SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
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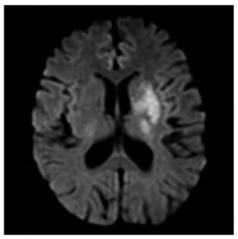
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Outcomes after endovascular therapy with procedural sedation vs general anesthesia in patients with acute ischemic stroke: The AMETIS randomized clinical trial. JAMA Neurol 2023; 80:474–83. PMID: 37010829.

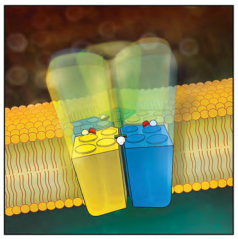
The optimal regimen for sedation of patients undergoing mechanical thrombectomy after acute ischemic stroke has not been delineated. This open-label, blinded endpoint, randomized trial (10 French university centers; between 2017 and 2020) evaluated use of procedural sedation or general anesthesia for this procedure. The primary outcome was a composite of functional independence at 90 days (no neurologic disability [score 0] to death [score 6]) and major periprocedural complications at day 7 including myocardial infarction, cardiogenic acute pulmonary edema, pneumonia, progression to malignant stroke, and procedure-related serious adverse events. Two hundred seventy-three patients undergoing internal carotid artery and/or proximal middle cerebral artery thrombectomy were enrolled (52% female; mean ± SD age, 72 ± 14 yr). There was no difference in the primary outcome between groups (28% general anesthesia *vs.* 36% sedation; absolute difference, 8.1 percentage points; 95% CI, –2.3 to 19.1; $P = 0.15$). In the general anesthesia group, 33% achieved functional independence *versus* 39% in the procedural sedation group (relative risk, 1.18; 95% CI, 0.86 to 1.61; $P = 0.32$). Periprocedural complications were comparable (66% *vs.* 67% respectively; relative risk, 1.02; 95% CI, 0.86 to 1.21; $P = 0.80$). *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

Take home message: This multicenter randomized trial of patients with large vessel occlusion acute ischemic stroke undergoing anterior circulation thrombectomy demonstrated comparable outcome between use of general anesthesia or procedural sedation with regard to functional independence including death, as well as periprocedural complications.

The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): An international, multicentre, pragmatic, registry-based randomised trial. Lancet 2023; 401:568–76. PMID: 36708732.

Survivors of critical illness develop protein malnutrition, which is associated with worse outcomes, but nutrition guidelines for protein dosing vary widely and are based on low-quality evidence. This international, pragmatic, single-blinded, randomized trial (85 intensive care units [ICUs] in 16 countries), enrolled 1,329 critically ill adult patients at risk for malnutrition and receiving mechanical ventilation between January 2018 and December 2021. Subjects were randomized to isocaloric nutrition with high-dose (more than 2.2 g/kg per day) or usual-dose (less than 1.2 g/kg per day) protein, which was continued up to 28 days, death, or transition to oral feeds. The primary outcome, time to discharge alive from hospital 60 days after ICU admission, was not different between high-dose and usual-dose groups (hazard ratio, 0.91; 95% CI, 0.77 to 1.07; $P = 0.27$). The secondary outcome, mortality at 60 days, was not different between high-dose and usual-dose (35% *vs.* 32%, respectively; relative risk, 1.08; 95% CI, 0.92 to 1.26). Subgroup analysis showed that high-dose protein was worse in patients with baseline acute kidney injury or higher organ failure scores. *(Article Selection: William G. Tharp, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: In this large-scale randomized trial in ventilated critically ill patients, high-dose protein did not improve time to discharge alive and may worsen outcomes in patients with acute kidney injury or high organ failure scores.



Control of contextual memory through interneuronal a5-GABA$_A$ receptors. PNAS Nexus 2023; 2:pgad065. PMID: 37056471.

Previous studies have posited that γ-aminobutyric acid type A (GABA$_A$) receptors containing a5 subunits, located on pyramidal neurons in the hippocampus, are implicated in the control of learning or memory. Utilizing neuronal cell–specific genetic knockouts of a5 subunit–containing GABA$_A$ receptors and innovative methods of cortical fluorescent calcium imaging in mice undergoing behavioral testing, this study demonstrates a critical role for these receptors on interneurons. Mice genetically deficient in a5 subunit–containing GABA$_A$ receptors in pyramidal neurons continue to form strong spatial engrams and are sensitive to etomidate suppression of place cells, a specialized pyramidal neuron in the hippocampus that becomes active when an animal enters a particular place. In contrast, mice genetically deficient in a5 subunit–containing interneurons no longer demonstrate etomidate-induced suppression of place cells and the strength of spatial engrams is reduced compared to control mice. Mice genetically deficient in a5 subunit–containing GABA$_A$ receptors in either interneurons or pyramidal neurons were resistant to etomidate's suppression of fear conditioning, suggesting that extra-hippocampal regions may contribute to contextual fear memory. The role of either neuronal subtype in contextual fear memory or the partial attenuation of place cell formation in GABA$_A$ a5-knockout interneuron mice suggests that etomidate's effect on memory may derive from contributions from both neuronal subtypes. *(Article Selection: Charles Emala, M.D. Image: J. P. Rathmell.)*

Take home message: Probing the function of a5 subunit–containing GABA$_A$ receptors using etomidate challenges the dogma that these receptors on hippocampal pyramidal neurons alone are implicated in the control of learning and memory, and instead implicate a critical role for these receptors located on interneurons in these cognitive processes. A better understanding of the role of a5 subunits on GABA$_A$ receptors on specific cell types in specific brain regions may guide therapeutics for a wide range of cognitive pathologies that involve memory and learning.

Randomized controlled trial of intrathecal oxytocin on speed of recovery after hip arthroplasty. Pain 2023; 164:1138–47. PMID: 36448974.

Intrathecal oxytocin has been shown to produce analgesia and to favor recovery after injury in animal models. This randomized controlled trial of adult patients undergoing primary unilateral total hip arthroplasty tested the hypothesis that intrathecal oxytocin (100 μg) at the time of surgery would speed recovery from postoperative pain. The primary outcome was the modeled trajectory in worst daily pain over the first 8 weeks after surgery evaluated *via* electronic diary. Secondary outcomes included postoperative opioid consumption and the speed of recovery in activity as measured by step numbers assessed *via* an electronic diary and accelerometer. A total of 90 patients completed the study (which was stopped early due to funding issues and COVID-19 short of the projected target of 120 patients) assigned to either intrathecal oxytocin (n = 44) or placebo (n = 46). Regarding the worst daily pain after surgery (primary outcome), no difference was observed between the groups. In a subset of patients (n = 23) receiving preoperative opioids, those who received oxytocin (n = 11) stopped using opioids faster after surgery than those receiving placebo. In addition, the oxytocin patients reported an increase in the daily step count over time (slope, 344 [95% CI, 173 to 515 daily steps · $\ln(\text{time})^{-1}$], $P > 0.001$). *(Article Selection: Cyril Rivat, Ph.D. Image: Adobe Stock.)*

Take home message: This prospective single-center analysis reported no effect of intrathecal oxytocin for the reduction of postsurgical pain after hip replacement surgery. Improvement in select secondary outcomes suggests the need for further study.

Hydrocortisone in severe community-acquired pneumonia. N Engl J Med 2023; 388:1931–41. PMID: 36942789.

It is uncertain whether glucocorticoids decrease mortality in patients with severe community-acquired pneumonia. In a double-blind randomized controlled trial, 800 adults in 31 French hospitals admitted to intensive care units with severe community-acquired pneumonia received 200 mg IV hydrocortisone daily for 4 or 8 days as determined by clinical improvement, then tapering for a total of 8 or 14 days or a placebo. All patients received standard antibiotics and supportive care. The primary outcome was death at 28 days. A battery of secondary outcomes was evaluated. Data from 795 patients were analyzed when the trial was stopped after the second planned interim analysis. A statistically significant decrease in the primary outcome was noted in the hydrocortisone group (6%; 95% CI, 3.9 to 8.6 *vs.* 12%; 95% CI, 8.7 to 15.1; absolute difference, −5.6 percentage points; 95% CI, −9.6 to −1.7; $P = 0.006$). Of the secondary outcomes, fewer patients receiving hydrocortisone not ventilated at baseline were intubated (18% *vs.* 30%; hazard ratio, 0.59; 95% CI, 0.40 to 0.86); vasopressor use was lower (15% *vs.* 25%; hazard ratio, 0.59; 95% CI, 0.43 to 0.82). Hospital-acquired infections and gastrointestinal bleeding were similar. Patients receiving hydrocortisone required higher doses of insulin in the first week of treatment. *(Article Selection: BobbieJean Sweitzer, M.D. Image: Adobe Stock.)*

Take home message: In this multicenter randomized trial, hydrocortisone significantly lowered the risk of death in patients with severe community-acquired pneumonia relative to placebo within 28 days.

Immobility-associated thromboprotection is conserved across mammalian species from bear to human. Science 2023; 380:178–87. PMID: 37053338.

With an incidence rate of 2 per 1,000 persons per year, venous thromboembolism (VTE) substantially contributes to global disease burden. VTE is an inflammatory process, which occurs in sterile and infectious states. While VTE is common with acute immobilization, the incidence of VTE in chronic immobilization owing to spinal cord injury equals that observed in the general population. In this translational study, the mechanism underlying thromboprotection during chronic immobilization was investigated in hibernating brown bears, which rarely suffer from VTE despite months of immobilization during hibernation. It was found that platelets from hibernating bears exhibit an antithrombotic signature, namely a decreased expression of heat shock protein 47 (HSP47) compared with those of active brown bears. Bone marrow chimeric mice with platelet-specific deletion of HSP47 were generated and subjected to venous flow restriction, confirming substantial reduction in thrombus frequency and size compared to controls. Subsequent *in vitro* studies revealed activation of neutrophils by HSP47 through a TLR2–myeloid differentiation primary-response protein 88 (MyD88)–dependent pathway. Additional study confirmed inhibition of platelet-neutrophil aggregate formation in the presence of HSP47-specific small molecule inhibitors. In human studies, HSP47 downregulation was confirmed in chronically immobilized patients with spinal cord injury and directly correlated with thrombogenicity. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: HSP47 is a promising target to protect against VTE in immobilized patients. This antithrombotic mechanism is evolutionarily conserved across species and thus may protect in other thrombogenic environments such as cancer or coagulation disorders.

Hypotension-avoidance versus hypertension-avoidance strategies in noncardiac surgery: An international randomized controlled trial. Ann Intern Med 2023; 176:605–14. PMID: 37094336.

The optimal targets for intraoperative blood pressure and perioperative management of chronic antihypertensive medications remain controversial. As part of a multicenter (110 centers, 22 countries) 2 × 2 factorial study, the POISE-3 investigators randomized 7,490 at-risk patients on at least one antihypertensive medication undergoing noncardiac surgery to either a hypotension or hypertension "avoidance" strategy by establishing specific intraoperative and postoperative target ranges for mean arterial pressure (MAP) (at least 60 mmHg *vs.* at least 80 mmHg, respectively) and by standardizing antihypertensive medication administration (withholding renin–angiotensin–aldosterone system inhibitors before and for 2 days postoperatively, others administered only for systolic blood pressures at least 130 mmHg *versus* administering all antihypertensive medications before and after surgery). General anesthesia was used in approximately 75% of each group. Intraoperative blood pressure management was at the discretion of the anesthetist. The primary outcome was a composite of vascular death and nonfatal myocardial injury, stroke, and cardiac arrest at 30 days. Approximately 73% of the hypotension avoidance group maintained their MAP target while 13% in the hypertension avoidance group exceeded their target. No statistically significant difference was noted in the primary outcome between strategies (14% *vs.* 14%; hazard ratio, 0.99 [95% CI, 0.88 to 1.12]; $P = 0.92$), respectively. Adherence to the assigned strategies, particularly in the postoperative period, was suboptimal. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: In a multicenter study of at-risk patients on at least one chronic antihypertensive medication, randomization to either a hypotension-avoidance or hypertension-avoidance strategy based on different intraoperative MAP targets and standardized perioperative administration of chronic antihypertensive medications, resulted in no statistically significant differences in major vascular complications at 30 days postoperatively.

Clinical thresholds in pain-related facial activity linked to differences in cortical network activation in neonates. Pain 2023; 164:1039–50. PMID: 36633530.

In neonates, facial expressions are used to determine the presence and severity of pain. But it is unclear whether facial expressions, which involve pontine reflexes, are linked with pain-related EEG activity, which is primarily cortical in origin and is the basis for any pain awareness. This study looked for correlations between pain-related facial activity as measured by the Neonatal Facial Coding System and patterns of brain activity in 78 neonates (0 to 14 days postnatal age) responding to a standard heel lance stimulus. The evolution of short-lived patterns of EEG power over different scalp regions after the stimulus (so-called EEG "microstates") were compared between those who showed pain behavior and the 71% who did not. All infants demonstrated a standard microstate network sequence in response to a heel lance for blood collection, with peaks of central EEG activity around 200 ms and 600 ms. In those term neonates who showed facial activity, there were additional interspersed early microstates (power 75 μV^2 vs. 472.59 μV^2; $P < 0.001$). In preterm neonates who showed pain-related facial responses, there was increased power around 600 ms (922 μV^2 *vs.* 1,280 μV^2; $P < 0.001$). *(Article Selection: Jamie Sleigh, M.D. Image: J. P. Rathmell.)*

Take home message: In neonates there is evidence of widespread covert cortical nociceptive processing, which may not manifest in clinically observable pain behaviors.

Effect of multimodal prehabilitation on reducing postoperative complications and enhancing functional capacity following colorectal cancer surgery: The PREHAB randomized clinical trial. JAMA Surg 2023; 158:572–81. PMID: 36988937.

Thirty-day morbidity after surgery is still high, with rates between 20% and 37%. Also, postoperatively impaired functional recovery favors bad outcomes after surgery. This multicenter, international randomized clinical trial of adult patients undergoing elective nonmetastasized colorectal cancer resection evaluated whether a 4-week in-hospital supervised multimodal prehabilitation program improves postoperative outcome. Colorectal cancer was chosen, as it ranks third among global cancer incidence rates. All participants were provided with perioperative standard care. The prehabilitation program consisted of a high-intensity exercise (three times per week) regimen, a nutritional intervention (*i.e.*, whey protein supplement), and psychological support. The primary outcomes were 30-day postoperative complications, defined by the comprehensive complication index greater than 20 (0 = no complications, 100 = death), and postoperative 6-min walking distance. A total of 251 subjects were enrolled (prehabilitation, n = 123; standard care, n = 128; median [interquartile range] age 69 yr [60 to 76 yr], 55% male). Due to the COVID-19 pandemic, the study with an original sample size calculation of 714 patients was terminated prematurely. Severe complications were significantly lower in the prehabilitation group (17% *vs.* 30%; odds ratio, 0.47 [95% CI, 0.26 to 0.87]; $P = 0.02$). Thirty-day 6-min walking distance was similar in the two groups (mean difference prehabilitation *vs.* standard care, 15.6 m [95% CI, –1.4 to 32.6]; $P = 0.07$). *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

Take home message: This randomized clinical trial of patients undergoing colorectal cancer surgery demonstrated benefit of a preoperative 4-week multimodal prehabilitation program with regard to postoperative severe complications within 30 days after surgery.