Succinylcholine Use and Dantrolene Availability: Comment

To the Editor:

We read with interest the study by Larach *et al.*,[1] which performed extensive and complex analyses of three databases (*i.e.,* Multicenter Perioperative Outcomes Group, the North American Malignant Hyperthermia Registry, and the Anesthesia Closed Claims Project) as well as performed a systematic review of literature. One of the conclusions of the study was that succinylcholine alone without volatile anesthetics may trigger malignant hyperthermia (MH). The authors seem to allude that this finding negates the Society for Ambulatory Anesthesia recommendation[2] that permits Class B ambulatory facilities to stock succinylcholine for rescue of laryngospasm without stocking dantrolene. However, the Larach *et al.* study[1] has significant limitations, particularly the fact that the analyses did not include data from Class B facilities or the use of succinylcholine for laryngospasm. The succinylcholine dose used for situations assessed in this study (*i.e.*, possible difficult airway or electroconvulsive therapy) is generally much higher, and extrapolating the conclusions to low-dose (20 to 30 mg) succinylcholine commonly used to treat laryngospasm may be inappropriate. Of note, there are no reports of MH with low-dose succinylcholine. Also, as stated in the accompanying editorial by Hopkins,[3] "the evidence presented in this article is insufficient to convince me that succinylcholine in the absence of volatile anesthetics can trigger a life-threatening progressive hypermetabolic response in MH–susceptible patients..."

Class B facilities provide for minimally or moderately invasive procedures not requiring general and/or regional anesthesia. These facilities, which are growing in number, typically do not stock dantrolene because they do not use (or have the ability to use) volatile anesthetics. To avoid the costs associated with carrying and replacing dantrolene, they often elect not to stock succinylcholine, as its presence is perceived to mandate the availability of dantrolene. Given that the use of succinylcholine for laryngospasm is under reported, although there is a high likelihood of overdiagnosis of MH, the prevalence of MH is credibly significantly lower than the incidence of laryngospasm, which makes this a significant patient safety issue. The Society for Ambulatory Anesthesia position statement acknowledges this reality. Therefore, offering the alternative to stocking succinylcholine without dantrolene is prudent from patient safety and cost-effectiveness perspectives.

In summary, the evidence presented in the Larach *et al.*[1] study is not enough to contradict the extensive arguments put forth in the pragmatic Society for Ambulatory Anesthesia recommendations.[2] In the era of escalating healthcare costs and changing surgical environments, any prudent guideline should balance the potential benefits of a recommendation with costs and risk mitigation. It should also be noted that the Society for Ambulatory Anesthesia recommendation does not extend to the pediatric age group and facilities that provide inhalation anesthesia or use of succinylcholine during induction of general anesthesia. Furthermore, this recommendation emphasizes precautions such as the need for MH drills and transfer arrangements.

Competing Interests

Dr. Joshi has received honoraria from Pacira Pharmaceuticals (Parsippany, New Jersey) and Baxter Pharmaceuticals (Deerfield, Illinois). The remaining authors declare no competing interests.

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DOI: 10.1097/ALN.0000000000002949

References

1. Larach MG, Klumpner TT, Brandom BW, Vaughn MT, Belani KG, Herlich A, Kim TW, Limoncelli J, Riazi S, Sivak EL, Capacchione J, Mashman D, Kheterpal S, on behalf of the Multicenter Perioperative Outcomes Group: Succinylcholine use and dantrolene availability for malignant hyperthermia treatment: Database analyses and systematic review. Anesthesiology 2019; 130:41–54
2. Joshi GP, Desai MS, Gayer S, Vila H Jr; Society for Ambulatory Anesthesia (SAMBA): Succinylcholine for emergency airway rescue in class B ambulatory facilities: The Society for Ambulatory Anesthesia position statement. Anesth Analg 2017; 124:1447–9
3. Hopkins PM: Succinylcholine and dantrolene: Inseparable in the emergency cupboard? Anesthesiology 2019; 130:6–8

(Accepted for publication May 18, 2019.)

Succinylcholine Use and Dantrolene Availability: Reply

In Reply:

We thank Drs. Joshi, Desai, Valedon, and Gayer for their interest in our database analyses and systematic literature review of succinylcholine use and dantrolene availability for malignant hyperthermia treatment.[1] Joshi *et al.* state that our analyses do not include data from Class B ambulatory care facilities. The American Association for Accreditation of Ambulatory Surgery Facilities (Gurnee, Illinois) defines Class B facilities as those that allow minimally or moderately invasive surgical, endoscopic and/or pain management procedures under moderate sedation with intravenous sedation, and/or parenteral sedation, and/or field and peripheral nerve blocks, and/or dissociative drugs excluding propofol.[2] Because the Multicenter Perioperative Outcomes Group (Ann Arbor, Michigan) uses different classifications for its participating institutions, we do not know how many of the 24 freestanding ambulatory surgery centers captured in our study also might have been Class B facilities.

Joshi *et al.* may have missed our systematic literature review of succinylcholine use for treatment of laryngospasm (appendix 2, query 5 and key words with combinations, supplemental digital content 3).[1] Unfortunately, we found no published studies containing data on succinylcholine administration rate in ambulatory surgery centers for airway rescue.

Joshi *et al.* are correct as regards our Multicenter Perioperative Outcomes Group investigation. We could not do a retrospective analysis of laryngospasm in the Multicenter Perioperative Outcomes Group database because laryngospasm is not reported in a consistent, discrete fashion across the millions of cases included in our study. We chose grades III/IV mask ventilation as a surrogate for airway rescue to facilitate examination of 6,938,341 anesthetic cases. Succinylcholine was administered in freestanding ambulatory surgery centers in 1,388 cases of documented grade III/IV airway (table 2). For all anesthetizing locations, the succinylcholine dose for the 560 grade IV (impossible to ventilate) mask ventilation cases with a recorded succinylcholine amount and weight was 1.2 mg/kg (first quartile, 0.97; third quartile, 1.44; range, 0.12 to 3.02 mg/kg).[1]

Malignant hyperthermia cases triggered by low-dose succinylcholine without volatile anesthetic administration have been reported by Riazi. Two adult patients developed "almost certain" malignant hyperthermia after receiving 0.5 mg/kg and 0.8 mg/kg of succinylcholine to facilitate electroconvulsive therapy. Both of these patients had positive malignant hyperthermia diagnostic biopsies; one had a malignant hyperthermia causative mutation (supplemental digital content 6, reference 27 [table 3]).[1]

Although Joshi *et al.* quote part of Dr. Hopkins' statement, the remainder of his observations were omitted. We cite the entire paragraph with the omitted portions italicized. "Although the evidence presented in this article is insufficient to convince me that succinylcholine in the absence of volatile anesthetics can trigger a life-threatening progressive hypermetabolic response in MH-susceptible patients, *the evidence is similarly insufficient to rule out that this is the case. My view, therefore, is that equipoise is retained on this issue, and while it remains, patient safety is served by mandating that dantrolene be stocked where succinylcholine is available.*"[3]

Although Joshi *et al.* state that there is a high likelihood of overdiagnosis of malignant hyperthermia, we cannot find evidence to support this comment. Also, we could not find data to support the statement that "offering the alternative to stocking succinylcholine without dantrolene is prudent from patient safety and cost-effective perspectives."

What will be included in a malignant hyperthermia drill for Class B facilities that have no dantrolene to administer? We reiterate that time to dantrolene administration affects the likelihood of complications including coagulation, heart, lung, liver, kidney, and brain dysfunction (reference 9 [table 6]). Malignant hyperthermia complications increase substantially with every 10-min delay in initiating dantrolene treatment. If clinicians wait more than 50 min, complications increase to 100% (reference 27 [fig. 1]).[1]

Drs. Joshi, Desai, Valedon, and Gayer emphasize the need for transfer arrangements at Class B Ambulatory Facilities. We agree that transfer arrangements are essential for all freestanding facilities so that appropriate care for unanticipated medical, anesthetic, and/or surgical issues may be obtained. In 2012, four physicians representing the Society for Ambulatory Anesthesia (Drs. Belani, Metz, Piccone, and Valedon) helped to create a guide for the transfer of care of the malignant hyperthermia patient from ambulatory surgery centers to receiving hospital facilities. These physicians agreed that IV dantrolene therapy should be initiated before patient transfer.[4] Why is this guide no longer relevant to the care of ambulatory surgery center patients?

We stand by our conclusion that our data support stocking dantrolene wherever succinylcholine or volatile anesthetics may be used, even when succinylcholine is used solely for airway rescue.

Competing Interests

Many of the authors are unpaid volunteers for the nonprofit Malignant Hyperthermia Association of the United States (MHAUS; Sherburne, New York). They have served variously as directors of The North American Malignant Hyperthermia Registry of MHAUS and members of the board of MHAUS, the Professional Advisory Council of MHAUS, and/or the Malignant Hyperthermia Hotline of MHAUS. All of these positions are voluntary and unpaid. Many participated in the drafting of the current MHAUS recommendation for dantrolene availability in anesthetizing locations. Many of the authors have traveled to malignant hyperthermia conferences in the United States or Canada with MHAUS financial support. MHAUS receives funding support from MHAUS members, customers, medical associations and societies, foundations, and various corporations, including Eagle Pharmaceuticals (Woodcliff Lake, New Jersey), PAR Pharmaceuticals (Chestnut Ridge, New York), and U.S. WorldMeds, LLC (Louisville, Kentucky). Dr. Belani received several vials of Ryanodex from Eagle Pharmaceuticals, Inc., for use in a research study. Dr. Mashman has received a grant from Eagle Pharmaceuticals, Inc., for three vials of Ryanodex to bring on a medical mission trip. Dr. Riazi has received a consulting fee from Norgine Pharmaceuticals (Amsterdam, The Netherlands) and is also a member of the scientific advisory board of the RYR1 Foundation (Pittsburgh, Pennsylvania). Dr. Sivak has been a principal investigator for a Merck (Kenilworth, New Jersey) sponsored study of sugammadex (November 7, 2017 through August 3, 2018).

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DOI: 10.1097/ALN.0000000000002950

References

1. Larach MG, Klumpner TT, Brandom BW, Vaughn MT, Belani KG, Herlich A, Kim TW, Limoncelli J, Riazi S, Sivak EL, Capacchione J, Mashman D, Kheterpal S, on behalf of the Multicenter Perioperative Outcomes Group: Succinylcholine use and dantrolene availability for malignant hyperthermia treatment: Database analyses and systematic review. Anesthesiology 2019; 130:41–54
2. AAAASF Surgical Version 14.5. Available at: http://www.aaaasf.org. Accessed May 5, 2019.
3. Hopkins PM: Succinylcholine and dantrolene: Inseparable in the emergency cupboard? Anesthesiology 2019; 130:6–8
4. Larach MG, Dirksen SJH, Belani KG, Brandom BW, Metz KM, Policastro MA, Rosenberg H, Valedon A, Watson CB: Creation of a guide for the transfer of care of the malignant hyperthermia patient from ambulatory surgery centers to receiving hospital facilities. Anesth Analg 2012; 114:94–100

(Accepted for publication May 18, 2019.)

Opioid-induced Ventilatory Depression in Sleep Apnea: Comment

To the Editor:

On the front page of the February 2019 issue of Anesthesiology, the article by Doufas *et al.* was encapsulated as, "Adults with Obstructive Sleep Apnea Do Not Have Increased Sensitivity to Opioid-induced Ventilatory Depression."[1] This is potentially misleading.

The complexity of the study design, pharmacokinetic/pharmacodynamic modeling, and the assumptions and limitations of the study may be beyond the understanding of the average reader. In their accompanying editorial, Henthorn and Olofsen did an admirable job explaining the many limitations.[2] They stated, "...we should be very cautious drawing conclusions in the language of pharmacokinetics–pharmacodynamics when there are no drug concentrations (pharmacokinetics) data and when there is non–steady-state effect data and either the onset effect or offset effect is missing."

The front page title, however, suggests the study endpoint of Doufas *et al.* can be broadly interpreted as applicable to all opioids in all clinical situations encountered by obstructive sleep apnea patients, which is overly simplistic. Is a target-controlled infusion of 4 ng/ml of remifentanil for 10 min in a well-lit and noisy operating room in a patient anticipating surgery an appropriate surrogate for the level of consciousness, airway, and respiratory dynamics of patients with obstructive sleep apnea on morphine patient-controlled analgesia in a quiet hospital ward at nighttime? Even