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Anesth Analg May 2013 116:994-1000

背景：肌肉的神經刺激後衰減被普遍認為是由於神經末梢突觸前乙醯膽鹼受體（AchRs）被阻滯而產生的突觸前現象，而顫搐張力的降低被認爲是由於肌肉 AchRs 被阻滯而產生的突觸後效應。本研究通過使用具有特異性突觸前或突觸後效應的配體，考察衰減並非僅是一個突觸前現象的假設。

方法：給予大鼠肌注（2.5U）或靜注（12U）肉毒桿菌毒素（Botx），或僅靜脈注射 α-金環蛇毒素（α-BTX）後測定神經肌肉功能。同樣測定單獨靜脈注射二氫 β 刺桐定（DhβE，2mg/kg）及同時給予 α-BTX 後的急性神經肌肉效應。BTX 減少 Ach 的囊泡釋放，α-BTX 僅結合突觸前煙鹼樣 AchRs，而 DHβE 僅僅特異性結合突觸前 α3β2 AchRs。由於 Botx 即使在靜脈注射後 2h 內也缺乏急性效應，因此評估其肌注（0.6U）24h 後的神經肌肉效應，並與肌注 α-BTX（25 μg/kg）或肌注生理鹽水 24h 後的效應進行比較。對坐骨神經-脛骨肌施加四個成串電刺激和強直刺激進行神經肌肉效應的在體試驗。

結果：靜脈注射和肌注 Botx 後 2h 並未發現神經肌肉效應。靜脈注射 α-Botx 後幾分鐘內產生了顫搐抑制，並在 75%的基線顫搐張力時有顯著的衰減（P = 0.002）；這些效應持續至 2h 的觀察期結束。單純靜脈注射 DHβE 對單次顫搐刺激（P = 0.899）或四個成串電刺激（P = 0.394）並不產生顯著的變化，但顯著增強了靜脈注射 α-BTX 後的衰減（P = 0.001，75%基線顫搐張力時）。肌注 Botx 或 α-Botx 24 小時後，產生了單次顫搐和強直收縮張力的降低（P<0.0001），但 Botx 並未造成衰減，而 α-Botx 在注射後 24h 引起了顯著衰減（P<0.0001）。24h 後脛骨肌重量以及 AchRα1 亞單位的蛋白表達（western blots）在 Botx, α-BTX 和生理鹽水注射組之間無差別，但在去神經支配的肌肉中則增加（陽性對照）。
BACKGROUND: Nerve-stimulated fade in muscle is generally accepted as a prejunctional phenomenon mediated by block of prejunctional acetylcholine receptors (AChRs) at the nerve terminal, whereas decrease of twitch tension is considered a postjunctional effect due to block of muscle AChRs. Using ligands with specific pre- or postjunctional effects only, we tested the hypothesis that fade is not necessarily a prejunctional phenomenon.

METHODS: Neuromuscular function in rats was evaluated after IM (2.5 U) or IV (12.0 U) injection of botulinum toxin (Botx), or IV (250 μg/kg) α-bungarotoxin (α-BTX) alone. The acute neuromuscular effects of IV 2 mg/kg dihydro-β-erythroidine (DHβE), alone and in combination with α-BTX, were also tested. Botx decreases vesicular release of ACh, and α-BTX binds to postjunctional nicotinic AChRs only, whereas DHβE binds specifically to prejunctional α3β2 AChRs only. In view of the lack of acute effects of Botx even at 2 hours after IV injection, its neuromuscular effects were also evaluated at 24 hours after IM injection (0.6 U) and compared with IM injection of α-BTX (25 μg/kg) or saline also given 24 hours earlier. The sciatic nerve-tibialis muscle preparation, during train-of-four and tetanic stimulation, was used to test neuromuscular effects in vivo.

RESULTS: IV and IM Botx had no observable neuromuscular effects at 2 hours. IV α-BTX caused twitch depression within a few minutes, and significant fade (P = 0.002) at 75% of baseline twitch tension; these effects persisted until the end of the observation period of 2 hours. IV DHβE alone caused no significant change in single twitch (P = 0.899) or train-of-four ratio (P = 0.394), but significantly enhanced the fade of IV α-BTX (P = 0.001 at 75% of baseline twitch tension). IM Botx or α-BTX, at 24 hours after their injection, resulted in a significant decrease of single twitch and tetanic tensions (P < 0.0001), but Botx did not cause fade, whereas α-BTX caused significant (P < 0.0001) fade at 24 hours. The tibialis muscle weights and protein expression of α1 subunit of AChR (Western blots) did not differ between Botx, α-BTX and saline-injected groups at 24 hours but increased in denervated muscle (positive control).

CONCLUSIONS: Botx-induced decreased ACh release in and of itself does not cause fade but does cause decrease of absolute tensions. Decrease of available (functional) postjunctional AChRs by α-BTX did induce fade. The prejunctional fade effects of DHβE on α3β2 AChRs become manifest only when the margin of safety was decreased by concomitant administration of α-BTX. Thus, fade during repetitive stimulation is not always a prejunctional phenomenon and may also reflect the decreased margin of safety of neurotransmission, which can be due to a pure postjunctional AChRs block or to a combination of both pre- and postjunctional AChRs block. Block of prejunctional α3β2 AChRs alone is not necessary and sufficient to cause fade.
BACKGROUND: Inadvertent arterial placement of a large-bore catheter during attempted placement of a central venous catheter (CVC) occurs at a rate of 0.1% to 1.0% and may result in hemorrhage, pseudoaneurysm, stroke, or death. Ultrasound guidance or observation of color and pulsatility of blood are not reliable methods for avoiding this serious complication. Measurement of pressure in the needle or short plastic catheter before insertion of the guidewire has been shown to be highly reliable; however, traditional pressure measurement methodology is cumbersome. Recently a compact, sterile, single-use pressure transducer with an integrated digital display has become available. In this study, we evaluated the performance of this new device (Compass® Vascular Access).

METHODS: In this prospective, observational study at 4 academic medical centers 298 CVCs were placed. Pressure was measured using the Compass transducer before and after guidewire insertion. Other details of the procedure were at the discretion of the clinician. Data describing the CVC placement and any complications were collected.

RESULTS: Trainees placed 279 of 298 CVCs. Ultrasound guidance was used for 286 of 298 CVCs. Seven of the CVC placements occurred in the intensive care unit, with the balance occurring in the operating room. Ten of the CVCs were placed in a subclavian vein, with the balance being internal jugular vein. Two hundred seventy-four of 298 CVCs were placed on the
right side. Venous pressure measured before and after guidewire insertion was 7.2 ± 4.3 (SD) and 6.5 ± 4.3 (SD) mm Hg respectively \( (P = 0.03) \). The satisfaction score recorded by the physician performing the procedure was 8.0 ± 2.1 (SD; visual analog scale 1–10, 10 being most satisfying). There were 5 inadvertent arterial punctures (1.7%). Ultrasound guidance was used in all 5 cases of arterial puncture. All of the arterial punctures were recognized before guidewire insertion by measurement of arterial pressure with the Compass transducer. No guidewires or CVC catheters were placed in arteries.

**CONCLUSION:** The Compass pressure transducer for CVC placement performed as intended in 298 cases from 4 academic medical centers. There were 5 inadvertent arterial punctures despite the use of ultrasound guidance, all of which were correctly identified by pressure measurement using the Compass. The device was easily used by trainees, and users expressed a positive level of satisfaction.
experimental noxious stimulus increases pupillary diameter (PD) and pupillary light reflex amplitude (PLRA), the difference between PD before and after light stimulation. Labor pain is an intense acute nonexperimental stimulus, effectively relieved by epidural analgesia. In this prospective observational study, we therefore describe the effects of labor pain and pain relief with epidural analgesia on PD and PLRA, determine their association with pain intensity and determine the ability of a single measurement of PD or PLRA to assess pain.

METHODS: In the first stage, pain (11-point NRS), PD, and PLRA were measured in 4 conditions in 26 laboring women: before and after epidural analgesia and in the presence and absence of a uterine contraction. Pupillometry values among the 4 conditions were compared, and the strength of the association between absolute values of pain and PD or PLRA and between pain and changes in PD or PLRA brought about by uterine contraction was assessed with $r^2$. In the second stage, 1 measurement was performed in 104 laboring women. The strength of the association between pain and PD or PLRA was assessed with $r^2$. The ability of PD or PLRA to discriminate pain (NRS > 4) was also assessed.

RESULTS: In the first stage, a statistically significant increase in pain, PD, and PLRA was observed during a contraction, and this change was abolished after epidural analgesia. The $r^2$ for the association between pain and changes in PD ($r^2 = 0.25$ [95% confidence interval, 0.07–0.46]) or PLRA ($r^2 = 0.34$ [0.14–0.56]) brought about by a uterine contraction was higher than the $r^2$ for the association between pain and absolute values of PD ($r^2 = 0.14$ [0.04–0.28]) or PLRA ($r^2 = 0.22$ [0.10–0.37]) suggesting a stronger association for changes than for absolute values. In the second stage, $r^2$ was 0.23 [0.10–0.38] for PD and 0.26 [0.11–0.40] for PLRA and the area under the receiver operating characteristics curve was 0.82 [0.73–0.91] and 0.80 [0.71–0.89], respectively.

CONCLUSIONS: Changes in PD and PLRA brought about by a uterine contraction may be used as a tool to assess analgesia in noncommunicating patients.
Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, which are available as “over-the-counter” medications in most countries, are widely used by both pregnant and lactating women. They are popular non-opioid analgesics for the treatment of pain after vaginal and operative delivery. In addition, NSAIDs are used for tocolysis in premature labor, and low-dose aspirin has a role in the prevention of preeclampsia and recurrent miscarriage in antiphospholipid syndrome. NSAIDs and aspirin may affect fertility and increase the risk of early pregnancy loss. In the second trimester their use is considered reasonably safe, but has been associated with fetal cryptorchism. In the third trimester, NSAIDs and aspirin are usually avoided because of significant fetal risks such as renal injury, oligohydramnios, constriction of the ductus arteriosus (with potential for persistent pulmonary hypertension in the newborn), necrotizing enterocolitis, and intracranial hemorrhage. Maternal administration or ingestion of most NSAIDs results in low infant exposure via breastmilk, such that both cyclooxygenase-1 and cyclooxygenase-2 inhibitors are generally considered safe, and preferable to aspirin, when breastfeeding.

頭皮區域阻滯在開顱術後鎮痛中的應用：一項系統性回顧和 Meta 分析

Regional Scalp Block for Postcraniotomy Analgesia: A Systematic Review and Meta-Analysis

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背景：據報告多達三分之二的患者在顱腦手術後手術部位存在中重度疼痛，並且考慮到對神經系統評估的影響，通過全身應用阿片類藥物來治療疼痛是有所顧慮的。此外，關於神經外科可替代的鎮痛策略缺少共識和證據。頭皮區域阻滯（RSB）是一項成熟的技術，包括在定義的解剖部位做局部浸潤麻醉，作用於支配頭皮的主要感覺神經。然而，RSB 的降低術後疼痛的療效仍不清楚。這項研究試圖系統地確定和回顧關於 RSB 的隨機對照試驗（RCT）和通過一項定量薈萃分析對其有效性進行總體估計。

方法：在 MEDLINE, EMBASE 和 Cochrane 中心對試驗註冊資料庫檢索了所有關於評估 RSB 對開顱術後疼痛效果的隨機對照試驗。標題，摘要，論文由兩個獨立的審閱者甄別預定義入選標準而確定。兩位作者獨立評估相關研究和患者報告疼痛評分所提取資料的品質，鎮痛需求和 RSB 的併發症。疼痛評分用一個通用的 0 至 10 的區間來衡量，得分越高表明疼痛越劇烈。通過一個隨機・效應、逆方差、加權模型進行匯總療效的 Meta 分析；異質性由 I² 參數來量化。

結果：文獻檢索發現了 138 個獨立引文，來自 7 個隨機對照實驗總共 320 名符合納入標準的患者。所有的研究都使用標準的局麻藥物（利多卡因，布比卡因，或羅呱卡因）；其中有 3 個研究中的局麻藥聯合了腎上腺素。在 3 個研究中，RSB 是在術前進行的，其他 4 個研究中，RSB 是在手術切口關閉後進行。歸因於 RSB 的併發症未見報告。Meta 分析發現術後一小時組疼痛評分有總體下降（5 項研究；平均差，-1.61；95%可信區間，-2.06 至 -1.15；p<0.001; I²=0%）。術前 RSB 應用的亞組分析顯示手術結束後 2、4 和 6-8h 的疼痛評分顯著降低，而術後 RSB 應用可顯著降低術後 2、4、6-8 和 12h 的疼痛評分。雖然這
BACKGROUND: Up to two-thirds of patients report moderate to severe surgical site pain after craniotomy procedures, and there is understandable reluctance to manage these symptoms with systemic opioids that may impair neurological assessment. Furthermore, there is a lack of consensus and evidence concerning alternative analgesia strategies for cranial neurosurgery. Regional scalp block (RSB) is an established technique that involves infiltration of local anesthetic (LA) at well-defined anatomical sites targeting the major sensory innervation of the scalp. However, the efficacy of RSB in reducing postoperative pain remains unclear. In this study, we sought to systematically identify and review randomized controlled trials (RCTs) of RSB and synthesize an overall estimate of efficacy in a quantitative meta-analysis.

METHODS: Medline, EMBASE, and the Cochrane Central Register of Controlled Trials databases were searched for all RCTs evaluating the effect of RSB on postoperative pain after craniotomy. Titles, abstracts, and papers were reviewed independently by 2 authors against predefined inclusion criteria. Two authors independently assessed the quality of included studies and extracted data on patient-reported pain scores, other analgesia requirements, and complications of RSB. Pain scores were scaled to a common 0 to 10 interval with higher scores indicating more severe pain. Meta-analysis of the pooled treatment effect was performed with a random-effects inverse-variance weighted model; heterogeneity was quantified with the I² statistic.

RESULTS: The literature search identified 138 unique citations, from which 7 RCTs with a total recruitment of 320 patients met the inclusion criteria. All studies used standard LA drugs (lidocaine, bupivacaine, or ropivacaine); in 3 studies, LA was combined with epinephrine. In 3 studies, RSB was performed preoperatively; in the other 4 studies, it was administered postoperatively after wound closure. No complications attributable to RSB were reported. Meta-analysis found a pooled reduction in pain score at 1 hour postoperatively (N = 5 studies; mean difference, −1.61; 95% confidence interval, −2.06 to −1.15; P < 0.001; I² = 0%). Subgroup analysis of preoperative RSB showed significant reduction in pain scores at 2, 4, and 6 to 8 hours after surgery whereas postoperative RSB was associated with significant reduction in pain scores at 2, 4, 6 to 8 and 12 hours assessments. There was also an overall reduction in the opioid requirements over the first 24 hours postoperatively, although with significant heterogeneity among the studies (N = 6 studies; standardized mean difference, −0.79; 95% confidence interval, −1.55 to −0.03; P = 0.04; I² = 86%).

CONCLUSION: Published RCTs of RSB are small and of limited methodological quality but meta-analysis shows a consistent finding of reduced postoperative pain. This evidence supports the use of RSB for patients undergoing craniotomy.

特約評論：中世紀的伊斯蘭醫師對氣管切開術的歷史貢獻

Special Article: Contributions of Medieval Islamic Physicians to the History of Tracheostomy
Tracheostomy was first described by Greco-Roman physicians, including Paulus of Aegina. Medieval Islamic clinicians extended the Greco-Roman ideas with substantial contributions to the field of surgery, including tracheostomy. Although Al-Zahrawi (936–1013 CE) stated that he had not heard or read of any Islamic physicians having performed tracheostomy, there is evidence that many prominent Islamic surgeons did practice this lifesaving procedure during medieval times. Throughout the Islamic Golden Age, Muslim physicians advanced the practice of tracheostomy with many modifications of the procedure, instrumentation, and adjuvant medicinal prescriptions.

**SNAP5114--γ氨基丁酸轉運體3的抑制劑，在大鼠實驗性疼痛模型中的鎮痛作用**

The Antinociceptive Effect of SNAP5114, a Gamma-Aminobutyric Acid Transporter-3 Inhibitor, in Rat Experimental Pain Models

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**背景：γ 氨基丁酸（GABA）是哺乳動物中樞神經系統中主要的抑制性神經遞質。γ 氨基丁酸對調節脊髓背角痛覺有重要作用。通過特定的 γ氨基丁酸轉運體（GATs），將 γ氨基丁酸這種神經傳遞介質從突觸間隙快速攝取到神經元及膠質細胞中，終止此作用。四種GATs 中，GAT-3 的表達量最大，在與痛覺傳輸密切相關的中樞神經系統區域，包括脊髓。這項研究考察了鞘內注射 GAT-3 的選擇性抑制劑—SNAP5114,在急性、炎性和神經痛性實驗模型中的鎮痛作用。**
METHODS: Male Sprague-Dawley rats were used to assess thermal, mechanical, and chemical nociception in the tail flick and hotplate tests, the paw pressure test, and the formalin test. A rotarod test was performed to assess motor function. Chronic constriction injury to the sciatic nerve was induced in the rats. The electronic von Frey test and the plantar test were then performed to assess mechanical allodynia and thermal hyperalgesia. SNAP5114 (10, 50, 100, or 200 μg) was administered intrathecally to examine antinociceptive activity. To confirm whether the action of SNAP5114 was mediated by GABAergic transmission, the GABA_A receptor antagonist bicuculline (0.3 μg) or the GABA_B receptor antagonist CGP35348 (30 μg) was administered intrathecally before 200 μg of SNAP5114 in the tail flick test, the formalin test, and the electronic von Frey test.

RESULTS: Spinally applied SNAP5114 in normal rats dose-dependently prolonged withdrawal latencies in the tail flick test and suppressed the late-phase response in the formalin test. SNAP5114 did not affect motor performance. In the chronic constriction injury rats, SNAP5114 inhibited mechanical allodynia dose-dependently. The antinociceptive action of SNAP5114 was partially reversed by bicuculline or CGP35348 at doses at which the antagonist alone did not affect baseline behavioral responses.

CONCLUSIONS: These results suggest that SNAP5114 exerts antinociceptive effects by activating GABA_A and GABA_B receptors in the spinal cord. The GAT-3 inhibitor may prove useful in treatment of various painful conditions.
The impact of hypothermia on emergence from isoflurane anesthesia in orexin neuron-ablated mice.

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BACKGROUND: Orexin neurons regulate the sleep/wake cycle and are proposed to influence general anesthesia. In animal experiments, orexin neurons have been shown to drive emergence from general anesthesia. In human studies, however, the role of orexin neurons remains controversial, owing at least, in part, to the fact that orexin neurons are multifunctional. Orexin neurons regulate not only the sleep/wake cycle, but also body temperature. We hypothesized that orexin neurons do not directly regulate emergence from anesthesia, but instead affect emergence indirectly through thermoregulation because anesthesia-induced hypothermia can greatly influence emergence time. To test our hypothesis, we used simultaneous measurement of body temperature and locomotor activity.

METHODS: We used male orexin neuron-ablated (ORX-AB) mice and their corresponding wild-type (WT) littermates to investigate the role of orexin neurons in emergence. Body temperature was recorded using an intraperitoneally implanted telemetric probe, and locomotor activity was measured using an infrared motion sensor. Induction of anesthesia and emergence from anesthesia were defined behaviorally as loss and return, respectively, of body movement. Mice received general anesthesia with 1.5% isoflurane in 100% oxygen for 30 minutes under 3 conditions. In the first experiment, the anesthesia chamber was warmed (32°C), ensuring a constant body temperature of animals during anesthesia. In the second experiment, the anesthesia chamber was maintained at room temperature (25°C), allowing body temperature to fluctuate. In the third experiment in WT mice, the anesthesia chamber was cooled (23°C) so that their body
Results: In the warmed condition, there were no significant differences between the ORX-AB and control mice with respect to body temperature, locomotor activity, induction time, or emergence time. In the room temperature condition, however, anesthesia-induced hypothermia was greater and longer lasting in ORX-AB mice than that in WT mice. Emergence time in ORX-AB mice was significantly prolonged from the warmed condition (14.2 ± 0.8 vs 6.0 ± 1.1 minutes) whereas that in WT mice was not different (7.4 ± 0.8 vs 4.9 ± 0.2 minutes). When body temperature was decreased by cooling in WT mice, emergence time was prolonged to 12.4 ± 1.3 minutes. Induction time did not differ among temperature conditions or genotypes.

Conclusions: The effect of orexin deficiency to impair thermoregulation during general anesthesia is of sufficient magnitude that body temperature must be appropriately controlled when studying the role of orexin neurons in emergence from anesthesia.
metabolic side effects. But evidence that routine use of N2O causes clinically important toxicity remains elusive. We therefore evaluated the relationship between intraoperative N2O administration and 30-day mortality as well as a set of major inpatient postoperative complications (including mortality) in adults who had general anesthesia for noncardiac surgery.

**METHODS:** We evaluated 49,016 patients who had noncardiac surgery at the Cleveland Clinic between 2005 and 2009. Among 37,609 qualifying patients, 16,961 were given N2O ("nitrous," 45%) and 20,648 were not ("nonnitrous," 55%). Ten thousand seven hundred fifty nitrous patients (63% of the total) were propensity score-matched with 10,755 nonnitrous patients. Matched nitrous and nonnitrous patients were compared on 30-day mortality and a set of 8 in-hospital morbidity/mortality outcomes.

**RESULTS:** Inhalation of N2O intraoperatively was associated with decreased odds of 30-day mortality (odds ratio [OR]: 97.5% confidence interval, 0.67, 0.46-0.97; P = 0.02). Furthermore, nitrous patients had an estimated 17% (OR: 0.83, 0.74-0.92) decreased odds of experiencing major in-hospital morbidity/mortality than nonnitrous (P < 0.001). Among the individual morbidities, intraoperative N2O use was only associated with significantly lower odds of having pulmonary/respiratory morbidities (OR, 95% Bonferroni-adjusted CI: 0.59, 0.44-0.78).

**CONCLUSIONS:** Intraoperative N2O administration was associated with decreased odds of 30-day mortality and decreased odds of in-hospital mortality/morbidity. Aside from its specific and well-known contraindications, the results of this study do not support eliminating N2O from anesthetic practice.
BACKGROUND: Dexamethasone is widely used for postoperative nausea and vomiting (PONV) prophylaxis. However, there are limited data on the risk of wound complications associated with single-dose dexamethasone use for this purpose. We performed this retrospective study to determine whether intraoperative dexamethasone for PONV prevention increases the risk or severity of postoperative wound complications.

METHODS: Women who underwent laparotomy for endometrial cancer between 2002 and 2007 were identified from a tumor registry. Perioperative records were reviewed to determine dexamethasone administration. Medical records were reviewed to identify wound complications including cellulitis, superficial surgical site infection, wound separation, and fascial dehiscence. Wound care needs and time to complete wound healing were compared based on dexamethasone exposure. The rate of wound complications was also compared based on dexamethasone dose. Baseline characteristics and perioperative details were evaluated for independent associations with wound complications. Logistic regression analyses were performed to predict the occurrence of wound complications.

RESULTS: Four hundred thirty-one patients met inclusion criteria; 192 (44.6%) received dexamethasone (4-12 mg) and 31.1% developed a wound complication. In unadjusted analysis, there was no difference in the risk of developing a wound complication based on dexamethasone exposure; 53 of 192 patients (27.6%) who received dexamethasone developed a wound complication, compared with 81 of 239 (33.9%) who did not receive dexamethasone: odds ratio (OR) (95% confidence interval [CI]) = 0.74 (0.49, 1.13), P = 0.16. There was no difference in the distribution of wound complication types based on receipt of dexamethasone (P = 0.71), or in the incidence of wound complications based on the dose of dexamethasone (P = 0.48). Of patients who developed a wound complication, there was no difference in the need for IV antibiotics, vacuum-assisted wound closure, or in the rate of fascial dehiscence based on dexamethasone exposure. The time to complete wound healing was not different between the 2 cohorts (P = 0.48). In univariate analysis, higher body mass index (BMI), higher estimated blood loss, smoking, and longer duration of surgery were predictors of wound complications. Smoking (OR [95% CI]: 2.0 [1.3, 3.2], P = 0.003) and BMI (OR [95% CI]: 1.2 [1.1, 1.3], P = 0.0003) were the only significant predictors of wound complications in the multivariate model, whereas dexamethasone remained a nonsignificant predictor (OR [95% CI]: 0.7 [0.5, 1.1], P = 0.12).

CONCLUSION: Intraoperative dexamethasone for PONV prophylaxis does not seem to increase the rate or severity of postoperative wound complications in women undergoing laparotomy for
endometrial cancer. BMI and smoking were significant predictors of wound complications in this patient population.

Ryanodine Receptor Type 1 Gene Variants in the Malignant Hyperthermia-Susceptible Population of the United States

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BACKGROUND: Mutations in the ryanodine receptor type 1 gene (RYR1) that encodes the skeletal muscle-specific intracellular calcium (Ca(2+)) release channel are a cause of malignant hyperthermia (MH). In this study, we examined RYR1 mutations in a large number of North American MH-susceptible (MHS) subjects without prior genetic diagnosis. METHODS: RYR1 was examined in 120 unrelated MHS subjects from the United States in a tiered manner. The α-1 subunit of the dihydropyridine receptor gene (CACNA1S) was screened for 4 variants in subjects in whom no abnormality was found in ≥100 exons of RYR1. RESULTS: Ten known causative MH mutations were found in 26 subjects. Variants of uncertain significance in RYR1 were found in 36 subjects, 16 of which are novel. Novel variants in both
RYR1 and CACNA1S were found in the 1 subject who died of MH. Two RYR1 variants were found in 4 subjects. Variants of uncertain significance were found outside and inside the hotspots of RYR1. Maximal contractures in the caffeine-halothane contracture test were greater in those who had a known MH mutation or variant of uncertain significance in RYR1 than in those who did not.

CONCLUSIONS: The identification of novel RYR1 variants and previously observed RYR1 variants of uncertain significance in independent MHS families is necessary for demonstrating the significance of these variants for MH susceptibility and supports the need for functional studies of these variants. Continued reporting of the clinical phenotypes of MH is necessary for interpretation of genetic findings, especially because the pathogenicity of most of these genetic variants associated with MHS remains to be elucidated.

Review article: estimating surgical case durations and making comparisons among facilities: identifying facilities with lower anesthesia professional fees.
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Consumer-driven health care relies on transparency in cost estimates for surgery, including anesthesia professional fees. Using systematic narrative review, we show that providing anesthesia costs requires that each facility (anesthesia group) estimate statistics, reasonably the mean and the 90% upper prediction limit of case durations by procedure. The prediction limits need to be calculated, for many procedures, using Bayesian methods based on the log-normal distribution. Insurers and/or governments lack scheduled durations and procedures and cannot practically infer these estimates because of the large heterogeneities among facilities in the means and coefficients of variation of durations. Consequently, the insurance industry cannot provide the cost information accurately from public and private databases. Instead, the role of insurers and/or governments can be to identify facilities with significantly briefer durations (costs to the patient) than average. Such comparisons of durations among facilities should be
performed with correction for the effects of the multiple comparisons. Our review also has direct implications to the potentially more important issue of how to study the association between anesthetic durations and patient morbidity and mortality. When pooling duration data among facilities, both the large heterogeneity in the means and coefficients of variation of durations among facilities need to be considered (e.g., using "multilevel" or "hierarchical" models).

**Background:** An alternative technique involving a “distal approach” can be used for lumbar medial branch radiofrequency denervation (LMBRFD). We described and assessed this technique by comparing it with a conventional tunnel vision approach in a prospective randomized trial.

**Methods:** Eighty-two patients underwent LMBRFD by a distal (n = 41) or a tunnel vision approach (n = 41). The primary end point was a comparison of the mean difference in the change of 11-point numeric rating scale (NRS) scores of low back pain from entry to the scores at 1 month (NRS at baseline—NRS at 1 month) and at 6 months (NRS at baseline—NRS at 6 months) between the distal approach group and the tunnel vision approach group. The secondary end points were a change of NRS and the Oswestry disability index over time.
RESULTS: Thirty-four patients in each group had complete time courses. There were no statistically significant differences in the change of NRS scores between the groups at 1 month (corrected \( P = 0.19; 97.5\% \) 2-sided confidence interval [CI], \(-1.37 \) to \( 0.37 \)) and 6 months (corrected \( P = 0.53; 97.5\% \) CI, \(-1.36 \) to \( 0.77 \)). Patients in both groups showed a statistically significant reduction in NRS and Oswestry disability index scores from baseline to that of the scores at 1 and 6 months (corrected \( P < 0.0001; 97\% \) CI, \(-2.00 \) to \(-0.23 \)).

CONCLUSIONS: Patients who underwent LMBRFD by the tunnel vision or distal approaches showed significant pain relief at the 6-month follow-up. Less periprocedural pain was reported in the distal approach group. We consider that the distal approach provides an improved option for LMBRFD.

BACKGROUND: In this prospective, randomized, observer-blinded trial, we compared ultrasound-guided subparaneural popliteal sciatic nerve blocks performed either at or proximal to
the neural bifurcation (B). We hypothesized that the total anesthesia-related time (sum of performance and onset times) would be decreased with the prebifurcation (PB) technique.

METHODS: Ultrasound-guided posterior popliteal sciatic nerve block was performed in 68 patients. All subjects received an identical volume (30 mL) and mix of local anesthetic agent (1% lidocaine-0.25% bupivacaine-5 µg/mL epinephrine). In the PB group, the local anesthetic solution was deposited at the level of the common sciatic trunk, just distal to the intersection between its circular and elliptical sonographic appearances, inside the paraneural sheath. In the B group, the injection was performed inside the sheath between the tibial and peroneal divisions. A blinded observer recorded the success rate (complete tibial and peroneal sensory block at 30 minutes) and onset time. The performance time, number of needle passes, and adverse events (paresthesia, neural edema) were also recorded. All subjects were contacted 7 days after the surgery to enquire about the presence of persistent numbness or motor deficit.

RESULTS: Both techniques resulted in comparable success rates (85%-88%; 95% confidence interval [CI] of the intergroup difference, -14% to 19%) and required similar performance times (8.1 minutes; 95% CI of the difference, -1.65 to 1.71 minutes), onset times (15.0-17.7 minutes; 95% CI of the difference, -7.65 to 2.31 minutes), and total anesthesia-related times (23.4-26.0 minutes; 95% CI of the difference, -7.83 to 2.74 minutes). The number of needle passes and incidence of paresthesia (25%-34%) were also similar between the 2 groups. Sonographic neural swelling was detected in 2 and 3 subjects in the PB and B groups, respectively. In all 5 cases, the needle was carefully withdrawn and the injection completed uneventfully. Patient follow-up 1 week after the surgery revealed 2 patients with residual numbness. In both instances, the latter had resolved by 1 month.

CONCLUSION: When local anesthetic is injected inside the paraneural sheath, B and PB posterior popliteal sciatic nerve blocks result in comparable success and total anesthesia-related times. However, in light of the 95% CIs, we cannot exclude the possibility that an intergroup difference of 19% and 7.83 minutes might have gone undetected for success rate and total time, respectively.

Decreased Erythrocyte Deformability After Transfusion and the Effects of Erythrocyte Storage Duration

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背景：紅細胞在儲存時細胞膜會發生形態學上的改變，但不清楚這種改變是否可逆。我們評估患者輸血前後紅細胞膜的變形性來判定儲存時間的影響以及變形性的改變能否在輸血後可逆轉。

方法：16個進行後路脊椎融合術的病人納入本研究中。我們對那些需要中等輸血量（≥5個單位紅細胞）的病人和那些需要少量輸血（0—4個單位紅細胞）的病人進行紅細胞變形性的比較。分別測定輸血前直接從儲血袋中取出來的血樣本、病人的血樣本以及病人輸
血後的血樣本（術後3天）的紅細胞變形性。對於從儲血袋中提取的血樣本，我們比較了長時間儲存的紅細胞（≥21天）、短時間儲存的紅細胞（<21天）以及自體血回收的紅細胞的變形性。變形能力是使用細胞變形計量法測出的延伸指數定量評估的，這是一種測定細胞在剪切應力下延伸能力的方法。

結果：病人在輸入中等血量之後，其紅細胞變形性較術前基線顯著下降（EI下降了12% ± 4%到20% ± 6%; P = 0.03），但輸小量血後無變化（EI下降了3% ± 1%到4% ± 1%; P = 0.68）。且此些改變術後3天不能恢復。保存時間≥21天的紅細胞變形性（EI = 0.28 ± 0.02）明顯差於保存時間<21天的（EI = 0.33 ± 0.02; P = 0.001）或是病人術前採集的紅細胞變形性（EI = 0.33 ± 0.02; P = 0.001）。回收血紅細胞變形性處於中間水準（EI = 0.30 ± 0.03），好於保存時間≥21 天的儲存血（P = 0.047），但差於保存時間<21天的儲存血（P = 0.03）。

結論：本研究證實紅細胞保存時間的延長與其細胞膜變形性的下降相關，並且這種改變在輸血後很難逆轉。

（王慧娟譯 馬皓琳 李士通 校）

BACKGROUND: Erythrocyte cell membranes undergo morphologic changes during storage, but it is unclear whether these changes are reversible. We assessed erythrocyte cell membrane deformability in patients before and after transfusion to determine the effects of storage duration and whether changes in deformability are reversible after transfusion.

METHODS: Sixteen patients undergoing posterior spinal fusion surgery were studied. Erythrocyte deformability was compared between those who required moderate transfusion (≥5 units erythrocytes) and those who received minimal transfusion (0–4 units erythrocytes). Deformability was measured in samples drawn directly from the blood storage bags before transfusion and in samples drawn from patients before and after transfusion (over 3 postoperative days). In samples taken from the blood storage bags, we compared deformability of erythrocytes stored for a long duration (≥21 days), those stored for a shorter duration (<21 days), and cell-salvaged erythrocytes. Deformability was assessed quantitatively using the elongation index (EI) measured by ektacytometry, a method that determines the ability for the cell to elongate when exposed to shear stress.

RESULTS: Erythrocyte deformability was significantly decreased from the preoperative baseline in patients after moderate transfusion (EI decreased by 12% ± 4% to 20% ± 6%; P = 0.03) but not after minimal transfusion (EI decreased by 3% ± 1% to 4% ± 1%; P = 0.68). These changes did not reverse over 3 postoperative days. Deformability was significantly less in erythrocytes stored for ≥21 days (EI = 0.28 ± 0.02) than in those stored for <21 days (EI = 0.33 ± 0.02; P = 0.001) or those drawn from patients preoperatively (EI = 0.33 ± 0.02; P = 0.001). Cell-salvaged erythrocytes had intermediate deformability (EI = 0.30 ± 0.03) that was greater than that of erythrocytes stored ≥21 days (P = 0.047), but less than that of erythrocytes stored <21 days (P = 0.03).

CONCLUSIONS: The findings demonstrate that increased duration of erythrocyte storage is associated with decreased cell membrane deformability and that these changes are not readily reversible after transfusion.

基於主動脈流速度和外周動脈壓力分佈圖的一種微創心輸出量監測系統
A Minimally Invasive Monitoring System of Cardiac Output Using Aortic Flow Velocity and Peripheral Arterial Pressure Profile
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BACKGROUND: In managing patients with unstable hemodynamics, monitoring cardiac output (CO) can provide critical diagnostic data. However, conventional CO measurements are invasive, intermittent, and/or inaccurate. The purpose of this study was to validate our newly developed CO monitoring system.

METHODS: This system automatically determines peak velocity of the ascending aortic flow using continuous-wave Doppler transthoracic echocardiography and estimates cardiac ejection time and aortic cross-sectional area using the pulse contour of the radial arterial pressure. These parameters are continuously processed to estimate CO (CO\text{est}). In 10 anesthetized closed-chest dogs instrumented with an aortic flowprobe to measure reference CO (CO\text{ref}), hemodynamic conditions were varied over wide ranges by infusing cardiovascular drugs or by random atrial pacing. Under each condition, CO\text{ref} and CO\text{est} were determined. Absolute changes of CO\text{ref} (ΔCO\text{ref}) and CO\text{est} (ΔCO\text{est}), and relative changes of CO\text{ref} (%ΔCO\text{ref}) and CO\text{est} (%ΔCO\text{est}) from the corresponding baseline values were determined in each animal. We calibrated CO\text{est} against CO\text{ref} to obtain proportionally scaled CO\text{est} (CO\text{est}\text{N}).

RESULTS: A total of 1335 datasets of CO\text{ref} and CO\text{est} were obtained, in which CO\text{ref} ranged from 0.17 to 5.34 L/min. Bland–Altman analysis between CO\text{ref} and CO\text{est} indicated that the limits of agreement (the bias ± 1.96 × SD of the difference) and the percentage error (1.96 × [SD of the difference]/[mean CO] × 100) were from −1.01 to 1.13 L/min (95% confidence interval,
−1.76 to 1.88 L/min) and 43%, respectively. The agreement between CO$_{\text{ref}}$ and CO$_{\text{est}}^N$ was improved, with limits of agreement from −0.53 to 0.49 L/min (95% confidence interval, −0.62 to 0.59 L/min) and the percentage error of 20%. Polar plot analysis between ΔCO$_{\text{ref}}$ and ΔCO$_{\text{est}}$ indicated that mean ± 1.96 × SD of polar angle was −2° ± 22°. Four quadrant plot analysis indicated that %ΔCO$_{\text{est}}$ correlated tightly with %ΔCO$_{\text{ref}}$ ($R^2 = 0.93$). The %ΔCO$_{\text{est}}$ and %ΔCO$_{\text{ref}}$ changed in the same direction in 95% of the datasets. Reliability of this system was well preserved under conditions of random atrial pacing and also in a continuous manner.

**CONCLUSION:** Over a wide range of hemodynamic conditions, irrespective of cardiac beat irregularity, this system may allow minimally invasive monitoring of CO with a good trending ability. The present results warrant further research and development of this system for future clinical application.

**POISE 試驗中氧化亞氮與嚴重的發病率及死亡率**

*Nitrous Oxide and Serious Morbidity and Mortality in the POISE Trial*

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BACKGROUND: In this post hoc subanalysis of the Perioperative Ischemic Evaluation (POISE) trial, we sought to determine whether nitrous oxide was associated with the primary composite outcome of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal cardiac arrest within 30 days of randomization.

METHODS: The POISE trial of perioperative β-blockade was undertaken in 8351 patients. Nitrous oxide anesthesia was defined as the coadministration of nitrous oxide in patients receiving general anesthesia, with or without additional neuraxial blockade or peripheral nerve blockade. Logistic regression, with inverse probability weighting using estimated propensity scores, was used to determine the association of nitrous oxide with the primary outcome, MI, stroke, death, and clinically significant hypotension.

RESULTS: Nitrous oxide was administered to 1489 (29%) of the 5133 patients included in this analysis. Nitrous oxide had no significant effect on the risk of the primary outcome (112 [7.5%] vs 248 [6.9%]; odds ratio [OR], 1.08; 95% confidence interval [CI], 0.82–1.44; 99% CI, 0.75–1.57; P = 0.58), MI (89 [6.0] vs 204 [5.6]; OR, 0.99; 95% CI, 0.75–1.31; 99% CI, 0.69–1.42; P = 0.94), stroke (6 [0.4%] vs 28 [0.8%]; OR, 0.85; 95% CI, 0.26–2.82; 99% CI, 0.17–4.11; P = 0.79), death (40 [2.7%] vs 100 [2.8%]; OR, 1.04; 95% CI, 0.6–1.81; 99% CI, 0.51–2.15; P = 0.51) or clinically significant hypotension (219 [14.7%] vs 544 [15.0%]; OR, 0.92; 95% CI, 0.74–1.15; 99% CI, 0.70–1.23; P = 0.48).

CONCLUSIONS: In this post hoc subanalysis, nitrous oxide was not associated with an increased risk of adverse outcomes in the POISE trial patients. This analysis was limited by the observational nature of the data and the lack of information on the concentration and duration of nitrous oxide administration. Further randomized controlled trial evidence is required.

妊娠期高血壓患者的動脈順應性改變與先兆子癇相關
Altered Arterial Compliance in Hypertensive Pregnant Women Is Associated with Preeclampsia
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BACKGROUND: Vascular alterations are present in pregnant women affected by preeclampsia. In this study, we assessed arterial compliance in women affected by hypertensive disorders of pregnancy. We hypothesized that arterial compliance is reduced in women affected by preeclampsia.

METHODS: Forty-three hypertensive pregnant women undergoing evaluation for preeclampsia were studied. Clinical data about each patient and pregnancy were collected. Large (C1) and small (C2) artery compliance were assessed by radial tonometry, while the patients underwent laboratory tests to diagnose preeclampsia. At the time of delivery, gestational age and newborn data were recorded.

RESULTS: Eighteen women were diagnosed with preeclampsia. C2 levels were lower among preeclamptic versus hypertensive aprotinuric women (mean ± SD, 4.5 ± 1.3 vs 5.9 ± 2.3 mL/mm Hg · 100, P = 0.013, 95% confidence interval [CI] of difference 0.32–2.55), whereas C1 levels did not differ. In the preeclampsia group, C2 levels correlated with urine total protein concentrations measured the same day (Spearman ρ = −0.49, P = 0.047, upper 95% CI −0.01) and with gestational age at first occurrence of hypertension (Spearman ρ = 0.59, P = 0.010, lower 95% CI 0.17). Among singleton gestations, C2 also correlated with newborn birth weight measured at delivery (Spearman ρ = 0.43, P = 0.009, lower 95% CI 0.11). Women who were...
hypertensive but aprotinin at the time of compliance assessment, but who subsequently developed preeclampsia (n = 6), had C2 levels similar to those with an early diagnosis of preeclampsia (mean difference 0.37 mL/mm Hg · 100, 95% CI −2.42 to 1.67) and lower C2 levels than women diagnosed with gestational hypertension (P = 0.019, 95% CI 0.33–4.42 mL/mm Hg · 100).

CONCLUSIONS: The noninvasive assessment of arterial elasticity may contribute toward characterization of the nature of the pathophysiology in pregnancy-induced hypertensive disorders. The vascular alterations of the small arteries, as assessed by C2, may reflect the extent of vascular alterations present with preeclampsia.

在預料靜脈通路開放困難的嬰兒和兒童中，靜脈可視血管成像系統使有經驗護士的首次嘗試置管成功率降低

The VeinViewer Vascular Imaging System Worsens First-Attempt Cannulation Rate for Experienced Nurses in Infants and Children with Anticipated Difficult Intravenous Access

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BACKGROUND: The VeinViewer (Luminetx, Memphis, TN) helps identify veins by projecting an image of subcutaneous vasculature on the skin surface. We tested the primary hypothesis that VeinViewer use improves cannulation success by skilled nurses in pediatric patients with anticipated difficult IV access. A secondary goal was to evaluate the relationship between obesity and cannulation success.
METHODS: Patients aged 0 to 18 years were included. Anticipated cannulation difficulty was evaluated with the difficult IV access score. All cannulations were performed by members of the Intravenous Access Team. Patients were randomized to: (1) routine IV catheter insertion; or (2) insertion facilitated by the VeinViewer. The primary outcome was first-attempt insertion success. The proportion of successful insertions was evaluated using Cochran-Mantel-Haenszel $\chi^2$ analysis to adjust for any imbalanced baseline variables. The effect of obesity on cannulation success was evaluated with multivariable logistic regression.

RESULTS: Two hundred ninety-nine patients (49%) were randomly assigned to VeinViewer and 301 (51%) to routine cannulation. First-attempt cannulation success was 47% in patients assigned to VeinViewer vs 62% in patients assigned to routine cannulation, with an adjusted relative “risk” (95% confidence interval), of 0.76 (0.63–0.91). The Z-statistic of $-3.6$ crossed the “harm” boundary ($Z < -2.41$), with corresponding $P$ value of 0.0003. The trial was stopped on statistical grounds since the harm boundary for the primary outcome was crossed. There was no association between first-attempt success and the 4-level categorization of obesity after adjusted for baseline variables ($P = 0.94$).

CONCLUSIONS: The VeinViewer worsened first-attempt IV insertion success by skilled nurses. Surprisingly, first-attempt success for IV cannulation was not worsened by obesity.

糖尿病和非糖尿病患者在非心臟大手術中的高血糖反應和甾類藥物的附加作用

The Hyperglycemic Response to Major Noncardiac Surgery and the Added Effect of Steroid Administration in Patients With and Without Diabetes

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背景：目前尚不清楚手術應激所致高血糖反應的模式和程度、低劑量甾類藥物的附加作用，以及這些情況在糖尿病和非糖尿病患者中是否存在差異。因此，本研究旨在驗證如下兩個假說：(1) 糖尿病患者從術前到術中的血糖濃度升高比非糖尿病患者更明顯；(2) 給予甾類藥物增進了術中血糖升高，在糖尿病患者比非糖尿病患者更明顯。

方法：研究納入物件為擇期在全麻下行非心臟大手術的患者，根據糖尿病診斷分層，隨機接受術前 8mg 地塞米松或安慰劑靜脈注射。患者為一項更大型試驗(地塞米松、淺麻醉和嚴格血糖控制[DeLiT]試驗)的一部分。當血糖濃度大於 215 mg/dL 時給予靜脈胰島素注射。主要測量指標為從術前到術中最大血糖濃度時的血糖變化。本研究也報導了術中血糖升高的時間依賴性模式。

結果：患者隨機分組，90 例患者 (23% 患有糖尿病) 給予地塞米松，95 例患者 (29% 患有糖尿病) 給予安慰劑。從術前血糖濃度到術中最大血糖濃度的變化均數±標準差在糖尿病患者為 63 ± 69 mg/dL，在非糖尿病患者為 72 ± 45 mg/dL。非糖尿病患者的平均變數調整後變化值 (95%可信區間) 比糖尿病患者高 29 (13, 46) mg/dL ($P < 0.001$)。對所有患者而言，平均血糖在從術前至切皮時升高輕微，從切皮至手術中點升高顯著，此後維持在高水準且在蘇醒過程中相當穩定，非糖尿病患者血糖升高更明顯 ($P < 0.001$)。非糖尿病患者給予地塞米松後平均血糖濃度增加值 (97.5%可信區間) 比給予安慰劑後高 29 (9, 49) mg/dL ($P = 0.0012$)。但糖尿病患者中無地塞米松效應。
結論：對於術中高血糖的治療，應考慮不同手術階段的高血糖手術應激反應趨勢和甾類藥物的附加效應。為了避免高血糖反應而拒絕使用甾類藥物預防術後噁心嘔吐的行為，必須根據甾類藥物對術中血糖濃度的有限作用而重新考慮。

（陳彬彬 譯，馬皓琳、李士通 审校）

BACKGROUND: The pattern and magnitude of the hyperglycemic response to surgical stress, the added effect of low-dose steroids, and whether these differ in diabetics and nondiabetics remain unclear. We therefore tested 2 hypotheses: (1) that diabetics show a greater increase from preoperative to intraoperative glucose concentrations than nondiabetics; and (2) that steroid administration increases intraoperative hyperglycemia more so in diabetics compared with nondiabetics.

METHODS: Patients scheduled for major noncardiac surgery under general anesthesia were enrolled and randomized to preoperative IV 8 mg dexamethasone or placebo, stratified by diagnosis of diabetes. Patients were part of a larger underlying trial (the Dexamethasone, Light Anesthesia and Tight Glucose Control [DeLiT] Trial). IV insulin was given when glucose concentration exceeded 215 mg/dL. The primary outcome measure was the change in glucose from the preoperative to maximal intraoperative glucose concentration. We also report the time-dependent pattern of intraoperative hyperglycemia.

RESULTS: Ninety patients (23% with diabetes) were randomized to dexamethasone, and 95 (29% with diabetes) were given placebo. The mean ± SD change from preoperative to maximal intraoperative glucose concentration was 63 ± 69 mg/dL in diabetics and 72 ± 45 mg/dL in nondiabetics. The mean covariable-adjusted change (95% confidence interval) in nondiabetics was 29 (13, 46) mg/dL more than in diabetics (P < 0.001). For all patients combined, mean glucose increased slightly from preoperative to incision, substantially from incision to surgery midpoint, and then remained high and fairly stable through emergence, with nondiabetic patients showing a greater increase (P < 0.001). For nondiabetics, the mean increase in glucose concentration (97.5% CI) was 29 (9, 49) mg/dL more in patients given dexamethasone than placebo (P = 0.0012). However, there was no dexamethasone effect in diabetics (P = 0.99).

CONCLUSIONS: Treatment of intraoperative hyperglycemia should account for the hyperglycemic surgical stress response trend depending on the stage of surgery as well as the added effects of steroid administration. Denying steroid prophylaxis for postoperative nausea and vomiting for fear of hyperglycemic response should be reconsidered given the limited effect of steroids on intraoperative blood glucose concentrations.
The use of local anesthetics to reduce acute postoperative pain has a long history, but recent reports have not been systematically reviewed. In addition, the need to include only those clinical studies that meet minimum standards for randomization and blinding must be adhered to. In this review, we have applied stringent clinical study design standards to identify publications on the use of perioperative local anesthetics. We first examined several types of peripheral nerve blocks, covering a variety of surgical procedures, and second, we examined the effects of intentionally administered IV local anesthetic (lidocaine) for suppression of postoperative pain. Thirdly, we have examined publications in which vascular concentrations of local anesthetics were measured at different times after peripheral nerve block procedures, noting the incidence when those levels reached ones achieved during intentional IV administration. Importantly, the very large number of studies using neuraxial blockade techniques (epidural, spinal) has not been included in this review but will be dealt with separately in a later review. The overall results showed a strongly positive effect of local anesthetics, by either route, for suppressing postoperative pain scores and analgesic (opiate) consumption. In only a few situations were the effects equivocal. Enhanced effectiveness with the addition of adjuvants was not uniformly apparent. The differential benefits between drug delivery before, during, or immediately after a surgical procedure are not obvious, and a general conclusion is that the significant antihyperalgesic effects occur when the local anesthetic is present during the acute postoperative period, and its presence during surgery is not essential for this action.