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室性心動過速消融: 一項給予麻醉醫生的系統綜述

Ventricular Tachycardia Ablation: A Comprehensive Review for Anesthesiologists

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Anesthesia & Analgesia 2015 120 737–748

經皮導管消融術越來越多運用於藥物治療無效的反復發作室性心動過速 (ventricular tachycardia, VT) 的患者。對於此類患者最佳的管理包括謹慎考慮潜在心臟疾病的嚴重程度，麻醉藥物相互作用以及在 VT 標測和消融過程中的技術問題。目標在於選擇一種致心律失常性最小的麻醉技術，這樣可以使得在電生理操作室內 VT 的發生具有可重複性。麻醉藥可以通過直接的作用於離子通道和縫隙連接作用，或間接通過對於自主神經系統作用改變動作電位和心室去極化過程。此外，在操作過程中維持血流動力學穩定以及監測終末器官灌注是另一項挑戰。本綜述全面地更新了當今 VT 消融的實施過程中的麻醉處理方法。

（俞芳 譯 陳傑 校）

Percutaneous catheter ablation is being increasingly performed in patients with recurrent ventricular tachycardia (VT) unresponsive to medical treatment. Optimal management of patients requires careful consideration of the severity of the underlying cardiac disease, the anesthetic drug interactions, and the procedural technique during VT mapping and ablation. The goal is to choose an anesthetic technique that has the least effect on arrhythmogenicity, allowing reproducibility of the VT in the electrophysiology laboratory. Anesthetics can alter action potential and ventricular depolarization directly through their effects on ion channels and gap junctions, as well as indirectly via their effects on the autonomic nervous system. Furthermore, maintaining hemodynamic stability and monitoring for adequate end-organ perfusion are additional challenges. In this review, we provide a comprehensive update on the currently performed VT ablation procedures and their anesthetic considerations.

丙泊酚對於高糖誘導的人臍靜脈內皮細胞凋亡和功能障礙的保護作用

Propofol Protects Against High Glucose–Induced Endothelial Apoptosis and Dysfunction in Human Umbilical Vein Endothelial Cells
背景：圍術期高血糖症是臨床上常見的一種代謝紊亂疾病。高血糖誘導內皮細胞凋亡和功能障礙。丙泊酚是一種臨床上廣泛使用的靜脈麻醉藥物。本研究檢測丙泊酚是否及如何減輕高糖誘導的人臍靜脈內皮細胞（HUVECs）凋亡和功能障礙。方法：用不同濃度（5, 10, 15 和 25 mM）的血糖體外培養 HUVEC，時間分別是 4, 8, 12 和 24 小時。為研究丙泊酚的效應，用不同濃度（0.2, 1, 5 和 25μM）的丙泊酚孵育 2 小時。在平行實驗中，細胞在 5 mM 葡萄糖中孵育作為對照。用硝酸還原酶法測定產生的一氧化氮（NO）。用細胞計數試劑盒-8 測定細胞活性。用 Western blot 法檢測 caspase 3、細胞色素 C、內皮型一氧化氮合酶（eNOS）、p-eNOS-Thr495、p66Shc、蛋白激酶 C βII（PKCβII）和 p-PKCβII-Ser660。用亞鐵細胞色素 c 減少法測定超氧陰離子（O₂⁻）積累。用末端去氧核苷酸轉移酶介導 dUTP 突變末端標記染色法測定細胞凋亡。

結果：與對照組相比，高糖減少 HUVEC 的 NO 產生（P < 0.0001），降低細胞活性（P < 0.0001）。與高糖處理相比，丙泊酚預處理細胞（5μM，2 h）減少了高濃度葡萄糖誘導的抑制性 p-eNOS-Thr495 磷酸化（P < 0.0001），增加 NO 的產生（P = 0.0007），降低高血糖誘導的 p66Shc 的表達（P < 0.0001）和 p66Shc 線粒體易位（P < 0.0001），O₂⁻ 積聚（P < 0.0001），線粒體細胞色素 C 與釋（P < 0.0001），活化 Caspase 3 的表達（P < 0.0001）和增強內皮細胞活性（P < 0.0001）。此外，異丙酚抑制高糖誘導的 PKC–βII 的表達（P = 0.0002）和 p-PKCβII-ser660 磷酸化（P < 0.0001）。丙泊酚的保護作用與 PKCβII 抑制劑十分相似。

結論：丙泊酚通過降低高糖誘導 PKCβII 的表達和 p-PKCβII-ser660 磷酸的機制，抑制高糖誘導的 p66Shc 線粒體易位。因此保護人臍靜脈內皮細胞免受高糖誘導的內皮細胞功能障礙和細胞凋亡。

（徐歡譯 陳傑校）

BACKGROUND: Perioperative hyperglycemia is a common clinical metabolic disorder. Hyperglycemia could induce endothelial apoptosis and dysfunction. Propofol is a widely used IV anesthetic drug in clinical settings. In the present study, we examined whether and how propofol reduced high glucose–induced endothelial apoptosis and dysfunction in human umbilical vein endothelial cells (HUVECs).

METHODS: HUVECs were cultured with different concentrations (5, 10, 15, and 25 mM) of glucose for different times (4, 8, 12, and 24 hours). To study the effect of propofol, cells were incubated with different concentrations (0.2, 1, 5, and 25 μM) of propofol for 2 hours. In parallel experiments, cells were incubated in 5 mM glucose as control. Nitric oxide (NO) production was measured with a nitrate reductase assay. Cell viability was determined with a Cell Counting Kit-8. Protein expression of active caspase 3, cytochrome c, endothelial NO synthase (eNOS), p-eNOS-Thr495, p66Shc, protein kinase C βII (PKCβII), and p-PKCβII-Ser660 was measured by Western blot analysis. Accumulation of superoxide anion (O₂⁻) was measured with the reduction of ferricytochrome c. Cell apoptosis was determined with terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling staining.

RESULTS: Compared with control, high glucose decreased NO production (P < 0.0001) and reduced cells viability (P < 0.0001) in HUVECs. Compared with high glucose treatment, pretreatment of cells with propofol (5 μM, 2 hours) reduced high glucose–induced inhibitory p-eNOS-Thr495 phosphorylation (P < 0.0001), increasing NO production (P = 0.0007), decreased high glucose–induced p66Shc expression (P < 0.0001) and p66Shc mitochondrial translocation (P < 0.0001), O₂⁻ accumulation (P < 0.0001), mitochondrial cytochrome c release (P < 0.0001), active caspase 3 expression (P < 0.0001), and enhancing endothelial viability (P < 0.0001). Furthermore, propofol inhibited high glucose–induced PKCβII expression (P = 0.0002) and p-
PKCβII-Ser660 phosphorylation (P < 0.0001). Moreover, the observed protective effect of propofol was quite similar to that of PKCβII inhibitor.

CONCLUSIONS: Propofol, by a mechanism of decreasing high glucose–induced PKCβII expression and p-PKCβII-Ser660 phosphorylation, inhibits high glucose–induced p66Shc mitochondrial translocation, therefore protecting HUVECs from high glucose–induced endothelial dysfunction and apoptosis.

The Epidemiology of Staphylococcus aureus Transmission in the Anesthesia Work Area

Loftus, Randy W. MD*; Koff, Matthew D. MS, MD*; Brown, Jeremiah R. MS, PhD†; Patel, Hetal M. BS; Jensen, Jens T. MS; Reddy, Sundara MD‡; Ruoff, Kathryn L. PhD§; Heard, Stephen O. MD∥; Yeager, Mark P. MD*; Dodds, Thomas M. MD*

Anesthesia & Analgesia 2015 120 807–818

BACKGROUND: Little is known regarding the epidemiology of intraoperative Staphylococcus aureus transmission. The primary aim of this study was to examine the mode of transmission, reservoir of origin, transmission locations, and antibiotic susceptibility for frequently encountered S aureus strains (phenotypes) in the anesthesia work area. Our secondary aims were to examine phenotypic associations with 30-day postoperative patient cultures, phenotypic growth rates, and risk factors for phenotypic isolation.

METHODS: S aureus isolates previously identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and analytical profile indexing
were subjected to antibiotic disk diffusion sensitivity. The combination of these techniques was then used to confirm S. aureus transmission events and to classify them as occurring within or between operative cases (mode). The origin of S. aureus transmission events was determined via use of a previously validated experimental model and links to 30-day postoperative patient cultures confirmed via pulsed-field gel electrophoresis. Growth rates were assessed via time-to-positivity analysis, and risk factors for isolation were characterized via logistic regression.

RESULTS: One hundred seventy S. aureus isolates previously implicated as possible intraoperative transmission events were further subdivided by analytical profile indexing phenotype. Two phenotypes, phenotype P (patients) and phenotype H (hands), accounted for 65% of isolates. Phenotype P and phenotype H contributed to at least 1 confirmed transmission event in 39% and 28% of cases, respectively. Patient skin surfaces (odds ratio [OR], 8.40; 95% confidence interval [CI], 2.30–30.73) and environmental (OR, 10.89; 95% CI, 1.29–92.13) samples were more likely than provider hands (referent) to have phenotype P positivity. Phenotype P was more likely than phenotype H to be resistant to methicillin (OR, 4.38; 95% CI, 1.59–12.06; P = 0.004) and to be linked to 30-day postoperative patient cultures (risk ratio, 36.63 [risk difference, 0.174; 95% CI, 0.019–0.328]; P < 0.001). Phenotype P exhibited a faster growth rate for methicillin resistant and for methicillin susceptible than phenotype H (phenotype P: median, 10.32H; interquartile range, 10.08–10.56; phenotype H: median, 10.56H; interquartile range, 10.32–10.8; P = 0.012). Risk factors for isolation of phenotype P included age (OR, 14.1; 95% CI, 3.12–63.5; P = 0.001) and patient exposure to the hospital ward (OR, 41.11; 95% CI, 5.30–318.78; P < 0.001).

CONCLUSIONS: Two S. aureus phenotypes are frequently transmitted in the anesthesia work area. A patient and environmentally derived phenotype is associated with increased risk of antibiotic resistance and links to 30-day postoperative patient cultures as compared with a provider hand-derived phenotype. Future work should be directed toward improved screening and decolonization of patients entering the perioperative arena and improved intraoperative environmental cleaning to attenuate postoperative health care–associated infections.

麻醉醫生的手衛生學知識和觀念
Hand Hygiene Knowledge and Perceptions Among Anesthesia Providers
Fernandez, Patrick G. MD*; Loftus, Randy W. MD*; Dodds, Thomas M. MD*; Koff, Matthew D. MS, MD*; Reddy, Sundara MD†; Heard, Stephen O. MD‡; Beach, Michael L. MD, PhD; Yeager, Mark P. MD*; Brown, Jeremiah R. MS, PhD§
Anesthesia & Analgesia 2015 120 837–843
與減少不完全知識相關，包括在接觸環境後積極回應洗手（比值比[OR] 0.23，0.14–0.37，P < 0.001），在對病人護理中消毒環境（比值比 0.54，0.35–0.82，P = 0.004），相信他們可以影響同事（比值比 0.43，0.27–0.68，P < 0.001），並打算堅持準則（比值比 0.56，0.36–0.86，P = 0.008）。這些協變數與受試者特徵曲線下面積相關性為 0.79 (95% 置信區間，0.74–0.83)。

結論：麻醉醫生在手衛生準則方面的知識缺乏頻繁發生，往往由於沒有認識到手衛生在於與污染的病人接觸和環境接觸後。術中手衛生改進方案應解決這些知識缺陷。本研究證實的不完備知識的相關預測因素應在未來的研究中進一步驗證。

（李慧 譯 陳傑 校）

BACKGROUND: Health care worker compliance with hand hygiene guidelines is an important measure for health care–associated infection prevention, yet overall compliance across all health care arenas remains low. A correct answer to 4 of 4 structured questions pertaining to indications for hand decontamination (according to types of contact) has been associated with improved health care provider hand hygiene compliance when compared to those health care providers answering incorrectly for 1 or more questions. A better understanding of knowledge deficits among anesthesia providers may lead to hand hygiene improvement strategies. In this study, our primary aims were to characterize and identify predictors for hand hygiene knowledge deficits among anesthesia providers.

METHODS: We modified this previously tested survey instrument to measure anesthesia provider hand hygiene knowledge regarding the 5 moments of hand hygiene across national and multicenter groups. Complete knowledge was defined by correct answers to 5 questions addressing the 5 moments for hand hygiene and received a score of 1. Incomplete knowledge was defined by an incorrect answer to 1 or more of the 5 questions and received a score of 0. We used a multilevel random-effects XTMELOGIT logistic model clustering at the respondent and geographic location for insufficient knowledge and forward/backward stepwise logistic regression analysis to identify predictors for incomplete knowledge.

RESULTS: The survey response rates were 55.8% and 18.2% for the multicenter and national survey study groups, respectively. One or more knowledge deficits occurred with 81.6% of survey respondents, with the mean number of correct answers 2.89 (95% confidence interval, 2.78–2.99). Failure of providers to recognize prior contact with the environment and prior contact with the patient as hand hygiene opportunities contributed to the low mean. Several cognitive factors were associated with a reduced risk of incomplete knowledge including providers responding positively to washing their hands after contact with the environment (odds ratio [OR] 0.23, 0.14–0.37, P < 0.001), disinfecting their environment during patient care (OR 0.54, 0.35–0.82, P = 0.004), believing that they can influence their colleagues (OR 0.43, 0.27–0.68, P < 0.001), and intending to adhere to guidelines (OR 0.56, 0.36–0.86, P = 0.008). These covariates were associated with an area under receiver operator characteristics curve of 0.79 (95% confidence interval, 0.74–0.83).

CONCLUSIONS: Anesthesia provider knowledge deficits around to hand hygiene guidelines occur frequently and are often due to failure to recognize opportunities for hand hygiene after prior contact with contaminated patient and environmental reservoirs. Intraoperative hand hygiene improvement programs should address these knowledge deficits. Predictors for incomplete knowledge as identified in this study should be validated in future studies.

來源於麻醉工作區域的細菌傳播事件的動態和影響

The Dynamics and Implications of Bacterial Transmission Events Arising from the Anesthesia Work Area

Loftus, Randy W. MD*; Koff, Matthew D. MS, MD*; Birnbach, David J. MD, MPH†

Anesthesia & Analgesia 2015 120 853–860
Health care–associated infections are a hospital-wide concern associated with a significant increase in patient morbidity, mortality, and health care costs. Bacterial transmission in the anesthesia work area of the operating room environment is a root cause of 30-day postoperative infections affecting as many as 16% of patients undergoing surgery. A better understanding of anesthesia-related bacterial transmission dynamics may help to generate improvements in intraoperative infection control and improve patient safety.

**Haloperidol Suppresses Murine Dendritic Cell Maturation and Priming of the T Helper 1–Type Immune Response**

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Anesthesia & Analgesia 2015 120 895–902

**BACKGROUND:** Haloperidol has immunomodulatory effects when used to treat patients with schizophrenia and also is used to sedate critically ill patients in the intensive care unit. Although the mechanism by which haloperidol affects immune function is unclear, one possibility is that it alters dendritic cell (DC) function. DCs are potent antigen-presenting cells that influence the activation and maturation of T lymphocytes. In this study, we investigated the in vitro and in vivo immunomodulatory effects of haloperidol on DC-mediated immune responses.
METHODS: Using bone marrow–derived DCs in cell culture, we evaluated the effect of haloperidol on expression of costimulatory molecules (CD80 and CD86), major histocompatibility complex class II molecules, and the DC maturation marker CD83. DC culture supernatants also were evaluated for interleukin-12 p40 levels. In addition, we analyzed the effect of haloperidol on a mixed cell culture containing DCs and lymphocytes and measured the secretion of interferon-γ in the culture supernatants. We also assessed the in vivo effects of haloperidol on hapten-induced contact hypersensitivity responses.

RESULTS: Haloperidol inhibited the expression of CD80, CD86, major histocompatibility complex class II, and CD83 molecules on DCs and the secretion of interleukin-12p40 in DC culture supernatants. In mixed cell cultures containing both T cells (CD4+ and CD8α+) and DCs, haloperidol-treated DCs suppressed the proliferation of allogeneic T cells and effectively inhibited the production of interferon-γ. In vivo, haloperidol reduced hapten-induced contact hypersensitivity responses. Furthermore, an antagonist to D2-like receptor suppressed the maturation of DCs in a manner similar to haloperidol.

CONCLUSIONS: The results of our study suggest that haloperidol suppresses the functional maturation of DCs and plays an important role in the inhibition of DC-induced T helper 1 immune responses in the whole animal. Furthermore, the effect of haloperidol on DCs may be mediated by dopamine D2–like receptors. Together, these results demonstrate that administration of haloperidol suppresses DC-mediated immune responses.

BACKGROUND: Fentanyl’s analgesic efficacy varies widely among individuals. The single-nucleotide polymorphisms (SNPs) of catechol-O-methyltransferase (COMT) modulate
sensitivity to pain. It remains unclear, however, whether COMT genetic variability affects postoperative fentanyl analgesia in patients undergoing radical gastrectomy.

METHODS: One hundred fifteen patients, ASA physical status I–III, who were scheduled for radical gastrectomy under general anesthesia, were enrolled in this study. Patient-controlled IV analgesia with fentanyl was administered during the first 48 hours after surgery. Visual analog scale score for patients’ pain was maintained at ≤30 mm. The amount of fentanyl consumed and side effects were recorded for the first 24 and 48 hours postoperatively. The SNPs of COMT (rs6269, rs4633, rs4818, and rs4680) of all patients were screened by DNA sequence analysis of polymerase chain reaction–amplified DNA or polymerase chain reaction-restriction fragment length polymorphism.

RESULTS: There were no significant differences in the doses of fentanyl used among patients possessing different SNPs of COMT rs6269, rs4633, rs4818, and rs4680 at 24 (all P > 0.207) and 48 (all P > 0.148) hours after surgery. COMT gene haplotypes combined by COMT rs6269, rs4633, rs4818, and rs4680, however, significantly affected fentanyl consumption at 24 (P = 0.029) and 48 (P = 0.032) hours after surgery. Among the haplotypes of COMT gene, patients with haplotype ACCG consumed more fentanyl than GCGG and ATCA haplotypes during the first 24 and 48 hours (all P < 0.042) after surgery. No significant differences were found in the incidence of nausea, vomiting, and dizziness among the 4 SNPs of COMT gene (all P > 0.079) and their haplotypes (all P > 0.482).

CONCLUSIONS: COMT gene haplotype constructed by rs6269, rs4633, rs4818, and rs4680 contributes to the individual variation of postoperative analgesia with fentanyl. Patients carrying the COMT gene haplotype ACCG consumed the most drug during the first 24 and 48 hours postoperatively.

體外膜式氧合引起高分子量血管性血友病因數多聚體短暫缺失

Extracorporeal Membrane Oxygenation Induces Short-Term Loss of High-Molecular-Weight von Willebrand Factor Multimers

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背景：高分子量（HMW）血管性血友病因數（vWF）多聚體在初期的止血過程中起重要作用。心室輔助裝置帶來的剪切力增加導致HMW vWF 多聚體過早降解。但是體外膜式氧合（ECMO）條件下是否同樣存在vWF多聚體的降解仍然是疑問。

方法：我們在頑固性心功能不全伴/不伴肺功能衰竭並且需要ECMO治療的患者進行了一項觀察性研究。觀察主要節點是在ECMO 前，ECMO 中和ECMO 後的HMW vWF的品質和數量。為了進一步研究初期止血的改變，針對入組的 38 例患者，在患者接受ECMO前（基礎值），經行ECMO 24 小時和48 小時時，以及ECMO 治療後 24h，我們同時檢測vWF抗原（vWF-Ag），vWF瑞斯托菌素輔因數（vWF-RCo）和VIII 因子的水準。

結果：與基礎水準相比，經過 24h ECMO 治療後，vWF-Ag 和 vWF-RCo 水準明顯下降（平均數±標準差，vWF-Ag，307±152% 到 261±138%，P=0.002; vWF-RCo 282±145% 到 157±103%，P＜0.0001）。同樣在後續治療過程中vWF-Ag和vWF-RCo 水準亦明顯下降（vWF-Ag 265±128%，P=0.025; vWF-RCo 163±94%，P＜0.0001）。在終止ECMO 治療後，vWF-Ag 高於基礎水準（359±131%，P=0.004），而vWF-RCo 與基礎水準持平（338±142%，P=0.046）。與基礎值相比，vWF-RCo/vWF-Ag 比值在 24h ECMO 治療後明顯下降（0.96±0.23 至 0.61±0.17，P≤0.0001），在 48h ECMO 治療後該比值亦明顯下降（0.63±0.18，P≤0.0001）。在終止治療後，該比值迅速與基礎值持平（0.94±0.19，P=0.437）。HMW vWF 多聚體的數量在24 h (21±1.4 至14
BACKGROUND: High-molecular-weight (HMW) von Willebrand factor (vWF) multimers are crucial for primary hemostasis. Increased shear stress from ventricular assist devices can provoke premature degradation of HMW vWF multimers. Whether similar loss of vWF multimers occurs during extracorporeal membrane oxygenation (ECMO) is not clear.

METHODS: We conducted a prospective observational study in a clinical cohort of patients who required ECMO for intractable cardiac and/or respiratory failure. The primary end point was the quantity and quality of HMW vWF multimer bands before, during, and after ECMO support. To investigate further changes in primary hemostasis, we also measured vWF antigen activity (vWF:Ag), vWF ristocetin cofactor activity (vWF:RCo), and factor VIII in 38 patients who required ECMO support before initiation of ECMO (baseline), after 24 and 48 hours on ECMO, and 24 hours after termination of ECMO therapy.

RESULTS: Compared with baseline, vWF:Ag and vWF:RCo decreased after 24 hours of ECMO (mean ± SD, vWF:Ag, 307% ± 152% to 261% ± 138%, P = 0.002; vWF:RCo 282% ± 145% to 157% ± 103%, P < 0.0001) and remained lower during ongoing support (vWF:Ag 265% ± 128%, P = 0.025; vWF:RCo 163% ± 94%, P < 0.0001). After termination of ECMO, vWF:Ag was greater than baseline (359% ± 131%, P = 0.004) and vWF:RCo was similar to baseline levels (338% ± 142%, P = 0.046). Compared with baseline, the calculated vWF:RCo/vWF:Ag ratio decreased after 24 hours on support (0.96 ± 0.23 to 0.61 ± 0.17, P ≤ 0.0001) and remained lower during 48 hours on ECMO (0.63 ± 0.18, P ≤ 0.0001). After termination of ECMO support (0.94 ± 0.19, P = 0.437), values rapidly returned to baseline. The number of HMW vWF multimers (n) decreased from baseline after 24 hours on ECMO (21 ± 1.4 to 14 ± 1.8, P ≤ 0.0001) and after 48 hours on ECMO (15 ± 2.1, P ≤ 0.0001). Twenty-four hours after termination of ECMO support, HMW vWF multimeric pattern had returned to baseline values (21 ± 1.8, P = 0.551).

CONCLUSIONS: Loss of HMW vWF multimer bands occurred in patients undergoing ECMO support and resolved after the termination of ECMO. Although not detectable with coagulation screening tests, a vWF:RCo/vWF:Ag ratio <0.7 during ECMO was highly indicative for loss of HMW vWF multimers. Our findings may at least in part explain increased bleeding tendency during ECMO therapy. Administration of vWF concentrates may support restoration of primary hemostasis in patients with relevant bleeding during ECMO support.
方法：病人按計劃行診斷性上消化道內鏡檢查，隨機、雙盲給予 3 種劑量中的 1 種的 remimazolam 或者咪達唑侖，每組 25 位病人。給予單次的藥物鎮靜滿意後，病人性胃鏡檢查。我們評估檢查的成功與否、鎮靜效果、蘇醒和安全性。

結果：低劑量組（0.10mg/kg）、中劑量組（0.15mg/kg）和高劑量組（0.20mg/kg）給予單次劑量 remimazolam 後的胃鏡檢查成功率分別是 32%、56%、64%，咪達唑侖組（0.075mg/kg）的成功率是 44%。Remimazolam 組的鎮靜起效時間是 1.5-2.5 分鐘，而咪達唑侖是 5 分鐘。因爲這項研究是給予單次劑量，必要時給予咪達唑侖或丙泊酚以維持鎮靜狀態完成檢查。所有治療組病人鎮靜後的蘇醒都非常迅速，但受單次劑量後選擇的追加藥物的影響。在 remimazolam 和咪達唑侖的安全性上沒有明顯的不同。

結論：這項劑量探索性研究表明在診斷性上消化道內鏡檢查中給予病人單次劑量 remimazolam （0.10-0.20mg/kg）能夠快速鎮靜和快速蘇醒。Remimazolam 的安全性良好，與咪達唑侖相似，保證了這個起效迅速的藥物的進一步發展。

（呂越昌譯 薛張綱校）

BACKGROUND: This exploratory study was the first study of remimazolam in patients to assess the safety and efficacy of different single doses for procedural sedation.

METHODS: Patients scheduled to undergo a diagnostic upper gastrointestinal endoscopy were randomized to receive 1 of 3 doses of remimazolam or midazolam(25 per group) in a double-blind manner. After a single dose of study drug to achieve sedation, patients underwent gastroscopy. We assessed the success of the procedure, sedation levels, recovery from sedation, and safety.

RESULTS: A single dose of remimazolam resulted in a successful procedure in 32%, 56%, and 64% of patients in the low (0.10), middle (0.15), and high (0.20 mg/kg) dose groups compared with 44% of patients in the midazolam (0.075 mg/kg) dose group. The onset of sedation was 1.5 to 2.5 minutes in there mimazolam dose groups compared with 5 minutes for midazolam. Because this was a single administration study, sedation could be maintained for as long as necessary to complete the procedure, using rescue midazolam or propofol. Recovery from sedation was rapid for all treatment groups but was influenced by the choice of rescue medication. There were no obvious differences in the safety profiles of remimazolam and midazolam.

CONCLUSIONS: This exploratory dose-finding study showed that a single administration of remimazolam (0.10-0.20 mg/kg) was capable of inducing rapid sedation with a quick recovery profile in patients undergoing a diagnostic upper gastrointestinal endoscopy. The safety profile was favorable and appeared to be similar to that of midazolam, warranting further development of this short-acting compound.

Needleless Connectors Substantially Reduce Flow of Crystalloid and Red Blood Cells During Rapid Infusion

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儘管無針連接元件 (NC) 被廣泛地用於圍術期，但現代無針連接元件減低輸注液體的速度的可能性並未被徹底研究。我們研究了 Level 1 通過不同的靜脈導管輸液的 5 種裝置及無針連接元件在加壓輸注晶體液以及紅細胞時的流速特點。在大於 18 號的導管中，晶體液的速度降低 29% to 85%。在這些導管中，紅細胞輸注流速下降 22% to 76%（P < 0.0050）。我們建議臨床實踐者在使用大管徑靜脈導管經行快速輸液時去除無針連接元件。
Although needleless connectors (NC) are frequently used in the perioperative setting, the potential of modern NCs to slow delivery of IV fluids has not been thoroughly studied. We examined flow characteristics of 5 NC models during pressurized delivery of crystalloid and banked red blood cells from a Level 1 warmer through various IV catheters. Crystalloid flow rates were reduced by 29% to 85% from control in catheters >18 gauge, while red blood cell flow reductions ranged from 22% to 76% in these catheters (all P < 0.0050). We suggest that practitioners consider eliminating NCs when large IV catheters are inserted for rapid fluid administration.

The Dynamics of Enterococcus Transmission from Bacterial Reservoirs Commonly Encountered by Anesthesia Providers

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BACKGROUND: Enterococci, the second leading cause of health care-associated infections, have evolved from commensal and harmless organisms to multidrug-resistant bacteria associated with a significant increase in patient morbidity and mortality. Prevention of ongoing spread of this organism within and between hospitals is important. In this study, we characterized Enterococcus transmission dynamics for bacterial reservoirs commonly encountered by anesthesia providers during the routine administration of general anesthesia.

METHODS: Enterococcus isolates previously obtained from bacterial reservoirs frequently encountered by anesthesiologists (patient nasopharynx and axilla, anesthesia provider hands, and the adjustable pressure-limiting valve and agent dial of the anesthesia machine) at 3 major academic medical centers were identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and phenotypic analysis (analytical profile indexing).
They were then subjected to antibiotic disk diffusion sensitivity for transmission event confirmation. Isolates involved in confirmed transmission events were further analyzed to characterize the frequency, mode, origin, location of transmission events, and antibiotic susceptibility of transmitted pathogens.

RESULTS: Three hundred eighty-nine anesthesia reservoir isolates were previously identified by gross morphology and simple rapid tests as Enterococcus. The combination of further analytical profile indexing analysis and temporal association implicated 43% (166/389) of those isolates in possible intraoperative bacterial transmission events. Approximately, 30% (49/166) of possible transmission events were confirmed by additional antibiotic disk diffusion analysis. Two phenotypes, E5 and E7, explained 80% (39/49) of confirmed transmission events. For both phenotypes, provider hands were a common reservoir of origin proximal to the transmission event (96% [72/75] hand origin for E7 and 89% [50/56] hand origin for E5) and site of transmission (94% [16/17] hand transmission location for E7 and 86% [19/22] hand transmission location for E5).

CONCLUSIONS: Anesthesia provider hand contamination is a common proximal source and transmission location for Enterococcus transmission events in the anesthesia work area. Future work should evaluate the impact of intraoperative hand hygiene improvement strategies on the dynamics of intraoperative Enterococcus transmission.

在靜脈通路中留下的不只是你的指紋：一項關於異丙酚麻醉和可能存在三通污染的前瞻性研究

Leaving More Than Your Fingerprint on the Intravenous Line: A Prospective Study on Propofol Anesthesia and Implications of Stopcock Contamination

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BACKGROUND: Acute care handling of IV stopcocks during anesthesia and surgery may result in contaminated IV tubing sets. In the context of widespread propofol use, a nutrient-rich hypnotic drug, we hypothesized that propofol anesthesia increases bacterial contamination of IV
stopcocks and may compromise safety of IV tubing sets when continued to be used after propofol anesthesia.

METHODS: We conducted an in vitro trial by collecting IV tubing sets at the time of patient discharge from same-day ambulatory procedures performed with and without propofol anesthesia. These extension sets were then held at room temperature for 6, 24, or 48 hours. We cultured 50 samples at each interval for both cohorts. Quantitative cultures were done by aspirating the IV stopcock dead space and plating the aspirate on blood agar for colony count and speciation.

RESULTS: Positive bacterial counts were recovered from 17.3% of propofol anesthesia stopcocks (26/150) and 18.6% of nonpropofol stopcocks (28/150). At 6 hours, the average bacterial counts from stopcocks with visible residual propofol was 44 colony forming units (CFU)/mL, compared with 41 CFU/mL with no visible residual propofol and 37 CFU/mL in nonpropofol anesthesia stopcocks. There was a 100-fold increase in bacterial number in contaminated stopcock dead spaces at 48 hours after propofol anesthesia. This difference remained significant when comparing positive counts from stopcocks with no visible residual propofol and nonpropofol anesthesia (P = 0.034).

CONCLUSIONS: There is a covert incidence and degree of IV stopcock bacterial contamination during anesthesia which is aggravated by propofol anesthetic. Propofol anesthesia may increase risk for postoperative infection because of bacterial growth in IV stopcock dead spaces.

The Use of a Novel Technology to Study Dynamics of Pathogen Transmission in the Operating Room

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BACKGROUND: Suction-generated expiratory ventilation assistance (EVA) has been proposed as a way to facilitate bidirectional ventilation through a small-bore transtracheal cannula (TC). In this study, we investigated the efficiency of ventilation with EVA for restoring oxygenation and ventilation in a pig model of acute hypoxia.

METHODS: Six pigs (61–76 kg) were anesthetized and ventilated (intermittent positive pressure ventilation) via a cuffed endotracheal tube (ETT). Monitoring lines were placed, and a 75-mm long, 2-mm inner diameter TC was inserted. After the baseline recordings, the ventilator was disconnected. After 2 minutes of apnea, reoxygenation with EVA was initiated through the TC and continued for 15 minutes with the ETT occluded. In the second part of the study, the experiment was repeated with the ETT either partially obstructed or left open. Airway pressures and hemodynamic data were recorded, and arterial blood gases were measured. Descriptive statistical analysis was performed.

RESULTS: With a completely or partially obstructed upper airway, ventilation with EVA restored oxygenation to baseline levels in all animals within 20 seconds. In a completely obstructed airway, PaCO2 remained stable for 15 minutes. At lesser degrees of airway obstruction, the time to reoxygenation was delayed. Efficacy probably was limited when the airway was completely unobstructed, with 2 of 6 animals having a PaO2 <85 mm Hg even after 15 minutes of ventilation with EVA and a mean PaCO2 increased up to 90 mm Hg.

CONCLUSIONS: In severe hypoxic pigs, ventilation with EVA restored oxygenation quickly in case of a completely or partially obstructed upper airway. Reoxygenation and ventilation were less efficient when the upper airway was completely unobstructed.
背景：這項 2 階段的專案的目的是為了對一項新開發的基於網路的簡明干預在父母和兒童術前準備的程式進行形成性評價和初步療效的測試(WebTIPS)。

方法：第 1 階段入組了13個接受門診擇期外科手術的2 - 7 歲兒童和他們的父母，對其進行 WebTIPS 的形成性評價。在定性研究中，家長參與集中研討小組是非常普遍的，而且這是詢問研究參與者對一個產品或概念看法和態度的一個方法。在第 2 階段中，來自兩個醫療中心的 2 － 7 歲兒童被隨機分配接受 WebTIPS (n = 38)和標準護理(n = 44)。第二階段的主要結果是孩子和家長的術前焦慮。

結果：在第二階段，父母認爲 WebTIPS 有效(P < 0.001)並且易於使用(P < 0.001)。在第二階段，在進入手術室時(P = 0.02; Cohen d= 0.59)和介紹麻醉面罩時(分別為 43.5±21.7 與 57.0±57.0,P = 0.01; Cohen d= 0.63)，WebTIPS 組的兒童(36.2±14.1)與標準護理組的兒童(46.0±19.0)相比，焦慮程度較低。術前等候區，WebTIPS 組的父母(32.1±7.4)較對照組父母(36.8±7.1)經歷更少的焦慮(P = 0.004; Cohen d = 0.65)。

結論：WebTIPS 受到了家長和孩子的廣泛認可，其可減少術前焦慮。

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結論：WebTIPS 受到了家長和孩子的廣泛認可，其可減少術前焦慮。
Cardiopulmonary bypass (CPB) required for cardiac surgery presents unique challenges to the cardiac anesthesiologist responsible for providing the 3 most basic facets of any anesthetic: amnesia, analgesia, and muscle relaxation. Unique pathophysiologic changes during CPB result in pharmacokinetic alterations that impact the serum and tissue concentrations of IV and volatile anesthetics. Similarly, CPB causes pharmacodynamic alterations that impact anesthetic efficacy. The clinical significance of these alterations represents a “moving target” as practice evolves and the technology of CPB circuitry advances. In addition, perfusionists choose, modify, and maintain the CPB circuitry and membrane oxygenator. Thus, their significance may not be fully appreciated by the anesthesiologist. These issues have a profound impact on the anesthetic state of the patient. The delivery and maintenance of anesthesia during CPB present unique challenges. The perfusionist may be directly responsible for the delivery of anesthetic during CPB, a situation unique to the cardiac suite. In addition, monitors of anesthetic depth—assessment of clinical signs, hemodynamic indicators, the bispectral index monitor, end-tidal anesthetic concentration, or twitch monitoring—are often absent, unreliable, or directly impacted by the unique pathophysiology associated with CPB. The magnitude of these challenges is reflected in the higher incidence of intraoperative awareness during cardiac surgery. Further complicating matters are the lack of specific clinical guidelines and varying international policies regarding medical device specifications that add further layers of complexity and introduce practice variability both within institutions and among nations. We performed a systematic survey of the literature to identify where anesthetic practice during CPB is evidence based (or not), identify gaps in the literature to guide future investigations, and explore the implications of evolving surgical practice, perfusion techniques, and national policies that impact amnesia, analgesia, and muscle relaxation during CPB.

曲馬多以及其代謝產物M1會選擇性的抑制瞬態電壓感受器陽離子通道受體1 (TRPV1)的活性，而不是瞬態受體電位香草酸受體1 (TRPA1)的活性，而不是瞬態受體電位香草酸受體1 (TRPA1)

Tramadol and Its Metabolite M1 Selectively Suppress Transient Receptor Potential Ankyrin 1 Activity, but Not Transient Receptor Potential Vanilloid 1 Activity

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背景: 暫態受體電位香草酸受體 1 (TRPV1) 和瞬態電壓感受器陽離子通道受體 1 (TRPA1) 都在感覺神經元處表達，他們是負責感受傷害性刺激的多形態非選擇性陽離子通道。最近的研究指出這些通道在炎性、神經病理性以及癌性疼痛中有非常重要的影響，從而在鎮痛藥的藥理學目標的研究方面起到了積極的作用。曲馬多是在臨床實踐中使用的一種有效的鎮痛藥。據研究，曲馬多和它的代謝產物 M1 和 μ 胺受體結合從而抑制單胺類受體在中樞神經系統的再攝取，從而啓動下行抑制系統。然而，曲馬多在疼痛控制方面的作用機制目前尚未研究清楚。TRPV1 和 TRPA1 也許是曲馬多的作用靶點，但是目前沒有被廣泛研究。

方法: 我們通過運用鈣離子成像檢測和全細胞膜片鉗記錄的方法研究了曲馬多和它的代謝產物 M1 對於人胚胎性腎 293 細胞是否以及如何表達暫態受體電位香草酸受體 1 (hTRPV1) 和瞬態電壓感受器陽離子通道受體 1 (hTRPA1)。

結果: 分別與辣椒素組（一種 TRPV1 激動劑）和異硫氰酸烯丙酯組（一種 TRPA1 激動劑）相比，曲馬多和它的代謝產物 M1 在人胚胎性腎 293 細胞中表達 hTRPV1 和 hTRPA1 的同時並未增加細胞內鈣離子濃度。而且，在辣椒素的作用下，人胚胎性腎 293 細胞表達的 hTRPV1，經過曲馬多或它的代謝產物 M1 預處理 5 分鐘後，也不會影響細胞內鈣離子濃度的增加。反之，在異硫氰酸烯丙酯的預處理後，曲馬多和它的代謝產物 M1 在人胚胎性腎 293 細胞表達 hTRPA1 的同時，則明顯抑制了細胞內鈣離子濃度的增加。另外，膜片鉗的研究發現，在異硫氰酸烯丙酯的作用下，曲馬多和它的代謝產物 M1 則降低了細胞的內向電流。

結論: 這些資料表明了曲馬多和它的代謝產物 M1 會選擇性的抑制 hTRPA1 的作用，而對 hTRPV1 無影響，而且 hTRPA1 在鎮痛藥的化合物中起到了重要的作用。

（王慧娟 譯，李士通 审校）

BACKGROUND: The transient receptor potential vanilloid 1 (TRPV1) and the transient receptor potential ankyrin 1 (TRPA1), which are expressed in sensory neurons, are polymodal nonselective cation channels that sense noxious stimuli. Recent reports showed that these channels play important roles in inflammatory, neuropathic, or cancer pain, suggesting that they may serve as attractive analgesic pharmacological targets. Tramadol is an effective analgesic that is widely used in clinical practice. Reportedly, tramadol and its metabolite (M1) bind to μ-opioid receptors and/or inhibit reuptake of monoamines in the central nervous system, resulting in the activation of the descending inhibitory system. However, the fundamental mechanisms of tramadol in pain control remain unclear. TRPV1 and TRPA1 may be targets of tramadol; however, they have not been studied extensively.

METHODS: We examined whether and how tramadol and M1 act on human embryonic kidney 293 (HEK293) cells expressing human TRPV1 (hTRPV1) or hTRPA1 by using a Ca²⁺ imaging assay and whole-cell patch-clamp recording.

RESULTS: Tramadol and M1 (0.01–10 μM) alone did not increase in intracellular Ca²⁺ concentration ([Ca²⁺]i) in HEK293 cells expressing hTRPV1 or hTRPA1 compared with capsaicin (a TRPV1 agonist) or the allyl isothiocyanate (AITC, a TRPA1 agonist), respectively. Furthermore, in HEK293 cells expressing hTRPV1, pretreatment with tramadol or M1 for 5 minutes did not change the increase in [Ca²⁺]i induced by capsaicin. Conversely, pretreatment with tramadol (0.1–10 μM) and M1 (1–10 μM) significantly suppressed the AITC-induced [Ca²⁺]i increases in HEK293 cells expressing hTRPA1. In addition, the patch-clamp study showed that pretreatment with tramadol and M1 (10 μM) decreased the inward currents induced by AITC.

CONCLUSIONS: These data indicate that tramadol and M1 selectively inhibit the function of hTRPA1, but not that of hTRPV1, and that hTRPA1 may play a role in the analgesic effects of these compounds.
Transmission Dynamics of Gram-Negative Bacterial Pathogens in the Anesthesia Work Area

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BACKGROUND: Gram-negative organisms are a major health care concern with increasing prevalence of infection and community spread. Our primary aim was to characterize the transmission dynamics of frequently encountered gram-negative bacteria in the anesthesia work area environment (AWE). Our secondary aim was to examine links between these transmission events and 30-day postoperative health care-associated infections (HCAIs).

METHODS: Gram-negative isolates obtained from the AWE (patient nasopharynx and axilla, anesthesia provider hands, and the adjustable pressure-limiting valve and agent dial of the anesthesia machine) at 3 major academic medical centers were identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and phenotypic analysis (analytical profile indexing). The top 5 frequently encountered genera were subjected to antibiotic disk diffusion sensitivity to identify epidemiologically related transmission events. Complete multivariable logistic regression analysis and binomial tests of proportion were then used to examine the relative contributions of reservoirs of origin and within- and between-case modes of transmission, respectively, to epidemiologically related transmission events. Analyses were conducted with and without the inclusion of duplicate transmission events of the same genera occurring in a given study unit.
(first and second case of the day in each operating room observed) to examine the potential effect of statistical dependency. Transmitted isolates were compared by pulsed-field gel electrophoresis to disease-causing bacteria for 30-day postoperative HCAIs.

RESULTS: The top 5 frequently encountered gram-negative genera included Acinetobacter, Pseudomonas, Brevundimonas, Enterobacter, and Moraxella that together accounted for 81% (767/945) of possible transmission events. For all isolates, 22% (167/767) of possible transmission events were identified by antibiotic susceptibility patterns as epidemiologically related and underwent further study of transmission dynamics. There were 20 duplicates involving within- and between-case transmission events. Thus, approximately 19% (147/767) of isolates excluding duplicates were considered epidemiologically related. Contaminated provider hand reservoirs were less likely (all isolates, odds ratio 0.12, 95% confidence interval 0.03-0.50, P = 0.004; without duplicate events, odds ratio 0.05, 95% confidence interval 0.01-0.49, P = 0.010) than contaminated patient or environmental sites to serve as the reservoir of origin for epidemiologically related transmission events. Within- and between-case modes of gram-negative bacilli transmission occurred at similar rates (all isolates, 7% between-case, 5.2% within-case, binomial P value 0.176; without duplicates, 6.3% between-case, 3.7% within-case, binomial P value 0.036). Overall, 4.0% (23/548) of patients suffered from HCAIs and had an intraoperative exposure to gram-negative isolates. In 8.0% (2/23) of those patients, gram-negative bacteria were linked by pulsed-field gel electrophoresis to the causative organism of infection. Patient and provider hands were identified as the reservoirs of origin and the environment confirmed as a vehicle for between-case transmission events linked to HCAIs.

CONCLUSIONS: Between- and within-case AWE gram-negative bacterial transmission occurs frequently and is linked by pulsed-field gel electrophoresis to 30-day postoperative infections. Provider hands are less likely than contaminated environmental or patient skin surfaces to serve as the reservoir of origin for transmission events.
BACKGROUND: Oral flora, blood-borne pathogens, and bacterial contamination pose a direct risk of infection to patients and health care workers. We conducted a study in a simulated operating room using a newly validated technology to determine whether the use of 2 sets of gloves, with the outer set removed immediately after endotracheal intubation, may reduce this risk.

METHODS: Forty-one anesthesiology residents (PGY 2-4) were enrolled in a study consisting of individual or group simulation sessions. On entry to the simulated operating room, the residents were asked to perform an anesthetic induction and tracheal intubation timed to approximately 6 minutes; they were unaware of the study design. Of the 22 simulation sessions, 11 were conducted with the intubating resident wearing single gloves, and 11 with the intubating resident using double gloves with the outer pair removed after verified intubation. Before the start of the scenario, we coated the lips and inside of the mouth of the mannequin with a fluorescent marking gel as a surrogate pathogen. After the simulation, an observer examined 40 different sites using a handheld ultraviolet light in the operating room to determine the transfer of surrogate pathogens to the patient and the patient’s environment. Residents who wore double gloves were instructed by a confederate nurse to remove the outer set immediately after completion of the intubation. Forty sites of potential intraoperative pathogen spread were identified and assigned a score.

RESULTS: The difference in the rate of contamination between anesthesiology residents who wore single gloves versus those with double gloves was clinically and statistically significant. The number of sites that were contaminated in the operating room when the intubating resident wore single gloves was 20.3 ± 1.4 (mean ± SE); the number of contaminated sites when residents wore double gloves was 5.0 ± 0.7 (P < 0.001).

CONCLUSIONS: The results of this study suggest that when an anesthesiologist wears 2 sets of gloves during laryngoscopy and intubation and then removes the outer set immediately after intubation, the contamination of the intraoperative environment is dramatically reduced.
Background: As a result of cost-containment efforts, preparation programs for outpatient surgery are currently not available to the majority of children and parents. The recent dramatic growth in the Internet presents a unique opportunity to transform how children and their parents are prepared for surgery. In this article, we describe the development of a Web-based Tailored Intervention for Preparation of parents and children undergoing Surgery (WebTIPS).

Development of Program: A multidisciplinary task force agreed that a Web-based tailored intervention consisting of intake, matrix, and output modules was the preferred approach. Next, the content of the various intake variables, the matrix logic, and the output content was developed. The output product has a parent component and a child component and is described in http://surgerywebtips.com/about.php. The child component makes use of preparation strategies such as information provision, modeling, play, and coping skills training. The parent component of WebTIPS includes strategies such as information provision, coping skills training, and relaxation and distraction techniques. A reputable animation and Web design company developed a secured Web-based product based on the above description.

Conclusions: In this article, we describe the development of a Web-based tailored preoperative preparation program that can be accessed by children and parents multiple times before and after surgery. A follow-up article in this issue of Anesthesia & Analgesia describes formative evaluation and preliminary efficacy testing of this Web-based tailored preoperative preparation program.

EN3427: A Novel Cationic Aminoindane with Long-Acting Local Anesthetic Properties

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BACKGROUND: Currently approved local anesthetic drugs provide relatively brief local anesthesia that is appropriate and even desirable in some settings, but an extended duration of action beyond their capabilities would be a distinct benefit in other clinical situations. We implemented a drug discovery program that sought to identify novel local anesthetic molecules that specifically demonstrated a long-acting, preferential action on nociceptor sensory afferents that expressed transient receptor potential (TRP) channels. The hypothesis we tested was whether relatively membrane-impermeant local anesthetic molecules could confer long-lasting anesthesia if neuronal access was facilitated by TRP channel activation. The current work describes in vivo studies on a lead molecule that emerged from the discovery program, EN3427, in several rodent pain models.

METHODS: Studies were performed on male Sprague-Dawley rats using 2 models of acute mechanical paw-pinch-evoked and pinprick-evoked nociceptive pain. Behavioral responses to noxious stimuli were assessed at baseline, that is, before any pharmacologic intervention, and at various timepoints after a single perisciatic or subcutaneous administration of either EN3427 alone or in combination with lidocaine. Paw withdrawal thresholds or cutaneous trunci reflexes were quantified, and pre-post drug values were compared statistically with analysis of variance followed by post hoc Dunnett multiple range test.

RESULTS: A single perisciatic injection of lidocaine (2%) produced relief of paw-pinch-evoked pain that was significantly different from baseline through to the 1-hour timepoint (Dunnett multiplicity-adjusted P = 0.0081), as assessed using paw withdrawal or vocalization end points. EN3427 (0.2%), in the same model, produced a long-lasting block, with pain thresholds being significantly above baseline through to the 18-hour timepoint (Dunnett multiplicity-adjusted P = 0.0002); the combination of EN3427 (0.2%) plus lidocaine (2%) produced even longer lasting analgesia, with pain thresholds being significantly above baseline through to the 24-hour timepoint (Dunnett multiplicity-adjusted P = 0.0073). Similar results were obtained with use of the pinprick approach. A single subcutaneous injection of lidocaine (2%) produced complete loss of sensation to cutaneous pinprick through 0.5 hours, but sensitivity thresholds were no different to baseline by the 1-hour timepoint, a similar injection of EN3427 alone (0.2%) produced a loss of sensation that was significantly different from baseline through the 8-hour timepoint (Dunnett multiplicity-adjusted P = 0.0045), and the combination of lidocaine (2%) plus EN3427 (0.2%) appeared to further enhance duration of analgesia, although this was significantly different from baseline only through the 10-hour timepoint (Dunnett multiplicity-adjusted P = 0.0048). Analgesic efficacy was dose related; using the combined injection approach, we found that increases in the dose of EN3427 with a fixed 2% lidocaine led to substantially extended analgesia and increasing doses of lidocaine combined with a fixed dose of EN3427 (0.2%) led to only modestly increased duration of action.

CONCLUSIONS: The present studies demonstrate that a new molecular entity, EN3427, produces effective and long-lasting analgesia in 2 rodent pain models. The analgesic effects of EN3427 are significantly longer-lasting than lidocaine and are further extended when EN3427 is combined with lidocaine. The results are discussed with respect to a possible lidocaine-mediated
TRP channel activation and facilitated neuronal access of EN3427, with subsequent entrapment conferring extended-duration efficacy.