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

Lin M, Han R, Hull X, Zhang K, Gelb A. Midazolam sedation induces upper limb coordination deficits that are reversed by flumazenil in patients with eloquent area gliomas. *Anesthesiology*. 2019;131:36–45.

Midazolam has been shown to exacerbate motor dysfunction in patients with brain tumors in the eloquent cortex (ie, the frontotemporal and parietal cortex areas that are involved in speech). Some slowly infiltrative gliomas in these regions do not show any clinically detectable deficits under normal conditions but appear when sedation is administered. The mechanism of this “unmasking” by sedation is unclear. This study sought to determine if this exacerbation was mediated by GABA receptors. Fifteen patients with gliomas in the eloquent cortex were compared with 15 volunteers without neurologic disease. All patients received moderate sedation with midazolam, followed by flumazenil. Motor function was assessed at 3 points in time: the preoperative period, after midazolam administration, and after flumazenil administration. Patients with gliomas experienced significant motor dysfunction following midazolam but also displayed reversal of the dysfunction following flumazenil administration. No significant change from preoperative motor function was observed in the control group. Patients with high-grade gliomas performed much worse than patients with low-grade gliomas. In addition to showing the role of GABA receptors in this phenomenon, the study emphasized that normal-appearing brain areas were not necessarily functionally normal and that under certain conditions, such as midazolam administration, abnormal cortical connectivity was exposed. The study was limited by differences in age between the intervention and control group (mean 46 years of age vs mean 35 years of age) and its limitation to patients with supratentorial gliomas in the eloquent cortex.

Comment: The accompanying editorial to this article by Drs Vlisides and Mashour¹ discusses 2 unexpected and exciting features of this study. Sedation-induced motor impairment has previously been demonstrated in patients with other types of neurologic deficits caused by brain tumors or cerebrovascular disease; however, this study supports the role of GABAergic receptors in this phenomenon as opposed to cholinergic receptors, the predominant receptor type found in the cortex. Equally intriguing, however, is the possibility that the protocol in this study could be used as a type of neurologic stress

test. Just as a treadmill or pharmacologic stress test may reveal subclinical heart vulnerability, the administration of moderate sedation with midazolam, reversed by flumazenil, may unmask neurologic vulnerability in patient populations beyond those with brain tumors. (MA Saxen)

Moness Ali AM, Hammuda AA. Local anesthesia effects on postoperative pain after pediatric oral rehabilitation under general anesthesia. *Pediatr Dent*. 2019;41(3):181–185.

This randomized, single-blinded, controlled prospective study examined 105 children between the ages of 3 and 6 years of age who were undergoing general anesthesia for complete oral rehabilitation. Participants were randomly allocated to 2 groups, one of which received perioperative intraligamentary and/or intrapulpal injection of 3% mepivacaine and the other of which received no local anesthetic. Pain was assessed preoperatively and postoperatively by the treating pediatric dentist, the oral and maxillofacial surgeon, and parents using the Universal Pain Assessment Tool at 7 separate time points. No significant difference was found in the assessments between any of the groups for pain at the preoperative, immediate postoperative, and delayed postoperative time periods. The authors concluded their results were consistent with prior studies that failed to show efficacy of perioperative local anesthetic for the mitigation of postoperative pain in children undergoing general anesthesia for oral rehabilitation.

Comment: As the authors indicate, the practice of administering perioperative local anesthesia during pediatric oral rehabilitation under general anesthesia continues to be debated among pediatric dentists and dentist anesthesiologists. One of the chief goals of this practice is to reduce postoperative pain. Unfortunately, the design of this study fails to address important considerations regarding the type and timing of local anesthesia, making it difficult to add any additional insight to the debate regarding the effectiveness of this practice. Local anesthetics produce pain relief by blocking sensation in sensory nerves. This blockade is highly dependent on having an adequate concentration of local anesthetic solution outside of the sensory nerve, allowing diffusion of the solution into the nerve. This diffusion into the nerve is driven by the concentration gradient between the outside and inside of the nerve.² Once inside the nerve, the local anesthetic inhibits

neuronal transmission, thereby producing numbness; however, the process is reversed once the concentration of local anesthetic outside of the nerve dissipates. Inflammation greatly impairs this process by lowering the pH of the affected area, as does the initiation of local edema. For this reason, intrapulpal injection of 3% mepivacaine into inflamed pulps and intraligamentary injection immediately preceding extraction would be expected to produce very brief and possibly incomplete sensory neural blockade. In addition, no mention is made of the typical intraoperative duration of the dental treatment rendered in this article. Based on published reports, one might assume the types of cases included in this study would require a minimum of 45–60 minutes of intraoperative working time. The expected pulpal anesthesia of 3% mepivacaine is approximately 20 minutes, under normal conditions.³ Finally, all subjects received 0.5–1.0 µg/kg of fentanyl during the induction of general anesthesia. Without knowing the duration of the case, one cannot determine if the administration of fentanyl contributed analgesia, no effect, or possible hyperalgesia to the patients. In light of these concerns, the lack of any significant difference in postoperative pain scores between groups is not surprising. No conclusions regarding the efficacy of perioperative local anesthetic administration on postoperative pain can be drawn, however, since it is highly unlikely that local anesthetic was present in clinically significant concentrations at the time of postoperative pain assessments in this study. (MA Saxen)

Saugel B, Reese PC, Sessler DI, et al. Automated ambulatory blood pressure measurements and intraoperative hypotension in patients having noncardiac surgery with general anesthesia. *Anesthesiology*. 2019;131:74–83.

Normal blood pressure varies among individuals across the circadian cycle. Preinduction blood pressure may not be representative of a patient's normal pressure or usual range of blood pressure. This observational study examined the relationship between ambulatory (home-based) blood pressure and preinduction, postinduction, and intraoperative blood pressures. Three hundred seventy American Society of Anesthesiologists I or II adults between the ages of 40 and 65 years who were undergoing elective noncardiac surgery were studied. Poor correlation was found between preinduction blood pressure and the patient's usual blood pressure. In two-thirds of the patients, the lowest postinduction and intraoperative pressures were lower than the patient's normal lowest nighttime pressure. In 71% of patients, the lowest nighttime mean arterial pressure (MAP) was

greater than 65 mm Hg. Furthermore, the MAP during surgery with general anesthesia was markedly lower than the mean daytime, nighttime, and preinduction MAPs. The authors conclude that preinduction blood pressure cannot be used as a surrogate for normal daytime mean arterial pressure and that intraoperative mean arterial pressures are lower than the lowest mean daytime or nighttime MAP in most patients.

Comment: Controlled hypotension is commonly requested during certain oral and maxillofacial surgeries to maximize surgical site conditions and minimize surgical blood loss. The definition of the lowest safe intraoperative pressure remains elusive, despite a growing body of evidence indicating an association between intraoperative hypotension and cardiac impairment, kidney injury, and death. A mean arterial pressure of 65 mm Hg is often considered the safe minimum threshold for controlled hypotension. The authors speculated that the lowest normal blood pressure in patients, typically experienced at night during sleep, represented a reasonable safe limit for intraoperative hypotension. This study presents data that show a poor correlation between normal physiologic pressures and perioperative pressures. Determining a patient's preoperative normal blood pressure well before the day of surgery is a plausible strategy for vulnerable patients; however, there are currently very little published data to aid the surgeon and anesthesiologist in interpreting and using this information. The importance of identifying and managing patients at elevated risk during intraoperative hypotension will grow as the general population continues to age and the number of older and geriatric oral surgery patients increases. (MA Saxen)

Lei H, Chao L, Miao T, et al. Serious airway-related adverse events with sevoflurane anesthesia via facemask for magnetic resonance imaging in 7129 pediatric patients: a retrospective study. *Pediatr Anesth*. 2019;29:635–639.

This retrospective records review of 7129 pediatric patients (median age 12 months) evaluated the safety and efficacy of sevoflurane anesthesia by face mask for magnetic resonance imaging scanning in a high-volume magnetic resonance imaging department. Eighty-two percent of the patients were classified as American Society of Anesthesiologists I, and 16% were classified as American Society of Anesthesiologists II. Anesthesia was induced with 8% sevoflurane, followed by 1.5–2% sevoflurane for induction. No intubation was performed; rather, a face mask was taped to the face for the duration of the scan. The mean induction time was 3.8 minutes, while mean scan time was 17.1 minutes and the mean recovery time 11.5 minutes. No emergency intubation was required, and no cardiac arrest or death

was reported. Twenty-eight severe airway-related adverse events were found, including 12 with severe apnea (0.25). The occurrence of apnea was significantly higher in preterm infants (2.4%). Sixteen patients (0.2%) had severe airway obstruction. All adverse events were within the moderate risk category according to the World SIVA International Sedation Task Force.⁴ While recommending that special attention be given to preterm infants under sevoflurane anesthesia, the authors concluded that sevoflurane anesthesia is safe and effective for use in children in a high-volume magnetic resonance imaging scanning service.

Comment: In the introduction, the authors discuss limitations of other commonly accepted protocols for this type of service. Nasal dexmedetomidine is associated with long onset and prolonged recovery times, while propofol, at higher doses, may increase the risk of hypoxia and obstruction. The rapid onset of effect and noninvasive administration make sevoflurane an attractive option for this type of high-volume service. Unlike dentistry, in which significant repeated manipulation of the airway is present, this study allows observation of the effects of nonintubated sevoflurane anesthesia when the airway is typically immobilized and undisturbed. The retrospective nature of the study requires caution in attempting to draw conclusions or extrapolate results to other types of settings. (MA Saxen)

Lamontagne C, Lesage S, Villeneuve É, Lidzorski É, Derstenfeld A, Crochetière C. Intravenous dexmedetomidine for the treatment of shivering during caesarean delivery under neuraxial anesthesia: a randomized controlled trial. *Can J Anaesth*. 2019;66:762–771.

Bhakta P, Karim H, Vassallo M. Is an intravenous bolus of dexmedetomidine really a safe and effective option in treating shivering following neuraxial anesthesia? *Can J Anaesthesia*. In press. doi:10.1007/s12630-019-01429-1

Lamontagne C, Lesage S, Villeneuve É, Lidzorski E, Derstenfeld A, Crochetière C. In reply: is an intravenous bolus of dexmedetomidine really a safe and effective option in treating shivering following neuraxial anesthesia? *Can J Anaesth*. In press. doi:10.1007/s12630-019-01430-8

In a prospective, randomized, double-blind trial published earlier this year in the *Canadian Journal of Anesthesia*, Lamontagne and colleagues investigated the use of dexmedetomidine as a treatment to control shivering following neuraxial anesthesia in 80 women undergoing caesarian section.⁵ After delivery, 40 patients received a single 30- μ g bolus of dexmedetomidine while 40 patients in the control group received saline. The duration of

shivering in the dexmedetomidine group was 2.6 ± 2.1 minutes, while the saline group lasted 17.9 ± 12.6 minutes. After 15 minutes, shivering had resolved in 90% of the dexmedetomidine group compared with 22.5% in the control group. No adverse effects, including bradycardia, were observed in either group.

In a subsequent Letter to the Editor, Bhatka and colleagues⁶ questioned the safety of this practice, noting the reports of bradycardia and even cardiac arrest associated with the use of dexmedetomidine. They continued by noting shivering was a non-life-threatening event and that subanalgesic doses of meperidine have been shown to be effective in managing shivering. Lamontagne and colleagues⁷ responded by pointing out that their study also used subanesthetic doses, which perhaps explained the absence of bradycardia and cardiac arrest.

Comment: This article, along with the subsequent letter and reply, is reminiscent of the early days of remifentanyl usage. In 1997, shortly after the introduction of remifentanyl, DeSouza and colleagues⁸ found that administration of the recommended 1 μ g/kg dose at induction resulted in several occurrences of significant bradycardia. The package insert had recommended administration of this dose over 30–60 seconds to avoid muscular rigidity; however, no mention of bradycardia was found in the insert. Upon further investigation, DeSouza et al discovered that the Medfusion 2010i syringe pump used to deliver the remifentanyl bolus did so over a 24-second period—shorter than the recommended 30 to 60 seconds. By reducing the dosage and lengthening the time of drug delivery, the bradycardia was attenuated to an acceptable level. Thus, refinement of dosing and dose delivery were needed to fine-tune clinical use of this very useful opioid. The same theme seems to be at work in this exchange regarding the use of dexmedetomidine. As clinicians broaden the spectrum of indications for dexmedetomidine, refinement in patient selection, concomitant drug administration, and other aspects of the clinical context for dexmedetomidine use are to be anticipated. (MA Saxen)

ADDITIONAL ARTICLES OF INTEREST FOR SUPPLEMENTAL READING

Priebe HJ. Another nail in the coffin of the practice of checking mask ventilation before administration of a muscle relaxant. *Anesth Analg*. In press. doi:10.1213/ANE.0000000000004260

In this Letter to the Editor, the author notes that muscle relaxants have been shown to improve but never worsen mask ventilation in multiple studies, leading him to question the conventional wisdom of checking face

mask ventilation after induction but prior to the injection of a neuromuscular blocking drug.

Cravero J, Agarwal R, Berde C, et al. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. *Pediatr Anesth*. 2019;29:547–571.

This document is the official report of a task force appointed by the Society for Pediatric Anesthesia to develop recommendations for opioid administration to children after surgery.

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1. Vlisides PE, Mashour GA. Pharmacologic unmasking of neurologic deficits: a stress test for the brain. *Anesthesiology*. 2019;131:5.

2. De Jong RH. Differential nerve block. In: *Local Anesthetics*. Philadelphia, PA: Mosby; 1994:81–97.

3. Becker DE, Reed KL. Local anesthetics: review of pharmacological considerations. *Anesth Prog*. 2012;59:90–102.

4. Mason KP, Green SM, Piacitelli Q; the International Sedation Task Force. Adverse event reporting tool to standardize the reporting and tracking of adverse events during procedural sedation: a consensus document from the World SIVA International Sedation Task Force. *Br J Anaesth*. 2012;108:13–20.

5. Lamontagne C, et al. Intravenous dexmedetomidine for the treatment of shivering during cesarean delivery under neuraxial anesthesia: a randomized-controlled trial. *Can J Anaesth*. 2019;66:762–771.

6. Bhakta P, Karim HMR, Vassallo MC. Is an intravenous bolus of dexmedetomidine really a safe and effective option in treating shivering following neuraxial anesthesia? *Can J Anaesth*. In press. <https://doi.org/10.1007/s12630-019-01429-1>

7. Lamontagne C, Lesage S, Villeneuve LE, Derstenfeld A, Crochetière C. In reply: is an intravenous bolus of dexmedetomidine really a safe and effective option in treating shivering following neuraxial anesthesia? *Can J Anaesth*. In press. doi: 10.1007/s12630-019-01430-8

8. DeSouza G, Lewis MC, TerRiet MF. Severe bradycardia after remifentanyl. *Anesthesiology*. 1997;87:1019–1020.