and median root mean squared error (MDRMSE), and for bias using median performance error (MDPE). The models were validated in a prospective group of 68 new patients receiving different combinations of propofol and remifentanyl. The predictive ability ( $P_k$ ) of AAI/2, BIS, and IoC with respect to the sedation level, RSS score, was also explored.

**RESULTS:** Data from 110 patients were analyzed in the training group. The resulting estimated models had an MDAPE of 32.87, 12.89, and 8.77; an MDRMSE of 17.01, 12.81, and 9.40; and an MDPE of -1.86, 3.97, and 2.21 for AAI/2, BIS, and IoC, respectively, in the absence of stimulation and similar values under stimulation.  $P_k$  values were 0.82, 0.81, and 0.85 for AAI/2, BIS, and IoC, respectively. The model predicted the prospective validation data with an MDAPE of 34.81, 14.78, and 10.25; an MDRMSE of 16.81, 15.91, and 11.81; an MDPE of -8.37, 5.65, and -1.43; and  $P_k$  values of 0.81, 0.8, and 0.8 for AAI/2, BIS, and IoC, respectively.

**CONCLUSION:** A model relating  $C_{e\text{pro}}$  and  $C_{e\text{remi}}$  to AAI/2, BIS, and IoC has been developed and prospectively validated. Based on these models, the ( $C_{e\text{pro}}$ ,  $C_{e\text{remi}}$ ) concentration pairs that provide an RSS score of 4 range from ( $1.8 \mu\text{g}\cdot\text{mL}^{-1}$ ,  $1.5 \text{ ng}\cdot\text{mL}^{-1}$ ) to ( $2.7 \mu\text{g}\cdot\text{mL}^{-1}$ ,  $0 \text{ ng}\cdot\text{mL}^{-1}$ ). These concentrations are associated with AAI/2 values of 25 to 30, BIS of 71 to 75, and IoC of 72 to 76. The presence of noxious stimulation increases the requirements of  $C_{e\text{pro}}$  and  $C_{e\text{remi}}$  to achieve the same degree of sedative effects.

### 在標準麻醉設備下行全身麻醉受試者的通氣死腔的測定

#### Measurement of Dead Space in Subjects Under General Anesthesia Using Standard Anesthesia Equipment

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**背景：**肺部通氣死腔是指被送入肺部但不參加氣體交換的氣體容積。瞭解全身麻醉患者的肺部通氣死腔在臨床上是非常有用的，因為它可以幫助檢測例如肺栓塞、低心輸出量狀態等疾病的進程。死腔可以簡單地運用波爾公式計算出來，然而使用標準麻醉機卻很難測定混合呼末二氧化碳。以往研究表明標準麻醉機風箱內二氧化碳濃度與呼末二氧化碳非常接近。本研究作者應用風箱呼氣末  $\text{CO}_2$  和  $\text{PaCO}_2$  計算肺死腔並通過麻醉期間加一已知死腔容積的設備加以驗證。

**方法：**受試者採用氣管內全身麻醉。採樣線被定位在呼吸機風箱內並連接到二氧化碳檢測儀。分別在基礎狀態、加入 100ml 及 200ml 死腔時呼末二氧化碳值，同時通過動脈導管測量血二氧化碳分壓。運用波爾公式（肺泡死腔/潮氣量= $\frac{\text{血二氧化碳分壓}-\text{呼末二氧化碳}}{\text{血二氧化碳分壓}}$ ）來分別計算基礎、加入 100ml 及 200ml 機械死腔後的死腔容積。

**結果：**10 位受試者基礎死腔值為  $265 \pm 47$  mL。加入 100ml 死腔後受試者死腔測量值增加  $110 \pm 46$  mL。加入 200ml 死腔後受試者死腔測量值增加  $158 \pm 39$  mL。

**結論：**全身麻醉下基礎死腔測定值在預期範圍內。當機械死腔增加時，可以計算到死腔值的增加。加入 100ml 機械死腔獲得的計算值比加入 200ml 機械死腔獲得的計算值更精確。作者介紹了一種簡單的方法檢測應用 Narkomed GS 麻醉機 (Dräger Medical, Lübeck, Germany) 機械通氣時通氣死腔的變化趨勢。

(曹強 譯 陳傑 校)

**BACKGROUND:** Pulmonary dead space is the volume of gas that is delivered to the lungs but does not participate in gas exchange. Knowing pulmonary dead space in patients under general anesthesia is clinically useful because it can aid in detecting disease processes such as pulmonary emboli or low cardiac output states. Dead space can be simply calculated by using the Bohr equation; however, it is difficult to measure mixed exhaled carbon dioxide (PECO<sub>2</sub>) with a standard anesthesia machine. Previously, a study at our institution demonstrated the carbon dioxide (CO<sub>2</sub>) concentration in the bellows of a standard anesthesia machine is an accurate approximation of PECO<sub>2</sub>. In this study, we used the bellows PECO<sub>2</sub> measurement and arterial CO<sub>2</sub> (PaCO<sub>2</sub>) to calculate pulmonary dead space. We verified the technique by adding known apparatus dead space volumes during anesthesia.

**METHODS:** Subjects were under general endotracheal anesthesia. A sampling line was positioned inside the ventilator bellows and connected to a capnometer. Measurements of PECO<sub>2</sub> and PaCO<sub>2</sub> from an arterial catheter were taken at baseline and after adding 100 mL and 200 mL of dead space to the endotracheal tube. Dead space was calculated using the Bohr equation (alveolar dead space/tidal volume = [PaCO<sub>2</sub> - PECO<sub>2</sub>]/PaCO<sub>2</sub>) at baseline and after adding 100 mL and 200 mL of apparatus dead space.

**RESULTS:** The dead space at baseline was  $265 \pm 47$  mL (mean  $\pm$  SD) in 10 study subjects. After adding 100 mL of dead space to the endotracheal tube, the measured dead space increased by  $110 \pm 46$  mL. The measured dead space increased by  $158 \pm 39$  mL after adding 200 mL.

**CONCLUSIONS:** Our baseline dead space measurements were in the expected range under general anesthesia. When dead space was added, we were able to calculate that an increase in dead space occurred. Our calculation was more accurate after adding a 100-mL volume than after adding 200 mL. We present a simple way to detect trends in dead space in ventilated patients using a Narkomed GS anesthesia machine (Dräger Medical, Lübeck, Germany).

### 狗出血性休克復蘇中輸注 6% 羥乙基澱粉-高張力氯化鈉液體的療效

#### The Effects of 6% Hydroxyethyl Starch–Hypertonic Saline in Resuscitation of Dogs with Hemorrhagic Shock

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**背景：**血流動力學參數及全身攜氧能力參數很難很好地反應出機體內臟灌注不足，從而導致延誤對失血性休克及時的處理。液體復蘇後容量擴充對增加失血性休克患者機體全身及局部氧含量頗為有效。此次實驗中，作者假設相對於傳統血漿擴容液體，對失血性休克患者輸注 7.5 氯化鈉/6% 羥乙基澱粉 (HHES) 會使攜氧能力下降並減少胃血流灌注。應用失血性休克的狗模型來比較幾種不同靜脈擴容液體快速輸注後其早期系統氧合以及胃腸道血流灌注。擴容液體包括臨床上廣泛應用於嚴重失血性休克病人的液體：7.5 氯化鈉/6% 羥乙基澱粉 (HHES)、乳酸鈉林格氏液 (LR)、以及 6% 羥乙基澱粉液體 (HES)。

**方法：**實驗入組 30 只失血量為  $30 \text{ mL} \cdot \text{kg}^{-1}$  的成年狗，維持其平均動脈壓在 40-50mmHg 持續 45 分鐘，並按照液體復蘇的方式分為不同的三組：LR 組 ( $n=10$ )，以 3 比 1 補充丟失容量；HES 組 (液體平均相對分子量 130kDa) ( $n=10$ )，以 1 比 1 補充丟失容量；HHES 組 ( $n=10$ )，以  $4 \text{ mL} \cdot \text{kg}^{-1}$  補充丟失容量。實驗記錄資料包括血管內容量擴張 (伊文氏藍法及血紅蛋白稀釋法)、血流動力、攜氧能力、動靜脈二氧化碳壓差 ( $P_v\text{-aCO}_2$ )，胃黏膜內動脈二氧化碳分壓差 ( $P_{\text{co}_2} \text{ gap}$ )，資料記錄時間包括各個基數值、失血後 45 分鐘、輸注液體後 5 分鐘、45 分鐘及 90 分鐘。

**結果：**實驗結果顯示 7.5 氯化鈉/6% 羥乙基澱粉 (HHES) 由於其高效的擴容能力大大提高了血容量，但其血管內容量擴張相比其他液體較小 ( $P < 0.05$ )。三種液體對機體血流動力學改變相似，但 HHES 相對於其他兩種液體其輸注後混合靜脈血氧分壓較低、其組織氧攝取能力、 $P_v\text{-aCO}_2$  及  $PCO_2$  有所升高。 ( $P < 0.05$ )

**結論：**在此次對成年狗實施失血性休克後容量復蘇的實驗中，可以看到：HHES 雖然其擴容效果最好，但其對系統攜氧及胃腸道灌注方面的恢復與 LR 及 HES 相比較差。

(趙嫣紅 譯 陳傑 校)

**BACKGROUND:** Hemodynamic and global oxygen transport variables have failed to reflect splanchnic hypoperfusion, resulting in a failure to recognize inadequately treated hemorrhagic shock. Volemic expansion after fluid resuscitation is essential to improve global and regional oxygen in hemorrhagic shock. We hypothesized that, in contrast to conventional plasma expanders, the smaller volemic expansion from 7.5 NaCl/6% hydroxyethyl starch (HHES) solution administration in hemorrhagic shock may provide lesser systemic oxygen delivery and gastric perfusion. We used hemorrhaged dogs to compare intravascular volume expansion and the early systemic oxygenation and gastric perfusion effects of fixed fluid bolus administration, which are usually used in clinical situations with severe hemorrhage, of HHES, lactated Ringer (LR), and 6% hydroxyethyl starch (HES) solutions.

**METHODS:** Thirty dogs were bled ( $30 \text{ mL} \cdot \text{kg}^{-1}$ ) to hold mean arterial blood pressure at 40 to 50 mm Hg over 45 minutes and were resuscitated in 3 groups: LR ( $n = 10$ ) at 3:1 ratio to shed blood; HES (mean molecular weight 130 kDa, degree of substitution 0.4) ( $n = 10$ ) at 1:1 to shed blood; and HHES ( $n = 10$ ),  $4 \text{ mL} \cdot \text{kg}^{-1}$ . Intravascular volume expansion (Evans blue and hemoglobin dilution), hemodynamic, systemic oxygenation, venous-to-arterial  $\text{CO}_2$  gradient ( $P_{\bar{v}}\text{-aCO}_2$ ), and gastric intramucosal-arterial  $\text{PCO}_2$

gradient (PCO<sub>2</sub> gap) variables were measured at baseline, after 45 minutes of hemorrhage, and 5, 45, and 90 minutes after fluid resuscitation.

**RESULTS:** HHES increased blood volume because of the high volume expansion efficiency, but intravascular volume expansion with this solution was the smallest of the solutions ( $P < 0.05$ ). All 3 solutions induced a similar hemodynamic performance but

HHES showed lower mixed venous PO<sub>2</sub> and higher systemic oxygenation extraction, P<sub>v</sub>-aCO<sub>2</sub>, and PCO<sub>2</sub> gap than LR and HES ( $P < 0.05$ ).

**CONCLUSIONS:** In dogs submitted to pressure-guided hemorrhagic shock and fixed-volume resuscitation, the smaller intravascular volume expansion from HHES solutions provides worse recovery of systemic oxygenation and gastric perfusion compared with LR and HES solutions despite its high volume expansion efficiency, which was limited by low infused volume.

### 長期灌注嗎啡後藥物在豬脊髓內的分佈

#### Morphine Distribution in the Spinal Cord After Chronic Infusion in Pigs

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**背景:** 連續鞘內給藥提供了一種長期脊髓靶向給藥的新方法，其療效差異很大。應用一種豬的急性模型，作者先前已經證實連續鞘內給藥療效可能差異巨大，其原因與藥物在腦脊液和脊髓中分佈相關。作者設計本研究以確定長期給藥是否存在急性研究中所觀察到的藥物分佈。

**方法:** 四個農場飼養的豬，植入鞘內注射泵，給予嗎啡（1 mg/mL），每小時 20 $\mu$ L。由於程式性錯誤，1 只豬接受嗎啡鞘內注射每小時 2 $\mu$ L。藥物輸注持續 14 天，在此期間，動物的活動不受限制。在 2 周後動物接受麻醉和安樂死，並分離脊髓。脊髓按照 1cm 為單位進行分割，分別測量嗎啡濃度。

**結果:** 與既往急性動物實驗相同，藥物分佈極為有限。嗎啡濃度從導管尖端開始，按照距離呈指數下降，導致僅僅 5-10cm 之內出現 5 - 10 倍的降低，。

**結論:** 在活動的豬中鞘內注射嗎啡的藥物分佈非常有限，並且從注射位置開始，按照距離呈現一個明顯的脊髓藥物濃度梯度。因此，導管尖端位置可能至關重要，尤其是當注入等比重溶液時。這些資料也支援一個假說，長期鞘內注射阿片類藥物會產生導管尖端位置炎症腫塊的併發症，是由於藥物有限分佈引起注射位置極高的藥物濃度。

(懷曉蓉 譯 陳傑 校)

#### Abstract

**BACKGROUND:** Continuous intrathecal drug delivery provides new options for chronic delivery of drugs that target the spinal cord, but therapeutic efficacy is highly variable. Using an acute porcine model, we have previously demonstrated that continuous intrathecal drug delivery efficacy may be highly variable because of severely limited drug distribution in the cerebrospinal fluid and spinal cord. We designed this study to determine whether the limited drug distribution observed in our acute studies occurs with chronic administration as well.

**METHODS:** Four farm-bred pigs were implanted with intrathecal infusion pumps delivering morphine (1 mg/mL) at 20  $\mu$ L per hour. Because of a programming error, 1 additional pig received intrathecal morphine at 2  $\mu$ L per hour. Drug infusion continued for 14 days, during which time animal activity was unrestricted. At the end of 2 weeks the animals were anesthetized and euthanized and their spinal cords removed. The spinal cords were divided into 1-cm sections and morphine concentrations measured.

**RESULTS:** As with previous acute animal studies, drug distribution was extremely limited. Morphine concentration decreased exponentially as a function of distance from the catheter tip, resulting in a 5- to 10-fold decrease over a distance of only 5 to 10 cm.

**CONCLUSION:** Morphine distribution is very limited during chronic intrathecal delivery in ambulatory pigs, and there are significant spinal cord drug concentration gradients as a function of distance from the infusion point. Consequently, catheter tip position may be critical, particularly when infusing isobaric solutions. These data also support the hypothesis that inflammatory masses complicating chronic intrathecal opioid delivery occur at the catheter tip because limited drug distribution results in extremely high drug concentrations at that point.

### 以鉛筆尖式或 Tough 針尖行外周神經穿刺後的組織學分析

#### Histological Analysis After Peripheral Nerve Puncture with Pencil-Point or Tuohy Needletip

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**背景：**典型的持續性外周神經阻滯通常是通過一種“通過穿刺針技術”實施的，要求穿刺針的內徑能通過留置導管。目前認為，當穿刺針與神經直接接觸時，鉛筆尖式針尖比其他模式的穿刺針的創傷性更小。本次研究中，作者將鉛筆尖式穿刺針與 Tough 穿刺針作比較，以觀察是否前者比後者更少地引起神經損傷。

**方法：**6 只豬接受麻醉後，暴露其雙側臂叢神經。用鉛筆尖式穿刺針或 Tough 穿刺針對總共 8 支神經進行刺激。48 小時後，在麻醉下切除這些神經。樣本被進一步送檢，包括目視檢查、檢測炎性細胞、髓鞘損傷和神經內血腫。神經損傷的程度是通過一項客觀評分確認，其中 0 分為無損傷，4 分為嚴重損傷。

**結果：**包括對照組在內共有 58 支神經接受了檢測。根據損傷評分，鉛筆尖式穿刺針組【中位數（四分位數間距）為 3（3-4）】和 Tough 穿刺針組【3（3-4），P=0.97】之間沒有明顯的統計學差異。兩組神經組織的創傷後局部炎症反應、髓鞘損傷和神經內血腫的程度均較之前有所增高。

**結論：**無論採用何種針尖式樣的穿刺針，鉛筆尖樣和 Tuohy 樣針尖均會導致神經組織發生相同程度的創傷後炎症反應和相似的組織學改變，兩種穿刺針之間沒有明顯的差異。

(周姝婧 譯 陳傑 校)

**BACKGROUND:** Continuous peripheral nerve blocks typically are performed with a “through-the-needle technique” and require needles with an inner diameter allowing catheter placement. In case of direct needle–nerve contact, the pencil-point needle tip is currently considered less traumatic than are other needle configurations. In this study we determined whether nerve puncture with pencil-point needles is associated with fewer nerve injuries in comparison with Tuohy needles.

**METHODS:** In 6 anesthetized pigs the brachial plexus were exposed bilaterally. Up to 8 nerves underwent nerve puncture with a pencil-point or a Tuohy needle. After 48 hours, the nerves were resected during anesthesia. The specimens were processed for visual examination and the detection of inflammatory cells, myelin damage, and intraneural hematoma. The grade of nerve injury was assessed using an objective score ranging from 0 (no injury) to 4 (severe injury).

**RESULTS:** Fifty-eight nerves, including controls, were examined. According to the applied injury score, there was no significant difference between the pencil-point needle group [median (interquartile range) 3 (3–4)] and the Tuohy needle group [3 (3–4)  $P = 0.97$ ]. The occurrence of posttraumatic regional inflammation, myelin damage, and intraneural hematoma was similarly high in both groups.

**CONCLUSIONS:** Regardless of the needle tip configuration applied for nerve puncture, pencil-point and Tuohy needle tips may both lead to comparable magnitude of posttraumatic inflammation and considerable structural changes within the nerve. No significant differences were found comparing pencil-point with Tuohy tip–configured needles.

### 圍術期應用艾司洛爾的安全性：隨機對照試驗的系統回顧和薈萃分析

#### The Safety of Perioperative Esmolol: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**背景：**雖然已發現  $\beta$  受體阻滯劑能減少圍術期心肌梗死 (MI) 的發生率，但是其引起的低血壓與術後中風及術後死亡率密切相關。在這個系統性回顧中，我們將對選擇性  $\beta_1$  腎上腺素受體阻滯劑艾司洛爾在非心臟手術中的安全性和有效性作一評估。安全性的評估是通過分析術後低血壓和心動過緩的發生率，而有效性的評估則是通過分析心肌缺血的發生率。

**方法：**我們通過電子資料庫檢索非心臟手術圍術期應用艾司洛爾的隨機安慰劑對照試驗。按照實驗設計、人口統計學資料、血流動力學改變（預料或非預料中的）、心肌缺血和 MI 等獲取相關資料。運用 meta 回歸分析來評估其不均一性。

**結果：**本研究納入了 67 項臨床試驗，均符合本研究的納入標準。研究的品質受到小樣本和盲法貫徹不力的限制。總的來說，本研究顯示，艾司洛爾的應用導致了意料之外的低血壓發生率的升高（OR=2.13，95% 置信區間為 1.48~3.04），並呈劑量相關（ $R^2 = 0.408$ ）。而心動過緩的發生率並沒有明顯上升（OR=1.18，95% 置信區間為 0.69~2.02）。同時發現艾司洛爾的劑量滴定對動脈血壓和心率的變化均有影響。7 個對照研究表明，與安慰劑組相比，艾司洛爾能減少心肌缺血的發生率（OR=0.17，95% 置信區間為 0.02~0.45）。我們並沒有評估艾司洛爾對 MI 或中風發生率的影響，因為在我們檢索的研究中，這些事件的發生率太低。

**結論：**本綜述提示，根據血流動力學指示滴定艾司洛爾劑量是安全有效的。需要從高危患者中研究得到的安全性資料來建立艾司洛爾的圍術期治療的安全性和有效性情況。

（徐妍君 譯，馬皓琳 李士通 校）

**BACKGROUND:** Although  $\beta$  blockers have been found to decrease perioperative myocardial infarction (MI),  $\beta$ -blocker-mediated hypotension is associated with postoperative stroke and mortality. In this systematic review we assessed the safety and efficacy of the  $\beta_1$ -specific, adrenergic receptor antagonist esmolol in noncardiac surgery. Safety was assessed by analyzing the incidence of postoperative hypotension and bradycardia, and efficacy was assessed by analyzing the incidence of myocardial ischemia.

**METHODS:** We searched electronic databases for randomized placebo-controlled trials of the perioperative use of esmolol in noncardiac surgery. We abstracted data on design, demographics, hemodynamic changes (planned or unplanned), myocardial ischemia, and MI. Heterogeneity was assessed via meta-regression.

**RESULTS:** Our search identified 67 trials, which were well matched for study characteristics. The quality of the studies was limited by small sample size and poorly defined allocation concealment. Overall, the analysis demonstrates an increased incidence of unplanned hypotension (OR 2.13; 95% confidence interval [CI], 1.48 to 3.04), which was found to be dose related ( $R^2 = 0.408$ ). An increased incidence of significant bradycardia was not demonstrated (OR 1.18; 95% CI, 0.69 to 2.02). Dose titration was shown to influence both the change in arterial blood pressure and heart rate. In comparison with placebo, esmolol decreased the frequency of myocardial ischemia in the 7 evaluating studies (OR 0.17; 95% CI, 0.02 to 0.45). We did not assess the effects of esmolol on the incidence of MI or stroke because the incidence of these events was too infrequent in the retrieved studies.

**CONCLUSION:** This review suggests that titration of esmolol to a hemodynamic end point can be safe and effective. Safety data from studies in higher-risk patients are needed to establish a perioperative safety and efficacy profile of esmolol.

**口服布洛芬和塞來考昔對預防門診手術後病人疼痛、改善恢復轉歸和病人滿意度的影響**

**The Effects of Oral Ibuprofen and Celecoxib in Preventing Pain, Improving Recovery Outcomes and Patient Satisfaction After Ambulatory Surgery**

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**背景：**非甾體類抗炎藥已日益廣泛成爲用於門診手術室病人疼痛處理的多模式鎮痛方式的一部分。我們設計了這個隨機、雙盲、安慰劑對照研究，以評估非選擇性非甾體類抗炎藥（布洛芬）或選擇性 COX-2 抑制劑（給予塞來考昔作爲多模式鎮痛的一部分）對門診手術後患者的疼痛分級、對補救性鎮痛藥的需要和患者臨床相關轉歸的影響。首要的觀察指標是恢復到日常生活活動正常的時間。

**方法：**180 名接受門診手術的患者被隨機分成 3 組：組 1（對照組）患者在恢復室接受了 2 顆安慰劑膠囊（與塞來考昔匹配）或 1 顆安慰劑片（與布洛芬匹配），於術日晚睡前口服 1 片安慰劑，出院後 3 天每次 1 顆膠囊或片劑安慰劑，1 日 3 次；組 2（塞來考昔）患者在恢復室口服 400mg 塞來考昔（2 顆膠囊），術日晚睡前 1 顆安慰劑膠囊和片劑，術後 3 天每日 2 次每次 200mg 塞來考昔（1 顆膠囊）加睡前 1 顆安慰劑膠囊；組 3（布洛芬）患者在恢復室口服 400mg 布洛芬（1 片），術日晚睡前加服一片，術後 3 日 1 天 3 次每次 400mg 口服。出院前記錄恢復時間、術後疼痛評分和補充鎮痛藥需要量。在術後 24h、48h、72h、7d 和 30d 進行隨訪評價以評定疼痛分級、鎮痛藥需要量、正常活動的恢復、阿片相關副作用、恢復品質以及用 5 點口頭評定量表評定的患者對術後疼痛處理的滿意度。

**結果：**3 組患者人口統計學均無差異。相比於安慰劑組，塞來考昔和布洛芬顯著減少出院後補充鎮痛藥的需要（ $P < 0.05$ ）。效用比（塞來考昔和布洛芬比對照組）分別爲 0.73 比 1 和 0.3 比 0.8。塞來考昔和布洛芬組恢復品質評分和病人對術後鎮痛滿意度均比對照組高（ $P < 0.05$ , 效用比[比對照組] = 0.67）。術後便秘的發生率在對照組（28%）明顯高於塞來考昔（5%）和布洛芬（7%）組（ $P < 0.05$ ）。服用藥物的兩組患者出院後耐受性均良好。然而，3 組患者恢復到日常生活活動正常的時間相似。

**結論：**在出院後階段早期布洛芬（1200 mg/d）和塞來考昔（400 mg/d）顯著減少補充鎮痛藥的需要，這導致門診手術後病人恢復品質和鎮痛滿意度提高。

（楊秀娟 譯 馬皓琳 李士通 校）

**BACKGROUND:** Nonsteroidal antiinflammatory drugs have become increasingly popular as part of multimodal analgesic regimens for pain management in the ambulatory setting. We designed this randomized, double-blind, placebo-controlled study to evaluate the effect of postoperative administration of either a nonselective nonsteroidal antiinflammatory drug (ibuprofen) or the cyclooxygenase-2 selective inhibitor (celecoxib when administered as part of a multimodal analgesic regimen) on the severity of pain, the need for rescue analgesics, and clinically relevant patient outcomes after ambulatory surgery. The primary end point was the time to resumption of normal activities of daily living.

**METHODS:** One hundred eighty patients undergoing outpatient surgery were randomly assigned to 1 of 3 treatment groups: group 1 (control) received either 2 placebo capsules (matching celecoxib) or 1 placebo tablet (matching ibuprofen) in the recovery room and 1

placebo tablet at bedtime on the day of surgery, followed by 1 placebo capsule or tablet 3 times a day for 3 days after discharge; group 2 (celecoxib) received celecoxib 400 mg (2 capsules) orally in the recovery room and 1 placebo capsule and tablet at bedtime on the day of surgery, followed by celecoxib 200 mg (1 capsule) twice a day + placebo capsule every day at bedtime for 3 days after surgery; or group 3 (ibuprofen) received ibuprofen 400 mg (1 tablet) orally in the recovery room and 400 mg orally at bedtime on the day of surgery, followed by 400 mg orally 3 times a day for 3 days after surgery. Recovery times, postoperative pain scores, and the need for rescue analgesics were recorded before discharge. Follow-up evaluations were performed at 24 hours, 48 hours, 72 hours, 7 days, and 30 days after surgery to assess postdischarge pain, analgesic requirements, resumption of normal activities, opioid-related side effects, as well as quality of recovery and patient satisfaction with their postoperative pain management using a 5-point verbal rating scale.

**RESULTS:** The 3 groups did not differ with respect to their demographic characteristics. Compared with the placebo treatment, both celecoxib and ibuprofen significantly decreased the need for rescue analgesic medication after discharge ( $P < 0.05$ ). The effect sizes (celecoxib and ibuprofen versus control group) were 0.73 to 1 and 0.3 to 0.8, respectively. Quality of recovery scores and patient satisfaction with their postoperative pain management were also improved in the celecoxib and ibuprofen groups compared with the control group ( $P < 0.05$ , effect size [vs control group] = 0.67). The incidence of postoperative constipation was significantly higher in the control group (28%) compared with the celecoxib (5%) and ibuprofen (7%) groups, respectively ( $P < 0.05$ ). Both active treatments were well tolerated in the postdischarge period. However, the time to resumption of normal activities of daily living was similar among the 3 groups.

**CONCLUSIONS:** Both ibuprofen (1200 mg/d) and celecoxib (400 mg/d) significantly decreased the need for rescue analgesic medication in the early postdischarge period, leading to an improvement in the quality of recovery and patient satisfaction with their pain management after outpatient surgery.

### 清醒的有自主呼吸的低血容量志願者的脈搏氧飽和度儀體積描記的波形變化

#### **Pulse Oximeter Plethysmographic Waveform Changes in Awake, Spontaneously Breathing, Hypovolemic Volunteers**

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**背景：**本研究的主要目的是為了確定脈搏氧飽和度儀波形特點的變化是否可追蹤中樞血容量的進行性減少。我們也評估了脈搏氧飽和度儀波形的變化是否可以在標準生命體征改變前提供出血患者血液流失的提示。

**方法：**從 18 例通過下體負壓 (LBNP) 誘導中樞血容量進行性減少的健康受試者中收集來自於手指、額頭以及耳朵的脈搏氧飽和度儀感受器的脈搏氧飽和度儀數據。同時運用心阻抗圖記錄心搏量。本研究在不受干預的研究工作實驗室裏進行。從每個脈搏波形記錄計算脈搏的波幅、寬度以及曲線下面積 (AUC) 特徵。計算

合併相關係數來確定脈搏氧飽和度儀波形特徵的變化與 LBNP 時的心搏量之間的關係。

**結果：**對於在耳朵、額頭的脈搏氧飽和度儀感受器，脈搏波幅、寬度以及曲線下面積的減少與 LBNP 期間心搏量的進行性減少明顯相關 (所有特徵均  $R^2 \geq 0.59$ )。脈搏氧飽和度波形特點的改變在動脈血壓降低前即可觀察到。從額頭感受器的曲線下面積得到了脈搏特點與心搏量之間的最佳關係 ( $R^2 = 0.97$ )。當中樞血容量恢復時脈搏氧飽和度儀波形特徵恢復到基線水準。

**結論：**這些結果支持脈搏氧飽和度儀波形分析作為一種潛在的診斷工具用於自主呼吸的患者，在心血管失代償出現前發現顯著的低血容量。

(龔寅 譯 馬皓琳 李士通 校)

**BACKGROUND:** The primary objective of this study was to determine whether alterations in the pulse oximeter waveform characteristics would track progressive reductions in central blood volume. We also assessed whether changes in the pulse oximeter waveform provide an indication of blood loss in the hemorrhaging patient before changes in standard vital signs.

**METHODS:** Pulse oximeter data from finger, forehead, and ear pulse oximeter sensors were collected from 18 healthy subjects undergoing progressive reduction in central blood volume induced by lower body negative pressure (LBNP). Stroke volume measurements were simultaneously recorded using impedance cardiography. The study was conducted in a research laboratory setting where no interventions were performed. Pulse amplitude, width, and area under the curve (AUC) features were calculated from each pulse wave recording. Amalgamated correlation coefficients were calculated to determine the relationship between the changes in pulse oximeter waveform features and changes in stroke volume with LBNP.

**RESULTS:** For pulse oximeter sensors on the ear and forehead, reductions in pulse amplitude, width, and area were strongly correlated with progressive reductions in stroke volume during LBNP ( $R^2 \geq 0.59$  for all features). Changes in pulse oximeter waveform features were observed before profound decreases in arterial blood pressure. The best correlations between pulse features and stroke volume were obtained from the forehead sensor area ( $R^2 = 0.97$ ). Pulse oximeter waveform features returned to baseline levels when central blood volume was restored.

**CONCLUSIONS:** These results support the use of pulse oximeter waveform analysis as a potential diagnostic tool to detect clinically significant hypovolemia before the onset of cardiovascular decompensation in spontaneously breathing patients.

### 探索性試驗中氧化亞氮和遠期發病率和死亡率的關係

#### Nitrous Oxide and Long-Term Morbidity and Mortality in the ENIGMA Trial

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**背景：**患者接觸大量氧化亞氮後，其更遠期的心血管發病率和死亡率升高可能存在有病理生理的基礎理論。然而這種關係臨床上並未確定。探索試驗隨機選取 2050 例行非心臟手術的患者，包括接觸 2 小時以上氧化亞氮和不接觸氧化亞氮的麻醉。我們進行隨訪研究以評估長期心血管事件的風險。

**方法：**回顧所有研究患者的病例報告表和醫療記錄進行審查。記錄死亡日期和原因以及心肌梗死或中風的發生。然後電話採訪所有倖存的患者。該研究主要終點是生存。

**結果：**該研究隨訪時間中位數是 3.5 年（0-5.7 年）。在整個隨訪期間，有 380 例（19%）手術後死亡，91 例（4.5%）發生心肌梗死，有 44 例（2.2%）發生中風。氧化亞氮並沒有顯著增加死亡風險（危險比=0.98，95%可信區間：0.80-1.20，P=0.82）。接受氧化亞氮的患者發生心肌梗死的比值比為 1.59（95%可信區間：1.01-2.51，P=0.04），發生中風的比值比為 1.01（95%可信區間：0.55-1.87，P=0.97）。

**結論：**在探索性試驗中，氧化亞氮的使用增加了遠期發生心肌梗死的風險，但與死亡率和中風發生無關。給予氧化亞氮與嚴重長期不良轉歸之間的确切關係尚需要通過一個合理設計的大樣本隨機對照試驗來確定。

（滕凌雅 譯 馬皓琳 李士通 校）

**BACKGROUND:** There is a plausible pathophysiologic rationale for increased long-term cardiovascular morbidity and mortality in patients receiving significant exposure to nitrous oxide. However, this relationship has not been established clinically. The ENIGMA trial randomized 2050 patients having noncardiac surgery lasting more than 2 hours to nitrous oxide-based or nitrous oxide-free anesthesia. We conducted a follow-up study of the ENIGMA patients to evaluate the risk of cardiovascular events in the longer term.

**METHODS:** The trial case report forms and medical records of all study patients were reviewed. The date and cause of death and occurrence of myocardial infarction or stroke were recorded. A telephone interview was then conducted with all surviving patients. The primary endpoint of the study was survival.

**RESULTS:** The median follow-up time was 3.5 (range: 0 to 5.7) years. Three hundred eighty patients (19%) had died since the index surgery, 91 (4.5%) were recorded as having myocardial infarction, and 44 (2.2%) had a stroke during the entire follow-up period. Nitrous oxide did not significantly increase the risk of death [hazard ratio = 0.98 (95% confidence interval, CI: 0.80 to 1.20; P = 0.82)]. The adjusted odds ratio for myocardial infarction in patients administered nitrous oxide was 1.59 (95% CI: 1.01 to 2.51; P = 0.04) and for stroke was 1.01 (95% CI: 0.55 to 1.87; P = 0.97).

**CONCLUSIONS:** The administration of nitrous oxide was associated with increased long-term risk of myocardial infarction, but not of death or stroke in patients enrolled in the ENIGMA trial. The exact relationship between nitrous oxide administration and serious long-term adverse outcomes will require confirmation by an appropriately designed large randomized controlled trial.

## 0-10 數字評分量表能作為臨床有意義的疼痛測量方法用於兒童嗎？

### Do 0–10 Numeric Rating Scores Translate into Clinically Meaningful Pain Measures for Children?

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**背景：**自我報告的疼痛評分已被廣泛地應用於臨床和研究工作中，但是對它們在兒童中的解釋能力尚知之甚少。在這個前瞻性、觀察性研究中我們評估了在術後兒童中 0-10 數字量表（NRS）疼痛評分與其他自我報告的，臨床有意義的結果之間的關聯。這些結果包括感到需要治療（PNM）、疼痛減輕（PR）和對治療感到滿意度（PS）。

**方法：**該研究選擇 7-16 歲經過手術並伴有術後疼痛的兒童。在術後第一個 24 小時中對每個兒童記錄 1 到 4 個觀察項目。在每次評估中，兒童根據 NRS 確定他們的疼痛度，並同時確定他們的 PNM 和他們對疼痛治療的滿意度。在 1-2 小時內重複一次評估，並進一步評定他們的 PR 與前次評估結果相比較是相同、更好還是更差。用受試者操作特徵曲線來檢查用於 PNM、PS 的潛在的 NRS 切割點，同時計算在疼痛評分中與 PR 有關的最小臨床顯著差異（MCSD）。

**結果：**在 113 個兒童中記錄 397 個觀察專案（包括 189 對）。與 PNM 有關的 NRS 評分顯著高於“不需要者”（中位數 6 比 3;  $P < 0.001$ ）。NRS 評分  $>4$  用於鑒別 PNM 有很好的靈敏度(0.81)和特異性(0.70)，但是有大量的假陽性和陰性（例如：評分  $>4$  的兒童有 42% 沒有要求鎮痛）。在 NRS 評分中與感覺“好一點”或“差一點”有關（ $P < 0.001$  比相同）的 MCSD 分別是 -1(95% 可信區間[CI]  $-0.5 \sim 1$ ) 或 +1 (CI  $0.5 \sim 2.7$ )。NRS  $>6$  用於鑒別對治療不滿意的敏感性為 0.82，特異性為 0.76，但是評分  $>6$  的兒童中分別有 46% 和 24% 對他們的鎮痛非常滿意。

**結論：**該研究對有關 NRS 疼痛評分在兒童中的臨床解釋提供了重要的資訊。資料進一步支援了 NRS 評分作為有效的疼痛強度測量方法在兒童急性術後狀態下與 PNM、PR 和 PS 有關。然而，該評分與其他臨床有意義的結果相關的變異性表明切點的應用對於個體治療的決定是不合適的。

（周潔譯 馬皓琳 李士通校）

**BACKGROUND:** Self-reported pain scores are used widely in clinical and research settings, yet little is known about their interpretability in children. In this prospective, observational study we evaluated the relationship between 0 to 10 numerical rating scale (NRS) pain scores and other self-reported, clinically meaningful outcomes, including perceived need for medicine (PNM), pain relief (PR), and perceived satisfaction (PS) with treatment in children postoperatively.

**METHODS:** This study included children ages 7 to 16 years undergoing surgery associated with postoperative pain. One to 4 observations were recorded in each child within the first 24 hours postoperatively. At each assessment, children rated their pain with the NRS, stated their PNM, and rated their satisfaction with pain management. Assessments were repeated within 1 to 2 hours, and children additionally rated their PR as the same, better, or worse in comparison with the earlier assessment. Receiver operator characteristic curves were developed to examine potential NRS cut-points for PNM and PS, and the minimum clinically significant difference (MCSD) in pain score associated with PR was calculated.

**RESULTS:** Three hundred ninety-seven observations (including 189 pairs) were recorded in 113 children. NRS scores associated with PNM were significantly higher than “no need” (median 6 vs. 3;  $P < 0.001$ ). NRS scores  $>4$  had good sensitivity (0.81) and specificity (0.70) to discriminate PNM, but with a large number of false positives and negatives (e.g., 42% of children with scores  $>4$  did not need analgesia). The MCS-D in NRS scores was  $-1$  (95% confidence interval [CI]  $-0.5$  to  $1$ ) or  $+1$  (CI  $0.5$  to  $2.7$ ) in relation to feel “a little better” or “worse,” respectively ( $P < 0.001$  vs. the same). NRS scores  $>6$  had a sensitivity of 0.82 and specificity of 0.76 in discriminating dissatisfaction with treatment, yet 46% and 24% of children with scores  $>6$ , respectively, were somewhat to very satisfied with their analgesia.

**CONCLUSIONS:** This study provides important information regarding the clinical interpretation of NRS pain scores in children. Data further support the NRS as a valid measure of pain intensity in relation to the child's PNM, PR, and PS in the acute postoperative setting. However, the variability in scores in relation to other clinically meaningful outcomes suggests that application of cut-points for individual treatment decisions is inappropriate.

### 依那西普恢復嗎啡耐受大鼠中嗎啡的鎮痛作用並抑制脊髓神經炎症

#### Etanercept Restores the Antinociceptive Effect of Morphine and Suppresses Spinal Neuroinflammation in Morphine-Tolerant Rats

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**背景：**在本實驗中，我們觀察在嗎啡耐受大鼠中，腫瘤壞死因數（TNF）- $\alpha$  拮抗劑依那西普對嗎啡鎮痛作用的影響。

**方法：**雄性 Wistar 大鼠鞘內埋入兩根導管，一根與迷你滲透泵連接，輸注嗎啡（ $15 \mu\text{g/h}$ ）或生理鹽水（ $1 \mu\text{L/h}$ ）五天。第五天，停止輸注嗎啡後，通過另一根導管注射依那西普（ $5 \mu\text{g}$ 、 $25 \mu\text{g}$  或  $50 \mu\text{g}/10 \mu\text{L}$ ）或生理鹽水（ $10 \mu\text{L}$ ）。三小時後，鞘內給予嗎啡（ $15 \mu\text{g}/10 \mu\text{L}$ ），並測量擺尾潛伏期來評估嗎啡的鎮痛作用。處死大鼠並取出脊髓，對其進行定量即時聚合酶鏈反應和免疫組織化學來檢測前炎症細胞因數表達。

**結果：**我們發現急性依那西普（ $50 \mu\text{g}$ ）治療能維持嗎啡耐受大鼠中嗎啡的鎮痛作用。另外，在嗎啡耐受大鼠脊髓背側中，TNF $\alpha$  mRNA 的表達增加了 2.5 倍，白介素（IL）- $1\beta$  mRNA 增加了 13 倍，IL-6 mRNA 增加了 111 倍。 $50 \mu\text{g}$  依那西普阻斷了 TNF $\alpha$ 、IL- $1\beta$  和 IL-6 mRNA 的表達增加。免疫組織化學分析表明： $50 \mu\text{g}$  依那西普抑制了小膠質細胞內前炎症細胞因數的表達和神經炎症。

**結論：**本實驗表明：依那西普通過抑制前炎症細胞因數 TNF- $\alpha$ 、IL-1 $\beta$  和 IL-6 的表達和脊髓的神經炎症，恢復了對嗎啡耐受大鼠中嗎啡的鎮痛作用。結果說明依那西普也能作為嗎啡耐受的輔助治療，這也拓展了阿片類鎮痛藥在臨床疼痛管理中的作用。

（王海濤 譯 馬皓琳 李士通 校）

**BACKGROUND:** In the present study we examined the effect of the tumor necrosis factor (TNF)- $\alpha$  antagonist etanercept on the antinociceptive effect of morphine in morphine-tolerant rats.

**METHODS:** Male Wistar rats were implanted with 2 intrathecal catheters, and 1 was connected to a mini-osmotic pump for either morphine (15  $\mu$ g/h) or saline (1  $\mu$ L/h) infusion for 5 days. On day 5, either etanercept (5  $\mu$ g, 25  $\mu$ g, and 50  $\mu$ g/10  $\mu$ L) or saline (10  $\mu$ L) was injected via the other catheter after morphine infusion was discontinued. Three hours later, morphine (15  $\mu$ g/10  $\mu$ L, intrathecally) was given and tail-flick latency was measured to evaluate the antinociceptive effect of morphine. Rats were then killed and their spinal cords were removed for quantitative real-time polymerase chain reaction and immunohistochemistry to measure proinflammatory cytokines expression.

**RESULTS:** We found that acute etanercept (50  $\mu$ g) treatment preserved a significant antinociceptive effect of morphine in morphine-tolerant rats. In addition, the expression of TNF $\alpha$  mRNA was increased by 2.5-fold, interleukin (IL)-1 $\beta$  mRNA increased by 13-fold and IL-6 mRNA by 111-fold in the dorsal spinal cord of morphine-tolerant rats. The increase in TNF $\alpha$ , IL-1 $\beta$ , and IL-6 mRNA expression was blocked by 50  $\mu$ g etanercept pretreatment. The immunohistochemistry analysis revealed that 50  $\mu$ g etanercept suppressed proinflammatory cytokines expression and neuroinflammation in the microglia.

**CONCLUSIONS:** The present study demonstrates that etanercept restores the antinociceptive effect of morphine in morphine-tolerant rats by inhibition of proinflammatory cytokine TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 expression and spinal neuroinflammation. The results suggest that etanercept could also be an adjuvant therapy for morphine tolerance, which extends the effectiveness of opioids in clinical pain management.

低劑量、低濃度左旋布比卡因加上芬太尼的選擇性脊髓麻醉用於膝關節鏡檢查：一個劑量探索的研究

### **Low-Dose, Low-Concentration Levobupivacaine Plus Fentanyl Selective Spinal Anesthesia for Knee Arthroscopy: A Dose Finding Study**

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**背景：**選擇性感覺脊髓麻醉保有下肢運動功能，因此便於免去 PACU 並減少離床行走恢復所需的時間。

**方法：**在一個由 90 名（ASA 體格狀態 I 級和 II 級）擇期行膝關節鏡檢查的患者構

成的雙盲研究中，我們比較了在 3 種低劑量、低濃度左旋布比卡因－芬太尼混合溶液（5、4、3mg+10µg）脊髓麻醉後離床行走時間和不用去 PACU 的比率。

**結果：**由於大量阻滯不全（50%），3mg 劑量被停止了。23%的 5mg 研究組和 80% 的 4mg 研究組的患者不用去 PACU(P = 0001)。5mg 組在 70 分鐘（30–130 分鐘）（中位數[範圍]）後能夠下地行走，4mg 組在 45 分鐘（23–120 分鐘）後能夠下地行走(P = 0006)。

**結論：**4mg 左旋利多卡因加上 10µg 芬太尼能夠提供足夠的外科手術麻醉，最短的下地行走的時間和最高的免去 PACU 比率。

（唐亮譯 馬皓琳 李士通校）

**BACKGROUND:** Selective sensory spinal anesthesia preserves lower limb motor function and thus facilitates postanesthesia care unit (PACU) bypass and reduces ambulation recovery time.

**METHODS:** We compared the ambulation time and PACU bypass rate after using 3 low-dose, low-concentration levobupivacaine-fentanyl spinal solutions (5, 4, and 3 mg + 10 µg) in a double-blind study consisting of 90 patients (ASA physical status I and II) scheduled to undergo knee arthroscopy.

**RESULTS:** The 3-mg dose was halted because of a large number of inadequate blocks (50%). Twenty-three percent and 80% of patients from groups 5 mg and 4 mg, respectively, bypassed the PACU (P = 0001). Ambulation took place after 70 minutes (30–130 minutes) (median [range]) in group 5 mg and 45 minutes (23–120 minutes) in group 4 mg (P = 0006).

**CONCLUSION:** Four milligrams levobupivacaine plus 10 µg fentanyl produced adequate surgical anesthesia with the shortest time to ambulation and the highest PACU bypass rate.

### 綜述：抗血小板藥物藥理學與圍手術期管理的文獻回顧

#### Review article: antiplatelet drugs: a review of their pharmacology and management in the perioperative period.

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在日常麻醉監護過程中，麻醉醫師經常會遇到許多正在使用影響血小板功能藥物的患者。這些藥物通常作為處理原發或繼發動脈粥樣硬化血栓疾病的基本組成部分。其中，一些抗血小板藥物正在臨床使用，而另有個別藥物尚處在試驗研究階段。作為被最為廣泛研究的抗血小板藥物，阿司匹林與氫吡格雷（單獨或聯合應用）於當前在用藥物中具有最出色的風險收益狀況。普拉格雷最近被批准用於接受經皮介入的急性冠狀動脈綜合症患者。其他藥物，例如雙嘧達莫與西洛他唑，目前尚未開展大規模的臨床研究。此外，還有諸如坎格雷洛與替卡格雷等新近臨床試驗藥物，但其是否具有顯著的額外收益仍有待進一步評估。在對接受抗血小板藥物患者進行圍

手術期管理時，要求臨床醫師充分掌握其基本病理學、給藥原理、藥理學與藥代動力學和藥物相互作用等相關知識。此外，在評估停止或繼續使用抗血小板藥物的風險收益狀況時，應始終牢記手術方式、不可避免的出血併發症與選擇適當的全麻或區域麻醉方式間的利弊關係。一般而言，防止血栓形成最安全的方法是在整個圍手術期持續使用抗血小板藥物，除非臨床醫師認為圍手術期出血的風險相對血栓阻塞的發展更為重要。抗血小板藥物藥效與藥代動力學的相關知識可以讓臨床醫師更早地預期包括潛在藥物相互作用在內的圍手術期停藥或繼續使用抗血小板藥物的風險與困難。

(范羽譯 薛張綱校)

In the normal course of the delivery of care, anesthesiologists encounter many patients who are receiving drugs that affect platelet function as a fundamental part of primary and secondary management of atherosclerotic thrombotic disease. There are several antiplatelet drugs available for use in clinical practice and several under investigation. Aspirin and clopidogrel (alone and in combination) have been the most studied and have the most favorable risk-benefit profiles of drugs currently available. Prasugrel was recently approved for patients with acute coronary syndrome undergoing percutaneous interventions. Other drugs such as dipyridamole and cilostazol have not been as extensively investigated. There are several newer investigational drugs such as cangrelor and ticagrelor, but whether they confer significant additional benefits remains to be established. Management of patients who are receiving antiplatelet drugs during the perioperative period requires an understanding of the underlying pathology and rationale for their administration, pharmacology and pharmacokinetics, and drug interactions. Furthermore, the risk and benefit assessment of discontinuing or continuing these drugs should be made bearing in mind the proposed surgery and its inherent risk for bleeding complications as well as decisions relating to appropriate use of general or some form of regional anesthesia. In general, the safest approach to prevent thrombosis seems to be continuation of these drugs throughout the perioperative period except where concerns about perioperative bleeding outweigh those associated with the development of thrombotic occlusion. Knowledge of the pharmacodynamics and pharmacokinetics of antiplatelet drugs may allow practitioners to anticipate difficulties associated with drug withdrawal and administration in the perioperative period including the potential for drug interactions.

### 丙泊酚及其類似物2,6-二異丙基-4-(1-羥基-2,2,2三氟)苯酚在6Hz部分驚厥發作模型中的抗驚厥作用

#### The anticonvulsant effects of propofol and a propofol analog, 2,6-diisopropyl-4-(1-hydroxy-2,2,2-trifluoroethyl)phenol, in a 6 Hz partial seizure model.

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**背景：**丙泊酚是一種具有良好抗驚厥作用的全麻藥。但是其潛在的麻醉鎮靜作用限制了它用於驚厥發作的治療。有研究發現重組丙泊酚分子的某些靶位可以改變2,6-二異丙基苯酚的結構，產生的新物質具有更低的毒性作用以及更好的抗驚厥

作用。本文的報導是關於丙泊酚取代合成的類似物，2,6-二異丙基-4-(1-羥基-2,2,2-三氟)苯酚(MB003)和2,6-二仲丁基苯酚(MB050)以及它們在國家神經疾病與中風研究所篩選的模型中抗驚厥作用的比較。

**方法：**丙泊酚或2,6-二仲丁基苯酚在碳酸鉀的催化下分別與三氟乙醛乙基半縮醛發生化學反應合成MB003和MB050。將產物純化至98%的純度。依據國家神經疾病與中風研究所抗驚厥篩查計畫，研究丙泊酚，MB003，2,6-二仲丁基苯酚和MB050在小鼠最大電休克，皮下衝擊 6Hz(32mA) 部分驚厥模型中的保護作用。所有化合物均給予腹腔注射。通過給藥後小鼠在轉棒取樣器上的駐留能力來評價藥物的毒性作用。

**結果：**丙泊酚，MB003和MB050對於6Hz模型的保護作用最好，但是對於小鼠最大電休克和皮下衝擊法模型的保護作用欠佳。在6Hz模型中，要具有50%的保護作用，丙泊酚所需劑量為32.8mg/kg；MB003所需劑量為38.4mg/kg；MB050則需要74.0mg/kg。丙泊酚具有明顯的毒性作用，並且2,6-二仲丁基苯酚的毒性作用更甚。相應的2,6-二甲基酚類似物為MB003和MB050，2,6-二甲基-4-(1-羥基-2,2,2-三氟)苯酚，在6Hz模型中不具有保護作用，在測試的劑量範圍內也不具有毒性作用。

**結論：**這些結果表明，麻醉劑異丙酚和2,6-二仲丁基苯酚可以用1-羥基-2,2,2-三氟基取代一個對位，由此產生的新的物質在6Hz模型中具有更好的抗驚厥活性同時具有更低的致共濟失調的副作用。在6Hz模型中丙泊酚，MB003，2,6-二仲丁基苯酚和MB050的有效性以及2,6-二甲基-4-(1-羥基-2,2,2-三氟)苯酚的無效性表明2,6-異丙基和2,6-二仲丁基酚的結構對於抗驚厥作用更為重要，而對位有沒有酚醛取代基則無關緊要。這些結果表明1-羥基-2,2,2-三氟基團取代的2,6-二烷基酚可能具有良好的抗驚厥活性並且具有良好的使用價值。

(黃劍譯 薛張綱校)

**BACKGROUND:** Propofol is a general anesthetic having good anticonvulsant properties, but is limited in antiseizure use because of its potent anesthetic/sedative properties. It is proposed that substitution of the propofol molecule in the para position may yield compounds having less toxicity, yet possessing anticonvulsant properties because of retention of the 2,6-diisopropylphenol configuration. Reported herein is the synthesis of a para-substituted analog of propofol, 2,6-diisopropyl-4-(1-hydroxy-2,2,2-trifluoroethyl)phenol (MB003), and a similar analog of 2,6-di-sec-butylphenol (MB050), and their comparative anticonvulsant effects in National Institute of Neurological Disorders and Stroke screening models.

**METHODS:** MB003 and MB050 were synthesized by the reaction of propofol or 2,6-di-sec-butylphenol, respectively, with trifluoroacetaldehyde ethyl hemiacetal in the presence of catalytic amounts of K<sub>2</sub>CO<sub>3</sub>. Compounds were purified to >98% purity. Propofol, MB003, 2,6-di-sec-butylphenol, and MB050 were screened for protective effects by the National Institute of Neurological Disorders and Stroke Anticonvulsant Screening Program in the mouse maximal electroshock, subcutaneous metrazol, and 6 Hz (32 mA) partial seizure models. All compounds were administered by IP injection. The toxicity of each compound was assessed by the ability of the animals to stay on a Rotorod after dosing.

**RESULTS:** Propofol, MB003, and MB050 were found to be most protective in the 6 Hz model with lesser protective effects in the mouse maximal electroshock and subcutaneous metrazol models. In the 6 Hz model, propofol yielded a 50% effective dose of 32.8 mg/kg; MB003, 38.4 mg/kg; and MB050, 74.0 mg/kg. Propofol, and to a greater degree, 2,6-di-sec-butylphenol, exhibited high toxicity. The corresponding 2,6-dimethylphenol analog to MB003 and MB050, 2,6-dimethyl-4-(1-hydroxy-2,2,2-trifluoroethyl)phenol, was not protective in the 6 Hz model and exhibited no toxicity at any dose tested.

**CONCLUSION:** These results show that the anesthetics propofol and 2,6-di-sec-butylphenol may be substituted in the para position with a 1-hydroxy-2,2,2-trifluoroethyl moiety and the resulting molecules have anticonvulsant activity in the 6 Hz model while exhibiting less toxicity (ataxia) than the parent 2,6-dialkylphenols. The effectiveness of propofol, MB003, 2,6-di-sec-butylphenol, and MB050 and the ineffectiveness of 2,6-dimethyl-4-(1-hydroxy-2,2,2-trifluoroethyl)phenol, in the 6 Hz model shows that the 2,6-diisopropyl or 2,6-di-sec-butyl phenolic configuration is more important to anticonvulsant activity than having the phenolic para position free of substituents. These results suggest that 1-hydroxy-2,2,2-trifluoroethyl substituted 2,6-di-alkylphenols may have useful anticonvulsant activities.

### **C-MAC D 型鏡片可視喉鏡在常規氣管插管和困難氣道處理的首個臨床評價**

#### **First Clinical Evaluation of the C-MAC D-Blade Videolaryngoscope During Routine and Difficult Intubation.**

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**摘要：**在本次初步研究中，我們在常規氣管插管和困難氣道處理中評估了 C-MAC D 型鏡片(Karl Storz, Tuttlingen, Germany)，這是一種用於困難氣道的新型 C-MAC 可視喉鏡片。首先，我們在連續 15 個正常氣道病人的常規誘導中分別使用傳統直接喉鏡和 D 型喉鏡片進行聲門暴露。之後，在連續 300 個病人中的 20 個病人(6.7%)中，當傳統直接喉鏡插管失敗後，我們使用 D 型喉鏡片作為困難氣道急救設備。在 15 個病人的常規誘導插管中，使用直接喉鏡可在 7-8 個病人中分別見到 Cormack-Lehane 分級 1 或 2a。而置入 D 型喉鏡片可在所有病人中一次性的在視頻中看到聲門；使用 D 型喉鏡片，所有 15 個病人 Cormack-Lehane 分級均為 1 級。使用 D 型喉鏡片成功插管所用平均時間為 15 秒(範圍 5-26 秒)。在使用傳統直接喉鏡發現未預計困難氣道 20 個病人中，Cormack-Lehane 分級 3 或 4 的分別有 15 和 5 和病人。使用 D 型喉鏡片後，通過視頻的 Cormack-Lehane 分級改進到了 1 級 15 個病人，2a 級 5 個病人。從拿起喉鏡到獲得最佳暴露的時間平均為 11 秒(範圍 5-45

秒)，成功插管時間平均 17 秒(範圍 3-80 秒)。在所有的 35 個病人中，使用 D 型喉鏡片沒有對聲門的直接暴露，接下來的氣管插管需要可半彎曲的管芯。

(任雲譯 薛張綱校)

In the present preliminary study we evaluated the C-MAC<sup>®</sup> D-Blade (Karl Storz, Tuttlingen, Germany), a new videolaryngoscopic C-MAC blade for difficult intubation, during both routine and difficult intubations. First, both the conventional direct laryngoscopy and the D-Blade were used in 15 consecutive patients with normal airways during routine induction of anesthesia. Second, the D-Blade was used as a rescue device in 20 of 300 (6.7%) consecutive patients, when conventional direct laryngoscopy failed. In the 15 patients during routine induction of anesthesia, with direct laryngoscopy, a Cormack-Lehane (C/L) grade 1 and grade 2a view was seen in 7 and 8 patients, respectively. It was possible to insert the D-Blade and to get a video view of the glottis on the first attempt in all patients; with the D-Blade, all 15 patients had a C/L 1 view. The time to successful intubation with the D-Blade was 15 (8-26) seconds (median (range)). In the 20 patients, in whom unexpected difficulty with direct laryngoscopy was observed, C/L grades 3 and 4 were present in 15 and 5 patients, respectively. With the use of the D-Blade, indirect C/L video view improved to C/L class 1 in 15 patients, and to 2a in 5 patients, respectively. The time from touching the laryngoscope to optimal laryngoscopic view was 11 (5-45) seconds and for successful intubation 17 (3-80) seconds. In all 35 patients, with the D-Blade no direct view of the glottis was possible and subsequently a semiflexible tube guide was required.

### 在早期嬰兒中行內鏡下剝離顱骨切除術：最早五年來的麻醉經驗

#### Endoscopic Strip Craniectomy in Early Infancy: The Initial Five Years of Anesthesia Experience

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**背景：**微創的內鏡下剝離顱骨切除術是治療嬰兒顱縫早閉的一種相對較新的外科技術。在這項研究中我們回顧了我們對這類手術的麻醉經驗。假設嬰兒有低體重或者其他的合併症，很有可能需要術中輸血，如果嬰兒有肺部併發症就很有可能進入重症監護室。

**方法：**我們回顧了從 2008 年 3 月到 2009 年 12 月最早實行內鏡下剝離顱骨切除術的 100 名嬰兒的病歷和麻醉記錄。研究結果包括術中輸血，靜脈栓塞，進入 ICU，顱面重建的第二次手術。我們使用多變數的統計回歸方法來決定對患者癒合的重要影響因素。

**結果：**所有患兒年齡從 4 周到 34 周（體重從 3.2-10.1 公斤），其中 87 例行單純的內鏡下剝離顱骨切除術和 13 例行複雜的內鏡下剝離顱骨切除術。有 4 例患兒有顱面綜合症。平均手術時間是 48 分鐘（從 26-86 分鐘）。92 名患兒有中度的失血，

平均約 23 毫升（四分位差 IQR：15-30 毫升）。8 名患兒接受了輸血，平均約 17.2 毫升/公斤（四分位差 IQR：10.1-21.2 毫升/公斤）。如果患兒的體重小於 5 公斤( $P = 0.04$ )，矢狀位行內鏡下剝離顱骨切除術( $P < 0.01$ )，有症狀的顱縫早閉( $P < 0.01$ )，過早的實行手術( $P < 0.01$ )，大都需要術中輸血。有 2 名患兒出現靜脈栓塞但是對臨床癒合沒有影響。8 名患兒進入重症監護室，患兒進入 ICU 的因素多為術中輸血 ( $P < 0.001$ )和肺部併發症( $P < 0.001$ )。82 名患兒在術後第一天就出院（從第一天到第三天）。6 名患兒進一步做了額眶部重建，1 名患兒做了顱頂重建。若患兒行多次顱縫早閉手術( $P < 0.01$ )，有併發症( $P = 0.03$ )，術後進入 ICU( $P = 0.04$ )，大都預示著要再次手術。

**結論：**20% 經歷內鏡下剝離顱骨切除術的患兒有以下一種或幾種情況：需要輸血，靜脈栓塞，肺部併發症，需進入 ICU。多變數的分析證實患兒的體重小於 5 公斤，矢狀位行內鏡下剝離顱骨切除術，有症狀的顱縫早閉，過早的實行手術，有很高的機率需要輸血。患兒進入 ICU 的因素多為術中輸血和肺部併發症。多次進行顱縫早閉手術的患兒很可能需要再進行顱面重建手術。

（翁梅琳譯 薛張綱校）

**BACKGROUND:** Minimally invasive endoscopic strip craniectomy (ESC) is a relatively new surgical technique for treating craniosynostosis in early infancy. In this study we reviewed our anesthesia experience with ESC. The hypothesis was that infants with low body weight and syndromes would have a higher risk of perioperative blood transfusion and that those with respiratory complications are more likely to be admitted to the intensive care unit (ICU).

**METHODS:** We retrospectively reviewed patient charts and anesthesia records of the first 100 consecutive infants who underwent ESC between May 2004 and December 2008 and follow-up evaluations until December 2009. Outcomes included (a) perioperative blood transfusion, (b) venous air embolism (VAE), (c) ICU admission, and (d) reoperation with craniofacial reconstruction procedures. Multivariable logistic regression was used to determine significant factors of patient outcomes.

**RESULTS:** Infants ranging from 4 to 34 weeks of age (weight: 3.2 to 10.1 kg), presented for 87 single and 13 multiple ESC. Four infants had a craniofacial syndrome. The mean surgical time was 48 minutes (range: 26 to 86 minutes). Ninety-two infants had a median estimated blood loss of 23 mL (interquartile ranges [IQR]: 15 to 30 mL). Eight infants who required blood transfusion received a median amount of 17.2 mL/kg (IQR: 10.1 to 21.2 mL/kg). Body weight  $\leq 5$  kg ( $P = 0.04$ ), sagittal ESC ( $P < 0.01$ ), syndromic craniosynostosis ( $P < 0.01$ ), and earlier date of surgery in the series ( $P < 0.01$ ) were factors associated with blood transfusion. VAE was detected in 2 infants with no changes in clinical outcome. Eight infants were admitted to the ICU. Factors associated with ICU admission were blood transfusion ( $P < 0.001$ ) and respiratory complications ( $P < 0.001$ ). Eighty-two infants were discharged on postoperative day 1 (range: 1 to 3 days). Six infants underwent subsequent fronto-orbital advancement and 1 cranial vault reconstruction. Multiple-suture craniosynostosis ( $P < 0.01$ ), associated syndromes ( $P = 0.03$ ), and ICU admission after ESC ( $P = 0.04$ ) were predictive of reoperation.

**CONCLUSIONS:** Twenty percent of infants undergoing ESC had 1 or more of the following: need for blood transfusion, VAE, respiratory complications, and ICU admission. Multivariable analysis confirmed that patients with lower body weight, those

with earlier date of surgery in the series, those undergoing sagittal ESC, and those with syndromic craniosynostosis had a higher rate of blood transfusion. ICU admissions often occurred in infants requiring transfusion and those with respiratory complications. Infants with multiple-suture craniosynostosis were more likely to require subsequent craniofacial reconstruction procedures.

### 兒茶酚-O-甲基轉移酶和阿片類 $\mu$ 受體基因多態性影響嗎啡術後鎮痛和中樞副作用 Combined Catechol-O-Methyltransferase and $\mu$ -Opioid Receptor Gene

#### Polymorphisms Affect Morphine Postoperative Analgesia and Central Side Effects

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**背景：**之前關於阿片類  $\mu$  受體的基因多態性對嗎啡鎮痛和阿片類相關副作用的影響研究有不同的結論。但是評價兩種以上基因多態性對於嗎啡影響的研究很少。本研究中探討了兒茶酚-O-甲基轉移酶和阿片類  $\mu$  受體基因多態性是否影響嗎啡的術後鎮痛。

**方法：**102 名手術病人入組了本前瞻性、觀察性研究。所有病人接受了全麻並運用血標本的 DNA 篩查  $\mu$  受體多態性 A118G (Asn40Asp) 和兒茶酚-O-甲基轉移酶多態性 G1947A (Val158Met)。術後給予病人自控鎮痛並保存使用記錄。量化表記錄病人的靜息痛和副作用。

**結果：**同  $\mu$  受體 A118 純合子相比，阿片類  $\mu$  受體 A118G 和兒茶酚-O-甲基轉移酶 G1947A 突變雜合子病人在蘇醒室和術後 48 小時使用的嗎啡量顯著減少。雜合子病人在術後觀察期內噁心和鎮靜評分顯著減少，且只有 2 個病人接受了鎮吐治療。

**結論：**本項研究顯示了在理解嗎啡在下腹部手術的不同反應時基因與基因之間的重要性。需要在多基因、人口學和臨床特徵上進行研究來預測正確的嗎啡劑量和相關的阿片類副作用。

(姚敏敏譯 薛張綱校)

**BACKGROUND:** Previous studies have generated controversial results regarding the influence of the genetic variations of  $\mu$ -opioid receptors on morphine analgesia and opioid-related side effects in the postoperative period. Few studies have been conducted attempting to assess the combined effects of variation within  $\geq 2$  genes in relation to morphine response. In this study, we investigated whether combined catechol-O-methyltransferase and  $\mu$ -opioid receptor polymorphisms contribute to the morphine response in postoperative analgesia.

**METHODS:** One hundred two surgical patients were enrolled in this prospective, observational study. All patients received general anesthesia and were screened for  $\mu$ -opioid receptor polymorphism A118G (Asn40Asp) and catechol-O-methyltransferase G1947A (Val158Met) polymorphism using a blood sample of DNA. Patient-controlled analgesia was provided postoperatively and morphine consumption was observed. Any pain at rest or side effects were measured with rating scales.

**RESULTS:** The heterozygous patients with  $\mu$ -opioid receptor A118G and catechol-O-methyltransferase G1947A mutation consumed significantly less morphine in the postanesthetic recovery room and 48 hours after surgery compared with homozygous patients of the A118 variant. Nausea and sedation scores were also significantly lower during all observed postoperative periods for heterozygous patients and only 2 patients (18%) from this group received anti-nausea treatment.

**CONCLUSION:** This study has demonstrated the importance of the gene-gene approach in understanding the morphine response in patients after lower abdominal surgery. More studies are needed to characterize the combined effects of multiple genes and demographic as well as clinical variables in predicting the correct morphine dosage and corresponding opioid-related side effects.

**1.5%甲呱卡因與 0.5%布比卡因混合液在超聲引導下肌間溝阻滯中對鎮痛的時效與阻滯起效延遲的影響。**

**The effect of mixing 1.5% mepivacaine and 0.5% bupivacaine on duration of analgesia and latency of block onset in ultrasound-guided interscalene block.**

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**背景：**爲了在神經阻滯中獲得快速起效和長時效的結果，短效與長效的局麻藥常常混合使用。然而，這樣的組合真的集合了上述兩大優點麼。我們假設甲呱卡因與布比卡因的混合液可以帶來比布比卡因更快起效速度和比甲呱卡因更長的阻滯時間。

**方法：**64 個接受肩關節鏡手術（18 到 65 歲；ASA1-2 級）在超聲引導下進行肌間溝臂叢阻滯作爲唯一的麻醉。研究物件隨機接受 3 種研究液體之一：30mL1.5%甲呱卡因，30mL0.5%布比卡因，或 15mL0.5%布比卡因和 1.5%甲呱卡因的混合液。記錄阻滯起效時間和運動感覺的阻滯時效。

**結果：**腋神經感覺（前幹）阻滯的起效三組相似（甲呱卡因  $8.7 \pm 4.3$  分鐘，布比卡因  $10.0 \pm 5.1$  分鐘，混合液  $11.3 \pm 5.3$  分鐘， $P=0.21$ ）。運動阻滯時效混合液組（ $11.5 \pm 4.7$  小時）處於布比卡因組（ $16.4 \pm 9.4$  小時）和甲呱卡因組（ $6.0 \pm 4.2$  小時）當中（布比卡因組和混合液組  $P = 0.03$ ；甲呱卡因組和混合液組  $P = 0.01$ ）。鎮痛時效甲呱卡因組最短（ $4.9 \pm 2.4$  小時），布比卡因組最長（ $14.0 \pm 6.2$  小時），混合液組居中（ $10.3 \pm 4.9$  小時）（甲呱卡因組和混合液組  $P < 0.001$ ；布比卡因組和混合液組  $P = 0.01$ ）。

**結論：**超聲引導下肌間溝阻滯中，0.5%布比卡因和 1.5%甲呱卡因混合液起效時間與任一局麻藥單用的起效時間相似。平均阻滯時效甲呱卡因-布比卡因混合液要顯著長於 1.5%甲呱卡因單用，但顯著短於 0.5%布比卡因單用。

（張玥琪譯，薛張綱校）

**BACKGROUND:** Short- and long-acting local anesthetics are commonly mixed to achieve nerve blocks with short onset and long duration. However, there is a paucity of

data on advantages of such mixtures. We hypothesized that a mixture of mepivacaine and bupivacaine results in a faster onset than does bupivacaine and in a longer duration of blockade than does mepivacaine.

**METHODS:** Sixty-four patients undergoing arthroscopic shoulder surgery (ages 18 to 65 years; ASA physical status I-II) with ultrasound-guided interscalene brachial plexus block as the sole anesthetic were studied. The subjects were randomized to receive 1 of 3 study solutions: 30 mL of mepivacaine 1.5%, 30 mL of bupivacaine 0.5%, or a mixture of 15 mL each of bupivacaine 0.5% and mepivacaine 1.5%. The block onset time and duration of motor and sensory block were assessed.

**RESULTS:** Onset of sensory block in the axillary nerve distribution (superior trunk) was similar among the 3 groups ( $8.7 \pm 4.3$  minutes for mepivacaine,  $10.0 \pm 5.1$  minutes for bupivacaine, and  $11.3 \pm 5.3$  minutes for the combination group;  $P = 0.21$  between all groups). The duration of motor block for the combination group ( $11.5 \pm 4.7$  hours) was between that of the bupivacaine ( $16.4 \pm 9.4$  hours) and mepivacaine ( $6.0 \pm 4.2$  hours) groups ( $P = 0.03$  between bupivacaine and combination groups;  $P = 0.01$  between mepivacaine and combination groups). Duration of analgesia was the shortest with mepivacaine ( $4.9 \pm 2.4$  hours), longest with bupivacaine ( $14.0 \pm 6.2$  hours), and intermediate with the combination group ( $10.3 \pm 4.9$  hours) ( $P < 0.001$  for mepivacaine vs. combination group;  $P = 0.01$  for bupivacaine vs. combination group).

**CONCLUSIONS:** For ultrasound-guided interscalene block, a combination of mepivacaine 1.5% and bupivacaine 0.5% results in a block onset similar to either local anesthetic alone. The mean duration of blockade with a mepivacaine-bupivacaine mixture was significantly longer than block with mepivacaine 1.5% alone but significantly shorter than the block with bupivacaine 0.5% alone.