ANESTHESIOLOGY

Succinylcholine Use and Dantrolene Availability for Malignant Hyperthermia Treatment

Database Analyses and Systematic Review

Marilyn Green Larach, M.D., F.A.A.P., Thomas T. Klumpner, M.D., Barbara W. Brandom, M.D., Michelle T. Vaughn, M.P.H., Kumar G. Belani, M.B.B.S., M.S., F.A.A.P., Andrew Herlich, D.M.D., M.D., F.A.A.P., F.A.S.A., Tae W. Kim, M.D., M.E.H.P., Janine Limoncelli, M.D., Sheila Riazi, M.Sc., M.D., FRCPC, Erica L. Sivak, M.D., John Capacchione, M.D., Darlene Mashman, M.D., Sachin Kheterpal, M.D., M.B.A., on behalf of the Multicenter Perioperative Outcomes Group*

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Malignant hyperthermia (MH) events are uncommon but potentially lethal adverse responses to volatile anesthetic agents or succinylcholine. Some question whether succinylcholine without volatile anesthetics triggers MH.[1] Dantrolene is an effective antidote.[2,3] Health Canada (Ottawa, Ontario) and the U.S. Food and Drug Administration (Silver Spring, Maryland) approved iv dantrolene for MH treatment in 1974 and 1979, respectively.[4]

Malignant Hyperthermia Association of the United States (MHAUS; Sherburne, New York) guidelines state that dantrolene must be available within 10 min of the decision to treat MH at all anesthetizing/sedating locations where MH-triggering agents are used.[5] MHAUS recommends an initial 2.5-mg/kg dantrolene dose repeated until adequate response is achieved.[6] MHAUS mandates that each institution stock at least 720 mg of dantrolene—sufficient to administer 10 mg/kg to a 70-kg patient.

In 2014, the American Association for Accreditation of Ambulatory Surgery Facilities (Gurnee, Illinois) created a "protocol to manage the possibility of malignant hyperthermia following its (succinylcholine) use." Dantrolene was required only if Class C-M/C facilities stocked volatile anesthetic agents. (Class C-M facilities may administer deep sedation, field/peripheral nerve blocks, spinal, and epidural anesthesia. Class C facilities have no anesthetic restrictions.)[7]

In 2017, the Society for Ambulatory Anesthesia (Chicago, Illinois) published a protocol for Class B ambulatory

ABSTRACT

Background: Although dantrolene effectively treats malignant hyperthermia (MH), discrepant recommendations exist concerning dantrolene availability. Whereas Malignant Hyperthermia Association of the United States guidelines state dantrolene must be available within 10 min of the decision to treat MH wherever volatile anesthetics or succinylcholine are administered, a Society for Ambulatory Anesthesia protocol permits Class B ambulatory facilities to stock succinylcholine for airway rescue without dantrolene. The authors investigated (1) succinylcholine use rates, including for airway rescue, in anesthetizing/sedating locations; (2) whether succinylcholine without volatile anesthetics triggers MH warranting dantrolene; and (3) the relationship between dantrolene administration and MH morbidity/mortality.

Methods: The authors performed focused analyses of the Multicenter Perioperative Outcomes Group (2005 through 2016), North American MH Registry (2013 through 2016), and Anesthesia Closed Claims Project (1970 through 2014) databases, as well as a systematic literature review (1987 through 2017). The authors used difficult mask ventilation (grades III and IV) as a surrogate for airway rescue. MH experts judged dantrolene treatment. For MH morbidity/mortality analyses, the authors included U.S. and Canadian cases that were fulminant or scored 20 or higher on the clinical grading scale and in which volatile anesthetics or succinylcholine were given.

Results: Among 6,368,356 queried outcomes cases, 246,904 (3.9%) received succinylcholine without volatile agents. Succinylcholine was used in 46% (n = 710) of grade IV mask ventilation cases (median dose, 100 mg, 1.2 mg/kg). Succinylcholine without volatile anesthetics triggered 24 MH cases, 13 requiring dantrolene. Among 310 anesthetic-triggered MH cases, morbidity was 20 to 37%. Treatment delay increased complications every 10 min, reaching 100% with a 50-min delay. Overall mortality was 1 to 10%; 15 U.S. patients died, including 4 after anesthetics in freestanding facilities.

Conclusions: Providers use succinylcholine commonly, including during difficult mask ventilation. Succinylcholine administered without volatile anesthetics may trigger MH events requiring dantrolene. Delayed dantrolene treatment increases the likelihood of MH complications. The data reported herein support stocking dantrolene wherever succinylcholine or volatile anesthetics may be used.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dantrolene effectively treats malignant hyperthermia, but there are discrepant recommendations for dantrolene availability in facilities that stock succinylcholine for airway rescue but do not use volatile anesthetics.

What This Article Tells Us That Is New

- The authors performed an analysis of data from three databases and a systematic literature review.
- Providers frequently use succinylcholine, including during difficult mask ventilation.
- Succinylcholine given without volatile anesthetics triggered 24 malignant hyperthermia events, 13 of which were treated with dantrolene. Fourteen patients experienced substantial complications, and one died.
- Delayed dantrolene treatment worsened patient outcomes.

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facilities that choose to not stock dantrolene and use "low-dose" succinylcholine for emergency airway rescue. (Class B facilities allow minimally or moderately invasive surgery with oral, parenteral, iv sedation, and/or analgesic or dissociative drugs.) The protocol states MH-susceptible individuals should not receive care in these facilities; providers should be "familiar with the early recognition and management of MH crisis," "conduct annual MH drills," and have an "agreement with the closest health care center carrying dantrolene."[8]

Along with MHAUS, the American Association for Accreditation of Ambulatory Surgery Facilities and the Society for Ambulatory Anesthesia emphasize MH preoperative screening to decrease MH events. However, the North American Malignant Hyperthermia Registry of MHAUS (Gainesville, Florida) studies show that taking a personal or family history will not prevent all MH cases. For 152 MH patients, the median number of unremarkable prior general anesthetics was 2 (first quartile, 1; third quartile, 2; range, 0 to 30). Further, 7.2% (24/332) of positive family histories were discovered after anesthetics triggered MH events. Three of these 24 patients died.[9,10] Finally, limited U.S./Canadian testing interferes with MH identification.[11]

In contrast to Society for Ambulatory Anesthesia recommendations, the Institute for Safety in Office-Based Surgery (Boston, Massachusetts) checklists state "36 vials of dantrolene sodium must be available wherever MH triggering agents are used."[12] Ontario, Massachusetts, and Tennessee mandate availability of succinylcholine for airway rescue and dantrolene to treat possible succinylcholine-induced MH.[13–15]

Given the discrepant guidance for MH preparation, we utilized targeted queries of three databases: (1) the Multicenter Perioperative Outcomes Group (Ann Arbor, Michigan) database of sedations/anesthetics administered in many institutions across multiple locations, (2) the North American Malignant Hyperthermia Registry, containing detailed MH event information, and (3) the Anesthesia Closed Claims Project (Seattle, Washington) of adverse anesthetic outcomes, paired with a systematic literature review to investigate three questions. What is the succinylcholine use rate, including for airway rescue, in various anesthetizing/sedating locations? Does succinylcholine without volatile anesthetics trigger MH including cases warranting dantrolene, and are these associated with morbidity/mortality? What is the relationship between dantrolene administration (time/dose) and U.S./Canadian MH morbidity/mortality rates?

Materials and Methods

Database Search Strategy

The Multicenter Perioperative Outcomes Group database was queried for frequency of succinylcholine use, including airway rescue, in various anesthetizing/sedating locations. The Multicenter Perioperative Outcomes Group's database includes observational electronic medical records data submitted by anesthesiology departments from an international medical center consortium. It does not include Canadian institutions, has few office-based locations, and does not include data from sedations/anesthetics administered without anesthesiology involvement.[16,17]

After Institutional Review Board (University of Michigan, Ann Arbor, Michigan) approval, we queried the Multicenter Perioperative Outcomes Group database for all patients receiving an anesthetic from January 1, 2005 through December 31, 2016. Anesthetics included monitored anesthesia care, neuraxial, regional block, and/or general anesthetics. We excluded anesthetic records with ambiguously defined or erroneously assigned locations, and locations with small sample sizes that would affect generalizability (*e.g.*, office-based locations). We grouped some locations (see Supplemental Digital Content 1 for Multicenter Perioperative Outcomes Group location classifications lists, http://links.lww.com/ALN/B798).

We calculated succinylcholine utilization, with and without volatile anesthetic administration, across various anesthetizing locations. We defined succinylcholine administration as succinylcholine dose greater than 0 and volatile anesthetic administration as expired desflurane, isoflurane, or sevoflurane values greater than 0.

A subgroup analysis evaluated anesthetics with difficult mask ventilation. A study author (T.T.K.) manually reviewed airway mask ventilation notes and categorized difficulty of mask ventilation based on established groupings.[18] We excluded cases without clear mask ventilation

Corresponding article on page 6. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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From The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States, University of Pittsburgh Medical Center, Mercy Hospital, Pittsburgh, Pennsylvania (2000 through 2017; M.G.L., B.W.B.); Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida (2018; M.G.L.); Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan (T.T.K., M.T.V., S.K.); Department of Nurse Anesthesia, University of Pittsburgh, Pittsburgh, Pennsylvania (2016 through 2018; B.W.B.); Department of Anesthesiology, School of Medicine (K.G.B., T.W.K., J.C.) and School of Public Health (K.G.B.), University of Minnesota, Minneapolis, Minnesota; Department of Anesthesiology, Children's Hospital of Pittsburgh (E.L.S.), and Department of Anesthesiology (A.H.), University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Department of Anesthesiology, Weill Cornell Medical College and New York–Presbyterian Hospital, New York, New York (J.L.); Department of Anesthesia and Pain Management, University Health Network, University of Toronto, Toronto, Canada (S.R.); Department of Anesthesiology and Pediatrics, Emory University School of Medicine, and Children's Healthcare of Atlanta, Egleston Hospital, Atlanta, Georgia (D.M.). Current positions: Dr. Larach is now at the Department of Anesthesiology, University of Florida, Gainesville, Florida. Dr. Sivak is now at the Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital and The Ohio State University, Columbus, Ohio.

*Members of the Multicenter Perioperative Outcomes Group are listed in appendix 1.

documentation from subgroup analysis. For cases with two different grades, we assigned the more severe grade. We determined succinylcholine use among cases with grade I/II difficulty, grade III/IV difficulty, and grade IV difficulty alone. We did not analyze whether succinylcholine was given before or after documentation of mask ventilation difficulty. A subgroup analysis of grade IV mask ventilation cases analyzed succinylcholine dosage. Another subgroup analysis compared frequency of succinylcholine use during grade IV mask ventilation among pediatric patients ages 0 to under 10 yr and 10 to under 18 yr.

The Anesthesia Closed Claims Project database consists of 11,035 cases from closed malpractice claims of participating malpractice insurance organizations with standardized evaluation of adverse anesthetic outcomes. This database was searched for cases from 1970 through 2014 in which succinylcholine without volatile anesthetic agents triggered an MH event.

The North American Malignant Hyperthermia Registry database contains more than 900 AMRA (Adverse Metabolic/Musculoskeletal Reactions to Anesthesia) forms submitted voluntarily by healthcare professionals. After Institutional Review Board (University of Pittsburgh, Pittsburgh, Pennsylvania) approval, the AMRA database was searched for reports submitted from 2013 through 2016 of (1) succinylcholine without volatile anesthetics agents triggering an MH event and (2) death associated with an MH event.

We searched North American Malignant Hyperthermia Registry and Anesthesia Closed Claims Project databases for relevant unpublished MH event data using the following criteria.

Inclusion criteria were human, MH triggered by volatile anesthetic agents or succinylcholine with severity graded as "somewhat greater than likely," "very likely," or "almost certain" (greater than or equal to 20) on the MH clinical grading scale or event judged "fulminant" by a clinician.[19] We limited morbidity/mortality rates to those calculated for U.S./Canadian acute event hospitalizations.

Exclusion criteria were nonhuman, events with severity graded as "almost never," "unlikely," or "somewhat less than likely" (less than 20) by the MH clinical grading scale or not "fulminant" as reported by a clinician, MH not triggered by the administration of volatile anesthetic agents/succinylcholine (*e.g.*, "awake" or "stress-induced" MH), and postdischarge and non-U.S./Canadian MH morbidity/mortality rates.

For database and literature searches, MH experts (M.G.L., B.W.B., S.R.) judged whether dantrolene treatment was warranted in succinylcholine without volatile anesthetic MH cases.

Literature Search Strategy

We prospectively registered our systematic review protocol with PROSPERO, International prospective register of systematic review, (York, United Kingdom) on April 30, 2017 (CRD42017064696) with a final revision approved on October 30, 2018. We used 11 queries to evaluate evidence concerning dantrolene availability for MH treatment in various anesthetizing/sedating locations (see appendix 2 for full text of each query).

We searched PubMed, EMBASE, and Cochrane Library databases for human studies including qualitative studies and case reports published in English or with an English abstract from January 1, 1969, through at least December 31, 2017. For selected queries, OVID, MEDLINE, Westlaw, and Google databases were also searched (see appendix 2 for key words/combinations). Our inclusion and exclusion criteria were identical to those listed above for the North American Malignant Hyperthermia Registry and Closed Claims Project queries.

We repeated literature searches before final analyses and retrieved 13 additional studies. Each query author prepared a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram, contacted principal authors for relevant unreported data, and created an evidence table summarizing relevant literature with Oxford Center for Evidence-based Medicine level and Cochrane Collaboration Tool bias assessment.[20–22] At least one additional author reviewed bias evaluations. We circulated evidence tables to all authors to elicit feedback.

Data Synthesis

For Multicenter Perioperative Outcomes Group data analysis, we summarized descriptive statistics including frequencies, percentages, and 95% CI. For the pediatric subgroup airway analysis, a two-sided Fisher exact chi-square test compared percentages across two age groups with a P value of less than 0.05 considered significant. We performed all analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina). For North American Malignant Hyperthermia Registry data analysis, we summarized descriptive statistics.

For the literature search, we prepared a narrative synthesis for included studies. A summary PRISMA flow diagram was created. We compiled individual query PRISMA flow diagrams and tables. We combined individual query results to answer the three study questions.

Results

We identified 6,938,341 sedative/anesthetic cases in the Multicenter Perioperative Outcomes Group database. Of these, 6,368,356 had valid sedative/anesthetic locations, with 95.7% occurring in U.S. institutions. Location and degree of mask ventilation difficulty (grades I through IV) was documented for 1,611,740 cases; 710 had grade IV mask ventilation and succinylcholine dose in milligrams recorded. Weight was available for 560 of these 710 cases

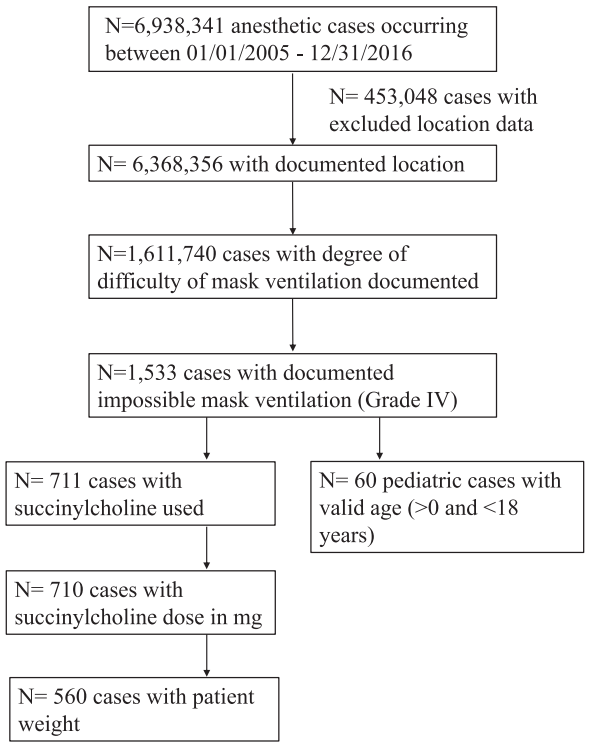

Fig. 1. This flow diagram depicts our examination of the Multicenter Perioperative Group database. We identified 6,938,341 sedative/anesthetic cases. Of these, 6,368,356 had a valid sedative/anesthetic location. For 1,611,740 cases, a location and degree of mask ventilation difficulty (grades I through IV) were documented. We identified 711 cases with grade IV mask ventilation documented and a recorded use of succinylcholine; 710 of these cases had the dose of succinylcholine recorded in milligrams. In 560 of these grade IV mask ventilation cases where a dose in milligrams of succinylcholine was provided, weight was available, permitting a milligrams per kilogram succinylcholine dose calculation. We also identified 60 pediatric cases with documented location, age, and grade IV mask ventilation.

permitting milligrams per kilogram succinylcholine dose calculation. We identified 60 pediatric cases with documented location, age, and grade IV mask ventilation (fig. 1).

We identified 91 AMRA reports in the North American Malignant Hyperthermia Registry from 2013 through 2016; 75 met inclusion criteria. Thirty MH cases were identified in the Anesthesia Closed Claims Project database; one met inclusion criteria.

We examined PubMed, Cochrane, EMBASE, OVID, MEDLINE, Google, and Westlaw databases, and identified 20,830 articles for possible inclusion. We screened 2,240 abstracts, reviewed 1,078 full-text manuscripts, and qualitatively synthesized 55 unique study results (fig. 2).

For our three primary questions, the results are as follows.

1. What Is the Succinylcholine Use Rate, Including for Airway Rescue, in Various Anesthetizing/Sedating Locations?

1a. Hospital-based Operating Suites (Including Delivery Suites), Intensive Care Units, and Emergency Departments

Multicenter Perioperative Outcomes Group Database Search. In hospital-based operating rooms, 20.2% (n = 859,294) of anesthetics included succinylcholine, and 4.7% (n = 201,347) included succinylcholine without volatile anesthetics. Among pediatric hospital–based operating rooms, 5.8% (n = 31,100) of anesthetics included succinylcholine, and 0.6% (n = 3,343) included succinylcholine without volatile agents. For obstetrics operating rooms, 7.5% (n = 7,894) of all anesthetics included succinylcholine, while 2.1% (n = 2,167) included succinylcholine in the absence of volatile anesthetics (table 1). The Multicenter Perioperative Outcomes Group database did not have sufficient location data to support an analysis of delivery suites, intensive care units, or emergency departments.

Literature Search. The succinylcholine administration rate varied between 0.7 and 94.3%. The highest succinylcholine use rate was reported in a 42-month prospective observational cohort of airway management in a tertiary care hospital emergency department.[23] Three studies reported succinylcholine administration in the operating room as part of airway management during general anesthesia.[24–26] Five studies performed in the emergency department, one in the pediatric intensive care unit, and one in the neonatal intensive care unit reported succinylcholine administration to facilitate endotracheal intubation. No studies examined obstetrics patients. Studies were designed to determine which drug facilitated endotracheal intubation. Therefore, cohorts reported were a small part of the entire population of hospitalized patients; no estimate of the overall succinylcholine administration rate per patient per unit of time could be made (Supplemental Digital Content 2, http://links.lww.com/ALN/B799).[27–34]

1b. Procedural Suites (Radiology, Electroconvulsive Therapy)

Multicenter Perioperative Outcomes Group Database Search. In acute care remote locations, 14.1% (n = 66,782) of all anesthetics included succinylcholine. Succinylcholine was used without volatile agents in 5.6% (n = 26,561) of cases. For pediatric hospital acute care remote locations, the frequency of succinylcholine use was 2.3% (n = 1,402); succinylcholine without volatile anesthetics was administered in 0.1% (n = 74) of cases (table 1). The Multicenter Perioperative Outcomes Group does not define how many of these acute care remote locations are in radiology suites or electroconvulsive therapy rooms.

Literature Search. No publications addressed this issue.

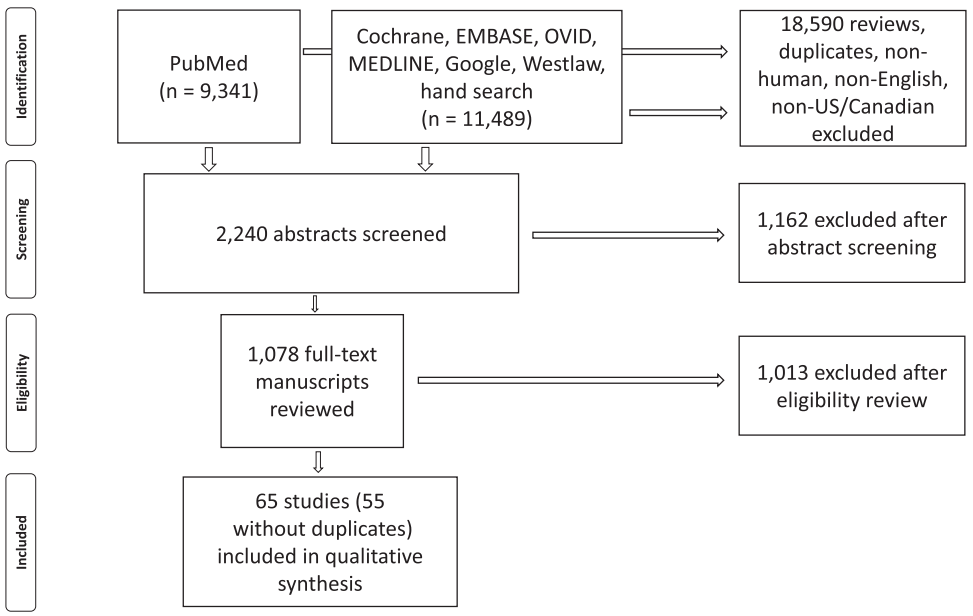

Fig. 2. This Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) figure for systematic literature search depicts summary statistics for our 11 queries. We examined PubMed, Cochrane, EMBASE, OVID, MEDLINE, Google, and Westlaw databases, and identified 20,830 articles for possible inclusion. We excluded 18,590 reviews, duplicate publications, nonhuman studies, studies lacking English abstracts, and for malignant hyperthermia morbidity and mortality queries, non-U.S. or Canadian studies. We screened 2,240 abstracts. After exclusion of 1,162 additional studies, we reviewed 1,078 full-text manuscripts. After eligibility review, an additional 1,013 studies were excluded. A total of 65 studies was analyzed. After 10 duplicates among queries were excluded, we performed a qualitative synthesis of 55 unique study results.

1c. Ambulatory Surgery Centers

Multicenter Perioperative Outcomes Group Database Search. For ambulatory surgery centers attached to hospitals, succinylcholine use frequency was 12.5% (n = 39,049). Succinylcholine without volatile anesthetics was used in 2.4% (n = 7,535) of cases. For freestanding ambulatory surgery centers, succinylcholine use frequency was 4.8% (n = 29,892); 0.9% (n = 5,877) of cases involved succinylcholine without volatile anesthetics (table 1).

Literature Search. No studies specifically addressed succinylcholine administration rate in ambulatory surgery centers. However, six studies compared succinylcholine (n = 202 subjects) with other agents with respect to intubating conditions, myalgias, and effectiveness, thereby implying succinylcholine is used in ambulatory surgery centers (Supplemental Digital Content 3, http://links.lww.com/ALN/B800).[35–40]

1d. Medical, Oral Surgery, and Dental Offices

Literature Search. One unblinded prospective Norwegian single-site 5-yr study measured laryngospasm treatment with succinylcholine in healthy pediatric patients anesthetized by a dedicated anesthetic team using total iv anesthesia with laryngeal mask airway for adenotonsillectomy. They found 10 of 1,126 patients experienced less than 90% oxygen saturation measured by pulse oximetry attributable to laryngospasm, and 9 of 1,126 (0.8%) required succinylcholine. No patient developed MH (Supplemental Digital Content 4, http://links.lww.com/ALN/B801).[41]

1e. Airway Rescue

Multicenter Perioperative Outcomes Group Database Search. Among the 59,762 patients of any age found to have grade III/IV difficult mask ventilation, the frequency of succinylcholine use was 33.8% (n = 20,175). In attached and free ambulatory surgery centers, the frequency of succinylcholine use with grade III/IV difficult mask ventilation was 32.9% (n = 701) and 36.7% (n = 509), respectively. For the 1,533 grade IV mask ventilation cases, frequency of succinylcholine use was 46.4% (n = 711; table 2). Among the 710 grade IV mask ventilation cases with a recorded milligrams of succinylcholine amount, the median dose was 100 mg (first quartile, 100; third quartile, 140; range, 10 to 320 mg). For the 560 grade IV mask ventilation cases with a recorded succinylcholine amount and weight, the dose was 1.2 mg/kg (first quartile, 0.97; third quartile, 1.44; range, 0.12 to 3.02 mg/kg). For the 60 pediatric patients (age less than 18 yr) with a grade IV mask, succinylcholine use frequency was 25% (n = 15). There was no difference in succinylcholine use between those aged 0 to 10 yr and those aged 10 to 18 yr ($P = 0.12$).

Literature Search. Eighteen studies reported succinylcholine use in 0.02 to 90% of individuals requiring "airway rescue" for predominantly laryngospasm. A large U.S. retrospective

Table 1. Frequency of Succinylcholine Use with and without Volatile Agents* during Sedations or Anesthetics† by Location

Location No. of Reporting Institutions‡	Cases with Succinylcholine and Volatile Agent Administration N % (95% CI)	Cases with Succinylcholine and without Volatile Agent Administration N % (95% CI)	Cases with Succinylcholine Administration N % (95% CI)	All Cases N % (95% CI)
Acute care hospital main OR	657,947	201,347	859,294	4,250,831
N = 38 institutions	15.5 (15.4–15.5)	4.7 (4.7–4.8)	20.2 (20.2–20.3)	65.6 (65.5–65.6)
Acute care hospital remote location	40,221	26,561	66,782	475,483
N = 29 institutions	8.5 (8.4–8.5)	5.6 (5.5–5.7)	14.1 (14.0–14.1)	7.3 (7.3–7.4)
Pediatric hospital main	27,757	3,343	31,100	536,780
N = 10 institutions	5.2 (5.1–5.2)	0.6 (0.6-0.6)	5.8 (5.7–5.9)	8.3 (8.3-8.3)
Pediatric hospital remote location	1,328	74	1,402	61,451
N = 7 institutions	2.2 (2.1–2.3)	0.1 (0.1–0.2)	2.3 (2.2–2.4)	1.0 (0.9–1.0)
ASC attached	31,514	7,535	39,049	313,743
N = 15 institutions	10.0 (9.9–10.2)	2.4 (2.4–2.5)	12.5 (12.3–12.6)	4.8 (4.8–4.9)
ASC free	24,015	5,877	29,892	624,750
N = 24 institutions	3.8 (3.8–3.9)	0.9 (0.9–1.0)	4.8 (4.7–4.8)	9.6 (9.6–9.7)
Obstetrics OR	5,727	2,167	7,894	105,318
N = 22 institutions	5.4 (5.3–5.6)	2.1 (2.0–2.2)	7.5 (7.3–7.7)	1.6 (1.6-1.6)
All locations	788,509	246,904	1,035,413	6,368,356
N = 40 institutions	12.4 (12.4-12.4)	3.9 (3.9-3.9)	16.3 (16.2–16.3)	

*Volatile agent defined by any nonzero value for expired desflurane, isoflurane, or sevoflurane. †Anesthetics include monitored anesthesia care, neuraxial, regional block, or general anesthetics. ‡A single institution may be reporting data from more than one physical entity, *e.g.*, a single institution may include more than one acute care hospital, remote location, obstetrics unit, or ASC.

ASC, ambulatory surgical center; free, freestanding; OR, operating room.

quality improvement study in a single institution examined 21,452 pediatric cases in which 21 laryngospasm episodes were reported; 38% (n = 8) required succinylcholine.[42] An Australian Incident Monitoring Study examined 189 laryngospasm events; 15% (n = 29) required succinylcholine.[43] Most studies demonstrated reporting bias with possible underreporting. Seven studies reported succinylcholine doses that varied significantly: 0.1 mg/kg (n = 2),[44] 0.25 mg/kg (n = 1),[45] 0.5 mg/kg (n = 45),[46,47] and 1 mg/kg (n = 8).[48–50] Studies were Oxford Center for Evidence-based Medicine levels 2 through 4 (Supplemental Digital Content 5, http://links.lww.com/ALN/B802).[41,44,48,51–58]

2. Does Administration of Succinylcholine without Concomitant Volatile Anesthetic Administration Trigger MH Including Cases Warranting Dantrolene, and Are These Associated with Morbidity/Mortality?

North American Malignant Hyperthermia Registry Database Search. Two MH events after succinylcholine without volatile anesthetic administration were reported in U.S. hospitals. Both cases received dantrolene warranted by clinical circumstances, although administration times were unclear. Both patients experienced MH morbidity (decreased level of consciousness) but survived.

Anesthesia Closed Claims Database Search. One fatal MH event followed administration of multiple doses of succinylcholine without volatile anesthetic administration in a U.S. hospital in 1984. Dantrolene was warranted and administered, but the time of administration was unknown.

Literature Search. The literature reported 21 MH events after the administration of succinylcholine without exposure to volatile anesthetic agents, 18 in the United States or Canada.[27,59–63] These cases did not overlap with the two North American Malignant Hyperthermia Registry events. Succinylcholine doses were 0.5 to 2.5 mg/kg (n = 12).[27] Ten cases received dantrolene. Its use was clinically indicated in all cases, although administration times were not well documented. MH morbidities in 12 cases included rhabdomyolysis, change in consciousness level, life-threatening arrhythmias, and renal dysfunction/failure. All articles have reporting bias attributable to selective reporting. See Supplemental Digital Content 6, http://links.lww.com/ALN/B803.

3. What Is the Relationship between Dantrolene Administration and MH Morbidity and Mortality Rates in the United States and Canada?

3a. MH Morbidity

Literature Search.

Description. MH morbidities included cardiac dysfunction including cardiac arrest, renal dysfunction, consciousness level change/coma, pulmonary edema, disseminated intravascular coagulation, and hepatic dysfunction. Other

Table 2. Frequency of Succinylcholine Use* during Graded Mask Ventilation

Location No. of Reporting Institutions†	Succinylcholine Use in Any Case with Grade I or II N % (95% CI)	Succinylcholine Use in Any Case with Grade III or IV N % (95% CI)	Succinylcholine Use in Any Case with Grade IV N % (95% CI)	Succinylcholine Use with All Grades N % (95% CI)	Cases with Documented Grade I or II N	Cases with Documented Grade III or IV N	Cases with Documented Grade IV N	Cases with Documented Grade N
Acute care hospital main OR	259,290	17,578	611	276,868	1,120,202	52,320	1,272	1,172,522
N = 20 institutions	23.1 (23.1–23.2)	33.6 (33.2–34.0)	48.0 (45.3–50.8)	23.6 (23.5–23.7)				
Acute care hospital remote	35,641	1,162	32	36,803	84,728	2,641	68	87,369
N = 15 institutions	42.1 (41.7–42.4)	44.0 (42.1–45.9)	47.1 (34.8–59.6)	42.1 (41.8–42.5)				
Pediatric hospital main	6,330	177	6	6,507	159,312	1,090	32	160,402
N = 6 institutions	4.0 (3.9–4.1)	16.2 (14.1–18.6)	18.8 (7.2–36.4)	4.1 (4.0–4.2)				
Pediatric hospital remote	547	20	1	567	24,717	158	6	24,875
N = 4 institutions	2.2 (2.0–2.4)	12.7 (7.9–18.9)	16.7 (0.4–64.1)	2.3 (2.1–2.5)				
ASC attached	12,577	701	38	13,278	74,666	2,130	116	76,796
N = 9 institutions	16.8 (16.6–17.1)	32.9 (30.9–35.0)	32.8 (24.3–42.1)	17.3 (17.0–17.6)				
ASC free	10,541	509	19	11,050	87,221	1,388	34	88,609
N = 14 institutions	12.1 (11.9–12.3)	36.7 (34.1–39.3)	55.9 (37.9–72.8)	12.5 (12.3–12.7)				
Obstetrics OR	763	28	4	791	1,132	35	5	1,167
N = 14 institutions	67.4 (64.6–70.1)	80.0 (63.1–91.6)	80.0 (28.4–99.5)	67.8 (65.0–70.5)				
All locations	325,689	20,175	711	345,864	1,551,978	59,762	1,533	1,611,740
N = 20 institutions	21.0 (20.9–21.0)	33.8 (33.4–34.1)	46.4 (43.9–48.9)	21.5 (21.4–21.5)				

*Succinylcholine could have been administered at any point at any dose during the anesthetic. †A single institution may be reporting data from more than one physical entity; *e.g.*, a single institution may include more than one acute care hospital, remote location, obstetrics unit, or ASC.

ASC, ambulatory surgical center; free, freestanding; OR, operating room.

complications included compartment syndrome and pleural effusion. Some may consider MH recrudescence as a morbidity.[9]

Rates. Complications not including recrudescence, cardiac arrest, or death occurred in 20 to 37% of 310 MH events. These rates were consistent across two nonoverlapping databases (North American Malignant Hyperthermia Registry and Toronto General MH Database). Overall, as MH event severity increased, morbidity rate increased.[9,10,27] The MH recrudescence rate was estimated to be 20%.[64]

Relationship to Dantrolene (Dose and Time). In the largest retrospective MH morbidity study, there was inadequate power to detect differences between the group receiving dantrolene and the one not receiving dantrolene.[9] Initial dantrolene dose was not significant in a model analyzing likelihood of complications (odds ratio, 1.13; 95% CI, 0.96 to 1.33; $P = 1.000$). For the group not experiencing complications, median initial dantrolene dose was 2.31 (95% CI, 1.47 to 2.67) mg/kg and for the group experiencing complications, median initial dose of dantrolene was 2.48 (95% CI, 2.00 to 2.89) mg/kg. However, the likelihood of an MH complication increased 1.61 (95% CI, 1.16 to 2.25) times for every 30-min increase in time between first MH sign and first dantrolene dose.[9] Complications increased with increasing minutes to dantrolene use from the first MH sign. Complications increased substantially for each 10-min delay in dantrolene administration. Complication rates increased to 100% when dantrolene was delayed beyond 50 min.[27] Studies were all Oxford Center for Evidence-based Medicine level 3 or 4 and may have been limited by possible selection bias, reporting, and recall bias (Supplemental Digital Content 7, http://links.lww.com/ALN/B804).[65]

3b. MH Mortality

Rates.

Literature Search and North American Malignant Hyperthermia Registry Database Search. There are three Oxford Center for Evidence-based Medicine level 3 studies of MH mortality derived from the North American Malignant Hyperthermia Registry, with one having an overlapping dataset. Mortality rates ranged from 1.4 to 9.5% in predominantly U.S. cases.[10,65,66] There are also unpublished North American Malignant Hyperthermia Registry deaths (3/75) from 2013 through 2016. For years 1987 through 2016, a total of 15 (n = 450 MH events) deaths were reported to the North American Malignant Hyperthermia Registry. Four of 15 MH-triggering anesthetics were administered in freestanding facilities. North American Malignant Hyperthermia Registry studies were limited by possible selection bias, reporting, and recall bias. We also identified four International Classification of Diseases, Ninth Revision–based MH studies reporting 4.6 to 11.7% mortality rates. As claims data do not differentiate between MH events and MH-susceptible individuals, these probably represent overestimates for U.S. populations (Supplemental Digital Content 8, http://links.lww.com/ALN/B805).[67–70]

Relationship to Dantrolene.

Literature Search. One study demonstrated that timely dantrolene administration (less than or equal to 6 h after initial MH sign) decreased mortality from 75 to 0%. This was a highly significant result in a small, unblinded prospective study that provided evidence for U.S. Food and Drug Administration approval of iv dantrolene to treat MH.[3] Subsequent retrospective North American Malignant Hyperthermia Registry studies (1987 through 2012) showed that initial dantrolene (mg/kg) doses did not differ between those who died of MH and those who did not. The time intervals between first MH sign and first dantrolene administration also did not differ, but low patient death rates resulted in low power (18%) to detect a difference. In a North American Malignant Hyperthermia Registry study with eight cardiac arrests and four deaths, total dantrolene dose was higher in those who arrested or died compared with those who did not (10 *vs.* 5 mg/kg).[10,66] All five references are Oxford Center for Evidence-based Medicine levels 3 and 4 (Supplemental Digital Content 9, http://links.lww.com/ALN/B806).[9,65]

Discussion

Providers use succinylcholine in modern anesthetic practice. Overall, 16% (n = 1,035,413) of Multicenter Perioperative Outcomes Group cases included succinylcholine; 4% (n = 246,904) included succinylcholine without volatile anesthetic agents. The black box warning against routine pediatric succinylcholine use may be partially responsible for its low frequency of use in pediatric institutions.[71]

In the setting of difficult (grades III/IV) mask ventilation, providers use succinylcholine. Thirty-four percent (n = 20,175) of Multicenter Perioperative Outcomes Group cases with grades III/IV mask ventilation received succinylcholine. In freestanding ambulatory surgery centers, 37% (n = 509) of cases with grades III/IV mask ventilation received succinylcholine. In 20 non–office-based institutions, a median dose of 1.2 mg/kg (first quartile, 0.97 mg/kg) succinylcholine was administered to 560 cases with grade IV mask ventilation.

Our study identified 24 MH events triggered by succinylcholine (0.5 to 2.5 mg/kg) without concomitant volatile anesthetics, 21 in the United States or Canada. At least 13 MH cases received clinically indicated dantrolene. Although 14 patients experienced MH complications and 1 patient died, because of the small sample size and biased reporting, we could not reliably estimate morbidity/mortality rates for these cases.

Our study revealed that time of dantrolene administration but not dose affected the likelihood of an MH complication (pulmonary edema, disseminated intravascular coagulation, and heart, liver, kidney, and brain dysfunction). Complications increased substantially with every 10-min delay in initiating dantrolene treatment. Likelihood of an MH complication increased 1.6 times for every 30-min increase in time between first MH sign and first dantrolene dose. If clinicians waited more than 50 min, complications increased to 100%. Because of low-powered studies, we do not know whether the dose or amount of dantrolene administered affects mortality. We found that MH killed at least 15 U.S. patients, four of whom received MH-triggering anesthetics in a freestanding facility.

Limitations

The Multicenter Perioperative Outcomes Group database, though large and capable of supporting population-based epidemiologic research, draws cases predominantly from the United States (4.3% of cases came from The Netherlands) and lacks Canadian cases. Many Multicenter Perioperative Outcomes Group–reporting institutions are teaching hospitals; few are office-based practices. The database does not inform us about succinylcholine use when non–anesthesiology department members administer the sedation/anesthetic or rescue the airway. Therefore, the succinylcholine use rate in private practice and office-based practices and by non–anesthesiology-affiliated individuals may differ from what we report. Because the Society for Ambulatory Anesthesia closed its Clinical Outcomes Registry, it may become more difficult to research future office-based practices.

While the Multicenter Perioperative Outcomes Group database facilitates large-scale retrospective analyses, manual review of 6 million charts to determine exact incidence of airway rescue was not possible. We chose to use grades III/IV mask ventilation as a surrogate. By excluding cases where ease of mask ventilation was not documented, we may have introduced bias in favor of higher grades. We do not know how well succinylcholine use rate for difficult mask ventilation approximates airway rescue use. Further, we cannot determine the proportion of cases where succinylcholine was administered *after* difficulty with mask ventilation was encountered.

Selection bias, selective reporting, and recall bias affect reporting to the North American Malignant Hyperthermia Registry. All MH deaths in the North American Malignant Hyperthermia Registry studies were defined clinically according to the MH clinical grading scale with diagnosis confirmed in some by MH causative mutation identification. Though informative, the Anesthesia Closed Claims Project does not capture all adverse anesthetic events and may not include the anesthesia record. We do not know succinylcholine doses for MH events reported to the North American Malignant Hyperthermia Registry and Closed Claims Project. Unreliable denominators render North American Malignant Hyperthermia Registry and Closed Claims data insufficient for population-based epidemiologic research.

The Food and Drug Administration approved sugammadex in December 2015. The Anesthesia Closed Claims Project does not currently contain cases since sugammadex release. Although we analyzed 2016 cases from both the North American Malignant Hyperthermia Registry and Multicenter Perioperative Outcomes Group databases, future succinylcholine use may change as clinicians become more accustomed to sugammadex.

Our systematic literature review analyzed predominantly Oxford Center for Evidence-based Medicine Class 3 and 4 studies, which were too few in number/query to support quantitative synthesis. Selection bias, selective reporting, and recall bias affected most of these investigations. We did not perform a cost-effectiveness study, but dantrolene's cost effectiveness in ambulatory surgery centers has been previously reported.[72] Given our new data, investigators may wish to pursue additional cost–benefit analyses, although MH incidence is still difficult to determine.[67,73,74]

Conclusions

This study presents evidence that succinylcholine is used frequently in many anesthetizing and sedating locations, including for cases in which difficult mask ventilation is encountered. Succinylcholine administered without volatile anesthetics triggers MH events that warranted dantrolene treatment. In the United States and Canada, MH still causes mortality and major morbidity. Delays in dantrolene treatment markedly increased the likelihood of MH complications. Our data support stocking dantrolene wherever succinylcholine or volatile anesthetics may be used.

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Competing Interests

Many of the authors are unpaid volunteers for the nonprofit Malignant Hyperthermia Association of the United States (Sherburne, New York). They have served variously as directors of the North American Malignant Hyperthermia Registry of Malignant Hyperthermia Association of the United States and members of the board of Malignant Hyperthermia Association of the United States, the Professional Advisory Council of Malignant Hyperthermia Association of the United States, or the Malignant Hyperthermia Hotline of Malignant Hyperthermia Association of the United States. All of these positions are voluntary and unpaid. Many participated in the drafting of the current Malignant Hyperthermia Association of the United States recommendation for dantrolene availability in anesthetizing locations. Many of the authors have traveled to MH conferences in the United States or Canada with Malignant Hyperthermia Association of the United States financial support. The Malignant Hyperthermia Association of the United States receives funding support from Malignant Hyperthermia Association of the United States members, customers, medical associations and societies, foundations, and various corporations including Eagle Pharmaceuticals (Woodcliff Lake, New Jersey), PAR Pharmaceutical (Chestnut Ridge, New York), and U.S. WorldMeds LLC (Louisville, Kentucky). Dr. Capacchione has received a consulting fee from Eagle Pharmaceuticals, Inc. 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). The remaining authors declare no competing interests.

Correspondence

Address correspondence to Dr. Larach: The North American Malignant Hyperthermia Registry of Malignant Hyperthermia Association of the United States at the Department of Anesthesiology, University of Florida College of Medicine, P.O. Box 100254, Gainesville, Florida 32610-0254. mlarach@gmail.com.

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Appendix 1: Multicenter Perioperative Outcomes Group Investigators and Affiliated Institutions

The authors gratefully acknowledge the valuable contributions to protocol and final manuscript review by the Multicenter Perioperative Outcomes Group Perioperative Clinical Research Committee:

Fabian Kooij, M.D. — Department of Anesthesiology, Academic Medical Center, Amsterdam, The Netherlands
Janet Wilczak, M.D. — Beaumont Health, Dearborn, Michigan
Roy Soto, M.D. — Beaumont Health, Royal Oak, Michigan
Joshua Berris, D.O. — Beaumont Health, Farmington Hills, Michigan
Zachary Price, M.D. — Beaumont Health, Grosse Pointe, Michigan
Steven Lins, M.D. — Bronson Healthcare, Battle Creek, Michigan
Peter Coles, M.D. — Bronson Healthcare, Kalamazoo, Michigan
John M. Harris, M.D. — CHOC Children's Hospital, Orange, California
Kenneth C. Cummings III, M.D., M.S. — Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio
Mitchell F. Berman, M.D. — Department of Anesthesiology, Columbia University Medical Center, New York, New York
Masakatsu Nanamori, M.D. — Henry Ford Health System, Detroit, Michigan
Bruce T. Adelman, M.D. — Henry Ford Health System, West Bloomfield, Michigan
Christopher Wedeven, M.D. — Holland Hospital, Holland, Michigan
John LaGorio, M.D. — Mercy Health, Muskegon, Michigan
Patrick J. McCormick, M.D., M.Eng. — Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, New York
Simon Tom, M.D. — Department of Anesthesiology, Perioperative Care, and Pain Medicine, New York University Langone Medical Center, New York, New York
Michael F. Aziz M.D. — Department of Anesthesiology & Perioperative Medicine, Oregon Health & Science University, Portland, Oregon
Traci Coffman, M.D. — St. Joseph Mercy, Ann Arbor, Michigan
Terri A. Ellis II, M.D. — St. Joseph Mercy Oakland, Pontiac, Michigan
Susan Molina, M.D. — St. Mary Mercy Hospital, Livonia, Michigan
William Peterson, M.D. — Sparrow Health System, Lansing, Michigan
Sean C. Mackey, M.D., Ph.D. — Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California

Wilton A. van Klei, M.D., Ph.D. — Department of Anesthesiology, University Medical Center Utrecht, Utrecht, The Netherlands
Adit A. Ginde, M.D., M.P.H. — Department of Anesthesiology, University of Colorado, Aurora, Colorado
Daniel A. Biggs, M.D., M.Sc. — Department of Anesthesiology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
Mark D. Neuman, M.D., M.Sc. — Department of Anesthesiology, University of Pennsylvania, Philadelphia, Pennsylvania
Robert M. Craft, M.D. — Department of Anesthesiology, University of Tennessee Medical Center, Knoxville, Tennessee
Nathan L. Pace, M.D., M.Stat. — Department of Anesthesiology, University of Utah, Salt Lake City, Utah
William C. Paganelli, M.D., Ph.D. — Department of Anesthesiology, University of Vermont, Larner College of Medicine, Burlington, Vermont
Marcel E. Durieux, M.D., Ph.D. — Department of Anesthesiology, University of Virginia, Charlottesville, Virginia
Bala J. Nair, Ph.D. — Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington
Jonathan P. Wanderer, M.D. — Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee
Scott A. Miller, M.D. — Department of Anesthesiology, Wake Forest Baptist Health, Winston-Salem, North Carolina
Daniel L. Helsten, M.D. — Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri
Zachary A. Turnbull, M.D. — Department of Anesthesiology, Weill Cornell Medical College, New York, New York
Robert B. Schonberger, M.D., M.H.S. — Department of Anesthesiology, Yale School of Medicine, New Haven, Connecticut

Appendix 2: Systematic Literature Review Queries and Key Words

Queries

1. What is the frequency of succinylcholine administration in hospital-based operating suites (including delivery suites), intensive care units, and emergency departments? What is the frequency of succinylcholine administration without volatile anesthetics in hospital-based operating suites (including delivery suites)?
2. What is the frequency of succinylcholine administration in procedural suites (*e.g.*, radiology, electroconvulsive therapy)? What is the frequency of succinylcholine administration without volatile anesthetics in hospital-based off-site locations?
3. What is the frequency of succinylcholine administration in ambulatory surgery centers? What is the frequency of succinylcholine administration without concomitant volatile anesthetic administration in ambulatory surgery centers?
4. What is the frequency of succinylcholine administration in medical, oral surgical, and dental offices that sedate/anesthetize patients?
5. How often is succinylcholine administered in perioperative and periprocedural settings for airway rescue? What is the utilization rate of succinylcholine in anesthetics with evidence of difficulty with mask ventilation (grade III or IV)? What is the utilization rate of succinylcholine for rescue of grade IV mask ventilation? During manuscript preparation, an additional analysis was performed to determine succinylcholine dosage for cases with documented grade IV mask ventilation. What is the incidence of succinylcholine rescue of difficulty with mask ventilation in patients who are 0 to <10 yr old *versus* those who are 10 yr to 18 yr old?
6. Does administration of succinylcholine without concomitant volatile anesthetic administration trigger malignant hyperthermia (MH)? During manuscript revision, an additional analysis was performed to determine whether dantrolene administration was warranted in these cases and whether they had associated MH morbidity and mortality.
7. What is the MH mortality rate in the United States and Canada?
8. What is the impact of dantrolene administration on MH mortality in the United States and Canada? Does time or initial dantrolene dosage affect likelihood of MH mortality?
9. What morbidities are associated with an acute MH event in the United States and Canada?
10. What is the MH morbidity rate in the United States and Canada?
11. What is the impact of dantrolene administration on MH morbidity in the United States and Canada? Does time or initial dantrolene dose affect likelihood of MH mortality?

Key Words with Combinations

Airway rescue: ambulatory surgery anesthetics, drugs, laryngospasm, medications, succinylcholine
Adverse events: surgery, medications, succinylcholine
Ambulatory surgery: adverse events, anesthetics, medications, sedation, succinylcholine
Cesarean section: dantrolene (initial dose/administration time), general anesthesia, succinylcholine
Dental or oral: adverse events dental or oral surgical anesthetic, drugs, medications, succinylcholine, surgical sedation
Electroconvulsive treatment: adverse events, anesthetic treatment, sedation, succinylcholine
Emergency department: adverse events, drugs, medications, sedation, tracheal intubation
Intensive care: drugs, medications, succinylcholine, tracheal intubations
Malignant hyperthermia: anesthetic triggers, dantrolene, epidemiology, mortality rate, morbidity rate, succinylcholine
Maternal: anesthetic, dantrolene, morbidity, mortality, treatment
Radiologic procedure: adverse events, anesthetic adverse events, malignant hyperthermia, sedation