A Review of Current Literature of Interest to the Office-Based Anesthesiologist

Wainwright CE, Vidmar S, Anderson V, et al. Long-term outcomes of early exposure to repeated general anaesthesia in children with cystic fibrosis (CF-GAIN): a multicentre, open-label, randomised controlled phase 4 trial. *Lancet Respir Med.* 2024;12:703–713.

Long-term effects of early, recurrent human exposure to general anesthesia remain unknown. The Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) trial provided an opportunity to examine children randomly assigned in infancy to either repeated bronchoalveolar lavage (BAL)-directed therapy with general anesthesia or standard care with no planned lavages up to 5 years of age. Children who completed the ACFBAL trial, with a mean age of 5.1 (SD, 0.18) years, received standardized neurobehavioral and health-related-quality-of-life assessment and brain MRI scans. The primary outcome was a composite score of performance on the Conners Continuous Performance test (CCPT), second edition, a computer-based assessment of attention, processing speed, and response inhibition skills. Secondary outcomes included intellectual function, other neurobehavioral measures, and brain imaging as an exploratory outcome. Cumulative general anesthesia exposure time was not prospectively collected, but for those with complete cumulative exposure time data to the end of the ACFBAL trial, the median cumulative exposure time for the BAL-directed therapy group (n = 29) was 180 (IQR, 140–285) minutes and for the standard-care group (n = 32) was 48 (IQR, 30–122) minutes. The mean CCPT composite score was 51 (SD, 8.1) in BAL-directed therapy group and 53 (8.8) in the standard-care group; difference −1.7 (95% CI, −5.2 to 1.7; $P = .32$) with similar performance on other neurobehavioral measures, including measures of executive function, intellectual quotient scores, and brain imaging. These findings suggest that repeated general anesthesia exposure in young children with cystic fibrosis is not related to functional impairment in attention, intellectual quotient, executive function, or brain structure.

Comment: Expert opinion on the risk of neurotoxicity to young children following exposure to general anesthesia has been divided for several years. In 2016, the US Food and Drug Administration issued a warning that prolonged or repeated exposure to general anesthesia and sedatives that block N-methyl-D-aspartate (NMDA) receptors or potentiate gamma-aminobutyric acid (GABA) activity could have a potentially negative impact on brain development in children. Although most of the evidence for toxicity was preclinical in nature, children undergoing multiple procedures and those younger than 3 years of age who were exposed to general anesthesia for more than 3 hours were deemed at risk for potential neurotoxicity from anesthesia exposure.[1] Subsequently, 3 separate, large-scale trials failed to reveal outcomes following general anesthesia in children that would suggest significant neurotoxicity occurs following exposure to general anesthesia. The Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study examined healthy children with a single anesthesia exposure before age 36 months, comparing them with healthy siblings with no anesthesia exposure, and found no statistically significant differences in IQ scores in later childhood.[2] The Mayo Anesthesia Safety in Kids (MASK) study tested unexposed, singly exposed, and multiply exposed children with multiple neuropsychological tests but failed to find statistically significant differences according to exposure status in IQ as a primary outcome.[3] The General Anesthesia compared to Spinal anesthesia (GAS) trial randomized 722 infants undergoing herniorrhaphy repair before 60 weeks' postmenstrual age to either awake-regional anesthesia or sevoflurane-based general anesthesia. No differences in neurocognitive outcomes were found between the general and the spinal anesthesia groups following this short surgical procedure.[3] Although compelling, each of these 3 studies contained important limitations. The study by Wainwright et al is unique in its utilization of a rare, prospective opportunity to follow children undergoing multiple general anesthetics in early childhood. Their inability to demonstrate negative outcomes is consistent with the PANDA, MASK, and GAS studies, although the authors cite significant limitations of their study and urge further investigation.

Vitin A, Egan T. Remifentanil-induced hyperalgesia: the current state of affairs. *Curr Opin Anaesthesiol.* 2024;37(4):371–378. doi:10.1097/ACO.0000000000001400

Remifentanil-induced hyperalgesia (RIH) is a part of a general opioid-induced hyperalgesia (OIH) syndrome, seemingly resulting from abrupt cessation of continuous remifentanil infusions at rates equal or exceeding 0.3 mcg/kg/min. The mechanisms of its development are still not completely understood. Several ways of prevention and management are described in this review, such as slow withdrawal of the remifentanil infusion, the addition of propofol, and pretreatment with or concomitant administration of ketamine, buprenorphine, cyclooxygenase-2 inhibitors (NSAIDs), methadone, or dexmedetomidine. In clinical and animal studies, these strategies exhibited varying success, and many are still being investigated.

Comment: The rapid clearance of remifentanil from the plasma causes its analgesic effects to diminish very quickly

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after an infusion is terminated. It is difficult to distinguish between opioid-induced hyperalgesia and the rapid loss of analgesia due to its clearance. Practitioners typically have a plan for restoring analgesia by administering a second analgesic medication to help account for the waning of remifentanil's effect after infusion cessation. It is also noteworthy that the remifentanil infusion dosing rates cited in reports for dental surgery often lie below the 0.3 mcg/kg/min threshold cited in this review. The combination of relatively low infusion dosing rates and the brief nature of many dental surgeries (less than 60 to 90 minutes) may limit the development of remifentanil-induced hyperalgesia in many dental surgeries.[4,5]

So V, Radhakrishnan D, MacCormick J, et al. Does celecoxib prescription for pain management affect post-tonsillectomy hemorrhage requiring surgery? A retrospective observational cohort study. *Anesthesiology*. 2024;141(2):313–325. doi:10.1097/ALN.0000000000005032

Postoperative hemorrhage and pain are known complications of tonsillectomy. Severe postoperative hemorrhage may require surgical hemostasis. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to provide effective postoperative pain control; however, controversy exists regarding NSAID-associated bleeding risk, caused by cyclooxygenase-1 inhibition and associated platelet dysfunction. Selective cyclooxygenase-2 inhibitors, such as celecoxib, are subclass of NSAIDs that effectively manage pain without adverse events including bleeding. This study was designed to investigate the association between postoperative celecoxib use and post-tonsillectomy hemorrhage requiring surgical hemostasis. This retrospective, observational cohort study examined charts from 5,846 children under 18 years of age who underwent tonsillectomy between January 2007 and December 2017. The primary outcome was the proportion of patients with postsurgical hemorrhage requiring surgical hemostasis. After adjusting for covariates, celecoxib was found to not significantly increase the odds of hemorrhage requiring surgical intervention. This large pediatric cohort study of celecoxib administered after tonsillectomy provides compelling evidence for the safety of celecoxib but requires confirmation with a multisite randomized controlled trial.

Comment: Readers are reminded that the magnitude and risk of bleeding following a soft-tissue surgery like tonsillectomy differ from bleeding associated with dentoalveolar surgery. An additional, important consideration is the number of postoperative NSAID doses required for pain relief. Many dental surgeries, such as tooth extraction, require a very limited number of NSAID doses following surgery. Platelet inhibition has not been shown to be clinically significant following short-term use of short-acting NSAIDs, such as ibuprofen which was not associated with increased risk of bleeding when used for acute postoperative pain management.[6]

Vellinga R, Koomen JV, Eleveld DJ, et al. Target-controlled Infusion of remimazolam in healthy volunteers shows some acute tolerance. *Anesthesiology*. 2024;140(2):207–219. doi:10.1097/ALN.0000000000004811. PMID: 37889844.

Remimazolam, an ultra-short-acting benzodiazepine, is administered as a bolus dose or continuous infusion but has not been studied using target-controlled infusion (TCI). This 3-period, dose-finding, crossover study in 24 healthy volunteers quantified the relationship between remimazolam concentration, Modified Observer's Assessment of Alertness and Sedation (MOAAS) score, and bispectral index (BIS) using TCI. Sedation was achieved using a step-up/step-down infusion protocol. Target concentration-dependent sedation was observed with little effect on vital signs in all subjects; however, a difference in the sedative effects at identical concentrations was observed between the step-up and step-down parts of this titration scheme. The authors concluded remimazolam sedation appears to be prone to tolerance development when titrated to effect.

Comment: Acute tolerance or tachyphylaxis has been described for midazolam and other short-acting benzodiazepines. In the case of midazolam, its active alpha-hydroxy metabolite likely contributes to the creation of tolerance via competitive antagonism. In comparison, the primary metabolite of remimazolam, CNS7054, has no activity at $GABA_A$ receptor sites unlike its parent compound. The exact mechanism for tolerance development with remimazolam remains unclear, so further studies are needed.

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REFERENCES

1. Smart Tots. Neurotoxicity outside the operating room: an evolving challenge for pediatricians and pediatric subspecialists. Accessed September 30, 2024. https://smarttots.org/neurotoxicity-outside-the-operating-room-an-evolving-challenge-for-pediatricians-and-pediatric-subspecialists

2. Sun LS, Li G, Miller TL, et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. *JAMA*. 2016;315(21):2312–2320. doi:10.1001/jama.2016.6967

3. McCann ME, de Graaff JC, Dorris L, et al; GAS Consortium. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an

international, multicentre, randomised, controlled equivalence trial. *Lancet*. 2019;393(10172):664–677. doi:10.1016/S0140-6736(18)32485-1. Erratum in: *Lancet*. 2019;394(10199):638.

4. Kramer KJ, Ganzberg S, Prior S, Rashid RG. Comparison of propofol-remifentanil versus propofol-ketamine deep sedation for third molar surgery. *Anesth Prog*. 2012;59(3):107–117. doi:10.2344/12-00001.1

5. Matsuura N, Okamura T, Ide S, Ichinohe T. Remifentanil reduces blood loss during orthognathic surgery. *Anesth Prog*. 2017;64(1):3–7. doi:10.2344/anpr-63-03-04

6. Kelley BP, Bennett KG, Chung KC, Kozlow JH. Ibuprofen may not increase bleeding risk in plastic surgery: a systematic review and meta-analysis. *Plast Reconstr Surg*. 2016;137(4):1309–1316. doi:10.1097/PRS.0000000000002027