Continued Updates to *Anesthesia Progress*

This past January officially marked the start of my sixth year serving as editor of *Anesthesia Progress*, a journey that has been both enjoyable and challenging. The journal has seen several changes throughout my tenure, and this year appears to be no different. Along with its editorial board, the journal is undergoing some noteworthy updates, of which some are exciting and others quite bittersweet.

With the recent passing of Stuart E. Lieblich, DMD, the journal lost a significant long-standing editorial board member. Among his multitude of achievements, Dr Lieblich was a past president of the American Dental Society of Anesthesiology (ADSA) and had countless publications and contributions within the fields of sedation and anesthesia for dentistry and oral surgery as well as patient safety. As evidenced by the moving words of his obituary found within this issue of *Anesthesia Progress*, Dr Lieblich was the consummate professional in every sense and will be greatly missed.

Morton B. Rosenberg, DMD, another generational talent and cornerstone of the ADSA, will also be moving off the editorial board as he delves further into his well-deserved retirement. Together with Joel M. Weaver, DDS, PhD, Dr Rosenberg helped ensure the viability and vitality of *Anesthesia Progress* during the 1990s and 2000s, a tumultuous prespecialty era for dental anesthesiology. Dr Rosenberg's substantial influence and legacy within the ADSA simply cannot be overstated, and his absence will echo throughout the organization and beyond.

While the voids left by the departures of Drs Lieblich and Rosenberg are vast, I am happy to announce that James A. Phero, DDS, MD, and Mana Saraghi, DMD, have agreed to serve in their stead. Dr Phero obtained his dental degree at the University of North Carolina (UNC). He then earned his medical degree at UNC, where he also completed his oral and maxillofacial surgery residency. He is currently serving as a full-time clinical assistant professor at the University of Cincinnati, where he works as a board-certified oral and maxillofacial surgeon. No stranger to the ADSA, Dr Phero also serves on its board of directors and has been a frequent lecturer for their review courses and course faculty for its simulation courses.

Dr Saraghi obtained her dental degree at the University of Pennsylvania before completing her dental anesthesiology residency at Jacobi Medical Center/Albert Einstein College of Medicine, where she now serves as a full-time clinical associate professor and board-certified dentist anesthesiologist. Dr Saraghi is the current program director overseeing the dental anesthesiology residency at Jacobi Medical Center, and, as of April 2024, is the immediate past president of the American Dental Board of Anesthesiology.

On behalf of the ADSA and the *Anesthesia Progress* Editorial Board, I express our sincere gratitude to Drs Lieblich and Rosenberg for their invaluable service. I also extend the warmest of welcomes to Drs Phero and Saraghi, both of whom will undoubtably exceed all expectations. On a personal level, I have long utilized their thoughts and expertise as peer reviewers and feel they are extremely well qualified to help guide the journal into the future as active members of its editorial board. I certainly anticipate leaning on them as we continue the work of improving the journal.

I am also happy to announce that *Anesthesia Progress* is initiating the process to obtain an impact factor (IF). The application procedure is multilayered and is expected to take several years. However, after many discussions with the journal's publisher, I am happy to report that we are striving to formally begin the work within the year. For those unfamiliar, IF is a metric calculated by Clarivate that can be used to help measure a journal's relevance. It is a numerical value derived from the number of articles cited over a set time. In essence, the higher the IF, the higher a journal's rank. Additional information on IFs along with an overview of the application timeline is presented in an article by Dr Takuro Sanuki et al that can be found in the Commentary section of this issue.

Many academic institutions, particularly those in Asia, hold journals with IFs in higher regard than those without. However, comparing journals based explicitly on IFs is rather tricky and nuanced, as the devil is in the details. A journal like *Anesthesia Progress* has a narrow focus and resides within a small niche of health care literature. Even if we are ultimately successful in this endeavor, it is unlikely that the journal will ever generate an IF anywhere near as high as those of other medical or dental journals with more generalized scopes. Nonetheless, obtaining an IF for the journal has long been an objective, as evinced by my editorial predecessors' efforts, and I am confident that recent modifications to the Clarivate application process should enable us to achieve our goals.

As your editor, I strive to deliver a journal of the highest quality, and I feel that the newest additions to our editorial board, Drs Phero and Saraghi, demonstrate the excellence and diligence necessary to help accomplish that goal. The assignment of an IF will be a further representation of the merit of *Anesthesia Progress*, and I will periodically apprise readers of our efforts to this end. Each of these updates reflects the perpetual growth and improvement of the journal, an endeavor the editorial board takes very seriously. We hope these changes will be felt favorably by the readership and that the content of *Anesthesia Progress* will continue to impact our practices and patients in a positive manner.

Kyle J. Kramer, DDS, MS
Editor-in-Chief, *Anesthesia Progress*

Anesth Prog 71:57 2024 | DOI 10.2344/746154

Comparison of Anesthetics for Laryngeal Mask Airway Insertion: A Network Meta-Analysis

Cameron Goertzen, DDS, MSc;[1] Erin Goertzen, DDS, MSc;[1] Maryam Zanjir, DDS, MSc;[1] Christopher Dare, DMD, MSc;[1] Amir Azarpazhooh, DDS, PhD;[1,2,3] and Michelle Wong, DDS, MSc, EdD[1,4]

[1]Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada; [2]Clinical Epidemiology & Health Care Research, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; [3]Department of Dentistry, Mount Sinai Hospital Toronto, Ontario, Canada; [4]Department of Dental and Maxillofacial Sciences, Sunnybrook Sciences Health Centre, University of Toronto, Toronto, Ontario, Canada

Objective: This study aimed to establish which anesthetic agents are associated with minimized adverse outcomes during laryngeal mask airway (LMA) insertion.

Methods: Databases were searched for randomized controlled trials (RCTs) with American Society of Anesthesiologists I or II adult patients (≥15 years of age) receiving general anesthesia (GA) with an LMA. Propofol only was the comparator to other anesthetics used during LMA insertion. The primary outcome was prolonged apnea, and secondary outcomes were adverse airway events, LMA insertion failure, inadequate depth of anesthesia, and hemodynamic events. A network meta-analysis was conducted to estimate the treatment effects (odds ratios, 95% credible intervals, and surface under the cumulative ranking curve [SUCRA]).

Results: A total of 28 anesthetic combinations used on 4695 patients for GA induction and LMA insertion were examined across 53 RCTs. Overall, there was an apnea incidence rate of 33.3% (849 of 2548) with a mean time of 3.74 ± 3.56 minutes (n = 3091). Propofol + dexmedetomidine had the highest overall summed score of SUCRA ranks in reducing adverse outcomes (apnea incidence: SUCRA = 37%, apnea time: SUCRA = 66%, airway adverse event: SUCRA = 67%, insertion failure: SUCRA = 73%, inadequate depth of anesthesia: SUCRA = 84%). In comparison among all propofol combinations, propofol alone ranked lowest for overall summed score of SUCRA in reducing adverse outcomes (apnea incidence: SUCRA = 47%, apnea time: SUCRA = 71%, airway adverse event: SUCRA = 9%, insertion failure: SUCRA = 20%, inadequate depth of anesthesia: SUCRA = 9%).

Conclusion: All anesthetic combinations, other than those with thiopental, reduced adverse outcomes as compared with propofol alone. The combination of propofol and dexmedetomidine infused over 10 minutes ranked as the most effective for reducing adverse outcomes during LMA insertion.

Key Words: Laryngeal mask airway; Propofol; Dexmedetomidine; Systematic review; Network meta-analysis.

The laryngeal mask airway (LMA) is a supraglottic airway device that can be inserted after induction of general anesthesia (GA) using either inhalational or intravenous (IV) agents. Propofol, a short-acting lipophilic agent, is the most widely used IV agent for GA induction because it is able to induce relaxation of the masticatory musculature and depression of the upper airway reflexes, and thus allow LMA insertion.[1,2] When used as the sole anesthetic, high-dose propofol can lead to profound hypotension, cardiorespiratory depression, and prolonged apnea.[3,4] To minimize these undesirable effects, other anesthetic agents such as opioids, benzodiazepines, inhaled anesthetics, and neuromuscular blocking agents have been used to reduce the dose of propofol required. Each anesthetic combination confers different benefits and risks that may improve or impair LMA placement.[5] Despite the use of LMAs for over 4 decades, there is no consensus on which anesthetic combination facilitates the greatest LMA insertion success while minimizing adverse events.

The aim of this study was to examine differences in adverse outcomes between anesthetic agents used during

Received September 11, 2022; accepted for publication September 18, 2023.

Address correspondence to Dr. Cameron Goertzen, 124 Edward Street, Department of Dental Anesthesia, Faculty of Dentistry, Toronto, Ontario, Canada M5G 1G6; cameron.goertzen@mail.utoronto.ca.

Anesth Prog 71:58–75 2024 | DOI 10.2344/22-00033

LMA insertion following GA induction. We performed a systematic review and network meta-analysis (NMA) comparing propofol as the sole anesthetic for GA induction with other anesthetic combinations used during LMA insertion. Our primary outcome was prolonged apnea, and our secondary outcomes were airway adverse events, LMA insertion failure, inadequate anesthetic depth, adverse hemodynamic events, unanticipated hospital admission, and patient mortality.

Anesthesia practice among clinicians is diverse in their selection of drug combinations and doses, which is challenging when creating evidence-based statements on airway management. The NMA creates a network of interventions with both direct and indirect comparisons.[6] By combining direct and indirect estimates across a network of interventions in a single analysis, a relative ranking of treatments for a given outcome can be made. This study uniquely employs an NMA to compare the variety of induction agents used during LMA insertion to establish which may reduce risks of prolonged apnea and other adverse outcomes the most.

METHODS

This study was registered at PROSPERO (CRD42020202474). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for NMA was used to report our methodology and results.[6] Eligibility criteria included the following:

- Population: American Society of Anesthesiologists I or II adult patients (≥15 years of age) receiving GA with an LMA for nonemergency medical or dental surgery in hospital or ambulatory clinical setting who are spontaneously breathing during the procedure
- Interventions: Any anesthetic agent(s) for induction of GA and LMA insertion
- Comparison: Propofol as sole anesthetic for GA induction and LMA insertion
- Outcomes:
  - Primary outcome: prolonged apnea, defined as duration (time from induction until first breath) or incidence (≥15 s without breath after LMA insertion)[7,8]
  - Secondary outcomes[9,10]:
    - Airway adverse event
      - Incidence of coughing or gagging
      - Incidence of breath holding
      - Incidence of laryngospasm
      - Incidence of hypoxia (oxygen saturation as measured by pulse oximetry <96%)[11]
      - Incidence of swallowing
    - Insertion failure of LMA
      - Proportion of LMAs unsuccessful placed on first attempt
      - Inadequate ease of insertion (difficult/impossible)
    - Inadequate depth of anesthesia
      - Incidence of additional/rescue anesthetic required
      - Inadequate jaw relaxation/mouth opening (Young's criteria[12]; full, partial, nil)
      - Incidence of excitatory (head or limb) or nonpurposeful movements
    - Adverse hemodynamic event
      - Bradycardia (<60 beats/min)[13]
      - Tachycardia (>100 beats/min)[13]
      - Hypotension (systolic arterial blood pressure <90 mm Hg[14] or mean arterial pressure decrease >20% of the baseline value)[15]
      - Hypertension (systolic arterial blood pressure >160 mm Hg[16] or mean arterial pressure increase >20% of the baseline value)[16]
    - Unanticipated hospital admission
    - Mortality
- Study design: Randomized controlled trials (RCTs)

Data Sources and Search Strategy

Our search strategy was constructed with the help of 2 medical librarians and was applied to the following electronic databases: Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Methodology Register), OVID MEDLINE, OVID EMBASE, CINAHL, and SCOPUS (Supplemental Information, Table S1; all supplemental information available online only). The main databases were initially searched on January 9, 2021, and updated on January 19, 2022. A search filter of 1983, the year of the first LMA publication, to present was used for each database.[17] The first 100 hits of Web of Science and ScienceDirect were also searched for additional relevant studies. Completed and ongoing trials were searched through clinicaltrials.gov and World Health Organization International Clinical Trials Registry Platform. Unpublished studies such as dissertations, reports, and conference abstracts were searched for in ProQuest, Google Scholar (the first 100 hits), and the OpenGrey database. Reference lists of previous reviews in the same topic and included studies were searched manually. There were no language or publication date restrictions. We attempted to contact the authors in case of missing information. Search results were imported into EndNote X9 (Clarivate) for duplication screening, then Covidence systematic review software (Veritas Health Innovation) for study screening and selection.[18,19]

Study Selection and Data Collection

Two review authors (C.G. and E.G.) independently reviewed and selected trials from screening. C.G. extracted the data from the selected trials and E.G. reviewed and confirmed all

extracted data. Disagreements were resolved through discussion and consensus or by consulting a third reviewer (M.W.). Reason for study exclusion and included study characteristics are found in the Supplemental Information (Tables S2 and S3).

Risk of Bias Assessment

The 2 review authors, C.G. and E.G., independently used Cochrane's risk of bias assessment tool to evaluate the methodological quality of included trials across 6 domains[20]: selection, performance, detection, attrition, reporting, and other biases. Studies were graded as low risk if all the domains were judged to be of low risk, moderate risk if any domain was judged to be of unclear risk, and high risk if any domain was judged to be of high risk or if all domains were judged to be unclear risk. Disagreements were resolved with discussion or with a third reviewer (M.W.).

NMA and Data Synthesis

The included studies' data were entered into a standardized spreadsheet. If the study contained an intervention with the same anesthetic but different doses, the intervention arms were combined. Anesthetics were grouped together based on related drug class (ie, pharmacodynamic properties) for analysis. Continuous outcome (apnea time) was analyzed with mean and SD. Binary outcomes (presence of an airway adverse event or inadequate depth of anesthesia) were analyzed using the odds ratio (OR). Ordinal outcomes were combined and analyzed as a binary outcome. Missing SDs were calculated from the available CI or standard error and the number of participants.[21] If mean and SD were unavailable, they were estimated using median and range (the formula presented by Hozo and colleagues[22] using median and range) or using range (the formula presented by Walter and Yao[23]). If numerical data were not reported, authors were contacted.

NMA was conducted using the program R (version 3.5.0; R Project for Statistical Computing) with the Gemtc version 0.8.2 and rjags packages, which interface with Just Another Gibbs Sampler software (version 4.0.0; developed by Martyn Plummer) for Markov chain Monte Carlo modeling. A Bayesian NMA was performed under a hierarchical random effects framework and unified generalized linear model. For continuous outcomes, a normal likelihood and identity link function was used. For binary outcomes, a binomial likelihood with logit link function was used.[24,25] The treatment effects were estimated as ORs or mean differences with associated 95% credible intervals (CrIs) and the surface under the cumulative ranking curve (SUCRA). Heterogeneity was assessed using the I^2 statistic. Node-splitting method was used to calculate the inconsistency of the model through direct and indirect evidence with its Bayesian P value.[24] Posterior probabilities were used and scored to rank the interventions for the overall conclusions. Sensitivity analysis was conducted by excluding any high–risk of bias studies. Subgroup analysis was conducted comparing (1) the effect of premedication and (2) the type of LMA.

Quality of Evidence

Two review authors (C.G. and E.G.) used the CINeMA web application (University of Bern) to evaluate the confidence of the main NMA results considering 6 domains: heterogeneity, imprecision, incoherence, indirectness, and within- and across-studies bias.[26] Results were judged as high, moderate, low, or very low confidence.[26] Consensus was reached by consulting the other reviewer or by third reviewer (M.W.) when necessary.

RESULTS

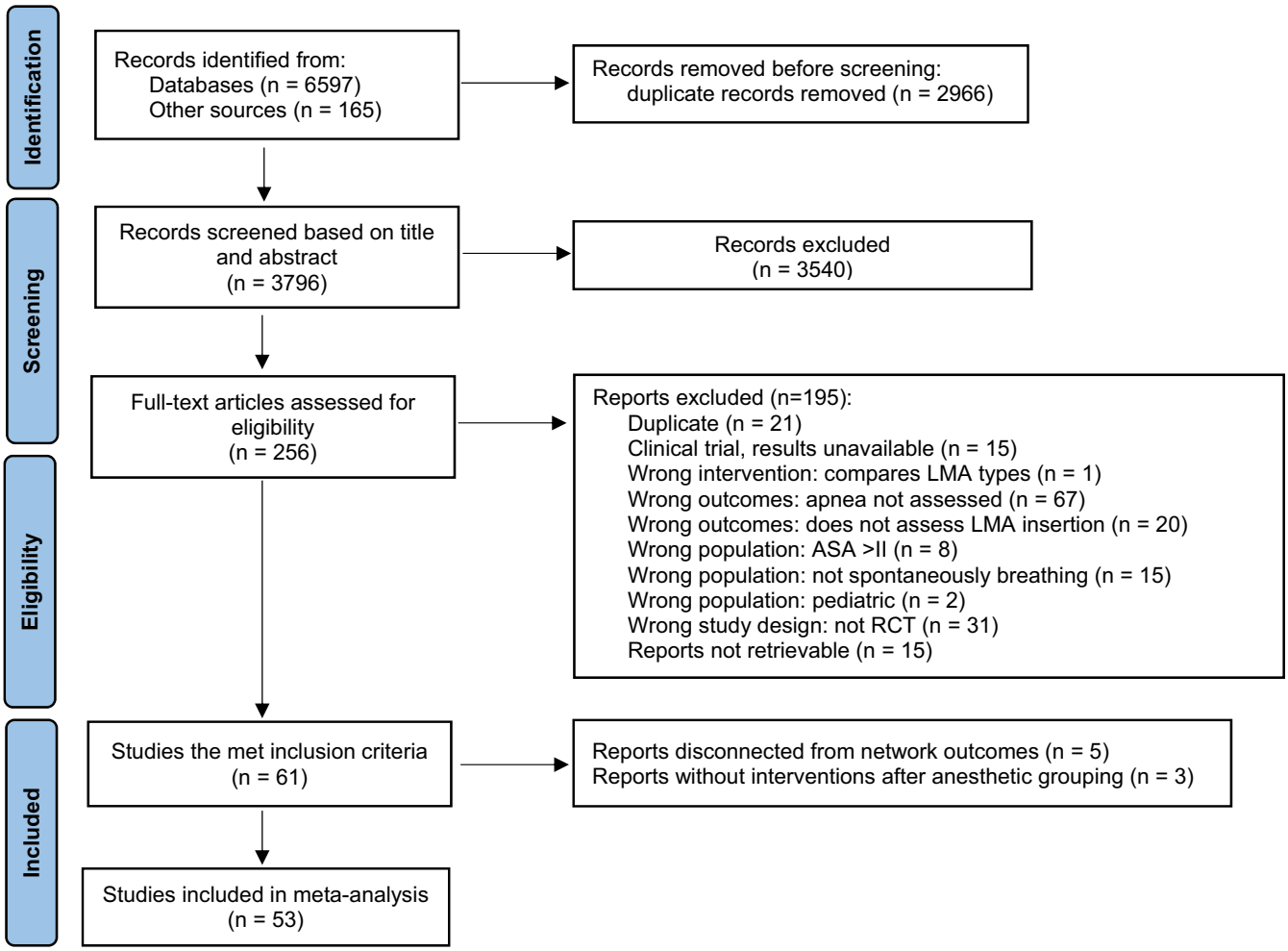
Search Results

In the initial screening stage, 6762 potentially eligible reports were retrieved, 2966 duplicates were removed, and 3540 records were excluded based on title and abstract (Figure 1). A total of 256 full-text trials were assessed for eligibility; 195 studies were excluded, and 61 RCT met the inclusion criteria (Supplemental Information, Tables S2 and S3). The included studies were from India (18), China (8), Turkey (6), Singapore (4), United Kingdom (4), Malaysia (3), South Korea (3), Brazil (2), Iran (2), Taiwan (2), Australia, Canada, Egypt, Ireland, Japan, Lebanon, Poland, Saudi Arabia, and Singapore (Supplemental Information, Table S3).

Study Characteristics

Population. All studies limited their patients to adults, although the minimal age of inclusion ranged from 15 years to 18 years of age (≥15 y, 3 studies; ≥16 y, 4 studies; ≥17 y, 1 study; and ≥18 y, 44 studies; Supplemental Information, Table S3). Nine studies did not specify their adult age range of inclusion. LMA types used were the first-generation LMA Classic (Teleflex; 14 studies) and second-generation ProSeal LMA (Teleflex; 5 studies) and I-gel (Intersurgical; 1 study). Forty-one studies did not specify LMA type used; however, 16 of these studies were conducted before the introduction of second-generation LMAs[27] in 2000. Twenty-nine studies did not use premedication prior to anesthetic induction. Of the 24 studies that reported premedication use, 12 used an anticholinergic (glycopyrrolate or atropine), 10 used an oral benzodiazepine (midazolam, lorazepam, or

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram



Flow diagram of study inclusion and exclusions. LMA indicates laryngeal mask airway; ASA, American Society of Anesthesiologists; and RCT, randomized controlled trial.

temazepam), and 2 used hydroxyzine. Eight studies did not specify if premedication was utilized. The surgical reasons for GA and LMA placement were elective general surgery, orthopedics, and plastic or gynecologic procedures (17 studies); lower abdominal or urologic operations (7 studies); oncological (4 studies); minor, elective, or short procedures (22 studies); and not specified (11 studies).

Interventions. A total of 48 different anesthetics and anesthetic combinations were identified. Of the 61 studies, 5 had intervention pairings that were disconnected from the comparator network across all outcomes, and were excluded from analysis. An additional 3 trials were excluded from analysis as they became single-arm trials following the anesthetic drug class grouping. In total, 4695 patients and 37 anesthetic treatments were combined into 28 anesthetic drug class groupings for inclusion in the NMA (Table).

Outcome Assessment. Figure 2 demonstrates the networks of each outcome. As reporting of outcomes differed across studies, analysis was completed for 31 studies for apnea incidence (2548 patients, 20 anesthetic combinations), 29 studies for apnea time (3091 patients, 17 anesthetic combinations), 41 studies for airway adverse events (3679 patients, 26 anesthetic combinations), 41 studies for LMA insertion failure (3853 patients, 26 anesthetic combinations), and 36 studies for inadequate depth of anesthesia (3888 patients, 20 anesthetic combinations). Supplemental Information, Figure S1 summarizes relative treatment effects for all possible comparisons as expressed by ORs with 95% CrIs.

In total, there was a 33% (849 of 2548) incidence of prolonged apnea overall (Table). For prolonged apnea, vapor + midazolam + short opioid demonstrated a high SUCRA score (OR, 0.02; 95% CrI, 4.0×10^{-3} to 0.64; SUCRA = 92%; Figure 3), which indicates a higher likelihood that combination is

Table. Anesthetic Interventions and Adverse Outcome Data

		Apnea						*Hemodynamic event*								
		Incidence			*Time*			*Bradycardia*			*Tachycardia*			*Hypotension*		
Anesthetic(s)	*Total patients, No.*	*Observed, No.*	*Patients, No.*	*Percentage*	*Mean time, min*	*SD*	*Patients, No.*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*
PPF	593	114	249	45.8	2.13	1.52	415	0	208	0.0				4	158	2.5
PPF + AA opioid																
PPF + butorphanol	50				0.96	0.22	50									
PPF + nalbuphine	30	16	30	53.3												
PPF + dexmedetomidine	143	34	143	23.8	3.10	1.63	143	7	103	6.8				1	77	1.3
PPF + ketamine	119	20	60	33.3	2.00	0.60	59	0	30	0.0				0	30	0.0
PPF + LIDO (IV)	48	11	34	32.4	4.20	1.50	10									
PPF + LIDO (topical)	30	1	30	3.3										4	30	13.3
PPF + MDZ	99	28	40	70.0	2.80	0.70	59									
PPF + MDZ + AA opioid																
PPF + MDZ + butorphanol	80	14	60	23.3	1.62	0.12	50	0	30	0.0				0	30	0.0
PPF + MDZ + dexmedetomidine	100	15	100	15.0	3.48	0.26	70	5	70	7.1				3	70	4.3
PPF + MDZ + ketamine	120	30	120	25.0	1.56	0.26	30	0	30	0.0				0	30	0.0
PPF + MDZ + LIDO (IV)	40	23	40	57.5												
PPF + MDZ + short opioid																
PPF + MDZ + fentanyl	270	88	250	35.2	3.11	1.07	120	0	100	0.0				5	130	3.8
PPF + NMBA																
PPF + succinylcholine	60	10	30	33.3												
PPF + mivacurium	109				3.70	1.08	109									
PPF + remifentanil	319	32	61	52.5	3.17	1.82	255	12	256	4.7				7	136	5.1
PPF + short opioid																
PPF + fentanyl	936	275	544	50.6	4.32	3.51	675	2	233	0.9	0	31	0.0	75	308	24.4
PPF + alfentanil	160	19	60	31.7	5.63	3.30	159	7	100	7.0						
PPF + short opioid + ketamine																
PPF + fentanyl + ketamine	40				6.85	2.80	40	0	40	0.0				14	40	35.0
PPF + short opioid + NMBA																
PPF + fentanyl + rocuronium	150				10.60	6.00	150									
PPF + fentanyl + succinylcholine	188				6.65	5.30	185									
PPF + THIO + short opioid																
PPF + THIO + fentanyl	41	17	41	41.5	2.81	0.63	41							21	41	51.2
PPF + vapor																
PPF + sevoflurane + N_2O	61	10	61	16.4	0.88	0.40	61									
PPF + N_2O	25				1.02	0.68	25									
PPF + vapor + short opioid																
PPF + fentanyl + N_2O	30	0	30	0.0												
PPF + sevoflurane + N_2O + fentanyl	40	4	40	10.0												
THIO	30				3.64	3.84	30									
THIO + NMBA																
THIO + succinylcholine	40				3.57	0.78	40									

Table. *(Continued)*

Anesthetic(s)	Total patients, No.	Apnea						Hemodynamic event								
		Incidence			Time			Bradycardia			Tachycardia			Hypotension		
		Observed, No.	Patients, No.	Percentage	Mean time, min	SD	Patients, No.	Observed, No.	Patients, No.	Percentage	Observed, No.	Patients, No.	Percentage	Observed, No.	Patients, No.	Percentage
THIO + short opioid + LIDO (IV)																
THIO + fentanyl + LIDO (IV)	60				1.95	1.15	60									
THIO + short opioid + LIDO (topical)																
THIO + fentanyl + LIDO (topical)	76				1.60	1.09	76									
Vapor																
Sevoflurane	73	27	73	37.0				0	33	0.0				0	33	0.0
Sevoflurane + N_2O	199	8	155	5.2	1.34	1.10	100	0	21	0.0				0	21	0.0
Vapor + MDZ + short opioid																
Sevoflurane + MDZ + fentanyl	40	13	40	32.5												
Vapor + remifentanil																
Sevoflurane + remifentanil	67	16	67	23.9				0	67	0.0				0	68	0.0
Vapor + short opioid																
Sevoflurane + fentanyl	39				4.61	3.52	39									
Sevoflurane + N_2O + fentanyl	150	21	150	14.0							0	30	0.0	16	30	53.3
Desflurane + N_2O + fentanyl	40	3	40	7.5	0.24	0.73	40									
Overall	**4695**	**849**	**2548**	**33.3**	**3.74**	**3.56**	**3091**	**33**	**1321**	**2.5**	**0**	**61**	**0.0**	**150**	**1232**	**12.2**

Anesthetic(s)	Airway adverse event														
	Coughing and/or gagging			Breath holding			Laryngospasm			Hypoxia			Swallowing		
	Observed, No.	Patients, No.	Percentage	Observed, No.	Patients, No.	Percentage	Observed, No.	Patients, No.	Percentage	Observed, No.	Patients, No.	Percentage	Observed, No.	Patients, No.	Percentage
PPF	141	370	38.1				55	369	14.9	0	40	0.0	138	214	64.5
PPF + AA opioid															
PPF + butorphanol															
PPF + nalbuphine	9	30	30.0				0	30	0.0				5	30	16.7
PPF + dexmedetomidine	5	103	4.9	14	77	18.2	0	40	0.0						
PPF + ketamine	15	89	16.9	0	59	0.0	1	119	0.8				4	89	4.5
PPF + LIDO (IV)	11	34	32.4				0	38	0.0						
PPF + LIDO (topical)	3	30	10.0				0	30	0.0						
PPF + MDZ	30	95	31.6	0	59	0.0	3	95	3.2				1	59	1.7
PPF + MDZ + AA opioid															
PPF + MDZ + butorphanol	6	50	12.0				0	80	0.0						
PPF + MDZ + dexmedetomidine	4	100	4.0	12	70	17.1	1	30	3.3						
PPF + MDZ + ketamine	14	30	46.7				7	60	11.7						
PPF + MDZ + LIDO (IV)	10	39	25.6				0	39	0.0						

Table. *(Continued)*

	Airway adverse event														
	Coughing and/or gagging			*Breath holding*			*Laryngospasm*			*Hypoxia*			*Swallowing*		
Anesthetic(s)	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*
PPF + MDZ + short opioid															
PPF + MDZ + fentanyl	33	150	22.0	34	70	48.6	5	140	3.6						
PPF + NMBA															
PPF + succinylcholine	12	60	20.0				2	60	3.3				6	60	10.0
PPF + mivacurium	11	109	10.1				4	110	3.6				24	109	22.0
PPF + remifentanil	18	96	18.8				5	75	6.7	2	101	2.0			
PPF + short opioid															
PPF + fentanyl	81	642	12.6	25	77	32.5	10	639	1.6	0	44	0.0	64	270	23.7
PPF + alfentanil	2	59	3.4				4	59	6.8				7	59	11.9
PPF + short opioid + ketamine															
PPF + fentanyl + ketamine	0	40	0.0				2	40	5.0				3	40	7.5
PPF + short opioid + NMBA															
PPF + fentanyl + rocuronium	1	150	0.7												
PPF + fentanyl + succinylcholine	8	188	4.3				0	188	0.0						
PPF + THIO + short opioid															
PPF + THIO + fentanyl	17	41	41.5				0	41	0.0						
PPF + vapor															
PPF + sevoflurane + N_2O	1	31	3.2				0	31	0.0						
PPF + N_2O															
PPF + vapor + short opioid															
PPF + fentanyl + N_2O	0	30	0.0				1	30	3.3						
PPF + sevoflurane + N_2O + fentanyl	2	40	5.0				2	40	5.0	3	40	7.5			
THIO	17	20	85.0				1	20	5.0						
THIO + NMBA															
THIO + succinylcholine	16	40	40.0				0	40	0.0						
THIO + short opioid + LIDO (IV)															
THIO + fentanyl + LIDO (IV)	33	60	55.0				14	60	23.3						
THIO + short opioid + LIDO (topical)															
THIO + fentanyl + LIDO (topical)	23	76					3	76	3.9	0	46	0.0			

Table. *(Continued)*

	Airway adverse event														
	Coughing and/or gagging			*Breath holding*			*Laryngospasm*			*Hypoxia*			*Swallowing*		
Anesthetic(s)	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*
Vapor															
Sevoflurane	13	73	17.8							0	73	0.0	2	33	6.1
Sevoflurane + N_2O	34	169	20.1				12	148	8.1	0	61	0.0			
Vapor + MDZ + short opioid															
Sevoflurane + MDZ + fentanyl	3	40	7.5							0	40	0.0			
Vapor + remifentanil															
Sevoflurane + remifentanil	3	67	4.5							0	68	0.0	4	67	6.0
Vapor + short opioid															
Sevoflurane + fentanyl															
Sevoflurane + N_2O + fentanyl	6	70	8.6				4	120	3.3	2	40	5.0			
Desflurane + N_2O + fentanyl	0	40	0.0				1	40	2.5						
Overall	**582**	**3261**	**17.8**	**85**	**412**	**18.2**	**137**	**2887**	**4.7**	**7**	**553**	**1.3**	**258**	**1030**	**25.0**

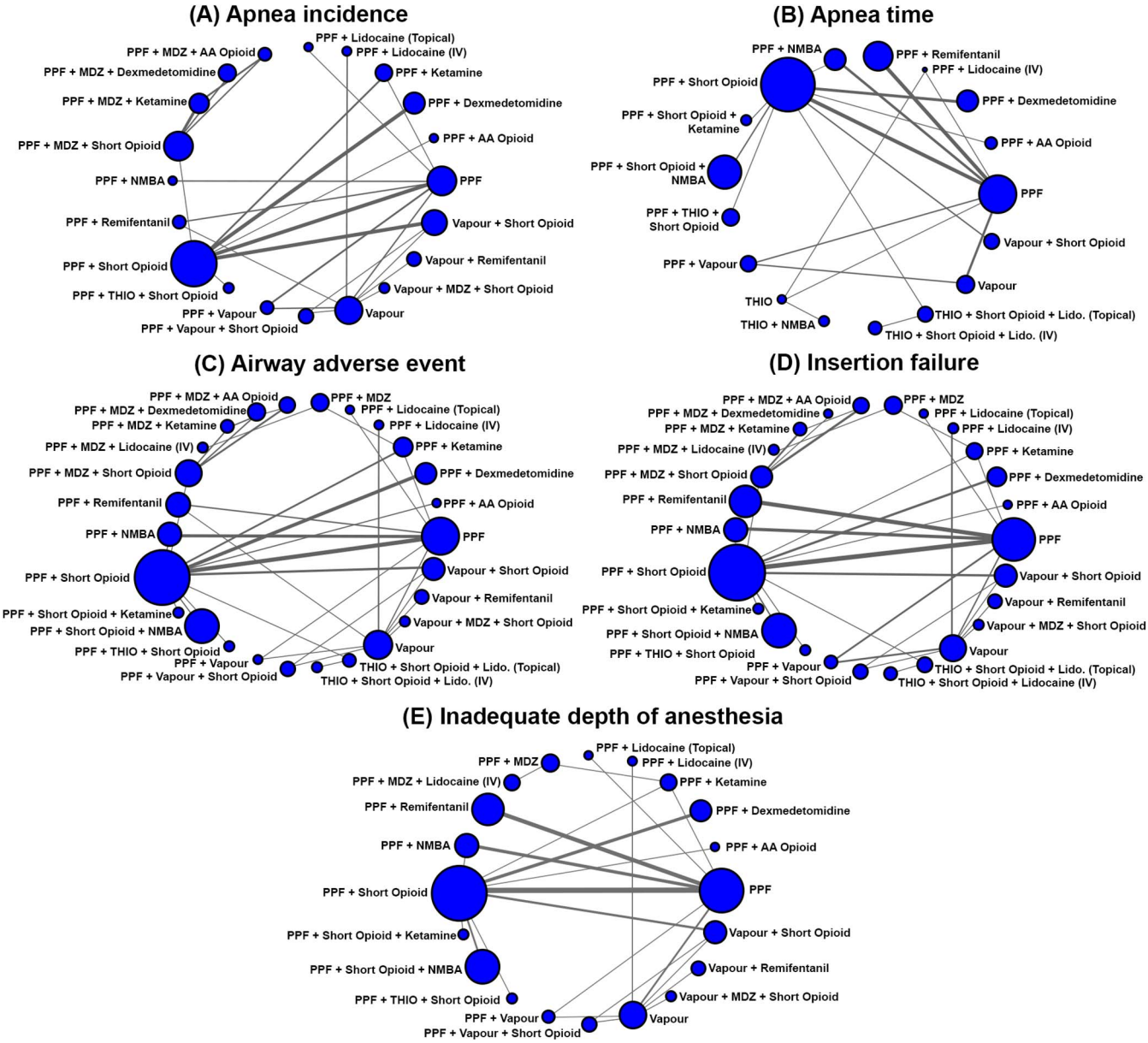
	Insertion failure						*Inadequate depth of anesthesia*								
	Unsuccessful first attempt			*Difficult insertion*			*Additional bolus required*			*Inadequate mouth opening*			*Head or limb movement*		
Anesthetic(s)	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*
PPF	145	476	30.5	182	458	39.7	122	300	40.7	168	288	58.3	225	389	57.8
PPF + AA opioid															
PPF + butorphanol															
PPF + nalbuphine	2	30	6.7	1	30	3.3				3	30	10.0	4	30	13.3
PPF + dexmedetomidine	5	77	6.5	3	80	3.8	2	37	5.4	2	143	1.4	0	26	0.0
PPF + ketamine	9	89	10.1	7	89	7.9	5	89	5.6	15	89	16.9	33	89	37.1
PPF + LIDO (IV)	11	38	28.9										18	34	52.9
PPF + LIDO (topical)	2	30	6.7	10	30	33.3	2	30	6.7				5	30	16.7
PPF + MDZ	10	99	10.1	14	99	14.1	9	59	15.3	28	99	28.3	36	99	36.4
PPF + MDZ + AA opioid															
PPF + MDZ + butorphanol	5	60	8.3	0	80	0.0	10	80	12.5	5	80	6.3	6	50	12.0
PPF + MDZ + dexmedetomidine	3	30	10.0	1	30	3.3				7	100	7.0			
PPF + MDZ + ketamine	27	60	45.0	7	60	11.7	35	60	58.3	28	60	46.7	18	30	60.0
PPF + MDZ + LIDO (IV)	1	40	2.5	4	40	10.0				8	40	20.0	19	40	47.5
PPF + MDZ + short opioid															
PPF + MDZ + fentanyl	33	120	27.5	1	110	0.9	31	80	38.8	41	180	22.8	22	50	44.0
PPF + NMBA															
PPF + succinylcholine	3	60	5.0	4	60	6.7				12	60	20.0	12	60	20.0
PPF + mivacurium	10	109	9.2	15	109	13.8				60	109	55.0	51	109	46.8
PPF + remifentanil	28	215	13.0	35	223	15.7	29	180	16.1	44	133	33.1	18	115	15.7
PPF + short opioid															
PPF + fentanyl	71	566	12.5	78	575	13.6	60	317	18.9	179	598	29.9	141	512	27.5
PPF + alfentanil	9	160	5.6	7	159	4.4	19	100	19.0	17	59	28.8	6	59	10.2

Table. *(Continued)*

	Insertion failure						*Inadequate depth of anesthesia*								
	Unsuccessful first attempt			*Difficult insertion*			*Additional bolus required*			*Inadequate mouth opening*			*Head or limb movement*		
Anesthetic(s)	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*	*Observed, No.*	*Patients, No.*	*Percentage*
PPF + short opioid + ketamine															
PPF + fentanyl + ketamine				3	40	7.5				3	40	7.5	3	40	7.5
PPF + short opioid + NMBA															
PPF + fentanyl + rocuronium				4	150	2.7	5	150	3.3	22	150	14.7	9	150	6.0
PPF + fentanyl + succinylcholine	10	188	5.3	14	188	7.4	16	188	8.5	57	188	30.3	21	188	11.2
PPF + THIO + short opioid															
PPF + THIO + fentanyl				11	41	26.8	5	41	12.2	15	41	36.6			
PPF + vapor															
PPF + sevoflurane + N_2O	5	61	8.2				2	31	6.5				8	31	25.8
PPF + N_2O							4	25	16.0						
PPF + vapor + short opioid															
PPF + fentanyl + N_2O				1	30	3.3	2	30	6.7	3	30	10.0	1	30	3.3
PPF + sevoflurane + N_2O + fentanyl	1	40	2.5										6	40	15.0
THIO				12	20	60.0				18	20	90.0			
THIO + NMBA															
THIO + succinylcholine				9	40	22.5				30	40	75.0			
THIO + short opioid + LIDO (IV)															
THIO + fentanyl + LIDO (IV)	22	60	36.7	25	58	43.1									
THIO + short opioid + LIDO (topical)															
THIO + fentanyl + LIDO (topical)	6	76	7.9	4	30	13.3									
Vapor															
Sevoflurane	7	40	17.5	7	33	21.2				6	33	18.2	32	73	43.8
Sevoflurane + N_2O	54	134	40.3				7	70	10.0				70	148	47.3
Vapor + MDZ + short opioid															
Sevoflurane + MDZ + fentanyl	1	40	2.5										18	40	45.0
Vapor + remifentanil															
Sevoflurane + remifentanil				8	67	11.9				3	67	4.5	4	67	6.0
Vapor + short opioid															
Sevoflurane + fentanyl															
Sevoflurane + N_2O + fentanyl	2	90	2.2	4	30	13.3				7	30	23.3	24	100	24.0
Desflurane + N_2O + fentanyl	8	40	20.0	15	40	37.5	2	40	5.0				1	40	2.5
Overall	**490**	**3028**	**16.2**	**486**	**2999**	**16.2**	**367**	**1907**	**19.2**	**781**	**2707**	**28.9**	**811**	**2669**	**30.4**

* PPF indicates propofol; AA, agonist-antagonist; LIDO, lidocaine; MDZ, midazolam; IV, intravenous; NMBA, neuromuscular blocking agent; THIO, thiopentone; and N_2O, nitrous oxide. Bold type indicates ???

Figure 2. Network Geometries of the Adverse Outcomes



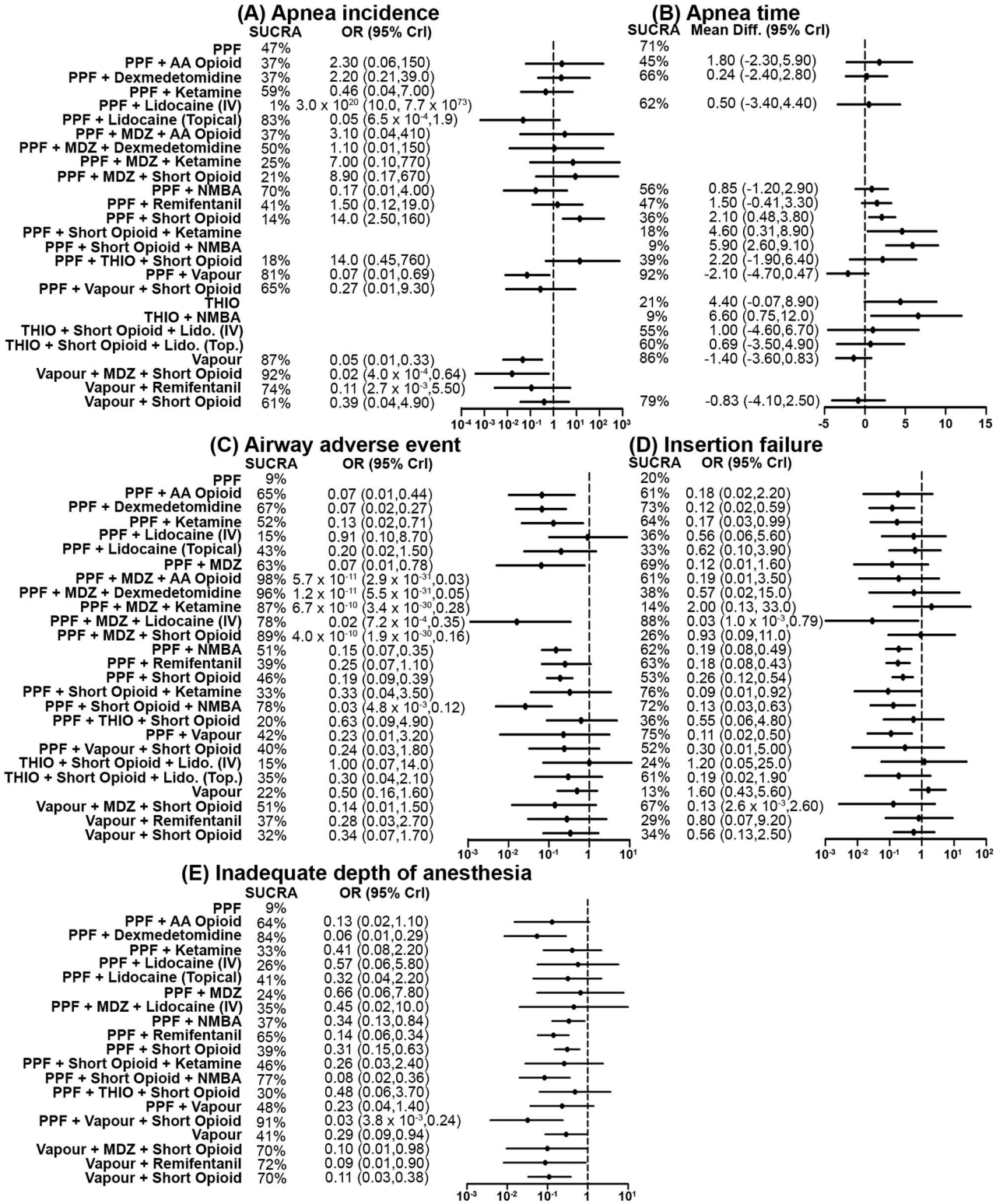
The network geometry of the primary, (A) apnea incidence and (B) apnea time, and secondary, (C) airway adverse events, (D) insertion failure, and (E) inadequate depth of anesthesia, outcomes during LMA placement. Gray connecting lines between circles indicate the direct comparison of interventions and the circle width is proportional to the number of studies evaluating the comparison. The circle volume is proportional to the number of patients who received the intervention. PPF indicates propofol; MDZ, midazolam; AA, agonist-antagonist; IV, intravenous; NMBA, neuromuscular blocking agent; and THIO, thiopentone.

one of the top ranked for reducing the risk of prolonged apnea. For comparison, propofol alone demonstrated a SUCRA score of 47% in this outcome (Figure 3).

Overall, the mean apnea time was 3.74 ± 3.56 minutes (Table). Propofol + vapor (mean difference = −2.10; 95% CrI, −4.70 to 0.47; SUCRA = 92%) ranked the top combination for reducing the risk of apnea time (Figure 3). For comparison, propofol alone demonstrated a SUCRA score of 71% in this outcome (Figure 3).

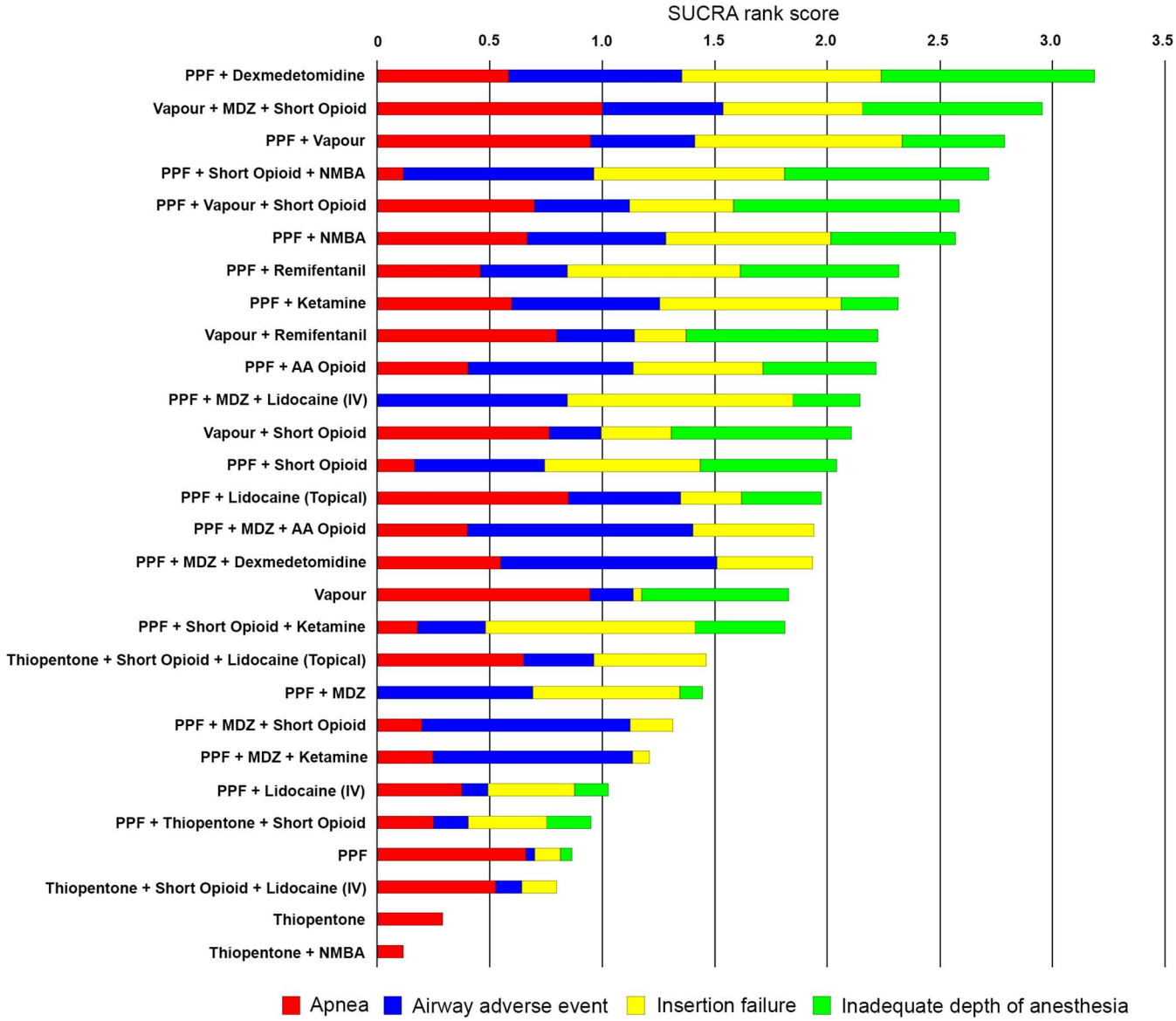
In the airway adverse event outcome, coughing and/or gagging was reported the most and had an incidence of 17.8% (582 of 3261; Table). Laryngospasm was examined among 2887 patients and had an incidence of 4.7%. Propofol + midazolam + agonist-antagonist opioid (OR,

Figure 3. NMA Outcome SUCRA Values and ORs



SUCRA values and forest plots of odds ratios and mean differences of NMA of (A) apnea time, (B) apnea incidence, (C) airway adverse event, (D) insertion failure, and (E) inadequate depth of anesthesia. NMA indicates network meta-analysis; SUCRA, surface under the cumulative ranking curve; OR, odds ratio; CrI, credible interval; PPF, propofol; MDZ, midazolam; AA, agonist-antagonist; IV, intravenous; NMBA, neuromuscular blocking agent; THIO, thiopentone; Lido., lidocaine; and Top., topical.

Figure 4. Cumulative SUCRA Scores of Anesthetic Interventions



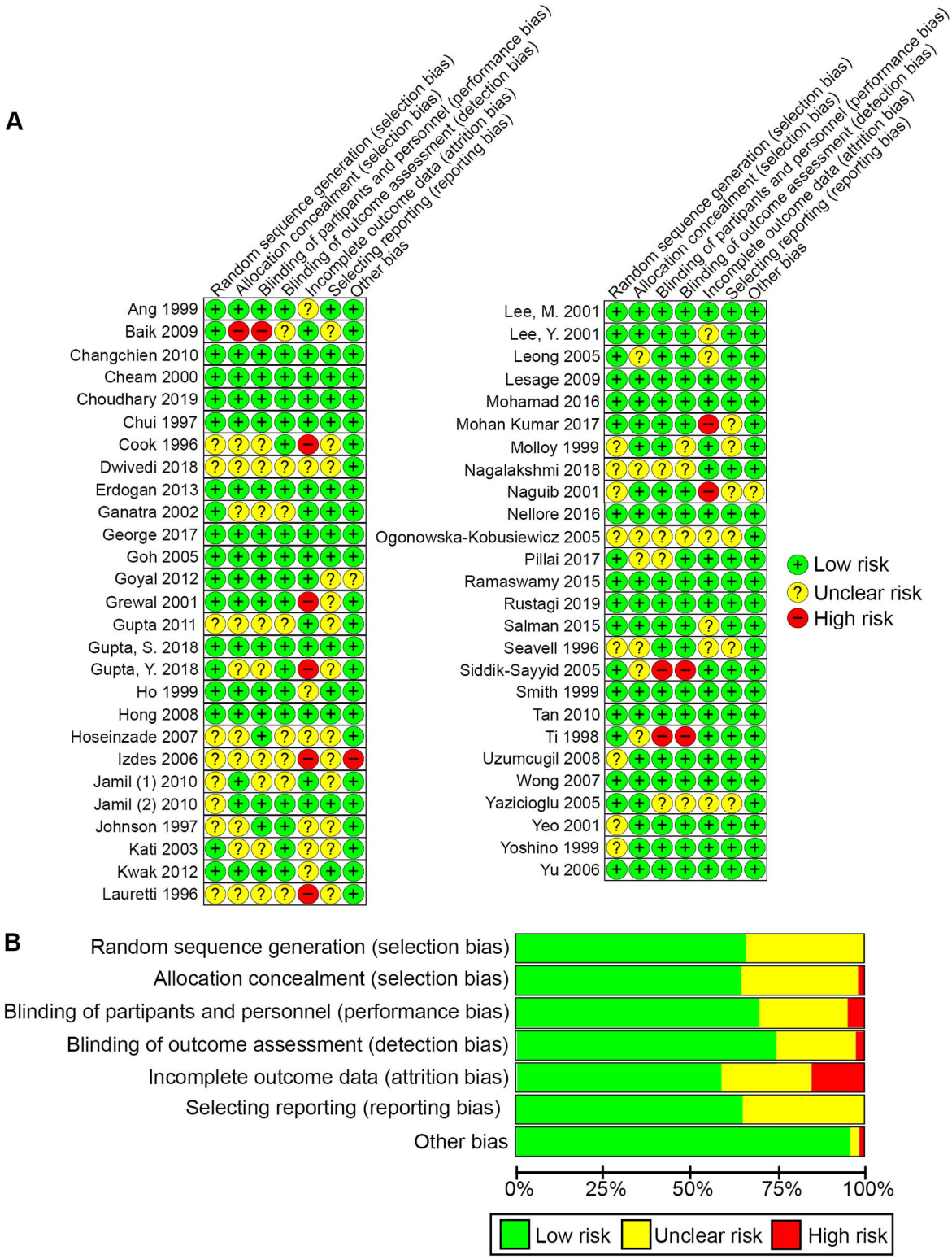
Summed scores of anesthetic intervention SUCRA ranks for apnea (red), airway adverse event (blue), insertion failure (yellow), and inadequate depth of anesthesia (green). SUCRA indicates surface under the cumulative ranking curve; PPF, propofol; MDZ, midazolam; NMBA, neuromuscular blocking agent; AA, agonist-antagonist; and IV, intravenous.

5.7×10^{-11}; 95% CrI, 2.9×10^{-31} to 0.03; SUCRA = 98%) ranked the top intervention for reducing the risk of airway adverse events (Figure 3). For comparison, propofol alone demonstrated a SUCRA score of 9% in this outcome (Figure 3).

Under the insertion failure outcome, failed LMA insertion on the first attempt occurred in 16.2% of patients (490 of 3028; Table). Furthermore, 16.2% (486 of 2999) were reported to have inadequate ease of LMA insertion. Propofol + midazolam + IV lidocaine (OR, 0.03; 95% CrI, 1.0×10^{-3} to 0.79; SUCRA = 88%) ranked the top intervention to reduce risk of insertion failure (Figure 3). For comparison, propofol alone demonstrated a SUCRA score of 20% in this outcome (Figure 3).

Within the inadequate depth of anesthesia outcome, head and/or limb movement had the highest incidence of occurrence and was reported in 30.4% (811 of 2669) of patients (Table). Propofol + vapor + short opioid (OR, 0.03; 95% CrI, 3.8×10^{-3} to 0.24; SUCRA = 91%) ranked the top intervention to reduce the risk of inadequate depth of anesthesia (Figure 3). For comparison, propofol alone demonstrated a SUCRA score of 9% in this outcome (Figure 3).

Figure 5. Risk of Bias Assessment



Each included study assessed by review authors' judgments for risk of bias and deemed as low risk of bias (+, green), unclear risk of bias (?, yellow), or high risk of bias (−, red).

Hemodynamic events (bradycardia, tachycardia, and hypotension) were reported in 19 studies, across 1613 patients and 15 anesthetic interventions. The most reported event was hypotension, which occurred in 12.2% (150 of 1232) of patients. However, 75 of 150 hypotension events occurred in the propofol + short opioid intervention. The OR and CrI demonstrated large variability across all interventions following analysis and was excluded in the summed scores of SUCRA ranks (Supplemental Information, Figure S2).

The SUCRA ranks were scored across all outcomes and summed (Supplemental Information, Table S4). Propofol + dexmedetomidine had the highest summed score (Figure 4), as it ranked among the top interventions across the outcomes for apnea incidence (OR, 2.20; 95% CrI, 0.21-39.0; SUCRA = 37%; rank 13 of 20), apnea time (mean difference 0.24; 95% CrI, −2.40 to 2.80; SUCRA = 66%; rank 5 of 17), airway adverse event (OR, 0.07; 95% CrI, 0.02-0.27; SUCRA = 67%; rank 7 of 26), insertion failure (OR, 0.12; 95% CrI, 0.02-0.59; SUCRA = 73%; rank 4 of 26), and inadequate depth of anesthesia (OR, 0.06; 95% CrI, 0.01-0.29; SUCRA = 84%; rank 2 of 20). Eighteen of 28 anesthetic interventions had scores across all outcomes, of which propofol had the lowest summed SUCRA score.

None of the included studies reported hypertension, unanticipated hospital admission, or mortality.

Risk of Bias

The overall risk of bias was graded as low in 19 studies (36%), moderate in 21 studies (40%), and high in 13 studies (24%) (Figure 5). Overall, high risk of bias was found in the domains of selection bias (1 study), performance bias (3 studies), detection bias (4 studies), and attrition bias (7 studies; Figure 5).

Sensitivity and Subgroup Analysis

When the high–risk of bias studies were removed, propofol + dexmedetomidine remained as having the highest overall cumulative SUCRA rank score in reducing adverse outcomes (Supplemental Information, Table S4). The results of the other subgroup analyses, (1) the effect of premedication and (2) the type of LMA (Supplemental Information, Table S4), were similar to those of the primary analysis. The quality of evidence ranged from very low to moderate (Supplemental Information, Table S5). Heterogeneity analysis demonstrated significant inconsistency (I^2 = 8.9-99.1%) with low to considerable heterogeneity (Supplemental Information, Tables S6 and S7).

DISCUSSION

This NMA attempted to identify the best anesthetic combination to avoid prolonged apnea and the other secondary outcomes of airway adverse events, inadequate anesthetic depth, LMA placement failure, and adverse hemodynamics after LMA insertion. Anesthesiologists often intend to have brief apnea to achieve sufficient anesthetic depth for LMA placement; however, anesthetic overdose during induction has been frequently identified by bispectral index monitoring.[28,29] Avoiding prolonged apnea and promptly resuming spontaneous breathing are desired; hence, prolonged apnea after LMA insertion was selected as the primary outcome for this study. Return of spontaneous breathing can be evaluated along with other physiology- and medication-related parameters to allow anesthesiologists to titrate their anesthetics by monitoring changes in their patients' respiration rates and tidal volumes, thereby decreasing risk of anesthetic overdose.

Preventing overdose may also avoid adverse outcomes such as hemodynamic instability, prolonged recovery time, and increased mortality.[29,30] In our study, it was difficult to determine if prolonged apnea was associated with other adverse outcomes such as hypoxia, as there was a lack of reporting in the included studies. Of the 53 studies included for meta-analysis, only 7 reported hypoxia as an outcome. Lack of reporting of hemodynamic events was also seen across the studies. In contrast, by reducing apnea time, the risk of inadequate depth of anesthesia is increased. In this NMA, 36 studies reported an outcome that suggests the risk of inadequate depth of anesthesia (ie, head or limb movement, inadequate jaw relaxation). Likewise, other more serious outcomes, such as laryngospasm, may be seen with insufficient anesthetic depth. Therefore, a balance exists between preventing anesthesia overdose and providing an adequate depth of anesthesia to reduce the risk of adverse events during LMA insertion.

Propofol as the only anesthetic agent for GA induction ranked near lowest for reducing adverse events during LMA insertion; only thiopental demonstrated a poorer ability to prevent adverse outcomes. The addition of other anesthetics with propofol improved the conditions for GA induction and LMA insertion. The combination of propofol + dexmedetomidine ranked the most effective anesthetic combination for reducing adverse events evidenced by SUCRA scores. This finding is supported by the recent meta-analysis completed by Ju and colleagues,[5] which demonstrated the use of dexmedetomidine in comparison with sedative agents, such as fentanyl or midazolam, improved the success rate of LMA placement, lessened respiratory depression, and reduced adverse events, such as coughing and limb movement. In our NMA study, the benefit of dexmedetomidine was compared with all anesthetic combinations used for LMA placement available in literature.

Dexmedetomidine is an α-2 adrenoreceptor agonist that has several beneficial properties for anesthesia induction that may have helped rank it as the top anesthetic when combined with propofol for LMA insertion.[31] Unlike other anesthetics that provide sedation (eg, opioids), dexmedetomidine has minimal negative effect on respiratory drive.[31] The respiratory-sparing effect makes dexmedetomidine ideally suited for the management of a difficult airway, and it has been used for awake fiberoptic intubation.[32,33] Dexmedetomidine has analgesic, antitussive, and anxiolytic properties that have been demonstrated to reduce patient reactivity during airway-stimulating events (eg, awake intubation), sparing the need for opioids or benzodiazepines.[32,33] Moreover, dexmedetomidine also has antisialagogue properties, potentially reducing the risk for cough and laryngospasm.[32,34]

In our study, the combination of propofol + dexmedetomidine ranked 13 of 20 in apnea incidence and 5 of 17 in apnea time. It is possible that the respiratory-sparing properties of dexmedetomidine were negated by the combined use of propofol. Despite the middle ranking of propofol + dexmedetomidine for apnea, the other desirable properties of dexmedetomidine may have helped it rank higher in the other outcomes of insertion failure, inadequate depth of anesthesia, and airway adverse events. Undesirable effects of dexmedetomidine include the potential for bradycardia and hypotension.[31] Of the 4 studies examining propofol + dexmedetomidine included in our meta-analysis, the incidences of bradycardia and hypotension were 6.8% and 1.3%, respectively. Overall, the quality of evidence of the included studies was low to moderate for propofol + dexmedetomidine, and further, better-quality studies are required to establish the full benefit of that anesthetic combination for LMA insertion.

The implication of this study is that propofol + dexmedetomidine could be seen as more favorable and have increased use among anesthesiologists because of its effectiveness for reducing adverse events during LMA insertion. The use of dexmedetomidine with propofol has clinical and economic considerations that go beyond reducing adverse events and increasing patient safety. First, the use of dexmedetomidine may increase the cost of GA compared with other commonly used anesthetics. Dexmedetomidine may cost twice as much as using propofol alone and as much as 4 times when compared with midazolam.[35] However, considering the total cost of managing some more serious adverse events, dexmedetomidine may prove more favorable. When used in the intensive care unit (ICU) for intubated patients, dexmedetomidine was associated with increased cost savings because of the reduction in ICU length of stay and the degree of monitoring and management.[36] Second, according to the product monograph, dexmedetomidine should be used as a slow induction bolus (1 μg/kg) given over 10 minutes to avoid adverse events such as bradycardia.[37] All studies that were included in this NMA utilized this suggested protocol of slow bolus of dexmedetomidine over 10 minutes for anesthesia induction before LMA placement. This required time for dexmedetomidine delivery compared with faster anesthetics, such as 30 seconds for remifentanil, may increase total anesthesia time and reduce the number of patients who can be seen in a clinical day. However, with optimal case organization and scheduling, the additional time required for dexmedetomidine use may be negated. Overall, the use of propofol + dexmedetomidine for LMA placement may prove to be an effective and efficient anesthetic combination for LMA insertion. Only through increased use and further clinical research can the full benefits of propofol + dexmedetomidine be appreciated.

The large number of included studies from Asia and the few from North America may be indicative of the LMA's popularity in each of the respective regions. In Europe and Asia, the LMA has become highly favored and is used more commonly over tracheal intubation, unlike in the US, where tracheal intubation is still the most used airway device.[38–40] Only 2 studies reported the use of second-generation LMAs. Our subgroup analysis of LMA type did not demonstrate any differences, mainly because of the lack of reporting. It is possible that with increased use of second-generation LMAs, the incidence of adverse events may be reduced.[41,42]

Inconsistency in what outcomes constituted successful LMA placement was notable. The most common reported set of outcomes was that of the modified scheme of Lund and Stovner,[43] examining mouth opening, ease of insertion, swallowing, coughing or gagging, head or limb movement, and laryngospasm. Another set of outcomes reported was those used by Muzi and colleagues,[44] which included jaw mobility, coughing, movement, spontaneous ventilation, breath holding, and lacrimation. Most of the included studies did not cite an existing set of LMA outcomes, and our NMA required grouping of outcomes into similar adverse event categories to permit analysis and comparison. Our study limited outcomes to only those that encompassed LMA insertion after GA induction and not outcomes that followed GA, such as patient satisfaction, sore throat, or incidence of postoperative nausea and vomiting (PONV). The meta-analysis by Joo and Perks[45] suggested that induction of GA with propofol for LMA insertion may be favored over sevoflurane due patient satisfaction and less frequent PONV. Further investigation is required to determine how the choice of anesthetics for LMA insertion may affect patient satisfaction and recovery.

A limitation of this NMA was that combining similar anesthetics into groups resulted in 3 one-arm studies without a comparator, preventing inclusion in the meta-analysis. By grouping anesthetics together, we made robust class comparisons at the expense of interdrug comparisons, such as alfentanil vs fentanyl. The ability to make comparisons is dependent on the sets of interventions being similar enough to be combined.[21] The heterogeneity analysis in this study demonstrated significant inconsistency with low to considerable heterogeneity; hence, caution is required for interpretation of the study's results.

Another limitation of the included studies was the lack of standardized dosing of anesthetics used. Propofol was used in doses that ranged from 1.5 mg/kg to 3.0 mg/kg. Higher doses of propofol are associated with hypotension, cardiorespiratory depression, and prolonged apnea.[5,41,42] Therefore, combining propofol with another anesthetic may be beneficial only if the propofol dose is reduced appropriately. Furthermore, a limitation of the included studies was the lack of preoperative standardization regarding the use of anticholinergics, sedatives, and anxiolytics. Though our subgroup analysis did not show any conclusive influence on the use of premedication with LMA insertion, we were limited by the number of studies that reported their use. The use of a benzodiazepine, such as midazolam, works synergistically with opioids and may potentially prolong apnea time following induction if an opioid is used.[46] Similarly, anticholinergics have been shown to improve the success of tracheal intubation by reducing oral secretions and preserving hemodynamic stability.[47,48] Likewise, antihistamines (eg, hydroxyzine) can be used as premedication to reduce anxiety, pruritus, and PONV as well as reduce oral secretions through their antisialagogue properties.[49] By reducing oral secretions, anticholinergics and antihistamines may potentially reduce the risk of laryngospasm during induction.[50] It is unclear how the role of premedication affects the success rate of LMA insertion, as different types of premedication can provide beneficial or unfavorable conditions for LMA insertion. Our subgroup analysis of premedications did not demonstrate a difference. If further study on anesthetics for LMA insertion is undertaken, we recommend that premedication be omitted for clear, uninfluenced comparison of the anesthetics. Finally, caution should be taken with interpretation of the SUCRA-ranked results. SUCRA does not take into consideration the magnitude of differences in effects between treatments.[51] Differences in top-ranked treatments may not be clinically appreciable. Likewise, this NMA weighed all outcomes equally during the overall SUCRA ranking. Some outcomes may be more relevant for the clinician in their setting and should be considered when selecting an anesthetic for LMA insertion given their respective clinical circumstances.

To the authors' knowledge, a strength of this study is that it is the first NMA to compare and rank all anesthetic combinations used for GA induction. The NMA method allows for direct and indirect comparisons of multiple treatments when head-to-head comparisons are not always available in the literature. In the studies that met our inclusion criteria, 48 different anesthetics and anesthetic combinations were identified. This study demonstrates that the comparison of different anesthetic combinations with an NMA is feasible and effective.

CONCLUSION

Our systematic review and meta-analysis of anesthetics used for GA induction and LMA insertion demonstrated that all anesthetic combinations, except for those used with thiopental, reduced adverse outcomes in comparison with propofol alone. In an NMA using cumulative SUCRA-ranked scoring, very low to moderate quality evidence suggests that the combination of propofol + dexmedetomidine is the most effective anesthetic combination for minimizing adverse outcomes during LMA insertion following GA induction according to the current literature.

ACKNOWLEDGMENTS

The authors would like to thank Madeline Gerbig and Maria Zych, Instruction and Liaison Librarians, University of Toronto Dental Library.

Disclosures

The authors have no interests to declare.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Aghamohammadi D, Eydi M, Hosseinzadeh H, Amiri Rahimi M, Golzari SE. Assessment of mini-dose succinylcholine effect on facilitating laryngeal mask airway insertion. *J Cardiovasc Thorac Res*. 2013;5(1):17–21.

2. Allsop E, Innes P, Jackson M, Cunliffe M. Dose of propofol required to insert the laryngeal mask airway in children. *Paediatr Anaesth*. 1995;5(1):47–51.

3. Goh PK, Chiu CL, Wang CY, Chan YK, Loo PL. Randomized double-blind comparison of ketamine-propofol, fentanyl-propofol and propofol-saline on haemodynamics and laryngeal mask airway insertion conditions. *Anaesth Intensive Care*. 2005;33-(2):223–228.

4. Lee MP, Kua JS, Chiu WK. The use of remifentanil to facilitate the insertion of the laryngeal mask airway. *Anesth Analg*. 2001;93(2):359–362.

5. Ju Q, Xiao Z, Sun W, Zhu M, Lv P. The anesthesia induction effect of dexmedetomidine in patients undergoing laryngeal mask intubation: a systematic review and meta-analysis of 7 RCTs. *Ann Palliat Med*. 2021;10(12):12358–12366.

6. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777–784.

7. Saunders R, Struys MMRF, Pollock RF, Mestek M, Lightdale JR. Patient safety during procedural sedation using

capnography monitoring: a systematic review and meta-analysis. *BMJ Open*. 2017;7(6):e013402.

8. Choi GJ, Kang H, Baek CW, Jung YH, Ko JS. Etomidate versus propofol sedation for electrical external cardioversion: a meta-analysis. *Curr Med Res Opin*. 2018;34(11):2023–2029.

9. Boonmak P, Boonmak S, Pattanittum P. High initial concentration versus low initial concentration sevoflurane for inhalational induction of anaesthesia. *Cochrane Database Syst Rev*. 2016;(6):CD006837.

10. Azarpazhooh A, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. *Cochrane Database Syst Rev*. 2016;(8):CD007095.

11. Mathew PJ, Mathew JL. Early versus late removal of the laryngeal mask airway (LMA) for general anaesthesia. *Cochrane Database Syst Rev*. 2015;(8):CD007082.

12. Young HSA, Clarke RSJ, Dundee JW. Intubating conditions with AH 8165 and suxamethonium. *Anaesthesia*. 1975;30(1): 30–33.

13. Kwon CH, Kim S-H. Intraoperative management of critical arrhythmia. *Korean J Anesthesiol*. 2017;70(2):120–126.

14. Südfeld S, Brechnitz S, Wagner JY, et al. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. *Br J Anaesth*. 2017;119(1):57–64.

15. Bijker Jilles B, van Klei Wilton A, Kappen Teus H, van Wolfswinkel L, Moons Karel GM, Kalkman Cor J. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology*. 2007;107(2):213–220.

16. Varon J, Marik PE. Perioperative hypertension management. *Vasc Health Risk Manag*. 2008;4(3):615–627.

17. Brain AI. The laryngeal mask—a new concept in airway management. *Br J Anaesth*. 1983;55(8):801–805.

18. Bramer W, Bain P. Updating search strategies for systematic reviews using EndNote. *J Med Libr Assoc*. 2017;105(3):285–289.

19. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc*. 2016;104(3):240–243.

20. Higgins JP, Altman DG. Assessing risk of bias in included studies. In: Higgins JP, Green S, ed. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2008:187–241.

21. Higgins JP, Thomas J, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.0. Cochrane; 2019.

22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5(1):13.

23. Walter SD, Yao X. Effect sizes can be calculated for studies reporting ranges for outcome variables in systematic reviews. *J Clin Epidemiol*. 2007;60(8):849–852.

24. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33(5):607–617.

25. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23(20):3105–3124.

26. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. *PLoS One*. 2014;9(7):e99682.

27. Brain AI, Verghese C, Strube PJ. The LMA "ProSeal"—a laryngeal mask with an oesophageal vent. *Br J Anaesth*. 2000;84(5): 650–654.

28. Giraldo JC, Acosta C, Giraldo-Grueso M. Frequency of anesthetic overdose with mean alveolar concentration-guided anesthesia at high altitude. *Med Gas Res*. 2019;8(4):150–153.

29. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev*. 2014;2014(6):CD003843-CD.

30. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg*. 2005;100(1):4–10.

31. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*. 2000;93(2):382–394.

32. Chopra P, Dixit MB, Dang A, Gupta V. Dexmedetomidine provides optimum conditions during awake fiberoptic intubation in simulated cervical spine injury patients. *J Anaesthesiol Clin Pharmacol*. 2016;32(1):54–58.

33. Bergese SD, Candiotti KA, Bokesch PM, et al. A phase IIIb, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of dexmedetomidine for sedation during awake fiberoptic intubation. *Am J Ther*. 2010;17(6):586–595.

34. Sasaki Y, Kato S, Miura M, Fukayama H. Correlation between body movements and salivary secretion during sedation. *Anesth Prog*. 2016;63(4):185–191.

35. Canadian Agency for Drugs and Technologies in Health. Dexmedetomidine for sedation in the ICU or PICU: a review of cost-effectiveness and guidelines. Publisher; 2014.

36. Aggarwal J, Lustrino J, Stephens J, Morgenstern D, Tang WY. Cost-minimization analysis of dexmedetomidine compared to other sedatives for short-term sedation during mechanical ventilation in the United States. *Clinicoecon Outcomes Res*. 2020;12:389–397.

37. Product monograph—Precedex. Pfizer Canada Inc. December 9, 2009. Updated March 30, 2023. https://www.pfizer.ca/files/Precedex_PM_EN.pdf

38. Woodall NM, Cook TM. National census of airway management techniques used for anaesthesia in the UK: first phase of the Fourth National Audit Project at the Royal College of Anaesthetists. *Br J Anaesth*. 2011;106(2):266–271.

39. Kadar S, Koshy R. Survey of supraglottic airway devices usage in anaesthetic practice in South Indian State. *Indian J Anaesth*. 2015;59:190.

40. Clark HM, Saxen MA, Yepes JF, et al. Comparison of intubated versus nonintubated airway management in children under general anesthesia provided by dentist anesthesiologists. *Pediatr Dent*. 2019;41(1):52–55.

41. Park SK, Choi GJ, Choi YS, Ahn EJ, Kang H. Comparison of the i-gel and the laryngeal mask airway proseal during general anesthesia: a systematic review and meta-analysis. *PLoS One*. 2015;10(3):e0119469.

42. de Montblanc J, Ruscio L, Mazoit JX, Benhamou D. A systematic review and meta-analysis of the i-gel® vs laryngeal mask airway in adults. *Anaesthesia*. 2014;69(10):1151–1162.

43. Lund I, Stovner J. Dose-response curves for tubocurarine, alcuronium and pancuronium. *Acta Anaesthesiol Scand Suppl*. 1969;37:238–242.

44. Muzi M, Robinson BJ, Ebert TJ, O'Brien TJ. Induction of anesthesia and tracheal intubation with sevoflurane in adults. *Anesthesiology*. 1996;85(3):536–543.

45. Joo HS, Perks WJ. Sevoflurane versus propofol for anesthetic induction: a meta-analysis. *Anesth Analg*. 2000;91(1):213–219.

46. Avramov MN, Smith I, White PF. Interactions between midazolam and remifentanil during monitored anesthesia care. *Anesthesiology*. 1996;85(6):1283–1289.

47. Shim JG, Cho EA, Ryu KH, et al. Effects of prophylactic atropine on the time to tracheal intubation with the pre-administration of remifentanil. *Acta Anaesthesiol Scand*. 2021;65(3):335–342.

48. Cho E-A, Hwang S-H, Lee SH, Ryu K-H, Kim Y-H. Does glycopyrrolate premedication facilitate tracheal intubation with a rigid videostylet? a randomized controlled trial. *Medicine*. 2018;97(32):e11834-e.

49. Sheen MJ, Chang F-L, Ho S-T. Anesthetic premedication: new horizons of an old practice. *Acta Anaesthesiol Taiwan*. 2014; 52(3):134–142.

50. Gavel G, Walker RW. Laryngospasm in anaesthesia. *Contin Educ Anaesth Crit Care Pain*. 2013;14(2):47–51.

51. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Syst Rev*. 2017;6(1):79.

SUPPLEMENTAL INFORMATION

(available online only)

Figure S1. Relative Treatment Effects of Primary and Secondary Outcomes

Figure S2. Adverse Hemodynamic Event Secondary Outcome

Table S1. NMA Search Strategy

Table S2. Exclusion Study Table

Table S3. Included Studies Table of Characteristics

Table S4. SUCRA Scores for Primary and Secondary Outcomes

Table S5. Grade for Top-Ranked Anesthetic Combinations

Table S6. Heterogeneity Analysis

Table S7. Inconsistency Analysis

Delayed Rocuronium Onset in a Patient Taking Levetiracetam for Epilepsy: A Case Report

Toru Yamamoto, DDS, PhD; Yuhei Koyama, DDS, PhD; Yutaka Tanaka, DDS, PhD; and Kenji Seo, DDS, PhD

Division of Dental Anesthesiology, Faculty of Dentistry & Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

Emerging evidence suggests that many conventional anticonvulsants, such as carbamazepine, phenytoin, and valproic acid, could cause cross-resistance to nondepolarizing muscle relaxants. However, there are few reports describing the interactions between levetiracetam and rocuronium. This case report describes the delayed onset of rocuronium in an adult patient with intractable epilepsy on long-term levetiracetam therapy. A 33-year-old man was scheduled for extraction of third molars and restorative dental treatment. His daily levetiracetam was continued preoperatively, and after a slow mask induction, rocuronium (20 mg; 0.66 mg/kg) was administered. Muscle relaxation was monitored by train-of-four (TOF) stimulation using the adductor muscle of the thumb. However, it took more than 9 minutes to finally obtain a TOF count of 0. This case report highlights that patients with intractable epilepsy taking levetiracetam may have resistance to rocuronium and should be carefully monitored to avoid harm triggered by prematurely initiated intubation maneuvers.

Key Words: Neuromuscular blockers; Muscle relaxant; Rocuronium; Anticonvulsant; Resistance; Intractable epilepsy; Levetiracetam.

Many drugs can impact nondepolarizing muscle relaxants (NDMRs), leading to prolonged or enhanced neuromuscular blockade. Long-term use of antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, and valproic acid has been reported to be associated with resistance to both the aminosteroidal (eg, rocuronium, vecuronium) and benzylisoquinolinium (eg, atracurium, cisatracurium) NDMRs.[1–10] Reports on the effects of newer AEDs (eg, lamotrigine, levetiracetam) on rocuronium are scarce and may not be well recognized.

Herein, we report a case of delayed rocuronium onset during general anesthesia in a patient on long-term anticonvulsant therapy because of intractable epilepsy. Written consent was obtained from the patient's legal guardian to publish the details of this case report.

CASE PRESENTATION

A 33-year-old man (height, 150 cm [59 in]; weight, 30 kg; body mass index, 13.3 kg/m^2) was scheduled for extraction of all 4 third molars and restorative treatment for dental caries. He was delivered at 37 weeks gestation with no perinatal abnormalities. However, 3 days after delivery, he contracted bacterial meningitis and suffered hydrocephalus which led to intractable epilepsy and intellectual disability, thereby hampering communication. Using the Oshima classification for patients with severe motor and intellectual disabilities, he was graded division 4 (very severe).[11]

Because of his history of status epilepticus, levetiracetam (1800 mg, twice a day) had been prescribed for over 10 years as his daily antiepileptic medication along with diazepam suppositories (10 mg) for emergent use in the event of unabated seizures. Despite his medications, epileptic seizures occurred often (ie, once a week) leading up to the week before hospital admission. He needed full-time assistance for the activities of daily living and utilized a wheelchair for transportation. The patient had no known drug allergies and no relevant family history.

Preoperatively, an anterior-posterior (AP) chest radiograph demonstrated severe scoliosis and a 12-lead electrocardiography revealed right-axis deviation. Routine preoperative blood tests were not obtained because of his uncooperative nature and therefore were planned to follow induction of general anesthesia.

The following risk factors for difficulty with mask ventilation were identified: male, beard, thick neck, and Mallampati class IV. Regarding difficult tracheal intubation

Received March 15, 2023; accepted for publication August 18, 2023.

Address correspondence to Dr Toru Yamamoto, Division of Dental Anesthesiology, Graduate School of Medicine and Dental Sciences, Niigata University, 2-5274, Gakkocho-dori, Chuo-ku, Niigata, 951-8514, Japan; toruyamamoto@dent.niigata-u.ac.jp.

Anesth Prog 71:76–80 2024 | DOI 10.2344/23-00018

risk factors, poor cervical spine mobility and difficulty with mouth opening were detected. Airway management was expected to be challenging because of tracheal deviation and his bent posture, which were observed at the preoperative assessment (Figure 1A and B). The patient was deemed an American Society of Anesthesiologists physical status class 3.

We planned for outpatient surgery rather than inpatient because of his difficulty adapting to different environments. The day of surgery, he took his usual dose of levetiracetam more than 2 hours before the induction of general anesthesia. He had fasted appropriately for more than 8 hours, and no other premedication was administered. Upon arrival to the operating room and application of the standard anesthesia monitors, including a muscle-relaxation monitor (NMT module, Philips; Figure 2A), his blood pressure was 95/70 mm Hg, pulse was 66 beats/min, and oxygen saturation was 97% at room air. Preoxygenation (6 L/min) was started, followed by a slow mask induction with sevoflurane (3%) that was started gradually and mixed with oxygen. After loss of consciousness, venous access was established in the left upper arm using a 22-gauge intravenous (IV) cannula. Boluses of fentanyl (50 μg) and rocuronium (20 mg; 0.66 mg/kg) were administered. Muscle relaxation was monitored using the train-of-four (TOF) test and the adductor muscle of the thumb (Figure 2B). Spontaneous ventilation was maintained and assisted mask ventilation was easy, so we opted to wait for a TOF of 0 using the muscle-relaxation monitor. However, it took over 9 minutes to obtain a TOF of 0.

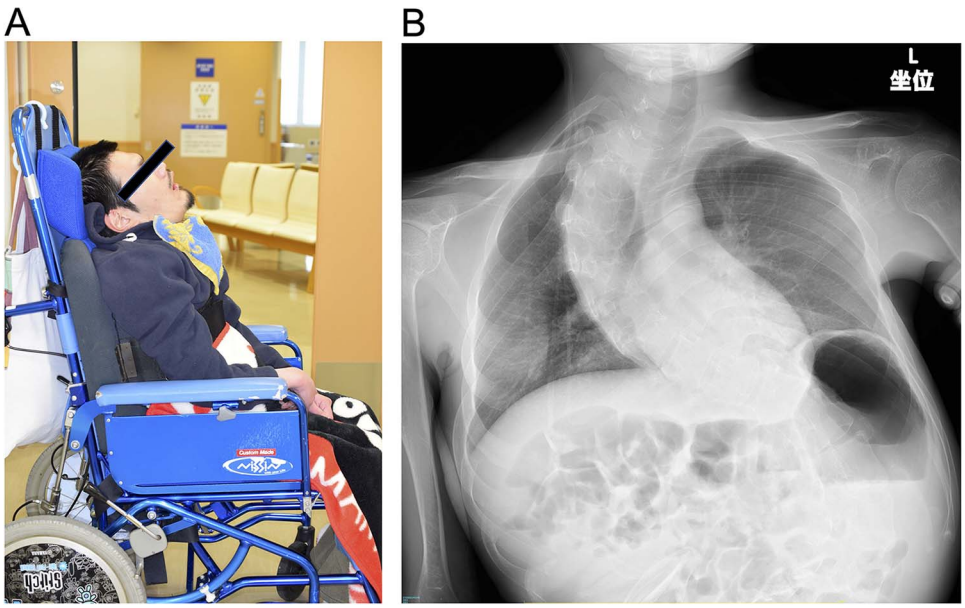
After sufficient muscle paralysis was confirmed, a video laryngoscope (McGRATH Mac, Medtronic) was employed, which produced a Cormack-Lehane grade 2 view. A flexible, wire-reinforced, endotracheal tube (internal diameter 7.0 mm) with a cuff (Shiley spiral tube, Covidien Japan) was used for the oral intubation. Adverse airway reflexes were not observed during the intubation. General anesthesia was maintained with oxygen (0.5 L/min), air (0.5 L/min), desflurane (4.5%), and a continuous infusion of remifentanil (0.2 μg/kg/min).

Rocuronium was not readministered during the dental procedure, and the patient's neuromuscular status prior to reversal at the end of the case was almost fully recovered with a TOF of 4 at 87%. However, sugammadex (200 mg) was administered preventively, and, after confirmation of adequate spontaneous breathing with airway patency, he was extubated. The duration of the dental procedure was 1 hour and 22 minutes. The duration of anesthesia was 3 hours and 2 minutes. The venous blood sample taken during the case showed hypoalbuminemia (3.1 g/dL; normal range, 4.1-5.1 g/dL), although his liver enzyme levels and serum Ca^{2+} were all on the low end of normal. The patient was discharged without complications on postoperative day 1.

DISCUSSION

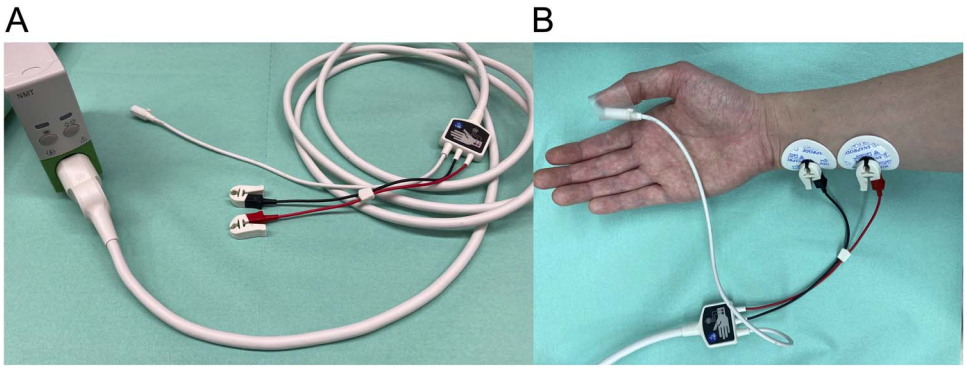
Intractable epilepsy can be associated with muscle weakness and impaired upper extremity coordination and dexterity. In general, rocuronium at 0.6 mg/kg should provide sufficient muscle relaxation for safe tracheal intubation approximately 2 minutes after IV administration.[12] However, in this case, it

Figure 1. Clinical Picture and Chest Radiograph of the Patient.



A, Side view of the patient. B, AP chest radiograph demonstrating significant scoliosis and tracheal deviation.

Figure 2. Muscle Relaxation Monitor.



A, NMT module with electrode clips and acceleration detection monitor. B, The acceleration detection monitor attached to the patient's thumb along with 2 electrodes used to stimulate the ulnar nerve.

took more than 9 minutes to obtain a TOF of 0. Intraoperative blood tests were performed to investigate whether the patient had any liver and/or kidney impairment due to long-term use of levetiracetam, but no abnormal values were found. Because Ca^{2+} levels can impact the effects of rocuronium, we checked his serum Ca^{2+} levels and found them to be within normal limits. The blood tests we obtained notably did not include Mg^{2+}, which can also impact muscle relaxation, so it remains unclear if that played a role.

Spontaneous ventilation was maintained while we were waiting for the TOF of 0, which was one of the clinical signs of the delayed paralysis onset we encountered. Although there was one report of delayed recovery from rocuronium-induced neuromuscular blockade in patients taking levetiracetam (1000 mg) acutely before operations,[13] there were few reports of long-term levetiracetam use (ie, over 10 years) that we were able to identify in the existing literature. Accumulation of findings in cases of long-term levetiracetam use is needed.

Anesthesiologists should assess neuromuscular function to avoid insufficient muscle relaxation, which can cause adduction or complete closure of the vocal cords (ie, laryngospasm) and a cough reflex during endotracheal intubation, endangering patient safety.[14–16] In such situation, the risks of a challenging intubation and vocal-cord injury due to glottis closure are high. Waiting patiently for the onset of sufficient muscle relaxation, as was done in this case, is important. Furthermore, adverse events (eg, glottis closure due to premature initiation of intubation) can be avoided by using a muscle-relaxation monitor, as was also done in this case. Careful assessment of the patient's neuromuscular status prior to intubation and throughout the surgical procedure, especially in patients with intractable epilepsy on long-term anticonvulsants like levetiracetam, is highly recommended because sufficient paralysis is essential for safe anesthesia management. The NMT monitor utilized in this study was approved as a medical device by the Japanese government and is widely used in daily clinical practice. We do not have any information on whether this device shows higher sensitivity vs traditional twitch monitors. Therefore, this device is anticipated to have the same sensitivity in detecting muscle relaxation as a traditional twitch monitor.

Deeper knowledge of drug interactions is becoming important, especially in anesthesiology and critical care. Emerging evidence suggests that AEDs such as phenytoin, carbamazepine, phenobarbital, and valproic acid can induce resistance to NDMRs like rocuronium. Delayed rocuronium onset has been reported in children taking the AEDs phenytoin and carbamazepine for a long time (eg, for more than 1 month).[17] However, few reports have described NDMR resistance in an adult taking AEDs for over 10 years.

It is thought that NDMR resistance associated with long-term antiepileptic therapy using conventional agents like carbamazepine, phenytoin, and valproic acid is due to 3 main factors operating alone or in combination: (1) induced hepatic drug metabolism, (2) increased protein binding of the NDMR, and (3) upregulation of acetylcholine receptors (AChRs).[18] These factors are discussed below.

Conventional AEDs such as carbamazepine, phenytoin, and valproic acid produce cytochrome P450 (CYP450) enzymatic induction, which can increase drug metabolism in the liver, leading to shorter duration of action.[19–21] Some reports have indicated that phenytoin increased alpha-1 glycoprotein (AAG) in human serum and rats.[22,23] Increased AAG blood levels promote plasma protein binding of cationic drugs, including all NDMRs (ie, the aminosteroids and benzylisoquinolines), which results in a decreased concentration of unbound, free drug capable of exerting its pharmacological effects (ie, paralysis), leading to delayed onset and shorter duration of action.[23–25] Decreased function of the neuromuscular junction with decreased receptor sensitivity and increased numbers of postsynaptic AChRs have been reported, which requires increased NDMR quantities

and can otherwise lead to delayed neuromuscular blockade onset.[26]

However, compared with other conventional antiepileptics, levetiracetam is an orally active drug with a unique profile. Its pharmacokinetics closely approximate the ideal characteristics expected of an AED: good bioavailability, rapid achievement of steady-state concentrations, linear and time-invariant kinetics, minimal protein binding, and minimal metabolism.

The major metabolic pathway of levetiracetam is not dependent on the hepatic CYP450 system, nor does it cause hepatic enzyme inhibition or induction. Sixty-six percent of an administered levetiracetam dose is eliminated unchanged in the urine; 24% is metabolized to an inactive metabolite that is detectable in the blood and excreted in the urine. Levetiracetam is not appreciably plasma protein–bound, nor does it affect the protein binding of other drugs. Thus, because of its minimal protein binding and lack of hepatic metabolism, the risk of drug interactions is very low.[27,28]

Regarding AAG, it is unclear whether levetiracetam elevates AAG in the same or similar ways as conventional AEDs. It has been reported, however, that AAG concentrations are higher in epileptic patients during periods of frequent seizures.[27] Therefore, it is possible that the patient in this report had elevated AAG levels secondary to his frequent seizures and that the resulting decrease in free, unbound rocuronium due to its binding with AAG may have attributed to the delayed onset of the muscle relaxant effects.

It is also unclear whether levetiracetam causes upregulation in AChRs similarly to phenytoin and carbamazepine.[30] However, previously published studies have demonstrated increased requirements for NDMRs after prolonged immobilization. Immobility is functionally comparable with denervation syndrome in that both result in muscle atrophy and AChR upregulation.[31] These could be associated with the delayed onset of rocuronium seen in this case. On the other hand, there is a report that fiber atrophy, but not changes in AChR expression, contributes to muscle dysfunction after immobilization.[26] Thus, the impact of immobilization remains unclear.

The possible impact of levetiracetam on the duration of action and recovery from rocuronium was unfortunately not examined in detail in this case. However, the TOF at the end of the operation (3 hours after rocuronium administration) was 87%, implying a slight residual muscle relaxant effect. A previous report has shown delayed recovery from rocuronium-induced neuromuscular blockade in patients taking levetiracetam.[13] However, this was a single-dose experiment; therefore, further investigation is necessary regarding NDMR recovery in cases of long-term levetiracetam use. Delayed recovery from rocuronium-induced neuromuscular blockade could be explained by interactions between levetiracetam and rocuronium because both agents are probable substrates of P-glycoprotein. P-glycoprotein is a transmembrane drug efflux pump that transports various drugs (ie, substrates that readily bind to P-glycoprotein) across the cell membrane, thereby excreting its substrates into bile, the gastrointestinal tract, and urine and playing an important role in drug elimination. It also facilitates excretion of rocuronium and might also transport levetiracetam. P-glycoprotein substrates might competitively inhibit the P-glycoprotein-mediated transport of other drugs. In the same context, levetiracetam inhibits efflux of rhodamine 123, a P-glycoprotein substrate, and thus could hinder the P-glycoprotein–mediated excretion of rocuronium, thereby leading to prolonged neuromuscular blockade. In view of previous findings that suggested vecuronium is a P-glycoprotein substrate and that decreases in P-glycoprotein activity resulted in reduced vecuronium elimination, a possible interaction between levetiracetam and neuromuscular blocking agents other than rocuronium cannot be discounted. However, this purported mechanism is speculative and requires further validation.

Levetiracetam is a relatively unique and somewhat newer AED, and thus its interaction with anesthetic agents has rarely been assessed, unlike other antiepileptics like phenytoin, carbamazepine, and valproic acid. Phenytoin is also a P-glycoprotein substrate, but, in contrast to levetiracetam, its chronic administration might reduce the duration of action of neuromuscular blocking agents, including rocuronium. A possible explanation is that phenytoin induces CYP450 isoenzymes, which could facilitate increased elimination of drugs that use CYP450 pathways. In addition, phenytoin increases plasma α1-acid glycoprotein, leading to decreased concentrations of free, unbound neuromuscular blocking agents with the potential to exert their effects at neuromuscular junctions. In contrast, levetiracetam neither induces CYP450 isoenzymes nor alters the protein binding of other drugs, unlike many of the other antiepileptics. The different pharmacokinetic characteristics of levetiracetam as compared with other AEDs might account for its different effects on neuromuscular blocking agents. Another explanation is that acute administration of antiepileptic agents may increase the clinical duration of neuromuscular blocking agents.[13] However, in this previous study, chronic use of anticonvulsants including levetiracetam was excluded. Therefore, chronic use of levetiracetam likely requires further investigation.

CONCLUSION

This case report suggests that patients with intractable epilepsy who are chronically taking levetiracetam may have resistance to rocuronium. Close assessment of neuromuscular function and reversal to ensure full return of function should be considered.

Conflict of Interest

The authors have no conflicts of interest relevant to the contents of this report.

Funding

None.

ACKNOWLEDGMENT

We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

REFERENCES

1. Kumar CM, Lawler PG. Phenytoin-induced resistance to vecuronium. *Anaesthesia*. 1989;44(3):263–264.
2. Gough JD, Smith A, Wise CC. Phenytoin-induced resistance to vecuronium. *Anaesthesia*. 1989;44(6):520.
3. Tempelhoff R, Modica PA, Jellish WS, Spitznagel EL. Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg*. 1990;71:665–669.
4. Platt PR, Thackray NM. Phenytoin-induced resistance to vecuronium. *Anaesth Intensive Care*. 1993;21(2):185–191.
5. Spacek A, Neiger FX, Krenn CG, Hoerauf K, Kress HG. Rocuronium-induced neuromuscular block is affected by chronic carbamazepine therapy. *Anesthesiology*. 1999;90(1):109–112.
6. Koenig MH, Edwards LT. Cisatracurium-induced neuromuscular blockade in anticonvulsant treated neurosurgical patients. *J Neurosurg Anesthesiol*. 2000;12(4):314–318.
7. Hernández-Palazón J, Tortosa JA, Martínez-Lage JF, Pérez-Ayala M. Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. *J Neurosurg Anesthesiol*. 2001;13(2):79–82.
8. Richard A, Girard F, Girard DC, et al. Cisatracurium-induced neuromuscular blockade is affected by chronic phenytoin or carbamazepine treatment in neurosurgical patients. *Anesth Analg*. 2005;100(2):538–544.
9. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord*. 2014;16:409–431.
10. Bloor M, Nandi R, Thomas M. Antiepileptic drugs and anesthesia. *Paediatr Anaesth*. 2017;27:248–250.
11. Oshima K. The fundamental problem of severe mentally and physically disabled person. Article in Japanese. *Kuoshuueisei*. 1971;35:648–655.
12. Kumar N, Rani D, Jain A. Evaluation of intubating conditions with rocuronium 0.6 mg/kg using train of four stimulation in elective surgery. *Indian J Anaesth*. 2022;66:S108–S114.
13. Jeon YJ, Kim MH. Effect of levetiracetam on rocuronium duration in patients undergoing cerebrovascular surgery. *Anesth Pain Med*. 2018;13(4):409–414.
14. Ghimouz A, Lentschener C, Goater P, Borne M, Esteve M. Adducted vocal cords relieved by neuromuscular blocking drug: a cause of impaired mechanical ventilation when using a laryngeal mask airway: two photographically documented cases. *J Clin Anesth*. 2014;26:668–670.
15. Kondo T, Izumi H, Kuroda M, Kitagawa M. Two cases of progressive vocal cord closure during desflurane-remifentanil anesthesia relieved after administration of propofol. *J Anesth*. 2013;27:791–792.
16. Kohno T, Ikoma M. Sudden vocal cord closure during general anesthesia using remifentanil. Article in Japanese. *Masui*. 2008;57:1213–1217.
17. Soriano SG, Kaus SJ, Sullivan LJ, Martyn JA. Onset and duration of action of rocuronium in children receiving chronic anticonvulsant therapy. *Paediatr Anaesth*. 2000;10:133–136.
18. Soriano SG, Martyn JA. Antiepileptic-induced resistance to neuromuscular blockers: mechanisms and clinical significance. *Clin Pharmacokinet*. 2004;43:71–81.
19. Anderson GD. A mechanistic approach to antiepileptic drug interactions. *Ann Pharmacother*. 1998;32:554–563.
20. Pirttiaho HI, Sotaniemi EA, Pelkonen RO, et al. Hepatic blood flow and drug metabolism in patients on enzyme-inducing anticonvulsants. *Eur J Clin Pharmacol*. 1982;22:441–445.
21. Soriano SG, Sullivan LJ, Venkatakrishnan K, et al. Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy. *Br J Anaesth*. 2001;86:223–229.
22. Bailey DN, Briggs JR. The binding of selected therapeutic drugs to human serum alpha-1 acid glycoprotein and to human serum albumin in vitro. *Ther Drug Monit*. 2004;26(1):40–43.
23. Kim CS, Arnold FJ, Itani MS, Martyn JA. Decreased sensitivity to metocurine during long-term phenytoin therapy may be attributable to protein binding and acetylcholine receptor changes. *Anesthesiology*. 1992;77(3):500–506.
24. Fink H, Luppa P, Mayer B, Rosenbrock H, et al. Systemic inflammation leads to resistance to atracurium without increasing membrane expression of acetylcholine receptors. *Anesthesiology*. 2003;98(1):82–88.
25. Fink H, Bogdanski R, Luppa P, Martyn JAJ, Blobner M. Nitric oxide is not a mediator of inflammation-induced resistance to atracurium. *Anesth Analg*. 2005;101(5):1362–1367.
26. Ibebunjo C, Martyn JA. Fiber atrophy, but not changes in acetylcholine receptor expression, contributes to the muscle dysfunction after immobilization. *Crit Care Med*. 1999;27:275–285.
27. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther*. 2000;85:77–85.
28. Patsalos PN. Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet*. 2012;43;707–724.
29. Morita K, Yamaji A. Changes in the concentration of serum alpha 1-acid glycoprotein in epileptic patients. *Eur J Clin Pharmacol*. 1994;46:137–142.
30. Jung KT, An TH. Updated review of resistance to neuromuscular blocking agents. *Anesth Pain Med*. 2018;13:122–127.
31. Ibebunjo C, Nosek MT, Itani MS, et al. Mechanisms for the paradoxical resistance to d-tubocurarine during immobilization-induced muscle atrophy. *J Pharmacol Exp Ther*. 1997;283:443–451.

Use of Rocuronium and Sugammadex for a Patient With Controlled Polymyositis: A Case Report

Hidetaka Kuroda, DDS, PhD; Tomomi Katayama, DDS; Atsuki Yamaguchi, DDS; Norika Katagiri, DDS, PhD; Shota Tsukimoto, DDS, PhD; Uno Imaizumi, DDS, PhD; and Takuro Sanuki, DDS, PhD

Department of Dental Anesthesiology, Kanagawa Dental University, Yokosuka, Japan

Muscle relaxants and their reverse drugs should be carefully administered to patients with acute polymyositis and/or dermatomyositis. However, the use of these drugs in controlled polymyositis and/or dermatomyositis is controversial. This case report describes the use of rocuronium and sugammadex in a 27-year-old female patient with controlled polymyositis who was scheduled for minor oral surgery under general anesthesia. General anesthesia was induced rapidly, and 0.66 mg/kg of rocuronium was administered prior to nasotracheal intubation. No additional muscle relaxants were administered during the surgery. At the end of surgery, approximately 2 hours after the rocuronium was administered, her train-of-four (TOF) ratio was still 49%. A dose of 3.3 mg/kg of sugammadex was administered, and it took 12 minutes for the TOF ratio to exceed 90%. The prolonged duration of muscle relaxation in patients with polymyositis may be due to a decrease in skeletal muscle and capillary volume. The slow onset of sugammadex may be caused by slow diffusion of rocuronium from the neuromuscular junction. Patients with polymyositis require close perioperative neuromuscular function monitoring, regardless of their disease control status.

Key Words: General anesthesia; Polymyositis; Rocuronium; Sugammadex.

Polymyositis, categorized as an inflammatory myopathy, is an autoimmune tissue disorder of skeletal muscle that involves infiltration of mononuclear cells around non-neurotic myofibers in skeletal muscle and the degeneration, necrosis, and regeneration of myofibers.[1,2] Polymyositis causes slow muscle weakness that mainly affects the trunk, proximal limb, neck, and pharyngeal muscles.[1,2] In addition to the symptoms of polymyositis, dermatomyositis is diagnosed when it is accompanied by characteristic skin rash, such as a heliotrope rash or Gottron sign or papules.[1,2] The pathogenesis of these diseases is understood to be the same, and they have poor prognoses when patients have rapidly progressive interstitial pneumonia or malignancy.[1–3]

Care should be taken with using muscle relaxants and reversal agents during general anesthesia for patients with polymyositis because of the potential for reduced or atrophied skeletal muscle.[4] Therefore, surgery should be performed under local anesthesia whenever possible.[5,6] The use of all types of muscle relaxants for patients with controlled polymyositis remains controversial, as it has long been discussed in the existing literature on general anesthesia for patients with acute polymyositis and dermatomyositis.[7,8] In this case report, we describe the management of a dental patient with controlled polymyositis undergoing intubated general anesthesia for dental extractions. Written informed consent was obtained from this patient and reported in accordance with the case reports guidelines.

CASE PRESENTATION

The patient was a 27-year-old woman (height, 167 cm; body weight, 60 kg; body mass index, 21.5 kg/m^2) with polymyositis who was scheduled to undergo general anesthesia for extraction of bilateral maxillary and mandibular third molars. Four years previously she experienced lower limb dyskinesia and general malaise while performing classical ballet and was diagnosed with polymyositis after magnetic resonance imaging and muscle biopsy. She was treated initially with prednisolone and cyclosporine, and once her acute symptoms were in remission, her polymyositis was controlled with prednisolone (2 mg/d). The patient reported no ongoing muscle weakness and had no daily limitations, with an estimated metabolic equivalent

Received April 30, 2023; accepted for publication October 9, 2023.

Address correspondence to Dr Hidetaka Kuroda, DDS, PhD, Department of Dental Anesthesiology, Kanagawa Dental University, 1-23 Ogawa-cho, Yokosuka, Kanagawa 2388570, Japan; kuroda@kdu.ac.jp.
Drs Kuroda and Sanuki contributed equally to this work.

Anesth Prog 71:81–84 2024 | DOI 10.2344/021627

task value of more than 6.0. Preoperative screening tests revealed a normal creatinine kinase level (71 U/L; normal, 30-145 U/L in females), C-related protein (0.08 mg/dL; normal, <0.3 mg/dL), and erythrocyte sedimentation rate (6 mm/h; normal: 0-20 mm/h in females), indicating that her polymyositis was under control. The patient had normal renal and hepatic function, and no other noteworthy findings were noted in review of her medical history. Her prednisolone was continued as usual during the perioperative period.

Upon the patient's arrival at the operating room, standard anesthetic monitors were applied, intravenous (IV) access was obtained, and she was appropriately preoxygenated. General anesthesia was rapidly induced with IV propofol (130 mg) and fentanyl (100 μg) followed by rocuronium (40 mg; 0.66 mg/kg) after confirming ease of mask ventilation. Nasotracheal intubation was successfully performed without difficulty, and general anesthesia was maintained with O_2 (1 L/min), air (3 L/min), and sevoflurane (1.5%–2%) along with a remifentanil infusion (0.1–0.2 μg/kg/min).

After induction and securing the airway, the neuromuscular blockade (NMB) depth was monitored using a peripheral nerve stimulator (TOF-Watch, Merck & Co, Inc,) placed along the ulnar nerve to stimulate the adductor pollicis brevis muscle. The train-of-four (TOF) mode, which applies 4 consecutive stimuli (ie, 2 Hz) every 0.5 seconds, is evaluated based on the ratio of the heights of the fourth stimulation (T4) to the first stimulation (T1). The TOF ratio (T4/T1) is almost 100% when no neuromuscular blocking agents are present but decreases as NMB deepens. The chronological results of the patient's NMB data are presented in the (Table). No additional rocuronium was administered during surgery. Sevoflurane was started at 2% after tracheal intubation, changed to 1.5% at 15 minutes before the end of surgery, and discontinued at the end of surgery. Although 2 hours had elapsed since rocuronium was administered during induction, the TOF ratio was 49%.

At the end of surgery (ie, 120 minutes after administration of rocuronium), IV sugammadex (200 mg) was administered to antagonize the rocuronium-induced NMB; however, it took 12 minutes for the TOF ratio to exceed 90%. The patient was extubated without difficulty after emerging from general anesthesia and confirming adequate spontaneous ventilation. The duration of the operation was 85 minutes, and the total duration of anesthesia was 140 minutes. No postoperative complications were observed. The patient was discharged the day after surgery.

Table. Changes in Muscle Relaxation State During General Anesthesia[a]

Time elapsed since administration, min	*TOF count, No./total, or TOF ratio, %*[b]
Rocuronium	
25	0/4
85	2/4
105	18%
115	38%
120	49%
Sugammadex	
1	64%
6	78%
11	82%
12	97%

[a] TOF indicates train of four.
[b] The number of twitches due to neuromuscular stimulation (TOF count) was determined when the height of the stimulation was undetectable or when the TOF ratio was <20%. TOF ratio = T4/T1; T1, height of first stimulation; T4, height of fourth stimulation.

DISCUSSION

In the present case, we experienced a prolonged duration of rocuronium-induced NMB and a delayed return of neuromuscular function following the administration of sugammadex during intubated general anesthesia for a patient with controlled polymyositis.

C-related protein and erythrocyte sedimentation rate are also used to diagnose polymyositis, but creatinine kinase level is used as the most sensitive responding muscle enzyme.[2] Creatine kinase concentration usually parallels disease activity and is always increased during active polymyositis phases, up to 50 times normal levels during acute active phases.[2] Creatine kinase is an enzyme present in skeletal and cardiac muscle that is released into the blood after cell damage. Reference values vary depending on sex because of differences in muscle mass (normal, 62–287 U/L for males and 45–163 U/L for females). In this case, preoperative screening showed that the patient's creatinine kinase level was within normal limits at 71 U/L. Her other lab values, continued prednisolone therapy, and lack of clinical signs or symptoms indicated that her polymyositis was under control, suggesting possible normal sensitivity to rocuronium and sugammadex.

In the histologic findings of polymyositis, it has been reported that intramuscular blood vessels show endothelial hyperplasia with tubulovesicular profiles, fibrin thrombi, and capillary obliteration, resulting in a reduction in capillary density.[2] Muscle fibers undergo phagocytosis and necrosis, resulting in perifascicular atrophy.[2] Moreover, in polymyositis, multifocal lymphocytic infiltrates surround and invade healthy muscle fibers.[2] These reports suggest that patients with polymyositis have not only reduced skeletal muscle volume but also decreased capillary volume, possibly indicating that delayed onset and prolonged duration of nondepolarizing muscle relaxants acting on the neuromuscular junction may occur. Rocuronium, which acts on the neuromuscular junction, has a shorter duration of

action than some nondepolarizing muscle relaxants (eg, pancuronium). In young, healthy adults, it has been reported that the time required for a TOF ratio greater than 90% to return following a 0.6 mg/kg dose of rocuronium was 50 to 70 minutes during propofol-maintained general anesthesia.[9] When 0.6 mg/kg of rocuronium was used, it has been reported that approximately 110 minutes were required for NMB recovery to a TOF ratio more than 90% when using sevoflurane for general anesthesia maintenance, as it enhances the NMB potency of rocuronium.[10,11] This NMB potentiation occurs with other volatile agents (ie, isoflurane and desflurane).[10] In this case rocuronium was administered at 0.66 mg/kg, and by 120 minutes the TOF ratio had recovered only to 49%, suggesting a prolonged duration of rocuronium-induced NMB.

Sugammadex is designed to reverse steroidal neuromuscular relaxants such as rocuronium.[12] It has been reported that the TOF ratio recovered to 90% within approximately 2 minutes when a 2.0 mg/kg dose of sugammadex was administered after the presence of 2 twitches was identified using peripheral nerve stimulation.[13] The dose of sugammadex administered in this case was 3.3 mg/kg; however, the TOF ratio still took 12 minutes to recover from 64% to 97%, indicating delayed onset of sugammadex in this patient with polymyositis. In patient with dermatomyositis, the slow onset of action of rocuronium and sugammadex is reportedly due to the slow diffusion of rocuronium from the neuromuscular junction to the plasma.[14]

A limitation of this case report is that the TOF ratio was not measured right after induction of general anesthesia prior to the administration of rocuronium. Furthermore, we did not monitor the onset of rocuronium-induced NMB either. Assessing the patient's neuromuscular status at these times would have helped to determine if the patient was overly sensitive to rocuronium. Because the onset of action of rocuronium has been reported to be delayed in patients with dermatomyositis, a similar reaction may have occurred in the present case.[14]

Monitoring the onset and depth of NMB during general anesthesia in patients with polymyositis is important. The choice of agents for maintenance of general anesthesia in this case may have been inappropriate given the possibility of sevoflurane's potentiating muscle relaxant effects.

Although neuromuscular responses to a depolarizing muscle relaxant (ie, succinylcholine) have been reported to be normal in patients with polymyositis,[15] hyperkalemia is a risk and could be induced if the muscle tissues are inflamed during an active phase.[7] Other nonsteroidal nondepolarizing muscle relaxants, namely benzylisoquinolines (ie, atracurium/cisatracurium), also act by competitive antagonism of acetylcholine receptors, similarly to rocuronium. Considering that delayed onset and/or prolonged action of muscle relaxants possibly results from impaired blood flow at the neuromuscular junction, close monitoring of muscle relaxation may be necessary when using any nondepolarizing muscle relaxants. Based on this case, it is suggested that sugammadex can be used safely with proper monitoring to patients with controlled polymyositis. In addition, use of nonsugammadex NMB reversal (ie, neostigmine/glycopyrrolate) has been reported to be safe.[16,17] Further studies are needed to identify ideal neuromuscular blocking agents and reversal drugs in patients with controlled polymyositis.

CONCLUSION

Patients with controlled polymyositis may be sensitive to nondepolarizing muscle relaxants (eg, rocuronium) and have prolonged action/paralysis and delayed recovery, likely due to impaired capillary blood flow. These patients should be closely monitored using a peripheral nerve stimulator throughout the perioperative period. Furthermore, muscle relaxant doses should be reduced/titrated carefully to effect to minimize risk of overdose/prolonged NMB, and full NMB reversal should be utilized to help ensure adequate neuromuscular function upon awakening.

ACKNOWLEDGMENTS

The authors declare that they have no conflicts of interest. The authors are grateful to Prof Kanta Kido, Department of Dental Anesthesiology, Hokkaido University, and Drs Ayako Mizutani and Keita Kagawa, Department of Dental Anesthesiology, Kanagawa Dental University, for their helpful discussions on this case report. We also thank Editage (www.editage.jp) for English language editing.

REFERENCES

1. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med*. 1975;292:344–347. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/1090839/

2. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. 2003;362:971–982. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/14511932/

3. Qiang JK, Kim WB, Baibergenova A, Alhusayen R. Risk of malignancy in dermatomyositis and polymyositis. *J Cutan Med Surg*. 2017;21:131–136. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/27534779/

4. You AH, Kang HY, Park SW, Kim Y. Delayed recovery of limb muscle power after general anesthesia with cisatracurium in a dermatomyositis patient. *J Clin Anesth*. 2018;50:59–60. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/29980001/

5. Yen CR, Tsou MY, Lin SM, Chan KH, Chu YC. Thoracic epidural anesthesia for a polymyositis patient undergoing awake mini-thoracotomy and unroofing of a huge pulmonary bulla. *Acta Anaesthesiol Taiwan*. 2008;46:42–45. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/18390401/

6. Gunusen I, Karaman S, Nemli S, Firat V. Anesthetic management for cesarean delivery in a pregnant woman with polymyositis: a

case report and review of literature. *Cases J*. 2009;2. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/20062684/

7. Ganta R, Campbell IT, Mostafa SM. Anaesthesia and acute dermatomyositis/polymyositis. *Br J Anaesth*. 1988;60:854–858. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/3134934/

8. Saarnivaara LH. Anesthesia for a patient with polymyositis undergoing myectomy of the cricopharyngeal muscle. *Anesth Analg*. 1988;67:701–702. Accessed Month 00, 0000. https://pubmed.ncbi.nlm.nih.gov/2898221/

9. Bjerring C, Vested M, Arleth T, Eriksen K, Albrechtsen C, Rasmussen LS. Onset time and duration of action of rocuronium 0.6 mg/kg in patients above 80 years of age: a comparison with young adults. *Acta Anaesthesiol Scand*. 2020;64:1082–1088. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/32462665/.

10. Bock M, Klippel K, Nitsche B, Bach A, Martin E, Motsch J. Rocuronium potency and recovery characteristics during steady-state desflurane, sevoflurane, isoflurane or propofol anaesthesia. *Br J Anaesth*. 2000;84:43–47. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/10740546/

11. Lee S, Ro YJ, Koh WU, Nishiyama T, Yang H-S. The neuromuscular effects of rocuronium under sevoflurane-remifentanil or propofol-remifentanil anesthesia: a randomized clinical comparative study in an Asian population. *BMC Anesthesiol*. 2016;16. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/27549387/

12. de Boer HD, van Egmond J, Driessen JJ, Booij LHD. Update on the management of neuromuscular block: focus on sugammadex. *Neuropsychiatr Dis Treat*. 2007;3:539. Accessed April 12, 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656290/

13. Shields M, Giovannelli M, Mirakhur RK, Moppett I, Adams J, Hermens Y. Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. *Br J Anaesth*. 2006;96:36–43. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/16357116/

14. Suzuki T, Nameki K, Shimizu H, Shimizu Y, Nakamura R, Ogawa S. Efficacy of rocuronium and sugammadex in a patient with dermatomyositis. *Br J Anaesth*. 2012;108:703. Accessed April 12, 2023. https://pubmed.ncbi.nlm.nih.gov/22419633/

15. Brown S, Shupak RC, Patel C, Calkins JM. Neuromuscular blockade in a patient with active dermatomyositis. Accessed July 31, 2023. *Anesthesiology*. 1992;77:1031–1033. https://pubmed.ncbi.nlm.nih.gov/1443721/

16. Ahn S, Lee JH, Yang EA, Park C, Shin DW. Anesthesia for flap surgery in a patient with polymyositis. *Korean J Anesthesiol*. 2014;67:S79–S80.

17. Bhargava JA, Tiwari RL, Goyal P, Jain S. Anesthetic challenges in a patient with polymyositis undergoing emergency laparoscopic appendicectomy. *J Anaesth Crit Care Case Rep*. 2017;3:7–12. Accessed July 31, 2023. https://jaccr.com/anesthetic-challenges-in-a-patient-with-polymyositis-undergoing-emergency-laparoscopic-appendicectomy-2/

Tracheal Stenosis Detected During Endotracheal Intubation in a Patient With Down Syndrome

Tomoaki Ujita, DDS, PhD;[1] Toru Yamamoto, DDS, PhD;[1] Yutaka Tanaka, DDS, PhD;[1] Shigenobu Kurata, DDS, PhD;[2] and Kenji Seo, DDS, PhD[2]

[1]Department of Dental Anesthesiology, Niigata University Medical and Dental Hospital, Niigata, Japan; [2]Division of Dental Anesthesiology, Graduate School of Medicine and Dental Sciences, Niigata University, Niigata, Japan

We report a case in which tracheal stenosis was discovered during endotracheal intubation. A 19-year-old woman with Down syndrome was scheduled to undergo treatment of multiple dental caries under intubated general anesthesia. During the first general anesthetic, we felt some resistance while advancing the endotracheal tube through the trachea. Prior to a second general anesthetic 2 years later, we performed 3-dimensional computed tomography to evaluate the tracheal stenosis and devised a strategy that established an airway without advancing the endotracheal tube over the stenotic lesion. Careful attention is required when performing endotracheal intubation because patients with Down syndrome sometimes have tracheal stenosis.

Key Words: Tracheal stenosis; Difficult intubation; Down syndrome; Airway management; Congenital heart disease.

Trisomy 21 (Down syndrome) is the most common chromosomal abnormality and is associated with multiple characteristic features and potential findings that warrant added consideration during anesthetic management. Patients with Down syndrome have an increased incidence of congenital cardiac and spinal abnormalities as well as more underappreciated airway anomalies such as subglottic stenosis. This case report presents the discovery of tracheal stenosis in a female patient with Down syndrome undergoing intubated general anesthesia for dental care.

CASE PRESENTATION

A 19-year-old woman (height, 130 cm; weight, 48 kg; body mass index, 28.4 kg/m^2) with Down syndrome was scheduled to undergo intubated general anesthesia for restorative dental treatment of multiple teeth due to dental caries. She had a history of patent ductus arteriosus surgical ligation performed under general anesthesia at the age of 1 year 6 months. There were no other pertinent medical or surgical history findings, and she was not taking any medications. An anteroposterior chest radiograph (Figure A) was obtained preoperatively, which showed a stenotic region between the glottis and the tracheal bifurcation. However, this radiographic finding was not readily appreciated preoperatively.

During her first general anesthetic for dental care at 19 years of age, the patient underwent slow mask induction followed by oral intubation with a size 7.0 (9.7-mm outer diameter), cuffed, reinforced oral/nasal endotracheal tube (ETT). However, some resistance was felt subglottically at a depth of 18 cm from the corner of the mouth, and it became difficult to advance the ETT further. A fiberoptic bronchoscope was used to confirm the stenotic area and to visualize that the tip of the tracheal tube could not be advanced further. We successfully changed to a size 5.0 (outer diameter 6.9 mm), cuffed, reinforced oral/nasal ETT and advanced it to a depth where its tip was beyond the stenotic area and 3 cm above the tracheal bifurcation. Stable ventilation was obtained, and surgery was performed as planned.

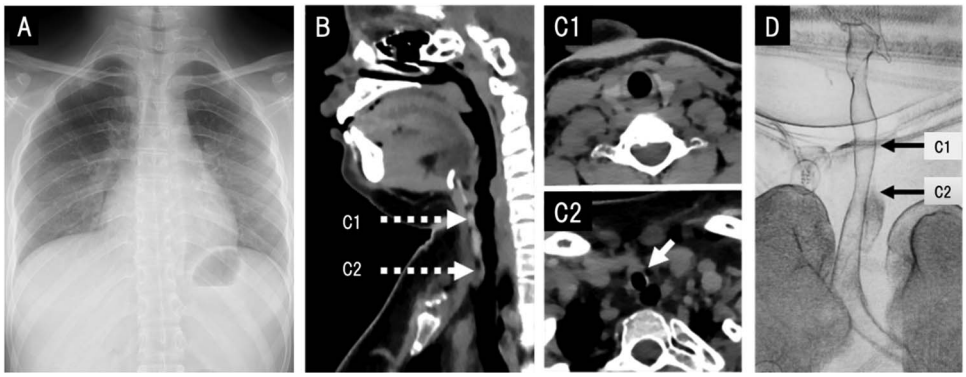
The patient returned for additional dental care requiring general anesthesia at 21 years of age and underwent computed tomography (CT) scans of her head, neck, and chest preoperatively. Tracheal stenosis was identified in the subglottic area (smallest diameter, 6.4 mm; widest diameter, 8.0 mm; Figure B–D). Therefore, we decided to perform oral intubation using another size 5.0 ETT and again examined her trachea during intubation with a fiberoptic bronchoscope. However, this time, the tip of the tracheal tube was positioned above the tracheal stenosis to prevent tracheal damage and edema caused by external forces. Its depth from the mouth

Received December 6, 2022; accepted for publication February 20, 2023.

Address correspondence to Dr Kenji Seo, Division of Dental Anesthesiology, Graduate School of Medicine and Dental Sciences, Niigata University, Niigata, Japan, 951-8514; seo@dent.niigata-u.ac.jp.

Anesth Prog 71:85–86 2024 | DOI 10.2344/anpr-63-16-65

Figure. Imaging Studies of the Airway



Images illustrating the patient's subglottic stenosis. (A) Preoperative anteroposterior chest radiograph with the detectable tracheal stenosis. (B) Sagittal CT image illustrating the tracheal stenosis and the location of the other horizontal CT images (C1 and C2 arrow). C1: normal area above the stenotic lesion. C2: stenotic area (C1: minor axis, 11.0 mm; major axis, 13.0 mm; C2: minor axis, 6.4 mm; major axis, 8.0 mm). (D) Three-dimensional reconstructed CT image with C1 and C2 arrows.

was 18 cm, but the ETT cuff was positioned past the glottis. The surgery was completed, and the patient was extubated without complications after visualizing the normal appearance of the tracheal mucosa with a fiberoptic scope.

DISCUSSION

Tracheal stenosis is a rare condition affecting 1 in 65,000 people[1] and is present in approximately 0.4% of people with Down syndrome. The diameter of the trachea tends to be 1.3 to 3.2 mm smaller than that of people without Down syndrome.[2] This trend applies not only to the tracheal stenosis but also to the entire trachea of patients with Down syndrome. Furthermore, 50% to 75% of cases of congenital tracheal stenosis also have concurrent congenital heart defects.[3] In this case, the patient had a patent ductus arteriosus that had been surgically corrected. Therefore, clinicians must be aware of the potential for airway management and intubation difficulties when managing anesthesia for patients with Down syndrome.

Expecting a difficult airway during the second general anesthetic, we determined the location of the stenotic area by measuring its distance from the glottis using CT imaging.[1,3] This imaging permitted precise morphological evaluation of the tracheal stenotic lesion, allowing us to determine whether the ETT could be placed above the stenotic area[4] and to prevent mechanical injury due to excessive pressure on the tracheal walls. The mechanism of tracheal stenosis or congenital heart disease in patients with Down syndrome remains unknown. However, close attention is needed when performing endotracheal intubation because tracheal stenosis can be present in some patients with Down syndrome.

This report was originally published in the *Journal of the Japanese Dental Society of Anesthesiology* (2023;51:30–32).

ACKNOWLEDGMENT

We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

REFERENCES

1. Hewitt RJ, Butler CR, Maughan EF, Elliott MJ. Congenital tracheobronchial stenosis. *Semin Pediatr Surg*. 2016;25(3):144–149.
2. Fockens MM, Hölscher M, Limpens J, Dikkers FG. Tracheal anomalies associated with Down syndrome: a systematic review. *Pediatr Pulmonol*. 2021;56(5):814–822.
3. Kylat RI. Tracheal stenosis and congenital heart disease in trisomy 21. *Children (Basel)*. 2019;6(9):98.
4. Kawabata M, Sakuraba S, Tagawa T, Sato K, Okuda M, Arisaka H. Severe but asymptomatic tracheal stenosis found during tracheal intubation in a patient with a normal preoperative chest X-ray [in Japanese]. *J Clin Anesth (Japan)*. 2009;33(11):1803–1804.

Review of Inherited Coagulation Disorders

Tiffany Hoang;[1] and Regina A. E. Dowdy, DDS, MS[2]

[1]Dental Student, Herman Ostrow School of Dentistry of University of Southern California, Los Angeles, California, [2]Adjunct Assistant Clinical Professor in Anesthesia and Emergency Medicine, Herman Ostrow School of Dentistry of University of Southern California, Los Angeles, California

Most invasive dental procedures elicit some degree of bleeding which ultimately leads to clotting and eventual hemostasis. However, patients with inherited coagulation disorders may exhibit prolonged or, in some cases, excessive bleeding requiring multiple perioperative interventions. Von Willebrand disease is the most common inherited coagulopathy and often manifests via easy bruising, epistaxis, or prolonged bleeding. Hemophilia A (factor VII) and B (factor IX) are factor deficiencies that are clinically indistinguishable and managed according to severity and the required dental treatment. Other coagulopathies are rare (ie, inheritance is autosomal recessive) and may only become evident in homozygotes or compound heterozygotes. Current lab values and medical consultation with the patient's hematologist are imperative prior to rendering invasive dental treatment. There are a myriad of sedation and general anesthesia considerations, including risks for epistaxis with nasal instrumentation and bruising with improper patient positioning. Preoperative treatment with desmopressin or factor replacement may be required and generally should facilitate normal hemostasis. Additional therapies should be considered to help ensure adequate postoperative hemostasis, including pressure dressings, resorbable clotting materials, laser therapy, and oral rinses.

Key Words: Von Willebrand disease; Hemophilia; Factor deficiencies; Clotting cascade; Anesthesia considerations; Dental considerations.

Hemostasis is the complex process of preventing and stopping bleeding from a damaged blood vessel. This mechanism involves an intricate series of events designed to seal a ruptured blood vessel quickly and effectively and is essential for preventing excessive blood loss and facilitating wound healing. Coagulation can be summarized in 4 major steps: vasoconstriction, formation of a platelet plug, activation of the clotting cascade, and formation of a fibrin clot that will gradually be dissolved once the damaged blood vessel is repaired.

HEMOSTASIS AND COAGULATION

Current understanding of normal hemostasis includes a series of well-regulated steps and a balanced system of proteolytic reactions.[1] Blood vessels are lined with endothelial cells which allow for the passage of fluids and solutes into the extracellular spaces but separate interstitial tissues from the blood.[2] When injury occurs to this endothelial layer, a chain of events that comprises the hemostatic process is initiated. Called *primary hemostasis*, this process results from exposure of the extracellular matrix in the injured vessel's epithelium. This highly thrombogenic environment attracts quiescent platelets which become activated and then release secretory granules that recruit additional platelets to aggregate, eventually forming a hemostatic plug. These secretory granules, understood now to fall within categories of dense granules or α-granules, contain more than 300 other substances involved in anti-inflammatory and proinflammatory processes, coagulation, and anticoagulation mechanisms.[2,3] There are 2 theories on how coagulation occurs in vivo: the *clotting cascade* and the *cell-based model* of coagulation. The clotting cascade is the classical paradigm that presents clotting as 2 distinct pathways that meet downstream to form a common pathway. The cell-based model paradigm, more physiologically accurate, describes the role of platelets and proposes that clotting occurs on the surface of tissue factor (TF)–presenting cells and on platelets.[4]

Coagulation Cascade

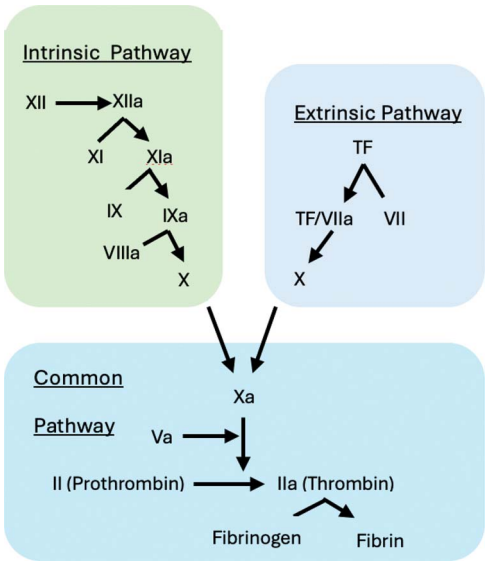
This classical paradigm was proposed in the 1960s and consists of sequential activation steps resulting in thrombin generation to form a blood clot. This cascade involves the extrinsic and intrinsic pathways (Figure), which are presented as being separate and distinct. The extrinsic pathway, which occurs outside the circulating blood, starts with the exposure of TF and activated factor VII (FVIIa). The

Received March 24, 2024; accepted for publication April 30, 2024.

Address correspondence to Dr Regina Dowdy, 925 W 34th St, Los Angeles, CA 90089; rdowdy@usc.edu.

Anesth Prog 71:87–95 2024 | DOI 10.2344/anpr-71-2_continuing_edu

Figure. Coagulation Cascade



The classic coagulation cascade model of hemostasis consisting of the intrinsic, extrinsic, and common pathways.

intrinsic pathway, which is an intravascular process, occurs via activation of FXII, FXI, and FIX.[2,4,5] The importance of the intrinsic coagulation cascade is evident in many patients with congenital bleeding disorders due to deficiencies in clotting factors, like hemophilia A (FVIII), hemophilia B (FIX), or FX deficiency.[1,2,5] At the juncture of the 2 pathways, activated FVIII (FVIIIa) is required to activate FX (FXa) and FV (FVa) which ultimately convert FII (prothrombin) to activated FII (thrombin). FI (fibrinogen) is converted by thrombin into activated FI (fibrin) which then helps cross-link platelets and strengthen the platelet plug.[1,5]

Cell-Based Model of Coagulation

The coagulation cascade describes clotting neatly and correlates well with laboratory tests such as prothrombin time (PT), which measures extrinsic pathway activity, and activated partial thromboplastin time (aPTT), which measures intrinsic pathway activity. However, it does not adequately explain coagulation in vivo because it does not describe coagulation as it occurs on the surface of fibroblasts, endothelial cells, and platelets.[1] Therefore, the cell-based model of coagulation was proposed to describe blood clotting in 3 overlapping phases—initiation, amplification, and propagation.

TF-bearing cells, such as fibroblasts and endothelial cells, are the site of the initiation phase. TF is an integral membrane protein that stays localized on the cell in which it was synthesized. In the initiation phase, TF binds to FVII and becomes activated whenever a vascular injury occurs.[4] The activated TF/FVIIa-complex then activates FIX and FX. FXa, in turn, activates FV which then converts a small amount of prothrombin into thrombin.

The amplification phase begins as circulating platelets are exposed to extracellular matrix proteins at the site of injury and begin to adhere. Platelet adhesion involves the binding of platelet surface glycoprotein (GP) Ib/IX to von Willebrand factor (vWF). In addition to activation of TF/FVII, vascular injury also causes the conformational conversion of vWF from its inactive, globulated configuration to its active, linear form. This activation exposes the GPIb-binding site on vWF, which is pivotal in thrombus formation. Additionally, FVIII is activated and binds to vWF and is then cleaved by thrombin to release it from vWF. The activated platelet now has FVa and FVIIIa bound on its surface, allowing for a significant amount of thrombin to be generated.

During the propagation stage, the Xase complex (activated FVIII/FIX) activates FX on the platelet surface, which binds to its cofactor FVa and generates the large amounts of thrombin required to convert fibrinogen to fibrin. Thrombin also activates FXIII, which cross-links adjacent fibrin monomers to one another and stabilizes the fibrin meshwork.[4]

Platelet Activation

The interaction between coagulation factors and platelets is integral to thrombus formation. Additionally, the initial thrombin generation from the TF/FVII pathway is important for converting the quiescent platelet into its active state. Subendothelial vWF, which is exposed by the vascular injury and endothelial damage, binds to platelet GPIb/IX/V, resulting in platelet adhesion to the damaged endothelium. The thrombin produced from the TF/FVII pathway then binds to protease-activated receptors on the platelet surface and results in the conversion of GPIIb/IIIa from a quiescent to an active state. This further attracts internal GPIIb/IIIa molecules to the platelet surface. Activated GPIIb/IIIa molecules bind to fibrinogen, linking activated platelets to one another and allowing for platelet aggregation and platelet plug formation. Certain molecules such as thromboxane A_2 (TX-A_2), serotonin, and adenosine diphosphate (ADP) help stabilize platelet aggregation. TX-A_2 binds to its receptors on the platelet surface and induces "inside-out" signal transduction of GPIIb/IIIa, which in turn amplifies platelet aggregation. ADP is then released from the platelet granules, contributing to the signal transduction for GPIIb/IIIa activation and binding to the G protein–coupled receptor P2Y12. This ADP release stabilizes and stimulates platelet plug formation, generating platelet aggregation and platelet plug formation.[4]

INHERETED COAGULOPATHIES

Building on the understanding of normal coagulation, it is crucial to explore inherited coagulopathies that represent deviations from the typical process. Inherited coagulopathies, such as von Willebrand disease (vWD) and hemophilia, arise from genetic mutations that affect different clotting factors. The severity and nature of these coagulopathies can vary widely, largely depending on the specific deficiency. Additionally, the pattern of inheritance, whether autosomal dominant, autosomal recessive, or X-linked, plays a crucial role in determining the likelihood and presentation of these disorders within families. Understanding these variances is essential for diagnosing and managing affected individuals.

Von Willebrand Disease

Present in 1% to 3% of the global population, vWD is the most common inherited bleeding disorder. VWD is a coagulopathy that result from quantitative or qualitative abnormalities of vWF and there are more than 20 distinct types of vWD. VWF is the largest circulating protein found in the blood plasma and is made up of multimers, or subunits, of varying sizes. In the absence of vWF, approximately 10% of circulating FVIII is present.[2,6] As a critical adhesive link in the process of platelets adhering to the damaged blood vessel in primary hemostasis and as a carrier for FVIII in secondary hemostasis, its role is clearly imperative if adequate clotting is to occur. This factor is stored in Weibel-Palade bodies in vascular endothelium or in alpha granules in megakaryocytes or platelets.[7] VWF functions by binding to GPIb receptors on platelets and subsequently to GPIIb/IIIa receptors on damaged vessel subendothelium.[6] Mucocutaneous bleeding is the most common clinical manifestation. Treatment for vWD is dependent upon the type and history as well as the clinical situation (ie, spontaneous vs surgical bleeding).

The gene coding for vWF is located on chromosome 12p13.3.[6] VWF is produced in endothelial cells and megakaryocytes and appears to have higher stored concentrations in the brain and lungs in comparison with the kidneys and liver.[6] Stimulation for endothelial secretion of vWF occurs in the presence of thrombin, fibrin, histamine, and complement factors C5b-9.[6] Presence of estrogen and circulating catecholamines is typically coupled with higher levels of vWF.[6] Type O blood experiences a 25% to 30% reduction in vWF and a mean antigen level of 75%; type AB blood has a mean antigen level of 123%.[6]

Type 1 vWD is of autosomal dominant inheritance and is the most common form, accounting for roughly 70% to 80% of diagnoses.[2] It accounts for approximately 1% of the general population, and clinically significant disease is seen in 1:1000 patients with type 1 vWD.[6,7] This type experiences a reduced quantity of vWF, 20% to 50% less than normal values, but a structurally and physiologically normal protein.[6] There is also an association of decreased levels of vWF antigen, FVII coagulant, and ristocetin (an additional agglutination cofactor).[6] Clinical manifestations of type 1 include epistaxis, easy bruising and/or hematomas, menorrhagia, gingival bleeding, and gastrointestinal bleeding.[6]

Type 2A vWD also has an autosomal dominant inheritance pattern but differs from type 1 in that it is a qualitative defect involving the loss of both intermediate and large plasma multimers, which are the functionally active subunits.[6] This loss appears to be related to retention within endoplasmic reticulum and proteolysis of the multimer proteins within the intracellular plasma. Type 2B vWD, also inherited via autosomal dominance, is classified separately with thrombocytopenia and loss of large vWF multimers.[6] Pseudo-vWD resembles type 2B. There is a mutation in GPI at the vWF binding site; mucocutaneous bleeding is a common presentation.[6] Type 2N vWD (Normandy) has an X-linked recessive inheritance pattern with decreased binding of FVIII to vWF. This diminished binding drastically reduces the half-life of FVIII coagulant from 12 hours to 1 hour, mimicking hemophilia A.[6] Type 2M vWD exhibits a decrease in the binding of vWF and platelet GPIb.

Type 3 vWD has an autosomal recessive inheritance that exhibits low to undetectable levels of plasma and platelet vWF antigen, diminished ristocetin cofactor activity, and significantly reduced levels of FVIII.[6] Clinical manifestations include spontaneous hemarthroses and muscle hematoma.[6]

Acquired forms of vWD also exist and are associated with lymphoproliferative diseases, tumors, autoimmune disease, hypothyroidism, and some medications like valproic acid or ciprofloxacin.[6] Probable mechanisms include decreased synthesis, rapid destruction and proteolysis, and tumor cell disruption.[6] Treatments for these acquired conditions depend on the mechanism of disruption and include cryoprecipitate, desmopressin, and fresh frozen plasma (FFP); however, these are only limited treatments, as they typically have a 3- to 5-hour working time.[6]

Hemophilia A (FVIII Deficiency)

Discovered in 1952, hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of FVIII.[5,6] Hemophilia is the most common severe bleeding disorder; it affects 1 in 5000 males in the United States, and affects all ethnicities.[5,8] The FVIII gene is one of the largest genes found in the human body, spanning 186 kb of genomic DNA and located on Xq28. Specifically, intron 22 of this gene is large and prone to inversion mutations, contributing to approximately 50% of all severe hemophilia A cases. The

other 50% of cases are caused by inversions, deletions, insertions, or point mutations of the other introns.[2,8,9]

FVIII, a component of the extrinsic pathway, is synthesized on hepatic and reticuloendothelial cells.[10] It is a single-chain polypeptide with 3 A domains (A1, A2, and A3), a large central B domain, and 2 C domains. The C2 domain is important for binding to vWF, thrombin, and FXa.[6] VWF protects FVIII from proteolytic degradation in the plasma and concentrates FVIII at the site of injury. The A2 and A3 domains are important sites for binding to activated FIX (FIXa). The B domain can be deleted without any consequences.[5,6,8]

FVIII circulates in the blood bound to vWF, is a cofactor for FIX, and allows for the activation of FX in the coagulation pathway. The normal coagulation pathway results in the conversion of fibrinogen to fibrin, stabilizing the clot at the site of injury. In hemophilia A, a deficiency or absence of FVIII produces a profound abnormality in the coagulation pathway, as FVIII is required for amplifying the production of FXa. In addition, FXa, which is generated by TF/FVIIa, is insufficient because this pathway is inhibited by TF pathway inhibitor as part of a negative feedback loop. Despite an abnormal coagulation pathway, the primary platelet plug formation and the initiation phases of coagulation are normal. Any clot that is formed from the initiation phase is friable and porous.[8]

The diagnosis of hemophilia A is often made following a bleeding episode or due to family history; however, 50% of cases show no family history of hemophilia A. Normal plasma levels of FVIII are 50% to 150%. Thus, hemophilia A is classified as mild (>5%), moderate (1%-5%), or severe (<1%). In patients with hemophilia A, approximately 65% have severe disease, 15% have moderate disease, and 20% have mild disease.[5,9] Most cases of severe disease show signs and symptoms by 4 years of age. Cases of moderate or mild disease are often diagnosed later in life following bleeding after trauma or surgery. Diagnosis of hemophilia A can also be made in the first trimester using chorionic villus sampling and gene analysis. In the second trimester, fetal blood sampling can be done.[8]

Hemophilia A and B are clinically indistinguishable, and thus specific factor assays are performed to differentiate and confirm the diagnosis. The PT, platelet function analysis (PFA)–100, and fibrinogen activity are normal.[6] The aPTT is prolonged when FVIII levels are less than 30%.[6,8]

Female carriers of the mutated gene may be asymptomatic unless extreme lyonization results in low FVIII levels. If FVIII levels are less than 40% in these female carriers, they are considered to have hemophilia A. If FVIII levels are at or above 40% in these female carriers, they are truly considered to be just carriers. Carriers are then further classified as symptomatic (ie, with bleeding manifestations) or asymptomatic. However, even carriers with an FVIII level of 40% to 60% may still experience bleeding episodes (eg, heavy menstrual bleeding, postpartum hemorrhage, or joint bleeding).[5,9] Asymptomatic females may become symptomatic with the onset of menarche. FVIII levels increase throughout pregnancy and drop to prepregnancy levels following delivery.[8]

Patients with severe hemophilia A often experience hemarthrosis (ie, bleeding in a joint) which can occur spontaneously or with minimal trauma. Hemarthrosis usually begins as mild joint pain and tenderness but rapidly progresses to excruciating pain, swelling, warmth, and muscle spasms.[5,9,10] A long-term effect of recurrent hemarthrosis is hemophilic arthropathy, which is characterized by synovial thickening and chronic inflammation, resulting in repeated hemorrhage. Common sites of target joints include the knees, elbows, ankles, hips, and shoulders. Joint stability may worsen due to disuse atrophy of surrounding muscles, thereby limiting the joint range of motion.[8]

Another characteristic includes muscle hematomas that can lead to compartment syndrome and can eventually cause fibrosis and peripheral nerve damage. Commonly, iliopsoas bleeds are accompanied by pain and flexion deformity, whereas gastrointestinal bleeding and hematuria are less common.[6] Intracranial hemorrhage rarely occurs but carries a 10% recurrence rate and is the leading cause of mortality in patients with hemophilia. Although most newborns with severe hemophilia do not experience complications following delivery, vaginal vacuum extraction is associated with an increased risk in central nervous system bleeds. The incidence of intracranial hemorrhage in newborns with hemophilia is 1% to 4%.[8]

The pattern of bleeding in hemophilia A tends to be coagulopathic rather than mucosal. Coagulopathic bleeding is often delayed in onset, meaning deep bruising is common and petechiae are rare. In the hemophilias, excessive bleeding from minor skin injuries is rare, but significant postsurgical bleeding is expected.[8]

Hemophilia B (FIX, Christmas Factor Deficiency)

Clinically, hemophilia B mimics hemophilia A with easy bruising, spontaneous muscle or joint hemorrhage, and excessive bleeding with trauma or surgical procedures. An X-linked, recessive coagulopathy, hemophilia B is a deficiency in FIX clotting. Prevalence is 1 in 25,000 to 30,000 male births.[6] Carriers are typically asymptomatic, as they retain greater than 50% of FIX activity, with exceptions being Turner syndrome, X-chromosome inactivation, X-mosaicism, and testicular feminization.[6] Bleeding episodes are similar to those found in hemophilia A. Severe disease is associated with less than 1% of normal factor activity, moderate is 1% to 5%, and mild is 5% to 40%. Inhibitors to FIX develop in less than 3% of patients who are severely affected.[6]

The gene for FIX is located on chromosome Xq27 and is responsible for encoding the vitamin K–dependent,

single-chain GP. Hemophilia B can be caused by point, frameshift, or deletion mutations resulting in either structural or functional changes to the FIX protein. The zymogen, or inactive, FIX becomes activated when cleaved by TF/FVIIa or FXIa, yielding FIXa.[6] In the presence of a phospholipid surface (such as platelets) and FVIIIa, FIXa will in turn activate FX.[6] Lab studies will typically yield normal PT, normal bleeding time, prolonged aPTT, and low FIX levels. Treatment typically involves FIX replacement.

Other Factor Deficiencies

FII Deficiency. Also known as hypoprothrombinemia or dysprothrombinemia, a deficiency in FII (prothrombin) is often unmasked by mild to moderate mucocutaneous and soft-tissue bleeding.[6] The gene responsible for this deficiency is found on chromosome 11p11-q12. Homozygotes of hypoprothrombinemia have less than 10% of normal quantity and homozygotes of dysprothrombinemia range from 1% to 20% of normal. Prothrombin is a protein synthesized in the liver and is vitamin K dependent. It is responsible for conversion of fibrinogen to fibrin, platelet aggregation, plasminogen activation, and activation of FV, FVIII, FXI, and FXIII, and protein C (when thrombomodulin is present).[6] A prothrombin level of 5% to 50% of normal is indicative of excessive bleeding only with surgery or trauma.[6] Lab values will show prolonged aPTT, prolonged PT, and a normal thrombin time.

FV Deficiency. A deficiency in FV is inherited in an autosomal recessive pattern. Clinical presentation includes ecchymosis, epistaxis, gingival bleeding, menorrhagia (in females), and excessive bleeding in the presence of trauma.[6] Coding for this factor is located on chromosome 1q21-25 and has some homology to FVIII. FV is produced in the liver and has a half-life of 12 to 15 hours. When activated, FV combines with FXa on the phospholipids of the platelets to create the prothrombinase complex, which is responsible for the conversion of prothrombin to thrombin.[6]

FVII Deficiency. FVII deficiency is rare with an autosomal recessive inheritance found on chromosome 13q34. Another vitamin K–dependent factor, FVII is secreted by the liver. This zymogen is activated by FXa, FIXa, FXIIa, thrombin, and FVIIa and is enhanced in the presence of TF.[6] The FVII half-life is 5 hours. Factor levels less than 1% of normal will mimic severe hemophilia A and B, and levels around 5% will have more mild symptoms such as epistaxis, gingival bleeding, menorrhagia, and easy bruising.

FX Deficiency. An autosomal recessive inherited disorder, FX deficiency can be qualitative or quantitative in nature. Clinical presentation includes spontaneous hemarthrosis, soft tissue and mucosal bleeding, or unusual bleeding following trauma. The gene coding for FX is located on chromosome 13q34 and is also vitamin K dependent. When activated, it will convert prothrombin to thrombin in the presence of a platelet-phospholipid surface, divalent calcium, and FVa.[6] Heterozygotes are typically able to maintain levels of more than 50% of normal and are therefore asymptomatic. Lab values will demonstrate normal thrombin time, prolonged PT and aPTT, diminished to absent FX levels, and a prolonged Russell viper venom time.[6] Acquired FX deficiency can be associated with amyloidosis, spindle cell thymoma, fungicide toxicity, renal or adrenal adenocarcinoma, and the use of methylbromide.[6]

FXI Deficiency (Rosenthal). Common amongst those of Ashkenazi Jewish descent and with an incidence of approximately 1:450, FXI deficiency is an autosomal recessive disorder. It affects both the intrinsic coagulation and fibrinolytic pathways. Located on chromosome 4q34-35, this factor is a GP that activates FIX via proteolysis. FXI plays a critical role of thrombin-activatable fibrinolysis inhibitor complex, which is initiated in the presence of thrombin.[6] This inhibitor downregulates fibrinolysis by disallowing binding of plasminogen to fibrin by removing the C-terminal lysine residues on partially degraded fibrin. Bleeding severity is related to the genotype. Spontaneous hemorrhage is rare, but mild to moderate bleeding is generally associated with injury.[6]

ANESTHETIC CONSIDERATIONS

The perioperative risks of patients with congenital coagulopathies undergoing surgery and sedation or general anesthesia include prolonged, and potentially fatal, hemorrhage and closed-space bleeding leading to nerve injury, vascular damage, or airway obstruction.[11] A hematologist must be involved during the perioperative care of patients with coagulopathies prior to undergoing surgery with or without sedation or general anesthesia. It is important to have a detailed plan to both measure and replace deficient factors as appropriate. Special care should be taken regarding airway maintenance. Video laryngoscopy is the preferred method when endotracheal intubation is required. Laryngeal mask airways should also be considered, if appropriate for the surgical procedure, to limit potential trauma to and bleeding in the airway. Any nasal cannulations (eg, passage of endotracheal or nasogastric tubes) should be avoided. For minor surgeries, noninvasive blood pressure monitoring is preferred; however, if multiple blood gases or labs are required throughout the procedure, invasive monitoring and site bleeding risk should be considered.

A coagulation profile including platelet count, PT, thrombin time, and aPTT should be performed. For major invasive surgery, point-of-care viscoelastic monitors, such as the thromboelastograph or rotational thromboelastograph, measure blood coagulation intraoperatively and help guide clinicians on the administration of blood products or recombinant

factors. These clinical tests, thromboelastography (TEG) and rotational thromboelastometry, assess platelet function, clot strength, and fibrinolysis.

With TEG, a small sample of the patient's blood is gently rotated in a cup at an angle of 4 degrees and 25 minutes, repeated 6 times a minute to imitate sluggish venous blood flow. A pin is then suspended from a torsion wire into the blood sample. The development of fibrin strands couples the motion of the cup to the pin, which is directly proportional to the clot strength. The increased tension in the wire is picked up by the electromagnetic transducer, and the electrical signal is amplified to create a trace. The shape of the trace generates various measurements to indicate the time and speed of clot formation, clot strength, and fibrinolysis. All these values are then analyzed to help clinicians decide which blood products need to be administered.[12]

Patients with vWD can undergo surgical procedures safely. Many type 1, 2A, and 2M vWD patients have success solely with desmopressin; however, upwards of 20% to 25% may not have an adequate response.[2,6] The typical infusion dose of desmopressin is 0.3 μg/kg (up to 20 μg) diluted into 50 mL of normal saline over 30 to 60 minutes.[6] Intranasal desmopressin (150-300 μg) can be given but has more of a limited response. In patients where desmopressin is insufficient, antifibrinolytics (eg, aminocaproic acid) can be administered rather than plasma products.[6] In patients with type 2B vWD, desmopressin is relatively contraindicated due to a potential to intensify thrombocytopenia.[6]

Patients who are unresponsive to desmopressin and those with types 2B, 2N, and 3 vWD require plasma-derived FVIII concentrates with vWF.[2,6] For major surgery, the ideal level of vWF is 0.8 to 1.0 U/mL or 80% to 100% of normal values; this can be achieved with 50 U/kg of body weight FVIII concentrate.[6] Postoperatively, the targeted vWF concentration is 0.4 U/mL for several days.[6]

Cryoprecipitate is commonly administered because it contains 40% to 70% of the original concentration of vWF. It is dosed at 1 bag/10 kg of body weight every 12 to 24 hours, and the duration of administration is bleeding dependent.[6] Purified plasma–derived vWF/FVIII is a US Food and Drug Administration–approved treatment with 2.5 IU of ristocetin cofactor to 1 U FVIII and a half-life of 11 hours.[6] Preoperatively, a loading dose is 60 to 80 ristocetin cofactor activity/kg body weight administered intravenously (IV) every 8 to 12 hours. Administration is continued for 7 to 10 days for major surgery and 3 to 5 days for minor surgery.[6] In some rare cases of type 3 vWD, patients may have developed alloantibodies to vWF. Combinations of recombinant FVIIIa, antifibrinolytics, and thrombin glue have been successfully administered for oral surgical procedures in these patients.[6]

For hemophilia A, current guidelines recommend that factor replacement therapy increase the preoperative plasma FVIII levels to 40% to 70% for elective surgeries and 80% to 100% for major surgeries.[9,10] After surgery, the target FVIII level is 50% until the surgical wound is healed or for about 6 to 10 days. Dosing calculations are dependent on many factors, including the targeted increase in factor levels, clinical expertise of the consulting hematologist, individual patient-level factors (eg, history of previous bleeding episodes), and hospital protocols. An example of the formula to determine the dose required to increase FVIII levels is as follows: FVIII dose = weight (kg) × 0.5 × (desired absolute percentage increase in factor levels). To rapidly increase FVIII levels to about 100%, the usual dose given is 50 units/kg.

Intramuscular injections are to be generally avoided in these patients.[13] In about 10% of patients, their body may produce an antibody that inactivates FVIII. These acquired anticoagulants are usually composed of immunoglobulin G, are poorly removed by plasmapheresis, and are responsive to immunosuppressive drugs. The use of prothrombin complex concentrates (PCCs) can be lifesaving to bypass this inhibitor.[10] For patients with mild hemophilia A, an IV infusion of desmopressin about 30 to 90 minutes before the procedure may be sufficient. Desmopressin stimulates the release of vWF and FVIII, increasing levels 3- to 5-fold and lasting up to 6 hours.[6,7,10] Inhibitors, or alloantibodies, develop in 20% to 30% of hemophilia A patients and are more common in severe cases. Immunosuppressive agents may need to be administered if alloantibodies develop.[2] Patients on emicizumab should be treated with FVIII concentrate if no inhibitors are present while continuously monitoring FVIII levels. In addition, FFP and cryoprecipitate can also correct FVIII levels.

In patients with hemophilia B, PCCs can be administered; these concentrates provide zymogen as well as activated prothrombin, FVIIa, FXa, and FIXa.[6] Concentrates have been associated with thrombotic events (eg, thrombophlebitis, deep venous thrombosis, pulmonary embolism, and disseminated intravascular coagulation) because of the combination of activated factors. These concentrates should not be administered if the FIX concentration is greater than 50% of normal, as the risk of thromboembolic events outweighs the benefits of infusion.[6] Highly purified FIX infusions can be administered in the perioperative period and have less of a risk of activating systemic coagulation.[6] Dosing is dependent upon whether the coagulant is derived from plasma or if it is recombinant. Recombinant has a lower recovery profile (37.8%) vs plasma derived (52.6%); recombinant is not exposed to human albumin or bovine serum and therefore may be preferred in some patient populations. With FIX replacement each 1 U/kg will increase circulating FIX levels by 0.01 U/mL. In a severely affected patient, approximately 100 U/kg will need to be administered every 12 to 18 hours. Plasma-derived FIX half-life is 17.7 hours, and recombinant FIX half-life is 18.1 hours.[6]

Patients with prothrombin deficiency can receive PCCs of FFP in the perioperative setting. Typically, only one administration is needed, as the half-life of prothrombin is 3 days.[6] The perioperative goal for FV is more than 25% of normal. This can be achieved with a fresh frozen plasma

Table. Factor Management for Coagulation Deficiencies[a]

Bleeding disorder	*Pretreatment for extraction and/or nerve blocks*
Hemophilia A (mild)	Desmopressin, 0.3 μg/kg (max 20 μg) IV over 20-30 min
Hemophilia A (moderate, severe)	Recombinant factor VIII concentrate, 20-25 IU/kg
Hemophilia B (mild, moderate, severe)	Recombinant factor IX concentrate, 40-60 IU/kg
Type 1 vWD	Desmopressin, 0.3 μg/kg (max 20 μg) IV over 20-30 min
Type 2A and 2M vWD	Desmopressin, 0.3 μg/kg (max 20 μg) IV over 20-30 min OR vWF/factor VIII, 50 IU of vWF:RCoF/kg
Type 2B and 3 vWD	vWF/factor VIII, 50 IU of vWF:RCoF/kg
Factor II	FFP
	PCC
Factor V	FFP
Factor VII	Factor VII concentrate
	Recombinant factor VIIa
Factor X	FFP
Factor XI	FFP
	Factor XI concentrate

FFP, fresh frozen plasma; IV, intravenous; max, maximum; PCC, prothrombin complex concentrate; RCoF, ristocetin cofactor; vWD, von Willebrand disease.

[a] Information from Israels et al.[2]

loading dose of 20 mL/kg and 5 to 10 mL/kg every 12 hours for 7 to 10 days.[6] The goal for hemostasis perioperatively is maintaining a level of greater than 25% of normal through administration of PCC and FFP. Recombinant FVIIa therapy has been successful with doses lower than what is required for treatment of hemophilia.[6] In patients with FXI deficiency, factor replacement is not generally required for dental procedures. However, antifibrinolytics are beneficial and should be considered.[6] See the Table for a full list of preoperative management considerations for dental and surgical procedures.

DENTAL CONSIDERATIONS

Determining the mechanism and severity of coagulopathy is important, but the type, location, and extent of the planned dental treatment are also extremely important. Access to the treatment site in question is critical for assessment and control of hemostasis. A simple anterior extraction can be directly visualized and, therefore, is more readily accessible for applying pressure, topical agents, and additional local hemostatic agents. Sinus elevation and bone grafting would create a different scenario in which there is essentially limited to no access to evaluate or control bleeding if hemostasis cannot be achieved. In the latter scenario, systemic factor replacement therapy will play a critical role. Location of surgical intervention (eg, mandibular tori removal elevating the floor of the mouth) can also cause a significant hematoma and subsequent airway obstruction. Administration of local anesthesia for inferior alveolar and posterior superior alveolar nerve blocks (ie, “deep blocks”) can also contribute to airway obstruction from an uncontrolled hematoma. An appropriate alternative to an inferior alveolar block is the Gow-Gates technique.[2] Other safe techniques include local infiltration, periodontal ligament injection, and intrapulpal injection. If these techniques are inadequate, the addition of sedation or general anesthesia can be considered, but these come with their own set of risks.

Consultation with a patient’s hematologist prior to any elective dental procedures should include discussions regarding plans for infusions of coagulation factors, blood products, and other measures prior to arrival at an outpatient, ambulatory, or office-based setting. Oftentimes, patients will have IV access established by the hematology service before arrival, and communication regarding using and maintaining the established IV access should focus upon additional anesthesia-related medications through the same access point.

Surgical interventions can occasionally be modified to create a less traumatic surgical field. Examples include electively sectioning a tooth that could be deemed a difficult extraction, limiting the number of teeth extracted in an appointment, avoiding soft tissue flaps whenever possible as they create a larger bleeding surface area that can be difficult to control postoperatively, and attaining primary closure.[2] In some scenarios it may be preferable to perform root canal therapy on unrestorable teeth with poor prognoses so the mucosa can be largely left intact.

Local Measures

There are local measures that can be employed for necessary surgical procedures. Suturing can be helpful to achieve primary closure if multiple adjacent teeth are extracted. However, each additional needle puncture is a potential source for bleeding, so the benefits must outweigh the risks. Electrocautery or CO_2 laser can be used for soft tissue biopsy or

for the purpose of achieving hemostasis, but these come with the risk of tissue necrosis which can become a source of postoperative bleeding. Gelfoam (Pfizer) is one example of an absorbable gelatinous sponge that allows for scaffolding effect for clot formation. It is placed directly into an extraction socket and will resorb over approximately 4 weeks. Gelfoam should not be placed under flaps as it will inhibit epithelial healing.[6]

Tranexamic acid (TXA) can be used as a mouthwash. The IV preparation of TXA can be diluted to 4.8% solution, which is used as a rinse 4 times a day for 7 days postoperatively. Consider contacting a compounding pharmacy for this preperation.[2] Aminocaproic acid is an antifibrinolytic agent available as oral and IV solutions, tablets, and a mouth rinse. Both agents function to inhibit fibrinolysis by blocking the plasminogen-fibrin bond, thereby inhibiting activation to plasmin. Oral mucosa is known to be rich in plasminogen activators, and saliva itself has fibrinolytic activity, which can increase the likelihood of clot breakdown following oral surgery procedures.[2,13] Sometimes these agents can be used as sole treatments (oral rinses are available) or in conjunction with replacement therapies. Combination therapies in more severe coagulopathies have demonstrated a decreased risk of delayed bleeding and reduced need for replacement factors postoperatively.[2] Oral doses can be started prior to surgery and continued 3 to 5 days postoperatively or until the surgical site is healed.[2]

Surgical stents can be fabricated that would allow for pressure to be exerted onto extraction sites.[2] A moist tea bag can also be useful for patients who continue oozing at home. Soaking a black tea bag in warm water, wringing it out, and then applying it as a pressure dressing for 30 minutes provides pressure and the added benefit of the astringent tannic acid (highest in black teas) which vasoconstricts capillaries and accelerates clot formation.

CONCLUSION

Patients with inherited coagulopathies have a wide array of complexities but are likely to require dental care at some time in their lives. Dental treatment can be safely rendered by collaborating with the patient's hematologist to manage and optimize the patient's coagulopathy. Recombinant factor replacement, desmopressin, and FFP are the primary preoperative treatment options for patients with factor deficiencies. However, administration may not be required depending upon the specifics of the procedure and the patient's coagulopathy. Other local measures that should be considered include laser therapy, collagen plugs, and specialized mouth rinses.

REFERENCES

1. Shevell L, Lee AI. Normal hemostasis. In: *Cecil Essentials of Medicine*. 10th ed. Elsevier; 2022:522-529.

2. Israels S, Schwetz N, Boyar R, McNicol A. Bleeding disorders: characterization, dental considerations and management. *J Can Dent Assoc*. 2006;72(9):827.

3. Golebiewska EM, Poole AW. Platelet secretion: from haemostasis to wound healing and beyond. Blood Rev. 2015;29(3):153-162. doi:10.1016/j.blre.2014.10.003

4. Nimjee SM, Crofton AR, Oh N, Kirsch W, Haglund MM, Grant GA. Coagulation for the neurosurgeon. In: *Younmans and Winn Neurological Surgery*. 8th ed. Elsevier; 2023:203-212.

5. Berntorp E, Fischer K, Hart DP, et al. Haemophilia. *Nat Rev Dis Primers*. 2021;7(1):45. doi:10.1038/s41572-021-00278-x

6. Lee JW. Von Willebrand disease, hemophilia A and B, and other factor deficiencies. *Int Anesthesiol Clin*. 2004;42(3):59-76. doi:10.1097/00004311-200404230-00007

7. Bharati KP, Prashanth UR. Von Willebrand disease: an overview. *Indian J Pharm Sci*. 2011;73(1):7-16. doi:10.4103/0250-474X.89751

8. Ozgonenel B, Kulkarni R, Chitlur M. Hemophilia and related conditions. In: *Conn's Current Therapy 2024*. Elsevier; 2024:458-466.

9. Martlew VJ. Peri-operative management of patients with coagulation disorders. *Br J Anaesth*. 2000;85(3):446-455. doi:10.1093/bja/85.3.446

10. Wake P. Blood, coagulation, and transfusion. In: *Smith and Aitkenhead's Textbook of Anaesthesia*. Elsevier; 2019:250-264.

11. Kiefer J, Mythen M, Roizen MF, Fleisher LA. Anesthetic implications of concurrent diseases. In: *Miller's Anesthesia*. 9th ed. Elsevier; 2020:999-1064.

12. Cowell VS. Hemophilia. In: Fleisher LA, Roizen MF, Roizen J, eds. *Essence of Anesthesia Practice*. Elsevier; 2018:194-195.

13. Wijeysundera DN, Finlayson E. Preoperative evaluation. In: *Miller's Anesthesia*. 9th ed. Publisher; 2020:918-998.

CONTINUING EDUCATION QUESTIONS

This continuing education (CE) program is designed for dentists who desire to advance their understanding of pain and anxiety control in clinical practice. After reading the designated article, the participant should be able to evaluate and use the information appropriately in providing patient care.

The American Dental Society of Anesthesiology (ADSA) is accredited by the American Dental Association and Academy of General Dentistry to sponsor CE for dentists and will award CE credit for each article completed. You must answer 3 of the 4 questions correctly to receive credit.

Submit your answers online at www.adsahome.org. Click on "On Demand CE."

CE questions must be completed within 3 months and prior to the next issue.

1) Which of the following inherited coagulopathies is the most common bleeding disorder?

   a. Factor II deficiency
   b. Hemophilia A
   c. Hemophilia B
   d. von Willebrand disease

2) Which of the following airway management techniques should be avoided in patients with clinically significant congenital coagulopathies?

   a. Nasotracheal intubation
   b. Natural airway (nonintubated deep sedation/general anesthesia)
   c. Placement of a laryngeal mask airway
   d. Video laryngoscopy

3) For patients with Type 1, 2A, or 2M von Willebrand disease, which of the following agents can be administered to improve coagulation during dental surgery?

   a. Desmopressin
   b. Normal saline
   c. Nonsteroidal anti-inflammatory drugs
   d. Plain local anesthetics

4) Which of the following intraoral local anesthetic techniques would be contraindicated in patients with clinically significant coagulopathy?

   a. Gow-Gates nerve block
   b. Inferior alveolar nerve block
   c. Intrapulpal injection
   d. Supraperiosteal infiltration

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

Chhabada S, Skinner C, et al. Association between age- and sex-specific body mass index percentile and multiple intubation attempts: a retrospective cohort analysis. *Anesth Analg*. 2024;138(4):821–828. doi:10.1213/ANE.0000000000006400

Obesity distorts airways and has been shown to slightly complicate intubation in adults, but whether obesity complicates pediatric intubations remains unclear. The authors tested the primary hypothesis that increasing age- and sex-specific body mass index (BMI) percentile is associated with difficult intubation, defined as more than 1 intubation attempt. A retrospective analysis of pediatric patients between 2 and 18 years of age undergoing noncardiac surgery with oral endotracheal intubation was conducted. The association between BMI percentile and difficult intubation, defined as more than 1 intubation attempt, using a confounder-adjusted multivariable logistic regression model was the primary focus of the study. Secondarily, the authors assessed whether the main association depended on preoperative substantial airway abnormality status or age group. A total of 9,339 patients were included in the analysis. Median (quartiles) age- and sex-specific BMI percentile was 70 (33, 93), and 492 (5.3%) patients had difficult intubation. There was no apparent association between age- and sex-specific BMI percentile and difficult intubation. The estimated odds ratio (OR) for having difficult intubation for a 10-unit increase in BMI percentile was 0.98 (95% CI, 0.95-1.005) and was consistent across the 3 age groups of early childhood, middle childhood, and early adolescence (interaction $P = .53$). Patients with preoperative substantial airway abnormalities had lower odds of difficult intubation per 10-unit increase in BMI percentile with OR (95% CI) of 0.83 (0.70-0.98), $P = .01$. The authors concluded age- and sex-specific BMI percentile was not associated with difficult intubation in children between 2 and 18 years of age. As in adults, obesity in children does not appear to significantly complicate intubation.

Comment: Obesity is associated with an increase in fat deposition in the tongue and pharynx. This results in the visual distortion of anatomic landmarks and possible impaired mobility of the head and pharynx during intubation. The authors point out that intubations are progressively more likely to fail as BMI increases from 18 kg/m^2 to about 30 kg/m^2, but the fraction of successful first-attempt intubations in adults hardly changes as BMI increases from 30 kg/m^2 to 80 kg/m^2. This study showed 1 in 20 of a sample of pediatric patients, age 2 to 18 years, required more than 1 intubation attempt, but increased age- and sex-specific BMI percentile was not associated with increased risk of difficult intubation. Children are thus like adults in that obesity minimally compromises laryngoscopy and intubation.

Schnetz MP, Reon BJ, Ibinson JW, et al. Bispectral index changes following boluses of commonly used intravenous medications during volatile anesthesia identified from retrospective data. *Anesth Analg*. 2024;138(3):635–644. doi:10.1213/ANE.0000000000006633

Although patients are commonly monitored for depth of anesthesia, it is unclear to what extent administration of intravenous anesthetic medications may affect calculated bispectral index (BIS) values under general anesthesia. In a retrospective analysis of electronic anesthesia records from an academic medical center, we examined BIS value changes associated with 14 different intravenous medications as administered in routine practice during volatile-based anesthesia using a novel screening approach. Discrete time windows were identified in which only a single drug bolus was administered, and subsequent changes in BIS values, concentration of volatile anesthetic, and arterial pressure were analyzed. Our primary outcome was change in the BIS value following drug administration. Adjusted 95% CIs were compared with predetermined thresholds for clinical significance. Secondary sensitivity analyses examined the same outcomes with available data separated according to differences in baseline volatile anesthetic concentrations, doses of the administered medications, and length of time window. The study cohort comprised data from 20,170 distinct cases; 54.7% of patients were men, with a median age of 55 years. In the primary analysis, ketamine at a median dose of 20 mg was associated with a median BIS increase of 3.8 (2.5-5.0). Midazolam (median dose 2 mg) was associated with a median BIS decrease of 3.0 (1.5-4.5). Neither of these drug administrations occurred during time periods associated with changes in volatile anesthetic concentration. Analysis for dexmedetomidine was confounded by concomitant decreases in volatile anesthetic concentration. No other medication analyzed, including propofol and common opioids, was associated with a significant change in BIS values. Secondary analyses revealed that similar BIS value changes occurred when midazolam and ketamine were administered at different volatile anesthetic concentrations and different doses, and these changes persisted 11 to 20 minutes after administration. The authors concluded that modest but persistent changes in BIS values occurred following doses of ketamine (BIS increase) and midazolam (BIS decrease) during periods of stable volatile anesthetic administration.

Anesth Prog 71:96–98 2024

Comment: The findings in this study are consistent with our understanding of the respective molecular mechanisms of action for ketamine and midazolam. Midazolam, like all benzodiazepines, acts as a positive allosteric modulator on γ-aminobutyric acid (GABA)–A receptors, resulting in hyperpolarization of central nervous system (CNS) neurons. GABA is the major inhibitory neurotransmitter in the CNS. Ketamine blocks the flow of glutamate through N-methyl-D-aspartate receptors in the CNS. Glutamate is a major excitatory neurotransmitter in the CNS. Ketamine and midazolam produce their anesthetic effects through 2 separate and distinct mechanisms, which is reflected in the 2 separate and distinct BIS patterns. The lack of a significant change in BIS values following the administration of other drugs, including propofol and common opioids, remains unclear.

A significant limitation of this study for dental anesthesia providers is the fact that the data were drawn from a population with a mean age of 55 years with each individual drug administered as an adjunct to inhalational anesthesia. Direct application of these results to dental anesthesia, which most often involves intravenous anesthesia administered to pediatric and young adult patients, is difficult.

Laferriere-Langlois P, Morisson L, Jeffries S, et al. Depth of anesthesia and nociception monitoring: current state and vision for 2050. *Anesth Analg*. 2024;138(2):295–307. doi:10.1213/ANE.0000000000006860

This narrative review article examines the current use of the bispectral index, Narcotrend monitor, Patient State Index, entropy-based monitoring, and Neurosense monitor, as well as middle latency evoked auditory potential, and explores how these technologies could evolve in the upcoming years. Whereas theoretical concepts such as minimal alveolar concentration and target-controlled infusions are currently used as surrogates for patient awareness, this review looks at the use of direct neural monitoring such as electroencephalography (EEG) and its derivatives (processed EEG [pEEG]) for monitoring anesthetic depth. Current studies appear to affirm that pEEG monitoring decreases the quantity of anesthetics administered, diminishes the time spent in the postanesthesia care unit, and may reduce the occurrence of postoperative delirium. Three strategies currently guide the application of these technologies: motor reflex monitoring, central nervous system activity, and autonomic nervous system activity. Generally, nociceptive monitors outperform basic clinical vital sign monitoring in reducing perioperative opioid use.

Comment: The adequacy of clinical anesthesia is typically based on factors such as patient movement, sympathetic nervous system activity, and hypnosis. Recent advances in the monitoring of depth of anesthesia and nociception suggest that these traditional indicators may be comparatively crude and result in the application of excessive levels of anesthesia for many types of surgeries. Combined with recent advances in anesthetic pharmacology and the diminished invasiveness of many types of surgery, it appears likely that depth of anesthesia monitoring and nociceptive monitoring will become an increasingly important part of non–operating room anesthesia practice in the near future.

Sawicki CM, Janal MN, Wade SD. Preoperative multisensory room use in pediatric patients with autism: a randomized clinical trial. *Pediatr Dent*. 2024;46(2):91–98.

This study evaluated the impact of multisensory room (MSR) use on preoperative anxiety and postoperative outcomes in children with autism spectrum disorder (ASD) undergoing dental treatment with general anesthesia. Forty children, ages 6 to 17 years, with ASD requiring general anesthesia for dental treatment participated in this study. The sample was predominantly male (62.5%) and identified as either white or black (53%) and non-Hispanic (60%). Participants were randomized to either the control group (standard preoperative waiting room) or intervention group (MSR) for 20 minutes prior to general anesthesia induction. Preintervention and postintervention preoperative anxiety were measured. Following surgery, postoperative emergence delirium was assessed. Short- and long-term postoperative pain and adverse behavioral effects were evaluated at 6 hours, 24 hours, 1 week, and 1 month postsurgery. Data analysis employed repeated measures analysis of variance with 2 groups and either 2 or 4 time periods. Preoperative behavioral anxiety levels increased postintervention in the control group ($P < .05$) and decreased in the MSR group ($P < .001$). Following surgery, pain intensity was greater in the control group compared with the MSR group at 6 hours ($P < .05$) and 24 hours ($P < .01$) and similar at 1 and 4 weeks. Preintervention and postintervention measures of preoperative heart rate, postoperative emergence delirium, and behavioral effects were similar between groups and over time. These findings suggested a novel, nonpharmacologic technique that can be utilized by various health care specialties to reduce preoperative anxiety and improve postoperative outcomes in children with ASD.

Comment: One of the dominant features of ASD is heightened sensitivity to environmental stimulation. This heightened sensitivity affects the way in which autistic individuals interpret and respond to their environment. Engineers, architects, and others have developed environments that reduce an autistic person's aversion to sensory overload, enhance meaningful sensory processing, and foster communication. Acoustic, auditory, tactile, and olfactory stimulation are the most critical design elements of these environments. An MSR is an example of this kind of engineered environment.

This study offers promise for the management of a population of patients frequently seen in the practice of dental anesthesiology. A limitation of the study included the ages of the participants, which ranged from 6 to 17 years. Future studies that examine the efficacy of this intervention in children 2 to 6 years of age would be particularly informative to dentist anesthesiologists.

Summaries and comments provided by

Mark A. Saxen, DDS, PhD
Department of Dental Anesthesiology
University of Pittsburgh School of Dental Medicine
Pittsburgh, PA

Impact Factor for Journals Specializing in Dental Anesthesiology

Impact factor (IF) is a quantitative measure of academic journal importance provided annually by Journal Citation Reports (Clarivate Analytics). Per the Clarivate website, the IF is calculated by "dividing the number of citations in the *Journal Citation Reports* year (the numerator) by the total number of citable items published in the two previous years (the denominator)."[1] In other words, IF is the average number of citations per year for articles published in a journal over the previous 2 years (Figure). It is important to note that for a journal to be assigned an IF, it must be included in the Web of Science by Clarivate Analytics.

IF is an indicator of a journal's relevance; a journal with a high calculated IF is generally considered to have high value, and the articles published in it are also considered to have a high value. Although journals with higher IFs likely have an advantage of being read by more researchers in the same field, it is meaningless to compare IFs for journals from different fields with different populations of researchers. This is like trying to compare the economic wealth of individual countries based on their gross domestic product without taking into consideration population differences.

However, despite much criticism, many academic institutions and research facilities still use IF as a component of personnel performance evaluations. This trend is particularly prominent in Asia, which leads to researchers seeking to publish in journals that have IFs over those that do not. Currently, there are 3 journals published by academic societies specializing in dental anesthesiology, but unfortunately, none of them have obtained an IF (Table). Therefore, even if a scientific article or case report that contains useful information directly related to dental anesthesiology is prepared and published after much effort in one of these journals that currently lack an IF, it may not be well received by scientists in other fields of study.

Anesthesia Progress is the oldest and most prestigious of the 3 journals specializing in dental anesthesiology. It has published many high-quality articles directly related to dental anesthesiology. It is our sincere desire that *Anesthesia Progress* obtain an IF, not only for the journal itself but also for the articles published. By extension, this would also benefit researchers specializing in dental anesthesiology to be legitimately recognized by other external researchers. We are convinced that obtaining an IF will stimulate meaningful research directly related to dental anesthesiology and ultimately lead to further scientific and clinical developments in dental anesthesiology. Above all, it will encourage researchers specializing in dental anesthesiology.

As mentioned above, the IF is calculated based on 3 years of data from journals included in the Web of Science, so newly included journals will not receive an IF for the first 3 years. Therefore, even if a journal takes action in 2024, the IF will not be calculated and assigned until 2027 (announced as an IF for 2026). First, the journal should apply for inclusion in the Web of Science. After acceptance, a more sophisticated peer-review process should be conducted for the next 3 years. Then, articles should be opened for free access simultaneously with publication. By following these steps, we anticipate that *Anesthesia Progress* should be expected to obtain an IF and become a more prestigious journal not only within dental anesthesiology and dentistry but also within all medical fields.

For the further development of dental anesthesiology worldwide and for the benefit of future dental anesthesiologists and researchers specializing in dental anesthesiology, we urge Dr Kyle J. Kramer, editor-in-chief of *Anesthesia Progress*, to consider obtaining an IF for the journal.

Comment from editor: I thank the authors for their submitted commentary detailing why Anesthesia Progress should obtain an Impact Factor. On behalf of the journal's editorial board and the American Dental Society of Anesthesiology Board of Directors, I am happy to report that we agree with the authors' recommendation and are taking steps toward working to accomplish that goal. Further details will be shared with the journal's readership as they become available.

Takuro Sanuki, DDS, PhD[1],
Shota Tsukimoto, DDS, PhD[2],
Hidetaka Kuroda, DDS, PhD[2],
and Kanta Kido, DDS, PhD[3]
[1] Professor and Chair, Department of Dental Anesthesiology, Kanagawa Dental University
[2] Associate Professor, Department of Dental Anesthesiology, Kanagawa Dental University
[3] Professor and Chair, Department of Dental Anesthesiology, Hokkaido University

REFERENCE

1. Clarivate. Journal Citation Reports: Documents Types Included in the Impact Factor Calculation. Accessed January 4, 2024. https://support.clarivate.com/ScientificandAcademicResearch/s/article/Journal-Citation-Reports-Document-Types-Included-in-the-Impact-Factor-Calculation?language=en_US

Received April 2, 2023; accepted for publication December 21, 2023.

Address correspondence to Dr Takuro Sanuki, Department of Dental Anesthesiology, Kanagawa Dental University, 1-23 Ogawa-cho, Yokosuka, Kanagawa, 2388570, Japan; sanuki@kdu.ac.jp.

Anesth Prog 71:99–100 2024 | DOI 10.2344/563377

Figure. Impact Factor Calculation Example

$$\text{Impact factor for 2026} = \frac{\text{Total count in 2026 of cited articles published in the journal from 2024 and 2025}}{\text{Total count of possible citable articles published in the journal from 2024 and 2025}}$$

Impact factor is calculated by "dividing the number of citations in the *Journal Citation Reports* year (the numerator) by the total number of citable items published in the two previous years (the denominator)."[1]

Table. Journals Published by Academic Societies Specializing in Dental Anesthesiology

Journal title	*Academic society issuing the journal*	*Annual issues, No.*	*Language*	*Impact factor*
Anesthesia Progress	American Dental Society of Anesthesiology	4	English	Not obtained
Journal of Dental Anesthesia and Pain Medicine	Korean Dental Society of Anesthesiology	6	English	Not obtained
Journal of Japanese Dental Society of Anesthesiology	Japanese Dental Society of Anesthesiology	4	Japanese	Not obtained

Joint Meeting of the IFDAS 17th Triennial Congress and the ADSA Annual Session Held in Las Vegas

In conjunction with the 2024 Annual Session of the American Dental Society of Anesthesiology (ADSA), the International Federation of Dental Anesthesiology Societies (IFDAS) held its 17th International Dental Congress on Anesthesia, Sedation, and Pain Control from March 15 to 16, 2024, at the Aria Resort and Casino in Las Vegas. Held every 3 years in various locations around the globe, IFDAS meetings are exciting opportunities for members of international dental anesthesia societies to present cutting-edge research and initiatives and exchange clinical advances in the areas of anesthesia, sedation, and pain control for dentistry.

With a diverse array of presenters from Europe, Asia, Australia, Canada, and the United States, the congress drew over 1,000 attendees to its training courses, which included sessions for general anesthesia/deep sedation, minimal/moderate sedation, and pediatric sedation and a course for assistants. A highlight was the ADSA High-Fidelity Human Simulation Course held at the Clinical Simulation Center of Las Vegas, a state-of-the-art educational facility located at University of Nevada, Las Vegas's Shadow Lane Campus, where international colleagues observed the usefulness of immersive simulation training for advancing patient safety.

The IFDAS General Assembly also celebrated the achievements of some exceptionally distinguished professionals. The Horace Wells Award, IFDAS's highest award, was given to Dr Idit Matot from Israel, Dr Kazu-Ichi Yoshida from Japan, and Dr Karen Crowley from the United States for their outstanding service. The Kubota Award was bestowed posthumously upon Dr Douglas Stewart, honoring his legacy of excellence. Dr Daniel Haas, an internationally renowned expert in dental anesthesiology and former dean of the University of Toronto faculty of dentistry, was honored by giving the Brienza Memorial Lecture.

The ADSA's highest achievement, the Heidbrink Award, was bestowed posthumously upon Dr Stuart Lieblich. A revered figure in the community for his contributions to the advancement of patient safety in anesthesia for dentistry, Dr Lieblich was a former president of the ADSA and a long-serving board member of the American Board of Oral and Maxillofacial Surgery. With a distinguished career that included teaching at the University of Connecticut and contributions to over 20 textbooks and 45 peer-reviewed papers, his impact on the field was immense. Dr Lieblich was instrumental in advancing ambulatory anesthesia and opioid reduction strategies in oral surgical procedures, leaving a lasting legacy that continues to influence practices worldwide. Sadly, he passed away recently following a months-long battle with cancer. His contributions were recognized posthumously with Dr Bob Bosack accepting the award on his behalf.

A significant highlight of this joint meeting was the debut of the new Ten Minutes Saves a Life collaborative learning modules. Part of a unique educational collaboration between the ADSA and the American Society of Anesthesiologists (ASA), these modules aim to enhance patient safety in dental sedation through team-based training. The Ten Minutes Saves a Life application featured in these modules provides an interactive platform for emergency drill practice that was highly praised by international attendees for its innovation and practical relevance.

Adding to the international scope of innovative training solutions, Dr Kenji Seo, professor at Niigata University Graduate School of Medical and Dental Sciences, Division of Dental Anesthesiology, shared details about a similar project being worked on at his university. Similar to the ADSA/ASA collaboration, the Japanese project also focuses on using simulation-based training to improve dental anesthesia safety and emergency preparedness.

The meeting featured numerous other informative lectures spanning a broad range of topics. Several other notable experts were present, including Dr Nigel Robb, dean of the Griffith University School of Medicine and Dentistry, whose lecture highlighted an international perspective to mitigating sedation risks. In addition to the rich discussions and presentations, the meeting also featured over 30 poster and abstract submissions from around the globe. The top 5 submissions were selected to present their research and clinical innovations in dental anesthesia live at the meeting.

The congress concluded with a critical and insightful panel discussion titled "Adverse Events Around the Globe & Implications for Safety." The panel featured experts from Canada, Israel, Brazil, India, Japan, and the United States. Each panelist shared their experiences and perspectives on managing safety in dental anesthesia, illustrating the universal challenges and collaborative solutions being developed worldwide.

It was also announced that the next IFDAS triennial congress will be held in Berlin, Germany, in the fall of 2027.

Jason Brady, DMD
Dentist anesthesiologist
Attending faculty, NYU-Langone
President, IFDAS
Vice President, ADSA

Anesth Prog 71:101–103 2024 | DOI 10.2344/025134

Figure 1. International Federation of Dental Anesthesiology Societies President Jason Brady presents the Horace Wells Award to Dr Karen Crowley.

Figure 2. Dr Greg Mahoney accepts the Y. Kubota Distinguished Service Award presented posthumously to Dr Doug Stewart.

Figure 3. Drs Lucia Santos, Andra Rettman, and Ariana Carillo, the top 3 International Federation of Dental Anesthesiology Societies poster presenters.

IFDAS Abstracts

Comparison of Circulatory Dynamics During Induction of General Anesthesia Between Propofol and Remimazolam: Clinical Research

Kanoko Hirata, DDS; Yozo Manabe, DDS, PhD; Akina Toya, DDS; Shigeru Iwamoto, DDS; and Yoshihiro Momota, DDS, PhD
Department of Dental Anesthesiology, Osaka Dental University, Osaka, Japan

Objective: Propofol is characterized by its relatively strong circulatory depressant effects. Basic studies have shown that remimazolam has less potent effects on circulatory dynamics than propofol. The purpose of this study was to clarify the cardiovascular effects of propofol and remimazolam in clinical practice.

Methods: Sixty patients aged 18 years to 39 years undergoing surgery under total intravenous anesthesia were included in the study. Patients were divided into 2 groups: group propofol (GP) and group remimazolam (GR). The following parameters were measured during induction of general anesthesia: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiac output (CO), cardiac index, stroke volume, stroke volume index (SVI), and anesthetic depth (BIS). After the control values were obtained, remifentanil was administered at 0.3 μg/kg/min for 1 minute. In GP, propofol was administered at 5 μg/mL with a target-controlled infusion. In GR, remimazolam was administered at 0.2 mg/kg and maintained at 1 mg/kg/h. The recording period was from control to 5 minutes after tracheal intubation.

Results: BIS was significantly lower in GP than in GR from 3 minutes after induction. SBP, DBP, HR, CO, and SVI were significantly lower in GP than in GR after tracheal intubation.

Conclusion: The doses of propofol and remimazolam used in this study did not cause any differences in the circulatory dynamics during induction of anesthesia. However, the invasion of tracheal intubation restored the hemodynamics of the GR to control values, whereas those of the GP remained depressed. The possibility of overdosing propofol cannot be ruled out, but the effects of remimazolam on circulatory depression were still considered to be less severe than those of propofol.

Anesth Prog 71:104–105 2024

Unlocking the Diagnostic Potential of the Basophil Activation Test in Patients with a History of Anaphylactic Shock: Timing and Clinical Utility

Takashi Goto, DDS, PhD; and Satoru Sakurai, DDS, PhD
Department of Dental Anesthesiology, Division of Oral Pathogenesis and Disease Control, Asahi University School of Dentistry, Mizuho, Gifu, Japan

Objective: Patients with a history of anaphylactic shock frequently seek dental care. However, patients who experience recurrent anaphylactic episodes are at risk for future reactions. The basophil activation test (BAT) has been gaining attention as an in vitro test to identify allergic triggers of anaphylaxis, facilitating prevention. However, BAT remains in the research stage, and several aspects need to be established, including the optimal testing time. Herein, we aimed to determine the efficacy and optimal testing time of BAT in patients with a history of anaphylactic shock and BAT positivity.

Methods: BAT was continuously performed on 2 patients who developed anaphylactic shock and had a positive BAT. The activation rate of basophils was observed over a prolonged period.

Results: For cefazolin sodium, BAT results were positive on days 33, 151, 161, 306, and 395 after the onset of anaphylactic shock but were negative on days 504 and 536. For latex products, BAT results were positive on days 133 and 1,779 after the onset of anaphylactic shock.

Conclusion: We successfully identified the causative agent of anaphylactic shock in 2 patients using BAT. Our findings suggest that the BAT response period may differ depending on the causative agent of anaphylactic shock.

Cerebral Oximetry: A Novel Approach to Resuscitation

Ariana Carillo, DDS
Second-Year Dental Anesthesia Resident, NYU Langone Health, Brooklyn, New York

The NYU Langone Health Parnia Lab seeks to improve standards of care, survival rates, and neurologic outcomes for cardiac arrest patients undergoing cardiopulmonary resuscitation (CPR) in fields ranging from critical care to dental anesthesia. The overall survival for adult in-hospital cardiac arrest has not significantly improved from the first multicenter study published in 1953 (28%) to current studies in the United States (18%) and the United Kingdom

(29%). These poor outcomes illustrate the need for innovation beyond CPR. Cerebral oximetry–guided CPR is a novel approach that measures real-time regional cerebral oxygen saturation (rSO2) during chest compressions to assess oxygen delivery, guide treatment, and predict neurologic outcomes. Using this approach, the Parnia Lab published outcomes for 183 CPR efforts at 5 participating centers. The results demonstrate that if cerebral oximetry–guided CPR maintained an rSO2 greater than 65%, there was a higher incidence of return of spontaneous circulation (ROSC), patient survival, and favorable neurologic outcomes. In contrast, an rSO2 less than 25% was associated with unlikely ROSC and patient survival. This poster highlights the research being conducted at Parnia Lab using goal-directed, cerebral oximetry–guided CPR to assess cerebral oxygen delivery during resuscitation in order to prognosticate patient survival and neurologic outcomes.

In Memoriam: Dr Stuart E. Lieblich
October 14, 1955–February 28, 2024

The American Society of Dental Anesthesiology (ADSA) is deeply saddened to report the passing of one of its most highly regarded members, Stuart E. Lieblich, DMD, after a 6-month battle with esophageal cancer. Dr Lieblich's extensive curriculum vitae places him among the brightest luminaries in many academic and clinical disciplines. As he was to receive the 2024 Heidbrink Award, the ADSA's highest honor, it was posthumously awarded on March 16, 2024, during the ADSA Annual Session in Las Vegas, NV.

Dr Lieblich was an accomplished surgeon from Avon, CT, spending more than 40 years in the private practice of oral and maxillofacial surgery. He was also a clinical professor and held faculty appointments at Connecticut Children's Medical Center and Weill Cornell School of Medicine. Dr Lieblich completed his predoctoral training at the University of Pennsylvania and his oral and maxillofacial residency at SUNY Downstate Medical Center in Brooklyn. He was a diplomate of the American Board of Oral and Maxillofacial Surgery (ABOMS) and the National Dental Board of Anesthesiology (NDBA). He was a past president of the ADSA (1999–2001) and the ABOMS (2009–2010). Dr Lieblich was a founding board member and a current director of the Dental Patient Safety Foundation and a current director of the NDBA. He published numerous articles and textbooks and was past section editor for the *Journal of Oral and Maxillofacial Surgery*. Dr Lieblich was a frequent contributor and peer reviewer for *Dental Anesthesia Online* and was a member of the American Dental Association Commission on Dental Accreditation.

Patient safety was Dr Lieblich's calling card. It is ironic that the countless people whose lives he may have indirectly saved are not even aware of his existence. But Stu persevered without hesitation or reward for he knew safety was the greatest legacy he could leave behind for others to follow. He was selfless, forever inclusive, and endlessly supportive of his countless friends and colleagues.

When you looked at Stu (and this was his secret sauce), it was impossible to tell if he was working or playing, and only in this sense can one appreciate the essence of his beautiful life—a true master in the art of living. Stu drew no distinction between labor and leisure, mind and body, or education and recreation. He hardly knew which was which. He simply pursued his vision of excellence as applied to whatever he was doing and left others to determine whether he was at work or play.

Dr Lieblich has bequeathed a significant donation to the ADSA Anesthesia Research Foundation (ARF). Memorial donations to the ADSA ARF in his name are welcome and will be used to advance patient safety.

Stu is survived by his wife, Dr Lisabeth Shlansky, and his 2 children, Brett and Margot. Someone like Stu comes around only once in a lifetime. May his memory be a blessing.

Submitted by:

Robert C. Bosack, DDS

Anesth Prog 71:106 2024 | DOI 10.2344/anpr-566035