A Review of Scientific Literature of Interest to Office-Based Anesthesiology Practitioners

Litman RS, Smith VI, Larach MG, et al. Consensus statement of the Malignant Hyperthermia Association of the United States on unresolved clinical questions concerning the management of patients with malignant hyperthermia. *Anesth Analg*. 2019;128:652–659.

At a recent consensus conference, the Malignant Hyperthermia Association of the United States addressed 6 important and unresolved clinical questions concerning the optimal management of patients with malignant hyperthermia (MH) susceptibility or acute MH. They include the following: (1) How much dantrolene should be available in facilities where volatile agents are not available or administered, and succinylcholine is stocked on site only for emergency purposes? (2) What defines masseter muscle rigidity? What is its relationship to MH, and how should it be managed when it occurs? (3) What is the relationship between MH susceptibility and heat- or exercise-related rhabdomyolysis? (4) What evidence-based interventions should be recommended to alleviate hyperthermia associated with MH? (5) After treatment of acute MH, how much dantrolene should be administered and for how long? What criteria should be used to determine stopping treatment with dantrolene? (6) Can patients with a suspected personal or family history of MH be safely anesthetized before diagnostic testing? This report describes the consensus process and the outcomes for each of the foregoing unanswered clinical questions.

Comment: A perennial point of discussion among office-based anesthesia providers concerns the amount of dantrolene a practitioner should have on hand while providing general anesthesia that involves no triggering agents, other than succinylcholine. This consensus statement states, “Facilities that stock and have the potential to administer any triggering agent, including succinylcholine without volatile agents, should have a full dose (at least 10 mg/kg corresponding to the estimated size of their patients) of dantrolene immediately available (ie, the ability to administer dantrolene within 10 min of the first sign of MH).” A detailed discussion of this issue, along with the other 5 questions stated above, is found in the article. (Summary MA Saxen)

Bourdon F, Simon N, Lannoy D. Quality control and stability of ketamine, remifentanyl and sufentanil syringes in a pediatric operating theater. *Pediatr Anesth*. 2019;29:193–199.

This study examined 151 syringes containing ketamine, remifentanyl, and sufentanil collected from the postanesthesia care unit over a 1-month period. High-performance liquid chromatography was used to quantify the amounts of drug and degradation products in the syringes. Seventy-three syringes contained a 10-fold dilution of the stock solutions and 78 were serial dilutions. A comparison between the actual and expected concentrations was performed. All stock solution syringes had good chemical stability throughout the working day. Overall, 15.3% (95% confidence interval) of syringes had a concentration outside of the $\pm 10\%$ acceptability range. The highest error rates were observed with sufentanil syringes. The error rate for serial dilution syringes was twice that of stock solutions. The study demonstrated that stock solution syringes prepared in advance are chemically stable throughout the day, unlike certain serial dilution syringes, indicating that the latter should be prepared just before administration to ensure accuracy.

Comment: This study shows that the preparation of stock solutions (ie, the initial dilution prepared from the original vial) was associated with an error rate of about 10%, whereas the preparation of serial dilutions (those prepared from stock syringes) was associated with an error rate of about 20%. Errors are more likely to occur when preparations are very dilute. Several aspects of this study have direct implications for practitioners who routinely use intravenous agents to induce and maintain general anesthesia. One should consider the effect of a 10 to 20% error in one's intravenous anesthetic delivery practices when using potent opioids such as remifentanyl and sufentanil. For example, the practice of preparing a mixture of remifentanyl and propofol in the same syringe or infusion commits the anesthesia provider to applying an unintended adjustment to one of the drugs (propofol) while attempting to adjust for a mixture that seems stronger (eg, 10 to 20% more opioid) or weaker (eg, 10 to 20% less opioid). Although this type of error may be relatively insignificant for anesthetizing healthy adults undergoing very short procedures, the potential for error becomes more problematic when one is anesthetizing more at-risk patient groups, such as pediatric, elderly, or medically complex or compromised patients, especially for longer cases. Additional variability is created if the practitioner draws up all mixtures for patient use at the beginning of the day, because a fixed-dose combination of anesthetic drugs will be used for patients with a variety of body compositions. The use of separate, dedicated infusion pumps to administer

remifentanyl or other potent opioids should be seriously considered as a safety strategy for minimizing this type of error. (Summary MA Saxen)

Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, and Riedel B. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia [published online ahead of print March 4, 2019]. *Can J Anesth*. doi:10.1007/s12630-019-01330-x.

Drawing from 7 large databases, the authors examined 9536 citations. After excluding animal studies, studies not published in English, studies with insufficient information or data, and studies focused on other outcomes, they deemed 1 prospective randomized controlled trial and 9 retrospective studies eligible for analysis. The primary outcome measures were recurrence-free survival and overall survival. Patients receiving propofol or remifentanyl infusion during their surgery were included in the total intravenous anesthesia (TIVA) group; patients receiving sevoflurane, isoflurane, desflurane, or enflurane were included in the volatile group. Collectively, the analysis examined over 21,000 cancer patients with multiple cancer types. Despite the heterogeneity of the studies, an association was found between improved cancer outcomes and the use of propofol-based TIVA when compared to inhalational, volatile-anesthetic anesthesia. The use of TIVA was associated with improved recurrence-free survival in all cancer types. Eight studies showed an association between TIVA and improved overall survival. The study had several limitations, including the large number of retrospective studies, differing follow-up intervals, and differences in study populations and study design.

Comment: The choice of anesthesia remains a controversial topic despite several large studies, mostly because of contradicting results as to the impact of anesthesia type and drugs used on cancer recurrence. There is a scientific basis to support why some drugs or techniques may impact cancer spread/recurrence, as they may affect systemic inflammatory processes and immunological mechanisms, affecting tumor growth rate and tumor recurrence. Although some retrospective studies suggest regional anesthesia is associated with lower cancer recurrence rates compared with general anesthesia, presumably because of its anti-inflammatory effect and preservation of the functionality of natural killer cells (which opioids appear to inhibit), there is still a need for prospective randomized trials. At the same time, it is still unclear from a mechanistic perspective how specific anesthetic drugs such as barbiturates,

inhalational agents, propofol, and etomidate contribute to tumor recurrence. (Summary RD Urman)

Bircher NG, Chan PS, Xu Y. Delays in cardiopulmonary resuscitation, defibrillation and epinephrine administration all decrease survival in in-hospital cardiac arrest. *Anesthesiology*. 2019;130:414–422.

The authors of this 9-year prospective study of 57,132 patients in 538 hospitals sought to determine if delays in the initiation of cardiopulmonary resuscitation (CPR), defibrillation, and epinephrine administration were each independent risk factors for surviving witnessed, in-hospital cardiac arrest. The 2 independent variables examined were (1) time to initiation of CPR and (2) time from initiation of CPR to treatment, defined as either defibrillation or epinephrine administration. For patients receiving both defibrillation and epinephrine, the earliest intervention was recorded. The mean age of patients was 67 years, and 61% of the cardiac arrests in the study occurred in an intensive care unit. Of the patients treated first with epinephrine, 94.3% had a nonshockable rhythm, whereas 83% of those treated first with a defibrillation had a shockable rhythm. The data demonstrated that delay in CPR reduces survival independently of defibrillation or epinephrine administration. The overall survival rate was 18% when CPR was initiated within 2 minutes, as compared to 16.4% when initiated between 3 and 5 minutes after cardiac arrest. The time to initiation of defibrillation was also a factor in survival, ie, the expected survival advantage of early CPR initiation can be reduced by subsequent delay in defibrillation. Although these findings are consistent with previously published studies, this study was the first to demonstrate that time from CPR initiation to epinephrine administration was also a determinant in survival.

Comment: Although this study examined witnessed, in-hospital cardiac arrest survival, the findings are more relevant to office-based anesthesia than studies of out-of-hospital cardiac arrests, where most arrests occur outside of a surgical setting and are nonwitnessed.¹ The study showed that even when personnel, equipment, and vigilance were optimized, survival occurred in less than 20% of cases. Three crucial elements evident in this study are directly applicable to office-based anesthesia emergency preparedness: the ability to instantly recognize and respond to cardiac arrest, the ability to immediately initiate effective CPR, and the immediate availability of a defibrillator and advanced cardiac life support drugs in the operatory. High-fidelity simulation and regular, routine emergency drills are also shown to

improve the outcomes when resuscitation is required in this setting.² (Summary MA Saxen)

Clark HM, Saxen MA, Yepes JF, et al. Comparison of intubation versus nonintubated airway management in children under general anesthesia provided by dentist anesthesiologists. *Pediatr Dent*. 2019;41:52–55.

This study compared the incidence of respiratory complications in intubated versus nonintubated general anesthesia (GA) dental cases when completed by a dentist anesthesiologist. The authors queried a final 9333 cases from the Society of Ambulatory Anesthesia Clinical Outcomes Registry for patients aged 2 to 7 years who had the American Society of Anesthesiologists physical status classification of I or II. Endotracheal intubation was used in 57.2% of cases. No significant association was found when comparing respiratory complication incidence in intubated versus nonintubated GA cases. Only 53 respiratory adverse events occurred in the 9333 cases, with the most common being laryngospasm (30 cases), followed by bronchospasm (19 cases).

Comment: This unique study is the first of its kind to compare the incidence of airway complications in the pediatric cases undergoing GA for dental treatment, including dental rehabilitation procedures. Although past literature has suggested that intubation with GA is associated with increased risk of complications, this study has found no significant difference in the incidence of respiratory complications between intubated and nonintubated GA cases. For dentist anesthesiologists, this also provides further knowledge when approaching the multifactorial decision of airway management, particularly in the dental office setting, where anesthetic gas machines are not routinely utilized for GA. The study also suggests that the choice of airway management technique by itself is not an independent risk factor for perioperative respiratory adverse events. (Summary JT Homs, RD Urman)

Segal S, Gunawan A, McLaughlin DH, Palavecino E. Microbial stability of anesthetic drugs prepared in the operating room. *J Clin Anesth*. 2019;55:20–23.

This study sought to determine if evidence of microbial contamination could be found in syringes prepared in the operating room, and if the contamination was evident in a time-dependent fashion. Microbial cultures were obtained from 400 syringes prepared by anesthesia personnel in the operating room under aseptic conditions. The syringes were sampled at 1, 2, 3, and 4

hours after preparation and analyzed for evidence of bacterial growth. Sampled drugs included propofol, rocuronium, ephedrine, glycopyrrolate, succinylcholine, ondansetron, and other commonly used anesthetic drugs. Colony-forming units (CFUs) per milliliter were calculated. Logistic regression was used to test the effect of time since preparation, the number of accesses of the syringe, and the identity of the drug. Overall, 9 of 400 syringes (2.25%) tested positive for bacteria. The median concentration of bacteria among positive cultures was 100 CFUs. All cultured species were generally nonpathogenic, common contaminants. There was no effect related to time since preparation, number of accesses of the syringe at the time of sampling, or type of drug (ie, propofol vs other drugs). The authors concluded that contamination of syringes is uncommon and occurs at a low overall concentration of bacteria. Contamination does not appear to be time related, calling into question the United States Pharmacopeia chapter 797 requirement to dispose of drugs not used within 1 hour of preparation.

Comment: This very practical study is a great example of an effort to apply scientifically controlled findings to regulations that are initially based solely upon expert opinion and/or a limited amount of evidence. However, the authors are quick to point out the limitations of this small, preliminary study. In the discussion they state that a definitive study would require a sample size approximately 10 times larger than that of this study (1010 samples per group to obtain a significance of $p < .05$ and β of .8). It is interesting that the investigators observed poor aseptic practices during the study, including failure to use hand hygiene and to cleanse injection ports prior to drug administration. Also interesting is their comparison of the amount of bacteria detected in these cultures to the amount of bacteria introduced into the circulation during dental procedures. The estimated bacterial load of such dental procedures is reported to be 5000 to 10,000 CFUs, approximately 2 orders of magnitude greater than the estimated load present during anesthetic injections. In healthy patients, the transient dental bacteremia is typically cleared rapidly by the patient's immune system.³ Dental offices, however, are not likely to undergo the same level of aseptic preparation before and between surgeries. Furthermore, the small size of dental operatories and operator ventilation, as compared to the typical operating room, may be a factor, as airborne contamination contributes to the risk of preparing syringes in the operating room.⁴ More dental-specific research remains to be done before dental office-based anesthesia providers can challenge current recommendations for safe drug

handling in the operating environment. (Summary MA Saxen)

Additional papers of interest:

Kattan S, Lee S-M, Hersh EV, Karabucak B. Do buffered local anesthetics provide more successful anesthesia than nonbuffered solutions in patients with pulpally involved teeth requiring dental therapy? *J Am Dent Assoc.* 2019;150:165–177.

This systematic review examined 5 double-blind, randomized clinical trials and concluded buffered local anesthetic preparations were more likely to achieve successful local anesthesia than nonbuffered preparations.

Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet.* 2019;393:183–198.

Review article.

Rebecca M, Cunningham RM, Walton MA, Carter PM. The major causes of death in children and adolescents in the United States. *N Engl J Med.* 2018;379:2468–2475.

Special report from the Wide-ranging Online Data for Epidemiologic Research (WONDER) system of the Centers for Disease Control and Prevention (CDC), known as CDC WONDER.

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3. Heimdahl A, Hall G, Hedberg M, et al. Detection and quantification by lysis filtration of bacteremia after different oral surgical procedures. *J Clin Microbiol.* 1990;28:2205–2209.
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