A New Dental Specialty in Canada

The pathway leading to specialty recognition for dental anesthesiology here in North America (the US and Canada) has been long and winding. Canada was actually first to have dental anesthesiology formally recognized as a specialty, although that recognition did not extend nationally and was limited to only the province of Ontario. In 2004, the Royal College of Dental Surgeons of Ontario (RCDSO) identified dental anesthesiology as a potential specialty and circulated a proposal for recognition to various stakeholders. The RCDSO ultimately determined that recognition of dental anesthesiology was in the best interest of the public, approved the proposal, and forwarded it to the Ministry of Health and Long-Term Care. As a result, dental anesthesiology was formally recognized as a dental specialty in 2007 within the province of Ontario.

More recently, efforts to expand dental anesthesiology's recognition beyond Ontario have gained significant traction. In February 2023, the Canadian Dental Regulatory Authorities Federation sent notice to the Canadian Academy of Dental Anaesthesia (CADA) that their application for specialty recognition submitted in late 2021 had been approved. This decision has paved the way for specialty recognition to expand into other provinces. Canadian provinces and their dental regulatory authorities, similar to their US state and state dental board counterparts, are now tasked with determining how to implement their newly approved dental specialty by way of provincial legislation amendments. In short, each Canadian province decides for itself how to incorporate dental anesthesiology into its provincial laws and regulatory rules. Additional ongoing steps in solidifying dental anesthesiology's place as a recognized dental specialty in Canada include formalizing accreditation standards for training programs and board certification nationwide. This will involve expansion of the Commission on Dental Accreditation of Canada to include standards for specialty training in dental anesthesiology and working with the Royal College of Dentists of Canada (RCDC) to establish a National Dental Specialty Examination in anesthesia as part of the pathway for specialty recognition licensure. Canada requires all dentists who complete specialty training to pass their respective RCDC exam prior to registering (ie, advertising) as a recognized specialist. Although there is still much work to be done, hats off to the CADA leadership and the application cochairs for their success thus far!

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The roots of dental anesthesiology as a specialty of dentistry in the US trace back to 1953 and the establishment of the American Dental Society of Anesthesiology (ADSA), which created a preliminary specialty application that was ultimately abandoned in the '90s because of political pressures within the organization. The American Society of Dentist Anesthesiologists (ASDA) picked up the ADSA's torch and submitted 4 specialty recognition applications to the American Dental Association (ADA), all of which passed every step along the way minus the last—approval by the ADA House of Delegates (1994, 1997, 1999, 2012).[1] In response to mounting pressures, the ADA altered its specialty recognition process in 2017 by forming the National Commission on Recognition of Dental Specialties and Certifying Boards (NCRDSCB) and effectively bypassing the ADA House of Delegates. The ASDA subsequently submitted a fifth application in 2018, which was evaluated by the newly formed NCRDSCB and formally approved on March 11, 2019, cementing dental anesthesiology as the 10th specialty recognized by the ADA. The American Dental Board of Anesthesiology was recognized a year later as the new specialty's official certifying board.[2]

In the years following the ASDA's successful application, the ADA has added 2 more recognized dental specialties, orofacial pain (2020) and oral medicine (2020), along with their respective certifying boards, to bring the number of dental specialties in the US to 12. There are now a total of 10 recognized dental specialties in Canada following the recent announcement of dental anesthesiology as the newest to gain such recognition.

What does the future hold for dental specialty areas? Will we continue to see the development of novel emerging dental specialties? It seems certain that dentistry will continue to grow in response to diagnostic and treatment innovations and changes in patient needs and demands. In 1963 the ADA recognized 8 dental specialties, and it took 36 years and another 20 years for it to recognize the 9th and 10th, respectively (oral and maxillofacial radiology, 1999; dental anesthesiology, 2019). In contrast, medicine had 4 recognized medical specialties in 1932, but now the American Association of Medical Colleges lists over 135 medical specialties and subspecialties.[3] If dentistry continues to follow the pathway set by our medical counterparts, the development of new dental specialties and possibly even new subspecialties appears likely. Per the NCRDSCB[4] website, "specialties are recognized in those areas where advanced knowledge, skills and training are greater than those taught in a predoctoral dental education program

and are separate and unique from the other specialties to maintain or restore oral health." Areas of interest with strong potential at this time could include special needs dentistry, implantology, laser dentistry, sleep dentistry, and possibly even geriatric dentistry. Looking to the future, one could even foresee dental genetics being another possibility. Prospective subspecialties for dental anesthesiology could include fellowships in simulation or chronic pain. Perhaps oral and maxillofacial surgery will end up developing another formal subspecialty such as temporomandibular joint surgery, allowing dedication to that singular area of interest.

It is clear, regardless of where dentistry goes next, that the redesigned process for specialty recognition in dentistry established by the ADA and the NCRDSCB has enabled dentistry within the US to continue marching forward and help stave off stagnation. The same can be said for Canada as well as Japan and a few other countries around the world. The trend of new dental specialties may be worrying for some, especially those who feel such changes may encroach upon their practices. However, it is your editor's opinion that dentistry must continue to innovate, adapt, and respond to ever-changing internal and external pressures. Developing emerging areas of interest into formal dental specialties and subspecialties is simply a much-needed part of that critical process. Such change should be celebrated for what it is: another step forward for dentistry as a whole.

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The Physical Compatibility of Glycopyrrolate and Rocuronium

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Objective: Scientific evidence has rarely, if at all, been reported in the literature demonstrating analytical confirmation of the physical compatibility and stability of glycopyrrolate and rocuronium combined. The purpose of this experiment was to determine if glycopyrrolate and rocuronium are physically compatible.
Methods: Glycopyrrolate and rocuronium were combined in various containers, observed over a 60-minute period, and compared against positive and negative controls. Measured metrics included color change, precipitate formation, Tyndall beam test, turbidity, and pH. Statistical analyses were used to assess significance of data trends.
Results: The combination of glycopyrrolate and rocuronium did not result in any color change, precipitate formation, a positive Tyndall beam test, or a significantly positive turbidity and did not result in any significant change in pH, regardless of container.
Conclusion: Per the protocol used in this study, glycopyrrolate and rocuronium were determined to be physically compatible.

Key Words: Glycopyrrolate; Rocuronium; Intravenous administration; Drug interactions; Drug compatibility.

Intravenous (IV) administration of incompatible drugs can go unrecognized and may lead to adverse outcomes, as medications are often administered simultaneously through the same IV line. Notably, not all medications can be mixed due to incompatibility, resulting in negative consequences and even death in some extreme cases when administered concurrently.[1] There are 3 types of incompatibilities associated with IV administration: physical, chemical, and therapeutic.[2] An example of physical incompatibility occurs when thiopental and rocuronium are combined, resulting in the formation of a precipitate due to discordant differences in pH.[3]

Glycopyrrolate, an anticholinergic agent, and rocuronium, a nondepolarizing neuromuscular blocking agent, are 2 drugs commonly used during general anesthesia although usually not concurrently as glycopyrrolate is used during reversal of rocuronium-induced paralysis. However, coadministration may occur if the anticholinergic effects of glycopyrrolate are indicated independent of rocuronium administration. If the patient's physiologic state (eg, excessive salivation, bradycardia) independently warrants an anticholinergic like IV glycopyrrolate at the time rocuronium is administered, unintended mixture may occur. Although coadministration is possible, the current literature is devoid of any discussion regarding the compatibility and stability of glycopyrrolate and rocuronium combined.

The objective of this study was to determine if glycopyrrolate and rocuronium are physically compatible when combined for up to 60 minutes. While these drugs are not usually mixed in the same syringe, residual drug present in the IV tubing could be incompatible with another drug delivered into the same tubing.[2] If incompatibility is noted, future research should be performed to determine whether there are circumstances under which glycopyrrolate and rocuronium can be administered without concern for incompatibility (eg, flushing the IV tubing between drug administrations). If

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physical compatibility is determined, coadministration can be performed with greater confidence.

The impact of this study will result in an increased availability of pharmacologic information useful for patient care. If incompatibility of these 2 drugs is suspected, avoidance of coadministration is warranted until further research determines what effects may come from coadministration. Anesthesia providers will benefit by having increased awareness of drug compatibility, which in turn improves patient safety. This research also provides examples of basic evaluations clinical providers can use to help determine drug compatibility in various settings.

METHODS AND MATERIALS

Conditions for compatibility were simulated and solutions were assessed over a 60-minute observation period in the 3 visual metrics of color change, precipitate formation, and a Tyndall beam test, the optical metric of turbidity, and the chemical metric of pH. Tyndall beam observes the scattering of a light source through a liquid medium. The Tyndall beam test was performed using a laser from a laser pointer directed through the solution to assess colloid formation. Turbidity measures the relative clarity or "haziness" of a liquid. The turbidity meter was calibrated using 0 nephelometric turbidity units (NTU) and 100 NTU calibration solutions. The pH meter was calibrated using a 7.0 pH buffer. Physical incompatibility was defined a priori as color change, precipitate formation, a positive Tyndall test, a significant difference in turbidity from the negative control, or a significant change in pH at any time during the 60-minute observation period (times 0, 15, 30, 45, and 60 minutes). Furthermore, incompatibility for pH was defined as a significant difference in pH attributed to a different container.

Four samples of glycopyrrolate and rocuronium were tested individually in test tubes to determine baseline values for the 5 metrics. Rocuronium is known to be physically compatible with lidocaine, and 3 specimens of this combination in a test tube served as the negative control. Rocuronium is known to be physically incompatible with ketorolac, so 3 specimens of this combination in a test tube served as the positive control.[4] Compatibility testing of the combination of glycopyrrolate and rocuronium in test tubes, syringes, and IV tubing was performed 5 times each.

Distilled water was used to clean the pH meter and turbidimeter sample vial between test runs. Normal saline was used to flush the IV tubing prior to injection of glycopyrrolate and rocuronium at the Y-site.

Drug doses, volumes, and concentrations used during compatibility testing mirrored those frequently utilized in vivo.

- Glycopyrrolate 0.4 mg; 2 mL of 0.2 mg/mL solution
- Rocuronium 50 mg; 5 mL of 10 mg/mL solution
- Lidocaine 50 mg; 5 mL of 10 mg/mL solution
- Ketorolac 30 mg; 1 mL of 30 mg/mL solution

To ideally simulate clinical conditions, 3 types of containers were used: (1) a 17-mL glass test tube, (2) a 10-mL plastic medical syringe, and (3) IV tubing with a 14-mL priming volume previously flushed with normal saline. Glass test tubes provided adequate containers for the testing of all 5 metrics but are not used clinically. Because of the enclosed nature of IV tubing and the medical syringe, pH and turbidity final values were obtained only at the end of the experimental time rather than being assessed at periodic intervals.

Test Tube

The individual or correct pair of drugs was sterilely removed from a previously unopened glass vial using a blunt-tip needle syringe and injected into a clean glass test tube. At time 0 minutes, color change and precipitate formation were evaluated visually, while the Tyndall beam test was performed using a laser pointer. A clean pH meter was inserted into the glass test tube. The solution was then transferred from the test tube into a clean sample vial to assess turbidity. After completing all metric measurements at time 0, the solution was transferred back into the original glass test tube for subsequent testing at each of the following four 15-minute intervals.

Syringe

Rocuronium was sterilely drawn up into a medical syringe from a previously unopened vial. Using the same syringe already containing rocuronium, glycopyrrolate was drawn up from a previously unopened vial to create a combined solution. Color change, precipitate formation, and the Tyndall beam test were performed at time 0 and repeated at the four 15-minute intervals. At time 60 minutes, the solution was transferred to a glass test tube for pH measurement and then to a clean sample vial for turbidity measurement.

IV Tubing

Rocuronium was sterilely drawn up from a previously unopened vial and injected into the IV tubing injection

Table. Results at 60 Minutes.

Drug(s)	*Container*	*Study metrics*			
		Color change†	*Precipitate formation‡*	*Tyndall beam test†*	*Turbidity (mean NTU)*
Glycopyrrolate, n = 4	Test tube	No	No	–	1.65
Rocuronium, n = 4		No	No	–	0.06
Rocuronium/lidocaine, n = 3		No	No	–	0.03
Rocuronium/ketorolac, n = 3		Yes (white)[a]	No	+†	719.33§
Glycopyrrolate/rocuronium, n = 5		No	No	–	0.40
Glycopyrrolate/rocuronium, n = 5	IV tubing	No	No	–	0.06
Glycopyrrolate/rocuronium, n = 5	Syringe	No	No	–	0.45

† $P = .001$ (Fisher exact test).
‡ Responses were not tested for significance, as no differences were found.
§ $P < .001$ (Tukey-Kramer test).

port previously flushed and filled with normal saline. Glycopyrrolate was sterilely drawn up and injected into the same port. The total volume of the medications injected (~10 mL) did not exceed the volume of the length of tubing found after the injection port. At time 0 minutes, color change and precipitate formation were evaluated visually. Subsequent repeat testing was performed at times 15, 30, 45, and 60 minutes from time 0. At 60 minutes from time 0, the solution was transferred to a glass test tube for Tyndall beam testing and pH measurement and then transferred to a clean sample vial for turbidity measurement.

Statistical Analysis

Separately, the results of color change, precipitate formation, and Tyndall beam test at 60 minutes were analyzed using Fisher exact test, followed by pairwise comparisons of the positive control (rocuronium/ketorolac) to each of the 3 glycopyrrolate and rocuronium combination test groups and the negative control (rocuronium/lidocaine). Turbidity values at 60 minutes were analyzed using a 1-way analysis of variance (ANOVA) over each of the test groups, with pairwise comparisons tested using the Tukey-Kramer method. The entire pH data set was first analyzed by a repeated-measures ANOVA with time as the within-subject factor. Then the mean pH of the test groups with the glycopyrrolate and rocuronium combination were compared for significant differences between all times and between all containers.

RESULTS

The positive control (rocuronium/ketorolac) produced a color change from clear to white upon mixing that persisted for all measured time intervals (time 0-60 minutes). However, there was no precipitate noted at any time during the experiment for this combination. A positive Tyndall beam test was also noted at all time intervals. The turbidity measurements for the positive control (mean 719.33 NTU) were significantly different at all time intervals during the experiment when compared with the other drugs and drug combinations ($P < .001$). There was no significant change in pH from time 0 to time 60 minutes within the positive control group (Table).

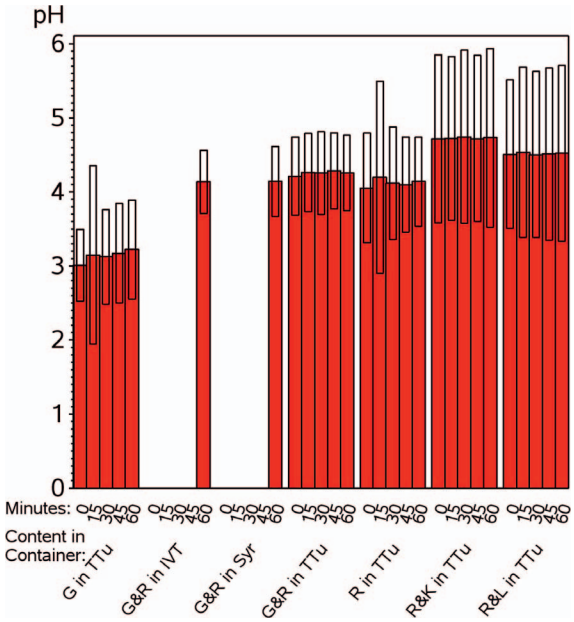
The negative control (rocuronium/lidocaine) produced no color change or precipitate formation, a negative Tyndall beam test, and a mean turbidity of 0.03 NTU that lacked statistical significance. The pH of the negative control did not significantly change throughout the experiment (Table).

The remaining individual drug and drug combinations did not produce color changes or precipitate formation in any of the containers at any time from 0 to 60 minutes. The lack of color changes and negative Tyndall beam test results were all significantly different compared with the positive control ($P < .001$). The mean turbidity measurements for the remaining individual drugs and drug combinations were all <1.66 NTU and found to be statistically significant when compared with the positive control ($P < .001$; Table). No significant pH changes were measured for any individual drug or drug combinations regardless of container type (Figure).

DISCUSSION

Drug incompatibility can be divided into 3 categories: physical, chemical, or therapeutic. Physical incompatibility refers to the metrics used within this study such as color change, turbidity, or precipitate formation.

Figure. pH values over time.



Mean and 95% confidence limits of pH values of each test group over the times tested. G, glycopyrrolate; R, rocuronium; G&R, glycopyrrolate and rocuronium; R&K, rocuronium and ketorolac; R&L, rocuronium and lidocaine; TTu, test tube; IVT, intravenous tubing; Syr, syringe.

Chemical incompatibilities are typically not visible and lead to degradation, formation of harmful by-products, or loss of drug potency.[5] Therapeutic incompatibility refers to a change in a drug's effectiveness as it pertains to its original therapeutic function due to the concurrent use or mixing with another drug.

The combination of rocuronium and glycopyrrolate demonstrated no change in color, positive Tyndall beam test, turbidity, or pH. As expected, there was an obvious color change, positive Tyndall beam test, and increased turbidity for the positive control (rocuronium/ketorolac). The negative control (rocuronium/lidocaine) produced no color change, no precipitate, a negative Tyndall beam test, and negligible turbidity. However, because of the sample size, there was no statistically significant difference detected between the positive and negative controls when pairwise comparisons were made. While no statistical difference was detected, the negative Tyndall beam test and lack of color change results that came from combining rocuronium and glycopyrrolate in the test tube were the same as the negative control, suggesting their physical compatibility.

The greatest pH change observed throughout the study was a change of 0.40 in a test tube sample. This fell beneath Hanifah's described change in pH of 0.5 required for incompatibility.[6] Furthermore, no significant pH changes were observed in any of the experimental groups with glycopyrrolate and rocuronium over the 60-minute period regardless of container, demonstrating the stability of glycopyrrolate and rocuronium.

The combination of rocuronium and ketorolac produced an extremely cloudy solution, resulting in a mean turbidity measurement >600 NTU. No other drug or drug combination produced a mean turbidity measurement >2 NTU, suggesting the combination of rocuronium and glycopyrrolate was physically compatible. No precipitate formation was noted during the experiment; therefore, no statistical analysis was performed regarding precipitate formation.

The physical compatibility of glycopyrrolate and rocuronium was previously untested, and scientific evidence of their compatibility will increase confidence of practitioners should coadministration occur in the clinical environment. No universally accepted protocol has been established for experimental design to test for drug compatibility; however, many studies use the 5 metrics employed in this study.[7] While glycopyrrolate and rocuronium appear physically compatible when combined in vitro, they may be incompatible in vivo. Testing to further evaluate physiochemical compatibility using high-performance liquid chromatography for example may be necessary to strengthen the results of this study.[8]

One weakness of this study was that the researchers were not blinded to the experiment, which could have created unintentional bias. In addition, only a total 5 trials were run for the experiment, which may have caused the study to have been underpowered. More trials could have been run to increase confidence in the data, making the study more robust.

CONCLUSION

Medications administered simultaneously must be physically compatible to avoid adverse drug interactions and reactions. The combination of glycopyrrolate and rocuronium produced no significant differences in any of the 5 metrics measured from baseline to 60 minutes. The data from this study suggest the physical compatibility of glycopyrrolate and rocuronium, 2 drugs that have potential for coadministration during anesthesia. Practitioners can now have more confidence should simultaneous administration of glycopyrrolate and rocuronium occur in the clinical environment.

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Involvement of α- and β-Adrenergic Receptors in Skeletal Muscle Blood Flow Changes During Hyper-/Hypocapnia in Anesthetized Rabbits

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Objective: This study investigated the involvement of α_1- and β_2-adrenergic receptors in skeletal muscle blood flow changes during variations in $ETCO_2$.

Methods: Forty Japanese White rabbits anesthetized with isoflurane were randomly allocated to 1 of 5 groups: phentolamine, metaproterenol, phenylephrine, butoxamine, and atropine. Heart rate (HR), systolic blood pressure (SBP), common carotid artery blood flow (CCBF), masseter muscle tissue blood flow (MBF), and quadriceps muscle tissue blood flow (QBF) were recorded and analyzed at 3 periods: (1) baseline, (2) during hypercapnia (phentolamine and metaproterenol groups) or hypocapnia (phenylephrine, butoxamine, and atropine groups), and (3) during or after receiving vasoactive agents.

Results: MBF and QBF decreased during hypercapnia. The decrease in MBF was smaller than that in QBF. SBP and CCBF increased, while HR decreased. Both MBF and QBF recovered to their baseline levels after phentolamine administration. MBF became greater than its baseline level, while QBF did not fully recover after metaproterenol administration. MBF and QBF increased during hypocapnia. The increase rate in MBF was larger than that in QBF. HR, SBP, and CCBF did not change. Both MBF and QBF decreased to ~90% to 95% of their baseline levels after phenylephrine or butoxamine administration. Atropine showed no effects on MBF and QBF.

Conclusion: These results suggest the skeletal muscle blood flow changes observed during hypercapnia and hypocapnia may mainly involve α_1-adrenergic but not β_2-adrenergic receptor activity.

Key Words: Adrenergic receptor; Hypercapnia; Hypocapnia; Skeletal muscle blood flow.

Skeletal muscle blood flow is regulated by various mechanisms.[1,2] In general, nitric oxide, carbon dioxide, lactate, adenosine, adenosine triphosphate, and serotonin have vasodilatory effects, while endothelin and serotonin have vasoconstrictive effects. Although carbon dioxide has direct vasodilatory effects, an elevation in $PaCO_2$ also enhances sympathetic nervous system (SNS) activity, which leads to vasoconstriction with a net result of reduced blood flow at the skeletal muscle tissue level.[1] In anesthetized rabbits, increases in end-tidal carbon dioxide ($ETCO_2$) tension reduced skeletal muscle blood flow while decreases in $ETCO_2$ resulted in increased skeletal muscle blood flow.[3–5] Because $ETCO_2$ values nearly equal $PaCO_2$ values,[6] it can be considered that decreases in skeletal muscle blood flow induced by $ETCO_2$ elevation are attributable to an enhancement of SNS activity rather than direct vasodilatory effects of carbon dioxide.

Constriction of skeletal muscle vessels induced by SNS activation is more profound in fast-twitch muscles than slow-twitch muscles.[7] Meanwhile, although the densities of vascular α1- and β-adrenergic receptors are similar in slow- and fast-twitch muscles, resistance

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arterioles are far more numerous in slow-twitch muscles.[8,9] Accordingly, it has been speculated that the differences in vascular regulation in fast- and slow-twitch muscles are attributable to the differences in vascular innervation or SNS activity and in the densities or functional reserves of vascular α-adrenergic receptors.[10]

If changes in skeletal muscle blood flow induced by variations in $ETCO_2$ arise primarily from altered SNS activity, then, as an example, the increase in skeletal muscle blood flow that occurs with decreased $ETCO_2$ may mainly involve the inhibition of α_1-adrenergic receptors rather than the activation of β_2-adrenergic receptors. Therefore, the purpose of this study was to investigate the activity of which adrenergic receptors, α_1 or β_2, is primarily involved in skeletal muscle blood flow changes during variations in $ETCO_2$. In this study, we targeted 2 skeletal muscles: the masseter muscle which predominantly has slow-twitch fibers, and the quadriceps muscle which predominantly has fast-twitch fibers.[11,12]

METHODS

Forty Japanese White rabbits (Sankyo Labo) weighing ~2.5 kg were used in this study. All animals received humane care in accordance with the National Institute of Health guidelines for the care and use of laboratory animals and The Guidelines for the Treatment of Experimental Animals of Tokyo Dental College.[13] The animals were randomly allocated evenly (n = 8) into 1 of 5 groups: (1) phentolamine, (2) metaproterenol, (3) phenylephrine, (4) butoxamine, and (5) atropine groups.

Anesthesia and Experimental Preparation

General anesthesia was induced with isoflurane (4%) and oxygen delivered using a mask. Before skin incisions for each of the experimental procedures, 2% lidocaine (0.5 mL) was injected into the surgical field. A #20 Fr, noncuffed, pediatric tracheal tube 10 cm in length[6] was inserted into the trachea through a tracheostomy. The left auricular marginal vein and right femoral artery were cannulated with 22- and 20-gauge indwelling catheters, respectively. After intravenous (IV) acetated Ringer's solution was started at 10 mL/kg/h, the animals were paralyzed with a rocuronium infusion (14 μg/kg/min).[14]

Animals were ventilated with a tidal volume of 35 to 50 mL and a respiratory rate of 35 to 45 breaths per minute to maintain the $ETCO_2$ at 30 mm Hg. However, supplemental CO_2 was added to the inhaled oxygen to maintain the study's baseline $ETCO_2$ of 40 mm Hg. To produce hypercapnic conditions, additional CO_2 was mixed in to maintain $ETCO_2$ at 60 mm Hg. To produce hypocapnic conditions, supplemental CO_2 was stopped, and $ETCO_2$ was maintained at 30 mm Hg. Thus, hypercapnic and hypocapnic conditions were achieved without any changes in the ventilator settings. Exhaled gas was sampled at the connector between a tracheal tube and an anesthesia circuit. $ETCO_2$ and isoflurane concentrations were continuously monitored using an anesthetic gas monitor (Capnomac Ultima, Datex). Femoral artery blood pressure was continuously monitored with a pressure transducer (P231D, Gould).

After the skin incision along the left lower margins of the mandible without local anesthesia, the fascia of the left masseter muscle was detached to expose muscle tissue. A needle probe of the hydrogen clearance tissue blood flowmeter (UHE-100, Unique Medical) was inserted 3-mm deep into the anterior portion of the left masseter muscle to measure masseter muscle tissue blood flow (MBF). Then, after a skin incision was made along the left femoral region without local anesthesia, the left quadriceps muscle was exposed. A needle probe of the hydrogen clearance tissue blood flowmeter was inserted 5-mm deep into the center of the left quadriceps muscle to measure quadriceps muscle tissue blood flow (QBF).

After completion of experimental preparations, isoflurane was reduced to achieve an end-tidal concentration of 1.0% (0.5 minimum alveolar concentration in rabbits)[15] and maintained at that level for more than 60 minutes to stabilize hemodynamic and respiratory variables. A heating lamp was used to maintain body temperature at ~39.0 °C.

Measurements

Heart rate (HR) was recorded by a tachograph triggered by blood pressure wave. Common carotid artery blood flow (CCBF) was measured with an ultrasound flowmeter (T108, Transonic). A flow probe (type 3SB) was applied to the isolated left common carotid artery. HR, systolic blood pressure (SBP), and CCBF were continuously recorded using a tachometer (HRM-100, Unique Medical). MBF and QBF were analyzed using a data collection analysis system (UCO, Unique Medical).

Measurements were performed at 3 periods: (1) baseline, (2) hypercapnia/hypocapnia, and (3) during or after receiving vasoactive agents. After baseline, $ETCO_2$ was changed to 30 or 60 mm Hg and maintained

Table 1. Hemodynamic and Tissue Blood Flow Changes During Hypercapnia ± Phentolamine.*

	Baseline	*Hypercapnia*	*Phentolamine*
HR, bpm	300.6 ± 17.0	286.9 ± 16.0†	297.5 ± 18.5‡
SBP, mm Hg	131.9 ± 10.3	140.6 ± 11.5†	125.6 ± 8.6‡
CCBF, mL/min	31.9 ± 6.1	37.1 ± 7.0†	33.5 ± 6.1‡
MBF, mL/min/100 g	45.4 ± 9.0	33.2 ± 6.7†	46.9 ± 7.4‡
QBF, mL/min/100 g	62.2 ± 7.2	37.9 ± 8.2†	63.1 ± 8.5‡

* Mean ± SD. CCBF, common carotid artery blood flow; HR, heart rate; MBF, masseter muscle tissue blood flow; QBF, quadriceps muscle tissue blood flow; SBP, systolic blood pressure.
† $P < .05$ versus baseline.
‡ $P < .05$ versus hypercapnia.

at this level for 15 minutes, and measurements were repeated for hypercapnia/hypocapnia. Thereafter, rabbits received 1 of 5 vasoactive IV agents.

During hypercapnic conditions, rabbits received phentolamine (an α_1- and α_2-receptor antagonist) or metaproterenol (a β_2-receptor agonist). In the phentolamine group, the third measurement was performed 3 minutes after an IV bolus of phentolamine (100 μg/kg; Regitine, Novartis Pharma). In the metaproterenol group, the third measurement was performed 15 minutes after starting an IV infusion of metaproterenol (0.2 μg/kg/min; metaproterenol sulfate, FUJIFILM Wako Pure Chemical Corporation).

During hypocapnic conditions, rabbits received phenylephrine (an α_1-receptor agonist), butoxamine (a β_2-receptor antagonist), or atropine (a muscarinic receptor antagonist). In the phenylephrine group, the third measurement was performed 15 minutes after starting an IV infusion of phenylephrine (0.1 μg/kg/min; Neo-Synesin Kowa, Kowa) infusion. In the butoxamine group, the third measurement was performed 15 minutes after starting an IV infusion butoxamine (750 μg/kg/min; butoxamine hydrochloride, Sigma-Aldrich-Merck) infusion. In the atropine group, the third measurement was performed 3 minutes after an IV bolus of atropine (100 μg/kg; Atropine Sulfate, Nipro ES Pharma). Finally, after the metaproterenol, phenylephrine, or butoxamine infusions were stopped and the $ETCO_2$ levels recovered to 40 mm Hg, rabbits were kept at rest for more than 30 minutes. The experiments were concluded after the observed variables recovered to baseline levels.

Statistical Analysis

Sample size was determined by an a priori power analysis (α error = .05, β error = .20, effect size = 1.2) using two masseter muscle tissue blood flow measurements at $ETCO_2$ levels of 30 mm Hg (33.3 ± 2.8 mL/min/100 g) and 40 mm Hg (27.4 ± 4.0 mL/min/100 g) from our previous study.[3] A total of at least 8 rabbits per group (N = 40) were calculated as the required sample size.

All data were expressed as mean ± standard deviation. One-way repeated-measures analysis of variance (ANOVA) using a linear mixed models was applied to compare values at baseline, hyper-/hypocapnia, and after IV agent administration for HR, SBP, and CCBF. Two-way repeated-measures ANOVA using a linear mixed model with (1) MBF/QBF and (2) values at baseline, hypercapnia/hypocapnia, and after IV agent administration as 2 variable factors was performed. In the case of a significant interaction, 1-way ANOVA was performed considering all groups as independent,[16] and, if significant, multiple comparisons of all groups were performed using the Tukey method. SPSS version 28.0.0.0 (IBM Japan) was used. Statistical significance was determined using $P < .05$.

RESULTS

In all 5 groups, 2-way repeated-measures ANOVA showed a significant interaction between 2 muscles and 3 observed periods.

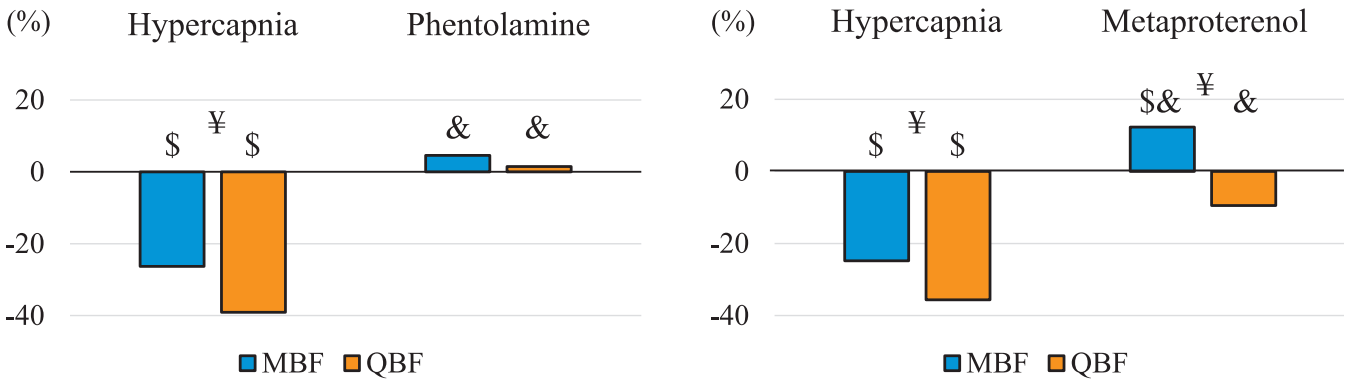
Hypercapnia Groups

Compared with baseline, both the phentolamine and metaproterenol groups had decreases in MBF and QBF during hypercapnia ($P < .05$). Decreases were larger in QBF than in MBF. SBP and CCBF increased, and HR decreased.

In the phentolamine group, all of these variables essentially recovered to baseline after phentolamine administration (Table 1, Figure 1).

In the metaproterenol group, both MBF and QBF increased relative to hypercapnia ($P < .05$), and although MBF increased beyond baseline ($P < .05$), QBF did not fully recover to baseline after metaproter-

Figure 1. Mean changes in muscle blood flow during hypercapnia and after phentolamine or metaproterenol administration.



MBF and QBF decreased during hypercapnia, while the decrease in MBF was smaller than that in QBF. Both MBF and QBF recovered to their baseline levels after phentolamine administration. In contrast, although MBF became greater than its baseline level, QBF did not fully recover to its baseline level after phentolamine administration. Data are expressed as the percentage change in respective baseline values. MBF, masseter muscle tissue blood flow; QBF, quadriceps muscle tissue blood flow. [a] $P < .05$ versus baseline; [b] $P < .05$ versus hypercapnia; [c] $P < .05$ between the 2 groups.

enol administration ($P < .05$; Table 2, Figure 1). HR remained decreased compared with baseline, SBP recovered to baseline, and CCBF increased as compared with baseline and hypercapnia ($P < .05$).

Hypocapnia Groups

As compared with baseline, the phenylephrine, butoxamine, and atropine groups had increases in MBF and QBF during hypocapnia ($P < .05$). Increases were greater in MBF than in QBF. On the other hand, there were no significant changes in HR, SBP, or CCBF.

In the phenylephrine group, MBF, QBF, and HR decreased after phenylephrine administration relative to baseline and hypocapnia ($P < .05$; Table 3, Figure 2).

Similar results were noted in the butoxamine group as both MBF and QBF decreased after butoxamine administration relative to baseline and hypocapnia ($P < .05$; Table 4, Figure 2).

In the atropine group, MBF and QBF showed no significant changes relative to hypocapnia but remained increased relative to baseline after atropine administration ($P < .05$; Table 5).

DISCUSSION

Results of this study demonstrated that MBF and QBF decreased during hypercapnia, while the decrease rate in MBF was smaller than that in QBF. During hypercarbic conditions, an increase in SNS tone occurs, which produces increased α- and β-adrenergic receptor activity; however, the overall decrease in MBF and QBF indicates constriction of the skeletal muscle blood vessels. General mechanisms of vasoconstriction include increased α_1-receptor activity or suppressed β_2-receptor activity. In fact, in the present study, the vasoconstriction that occurred during hypercarbia was corrected by suppressing α-receptor activity with phentolamine (an α blocker) or increasing β_2-receptor activity with meta-

Table 2. Hemodynamic and Tissue Blood Flow Changes During Hypercapnia ± Metaproterenol.*

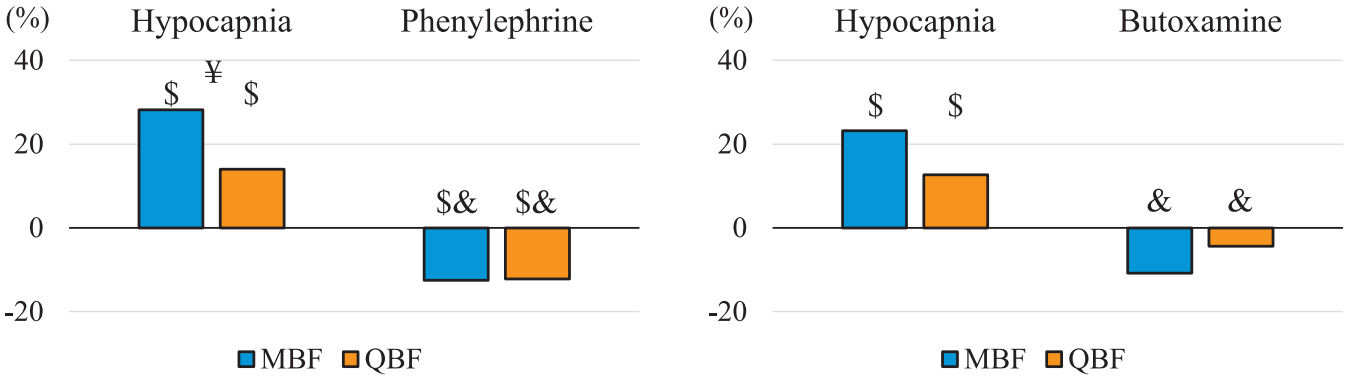
	Baseline	*Hypercapnia*	*Metaproterenol*
HR, bpm	301.3 ± 15.5	291.3 ± 15.8†	293.1 ± 15.6†
SBP, mm Hg	132.5 ± 17.9	141.3 ± 17.9†	135.6 ± 16.2‡
CCBF, mL/min	30.6 ± 7.0	37.1 ± 7.5†	42.0 ± 9.4†,‡
MBF, mL/min/100 g	42.0 ± 6.5	31.5 ± 5.7†	47.0 ± 6.9†,‡
QBF, mL/min/100 g	63.5 ± 8.4	41.1 ± 7.7†	57.4 ± 9.0†,‡

* Mean ± SD. CCBF, common carotid artery blood flow; HR, heart rate; MBF, masseter muscle tissue blood flow; QBF, quadriceps muscle tissue blood flow; SBP, systolic blood pressure.

†$P < .05$ versus baseline.

‡ $P < .05$ versus hypercapnia.

Figure 2. Mean changes in muscle blood flow during hypocapnia and after phenylephrine or butoxamine administration.



MBF and QBF increased during hypocapnia, while the increase in MBF was larger than that in QBF. Both MBF and QBF decreased to about 90% to 95% of their baseline levels after phenylephrine or butoxamine administration. Data are expressed as the percentage change in respective baseline values. MBF, masseter muscle tissue blood flow; QBF, quadriceps muscle tissue blood flow. [a] $P < .05$ versus baseline; [d] $P < .05$ versus hypocapnia; [c] $P < .05$ between the 2 groups.

Table 3. Hemodynamic and Tissue Blood Flow Changes During Hypocapnia ± Phenylephrine.*

	Baseline	*Hypocapnia*	*Phenylephrine*
HR, bpm	301.3 ± 16.4	295.0 ± 14.1	282.5 ± 12.8†,‡
SBP, mm Hg	125.6 ± 8.6	125.0 ± 8.0	128.4 ± 9.2
CCBF, mL/min	30.5 ± 8.8	32.1 ± 8.7	28.3 ± 7.1
MBF, mL/min/100 g	42.0 ± 7.7	53.2 ± 6.2 [a]	36.5 ± 7.0†,‡
QBF, mL/min/100 g	57.3 ± 4.5	65.3 ± 6.3 [a]	50.4 ± 7.5†,‡

* Mean ± SD. CCBF, common carotid artery blood flow; HR, heart rate; MBF, masseter muscle tissue blood flow; QBF, quadriceps muscle tissue blood flow; SBP, systolic blood pressure.
† $P < .05$ versus baseline.
‡ $P < .05$ versus hypocapnia.

Table 4. Hemodynamic and Tissue Blood Flow Changes During Hypocapnia ± Butoxamine.*

	Baseline	*Hypocapnia*	*Butoxamine*
HR, bpm	288.8 ± 26.4	286.9 ± 22.5	281.3 ± 19.6
SBP, mm Hg	131.3 ± 15.5	131.3 ± 15.5	130.0 ± 13.6
CCBF, mL/min	30.1 ± 6.7	29.1 ± 6.2	28.8 ± 4.9
MBF, mL/min/100 g	43.3 ± 5.2	53.4 ± 7.5†	39.0 ± 9.8†,‡
QBF, mL/min/100 g	60.9 ± 5.0	68.5 ± 4.7†	58.0 ± 3.7†,‡

* Mean ± SD. CCBF, common carotid artery blood flow; HR, heart rate; MBF, masseter muscle tissue blood flow; QBF, quadriceps muscle tissue blood flow; SBP, systolic blood pressure.
† $P < .05$ versus baseline.
‡ $P < .05$ versus hypocapnia.

Table 5. Hemodynamic and Tissue Blood Flow Changes During Hypocapnia ± Atropine.*

	Baseline	*Hypocapnia*	*Atropine*
HR, bpm	287.5 ± 23.8	285.6 ± 19.2	286.9 ± 23.1
SBP, mm Hg	128.8 ± 13.9	128.8 ± 14.6	128.8 ± 13.0
CCBF, mL/min	29.8 ± 7.0	29.1 ± 6.2	29.1 ± 5.8
MBF, mL/min/100 g	43.0 ± 5.5	53.0 ± 7.0†	52.3 ± 7.4†
QBF, mL/min/100 g	60.3 ± 6.0	68.6 ± 4.6†	68.0 ± 5.2†

* Mean ± SD. CCBF, common carotid artery blood flow; HR, heart rate; MBF, masseter muscle tissue blood flow; QBF, quadriceps muscle tissue blood flow; SBP, systolic blood pressure.
† $P < .05$ versus baseline.

proterenol (a β_2 agonist). However, since SNS tone increases during hypercarbia and both α- and β-receptor activity increases as a result, vasoconstriction by suppressing β_2-receptor activity is not possible. Thus, results of this study suggest that the decreased skeletal muscle blood flow during hypercarbia is mainly attributable to α_1-adrenergic receptor stimulation via increased SNS activity.

In addition, it has been reported that the vasoconstrictor effects of lumbar sympathetic stimulation on the resistance vessels of the soleus muscle, a slow-twitch muscle, were much smaller than seen in fast-twitch muscles.[17] It has also been reported that SNS-mediated vasoconstriction was greater in fast-twitch muscles than in slow-twitch muscles,[18] and the same results were obtained in this study. Both MBF and QBF recovered to baseline after administering phentolamine (an α blocker). In contrast, although MBF increased beyond baseline and CCBF also increased, QBF failed to fully recover to baseline after metaproterenol (a β_2 agonist) administration. When an α blocker was applied, the vasoconstrictive effects seemed to be reversed, suggesting that α-adrenergic receptor activity was primarily responsible for the vasoconstriction seen during hypercarbia. In addition, vasodilation by the β_2 agonist was shown to correct the decreased skeletal muscle blood flow due to increased α-adrenergic receptor activity. Since MBF increased beyond baseline level and QBF failed to fully recover to baseline after metaproterenol administration, there may be an increased distribution of β_2-adrenergic receptors in the masseter than in the quadriceps vasculature.

Contrary to hypercarbia, MBF and QBF increased during hypocarbia, indicating dilation of the skeletal muscle vessels. General mechanisms of vasodilation include suppressed α_1-adrenergic receptor activity or increased β_2-adrenergic receptor activity; however, SNS tone is decreased during hypocarbia, so vasodilation by increased β_2-adrenergic receptor activity is not possible. Therefore, the increase in skeletal muscle blood flow during hypocarbia is likely attributed to suppressed SNS tone, leading to decreased α_1-adrenergic receptor activity. The results of this study also indicate that both phenylephrine (an α_1-adrenoceptor agonist) and butoxamine (a β_2 blocker) inhibit the increase in skeletal muscle blood flow during hypocarbia by α_1-mediated vasoconstriction and by inhibiting β2-mediated vasodilation.

On the other hand, it has been reported that sympathetic denervation resulted in a 2.7-fold increase in blood flow to the soleus muscle (fast-twitch muscle) and an 8.7-fold increase in flow to the white portion of the gastrocnemius muscle (slow-twitch muscle).[18] In addition, α blockade by phentolamine caused increased blood flow in fast-twitch muscles, whereas muscles composed of greater than 20% slow-twitch fibers showed no effect.[19] Thus, the increases in skeletal muscle blood flow during hypocarbia observed in this study cannot be fully explained by only suppressed α_1-adrenergic receptor activity due to decreased SNS tone. One possible mechanism is the redistribution of tissue blood flow in oral and maxillofacial tissues. It is suggested that tissue blood flow in the mandibular bone marrow redistributes to the masseter muscle during hypocarbia and remifentanil infusion. This mechanism may explain the results obtained in this study.[3–5,20] In addition, the involvement of β_2-receptors in vasodilatation observed during low-dose epinephrine infusion (0.01 μg/kg/min)[21] and sympathetic cholinergic fibers is negligible.

In this study, the masseter muscle and the quadriceps muscle were utilized. Skeletal muscles consist of slow- and fast-twitch fibers, and 50% to 90% of the total muscle fibers in the anterior and deep portion of the masseter have slow-twitch properties.[11] In contrast, 90% of the total muscle fibers in the quadriceps muscle have fast-twitch properties.[12] Thus, we believe that the masseter and quadriceps muscles would be good indicators for the slow- and fast-twitch muscles, respectively. Phentolamine, a nonselective α-adrenergic receptor antagonist, was used in this study due to the lack of an available injectable, selective α1-adrenergic receptor antagonist in Japan. Therefore, the involvement of α_2-adrenergic receptors during vasoconstriction and vasodilatation could not be ruled out. In fact, it is reported that SNS control of blood flow in muscle appeared to be mediated through postsynaptic α_1- and α_2-adrenergic receptors located on the vascular smooth muscle.[18]

In this study, anesthesia was maintained with 1.0% isoflurane throughout the experiment. This concentration was equal to 0.5 minimum alveolar concentration (MAC) of isoflurane in the rabbit.[15] No major differences in tissue blood flow were observed during anesthesia with isoflurane, sevoflurane, or desflurane at a 0.5 MAC level.[22] Therefore, the effects of vasodilatation induced by isoflurane use in this study should be minimal.

CONCLUSION

The findings from this study suggest that α_1-receptor activity but not β_2-receptor activity may be mainly involved in the changes in skeletal muscle blood flow during hypercapnia and hypocapnia. Redistribution mechanisms in oral and maxillofacial tissues may also be associated with MBF changes.

DISCLOSURE

None of the authors have any relevant financial relationship(s) with a commercial interest.

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Anesthetic Management Using Remimazolam in a Hemodialysis Patient

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Remimazolam, an ultra-short-acting benzodiazepine, is a new intravenous anesthetic used for sedation and general anesthesia. Because remimazolam is primarily metabolized by carboxylesterases in the liver and other tissues including the lung and has metabolites with little or no bioactivity, its anesthetic effect is not significantly influenced by renal dysfunction. Therefore, remimazolam may be considered an appropriate agent for hemodialysis patients and may have added benefits beyond midazolam and propofol. Remimazolam has also been suggested to cause less cardiac depression than propofol. This case report presents an 82-year-old female hemodialysis patient with chronic heart failure who underwent partial glossectomy for squamous cell carcinoma of the tongue under general anesthesia with remimazolam and remifentanil. Hemodynamic control was stable during the anesthetic, which was safely completed without any adverse events and resulted in a rapid, clear emergence without flumazenil. Remimazolam and remifentanil may be appropriate as first-line general anesthetic agents for hemodialysis patients with heart failure.

Key Words: Remimazolam; Anesthetic management; General anesthesia; Hemodialysis; Heart failure; Oral surgery; Remifentanil.

INTRODUCTION

Remimazolam, an ultra-short-acting benzodiazepine, was developed as a new intravenous (IV) agent for general anesthesia and sedation. It is rapidly metabolized by carboxylesterases (CES) in the liver and other tissues including the lung. Combined with its rapid onset, remimazolam's unique metabolism facilitates easy and accurate titration, quick recovery, and few adverse events.[1] In recent clinical trials, the pharmacokinetics and pharmacodynamics, efficacy, and safety of remimazolam were evaluated in patients undergoing general anesthesia, demonstrating its usefulness as an IV anesthetic.[2–4] Remimazolam was approved in Japan for use via continuous IV infusion for general anesthesia in adult patients in 2020.[5]

Because remimazolam's metabolism is independent of organ (i.e., renal) function, it may be considered an appropriate agent for the anesthetic management of hemodialysis patients and may have added benefits beyond other IV anesthetics like midazolam and propofol. However, to our knowledge, there has been no report on general anesthesia using remimazolam in hemodialysis patients with heart failure. This case report presents the successful use of remimazolam for general anesthesia in a hemodialysis patient with a history of chronic heart failure undergoing oral surgery. Written informed consent was obtained from the patient for this report.

CASE PRESENTATION

An 82-year-old female (height, 147 cm; weight, 42.9 kg; body mass index, 19.85 kg/m^2) was scheduled to undergo partial glossectomy for T1N0M0 squamous cell carcinoma (SCC) of the tongue. The patient had hypertension, history of stroke, and end-stage kidney disease for which she had been undergoing hemodialysis for 4 years. In addition, she had a history of acute heart

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Table 1. Patient's Echocardiographic Data.

	Patient's values	*Abnormal cutoff values*[6]
Left ventricular ejection fraction, %	70	<50
Septal e′, cm/s	5.0*	<7.0
Lateral e′, cm/s	7.7*	<10.0
Septal E/e′	26.4*	>15.0
Mitral regurgitation (MR)	mild	
Aortic regurgitation (AR)	mild	
Tricuspid regurgitation (TR)	mild	
Peak velocity of TR, m/s	2.7	>2.8
TR pressure gradient (TRPG), mm Hg	30	>40

Echocardiography demonstrated preserved left ventricular function and diastolic dysfunction, although there were no congestive findings. The patient appeared to have had chronic diastolic heart failure with preserved ejection fraction. Her echocardiographic data had remained stable for over 1 year.

* Abnormal values.

failure 11 years earlier and a diagnosis of atrial fibrillation for which she was being followed by a cardiologist. Her regular medications were amlodipine (2.5 mg/day), diltiazem (200 mg/day), clopidogrel, ascorbic acid/pantothenic acid combination tablets, *Enterococcus faecium*/*Clostridium butyricum*/*Bacillus subtilis* combination powder, lanthanum carbonate, sennoside A+B, and nalfurafine.

An electrocardiogram and anterior-posterior chest radiograph obtained during preoperative examination ~1 week before the scheduled surgery showed atrial fibrillation and cardiomegaly, and her brain natriuretic peptide (BNP) level at that time was 882 pg/mL (normal <18.4 pg/mL). In addition to her BNP, we also performed echocardiography to assess her known heart failure. Echocardiography revealed her left ventricular function was preserved with an ejection fraction of 70% and diastolic dysfunction although there were no congestive findings. Other significant findings on echocardiography are presented in Table 1. Based on the patient's BNP level and echocardiography results, she appeared to have chronic diastolic heart failure. The echocardiography data had been maintained for a year with no significant changes, and she demonstrated no signs or overt symptoms of decompensation. Furthermore, the cardiologist judged that her heart function was stable and that surgery was feasible, thus we decided to proceed with the operation.

Surgery was scheduled for the day following one of her regular hemodialysis sessions. All her regular medications were continued preoperatively, and adherence to standard fasting guidelines were confirmed. In addition to the standard anesthetic monitoring, an arterial line was inserted into her right radial artery before induction of general anesthesia. The patient's blood pressure (BP) and heart rate (HR) before induction were 167/69 mm Hg and 65 beats per minute (bpm), respectively.

General anesthesia was induced with continuous IV infusions of remimazolam at 6 mg/kg/h and remifentanil at 0.25 μg/kg/min along with 100% oxygen (6 L/min) via facemask. After the patient lost consciousness, the remimazolam infusion rate was decreased to 1 mg/kg/h. Neuromuscular blockade was performed with an IV bolus of rocuronium (25 mg), and nasotracheal intubation was successfully performed without difficulty. Before tracheal intubation, the patient's lowest BP and HR were 118/55 mm Hg and 62 bpm, respectively. There were no significant hemodynamic changes during induction or after tracheal intubation. General anesthesia was maintained with continuous infusions of remimazolam at 0.3 to 0.4 mg/kg/h and remifentanil at 0.05 to 0.3 μg/kg/min along with oxygen/air (0.7/2.3 L/min). Ephedrine was administered via 4 mg boluses to raise the patient's BP twice, after induction and during surgery. Prior to the start of the surgical procedure, 4 mL of 2% lidocaine with 1:80,000 epinephrine was injected via infiltration into the surgical field at the start of the surgery, with an additional 1.5 mL given 1 hour later. The total dose of lidocaine and epinephrine were 110 mg and 68.75 μg, respectively. After local anesthetic injection, modest elevations in BP and HR temporarily occurred, ranging from a BP of 137/70 mm Hg and HR of 77 bpm to a BP of 161/73 mm Hg and a HR of 105 bpm. However, the patient's cardiovascular vital signs quickly returned to their normal ranges.

Immediately after completion of the surgery, the remimazolam and remifentanil infusions were discontinued. Because residual muscle relaxation remained as evident by the train-of-four (TOF) ratio of 0.38, an IV bolus of sugammadex (80 mg) was administered, and 5 minutes later, the TOF ratio was ~1. Twelve minutes after discontinuing the infusions, spontaneous breathing, cough reflex, eye opening, and obedience to verbal commands were observed, and the tracheal tube was immediately removed. Flumazenil was not required to help facilitate more rapid emergence from general anesthesia. The total duration of the surgical procedure was 1 hour and 13 minutes, and the total anesthesia time was 2 hours and 21 minutes. For postoperative analgesia, 600 mg of IV acetaminophen was administered at the end of surgery. Thereafter, additional doses (a total of 2) were administered at 6-hour intervals, producing adequate postoperative pain control.

Postoperatively, modest tachycardia (a HR of 100–120 bpm) was observed but improved with the administration of diltiazem (100 mg), one of the patient's regular medications. Thereafter, her HR remained around 70 to 80 bpm, and her cardiovascular

Table 2. Comparing Midazolam and Remifentanil Pharmacokinetic Parameters.

	Midazolam (0.075 mg/kg)	*Remimazolam (0.01–0.30 mg/kg)*
$t_{1/2}$ (hours)	4.290	0.597–0.804
CL (L/h)	23.02	70.24–75.35
V_{ss} (L/kg)	81.78	28.80–44.60

The $t_{1/2}$ of remimazolam is considerably more rapid, and its CL and V_{SS} are ~3 times and ~½ that of midazolam, respectively. Therefore, remimazolam is more rapidly metabolized and expected to promote more accurate titration and a faster recovery than midazolam. $t_{1/2}$, terminal phase half-life; CL, clearance; V_{SS}, volume of distribution at steady state.

condition stabilized rapidly during an otherwise unnoteworthy recovery. The patient was discharged from the hospital 12 days after the surgery.

DISCUSSION

In general, renal impairment can affect pharmacokinetics, including distribution, metabolism, elimination, and protein binding.[7] Chronic hemodialysis patients undergoing nonemergent surgeries are at significantly elevated risks for perioperative complications and death,[8] and anesthesiologists need to pay close attention to their perioperative management. Importantly, remifentanil and inhaled anesthetics like sevoflurane are not renally metabolized or excreted. However, IV anesthetics, other than remimazolam, as well as many other anesthesia-related drugs can accumulate due to impaired renal function, leading to enhanced or prolonged drug effects, delayed awakening, and other unexpected adverse events.[7]

Remimazolam is primarily metabolized by tissue CES, primarily carboxylesterase 1 (CES1), which is highly expressed in not only the liver but also the gallbladder and the lungs as well as other tissues. However, the liver has the highest genetic expression of CES1, while the lung is second highest. So, rapid metabolism of remimazolam is considered to be conducted in the liver and other tissues including the lung,[9] and its metabolic byproducts have virtually no relevant bioactivity.

The anesthetic effects of remimazolam are not significantly influenced by renal dysfunction.[9] Regarding the effect of impaired renal function, the pharmacokinetics of remimazolam in patients with an estimated Glomerular Filtration Rate (GFR) (uncorrected GFR for body surface area) <30 mL/min were compared with otherwise healthy subjects by measuring the blood concentration of remimazolam up to 24 hours after bolus administration.[10] The results of that study indicated that remimazolam pharmacokinetics in patients with impaired renal function did not differ from healthy patients. Furthermore, there was no delay in awakening time and no adverse events in patients with renal impairment.[10] This suggests that remimazolam may be a useful alternative for patients with severely impaired renal function.

Midazolam, a short-acting benzodiazepine similar to remimazolam, is used worldwide as an IV agent for general anesthesia and sedation management. Unlike remimazolam, midazolam is metabolized in the liver by cytochrome P450 3A4, which leads to a slower comparative rate of metabolism. Comparing the key pharmacokinetic parameters for midazolam and remimazolam,[11] the terminal phase half-life of remimazolam is considerably more rapid, and its clearance and steady state volume of distribution are ~3 times and ~½ that of midazolam, respectively (Table 2).

Midazolam metabolism in patients with severely impaired renal function reportedly does not differ considerably from that in healthy subjects.[12] However, midazolam's pharmacologically active metabolite, α-hydroxymidazolam, is excreted by the kidneys.[13] Its elimination can be prolonged in patients with renal impairment.[14] On this point, the remimazolam's carboxylic acid metabolite (CNS7054) has a benzodiazepine binding site affinity ~300 times lower and exhibits almost no bioactivity.[1] Therefore, the actions of remimazolam and its metabolites are not affected by excretory ability of the kidneys. Remimazolam is more rapidly metabolized and expected to promote more accurate titration and a faster recovery than midazolam, even in patients with renal impairment.

Propofol is also often used as a general anesthetic and sedative agent because it is quickly redistributed into peripheral tissues and metabolized, resulting in the rapid onset and disappearance of its anesthetic effects. Unlike midazolam and remimazolam, propofol is not a benzodiazepine although it does similarly act as a positive allosteric modulator to enhance the actions of GABA at GABA-A receptors and induce an anesthetic action.[15] The action of propofol on the GABA-A receptors cannot be antagonized by a benzodiazepine receptor antagonist (flumazenil) due to the different binding sites that propofol and benzodiazepines have on GABA-A receptors.[15] Propofol is extensively metabolized in the liver through the cytochrome P450 system and glucuronidation, and less than 1% is excreted unchanged.[15] Because propofol exhibits a high systemic clearance that exceeds hepatic blood flow, other organs are thought to contribute to its extrahepatic clearance.[15] A past study[16] demonstrated that renal clearance of propofol was ~30% of total body clearance and suggested the human kidneys play an important role in

propofol elimination. However, another study[17] that investigated the influence of renal impairment on propofol metabolism reported that severe renal impairment did not significantly affect the pharmacokinetic and pharmacodynamic profiles of propofol. Therefore, propofol may also be considered a useful anesthetic agent when managing hemodialysis patients.

However, the patient in the present case had the added complication of chronic diastolic heart failure. Patients with chronic renal failure undergoing hemodialysis frequently have cardiovascular complications.[8] The occurrence of serious cardiovascular complications during anesthesia needs to be considered in patients with severely impaired renal function, especially hemodialysis patients. Because propofol has been demonstrated to depress cardiac function,[18] it should be administered cautiously to patients with heart failure. On the other hand, remimazolam was reported to have a lower incidence of hypotension and cumulative norepinephrine doses during induction of general anesthesia compared with propofol in patients undergoing cardiac surgery.[19] Furthermore, the safe anesthetic management of a patient with severe cardiovascular disease using remimazolam has also been reported.[20] These findings suggest that remimazolam causes less cardiac depression than propofol. Therefore, we considered remimazolam to be a more suitable option than propofol for the present patient with chronic diastolic heart failure.

In the past studies,[3,4] the initial remimazolam infusion rate for general anesthesia was 6 or 12 mg/kg/h until loss of consciousness, followed by an infusion maintenance rate of 1 mg/kg/h. This method was applied during this case without any significant hemodynamic changes being observed during the induction of anesthesia, and the patient's hemodynamics were generally stable throughout. There was no delay in awakening from general anesthesia and no need to consider administering flumazenil. In the present case, anesthetic management was performed safely using the combination of remimazolam and remifentanil.

CONCLUSION

The effects and pharmacokinetics of remimazolam are independent of renal function, and it appears that remimazolam can be used safely for hemodialysis patients with heart failure. In addition, the combination of remimazolam and remifentanil produced a rapid and clear emergence from general anesthesia without the need for reversal agents. Remimazolam and remifentanil may be appropriate as first-line agents for the anesthetic management of hemodialysis patients with heart failure.

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Cardiac Arrest Due to Pacing Failure From Pilsicainide Poisoning

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Key Words: Pilsicainide; Poisoning; Cardiac arrest; Pacing failure; Pacing threshold.

We experienced a case of accidental pilsicainide poisoning suspected as the cause of pacing failure leading to cardiac arrest. The patient was a 36-year-old woman with a history of refractory multifocal supraventricular tachycardia who had previously undergone multiple cardiac ablations requiring placement of a pacemaker. Upon her arrival on the day of dental treatment, the patient's condition deteriorated rapidly, with a heart rate of approximately 30 beats/min, pacing failure, and an idioventricular rhythm upon electrocardiographic examination. During transportation for emergency medical care, the patient experienced clonic convulsions, and ventricular tachycardia was observed. Cardiopulmonary resuscitation, large-volume infusion, and percutaneous cardiopulmonary support were rapidly performed after arrival at a nearby medical hospital. This elicited a pacing response and successful resuscitation of the patient. No abnormalities were found during pacemaker interrogation; however, the patient's serum pilsicainide concentration was 1.46 μg/mL. Accidental ingestion of pilsicainide likely led to an increase in pacing threshold and ultimately to cardiac arrest. In the event of pacing failure, it is important to judge the degree of urgency, take appropriate emergency measures, and collaborate with other medical colleagues as soon as possible.

Pilsicainide is an antiarrhythmic drug developed and frequently used in Japan and classified as Vaughan-Williams class Ic because of its particularly strong sodium channel blockade effects.[1,2] There have been reports of poisoning associated with increased blood levels of pilsicainide, and cases of pilsicainide-associated mortality exist.[3–13] Here, we report a case of accidental pilsicainide poisoning as the suspected cause of cardiac arrest due to pacing failure.

We have obtained written consent from the patient for the publication of this case report.

CASE PRESENTATION

The patient was a 36-year-old woman (height 162 cm; weight 47 kg; body mass index 17.9 kg/m^2) scheduled for restorative dental treatment because of dental caries. Her medical history was significant for refractory multifocal supraventricular tachycardia, and she reported a total of 6 ablation surgeries for atrioventricular (AV) node reentrant tachycardia, inappropriate sinus tachycardia, and junctional tachycardia. No other relevant medical history, medications, or allergies were reported.

Eight months before the scheduled dental treatment, ablation near the sinus node and superior vena cava isolation was performed, resulting in severe sinus bradycardia with almost no intrinsic automaticity; thus,

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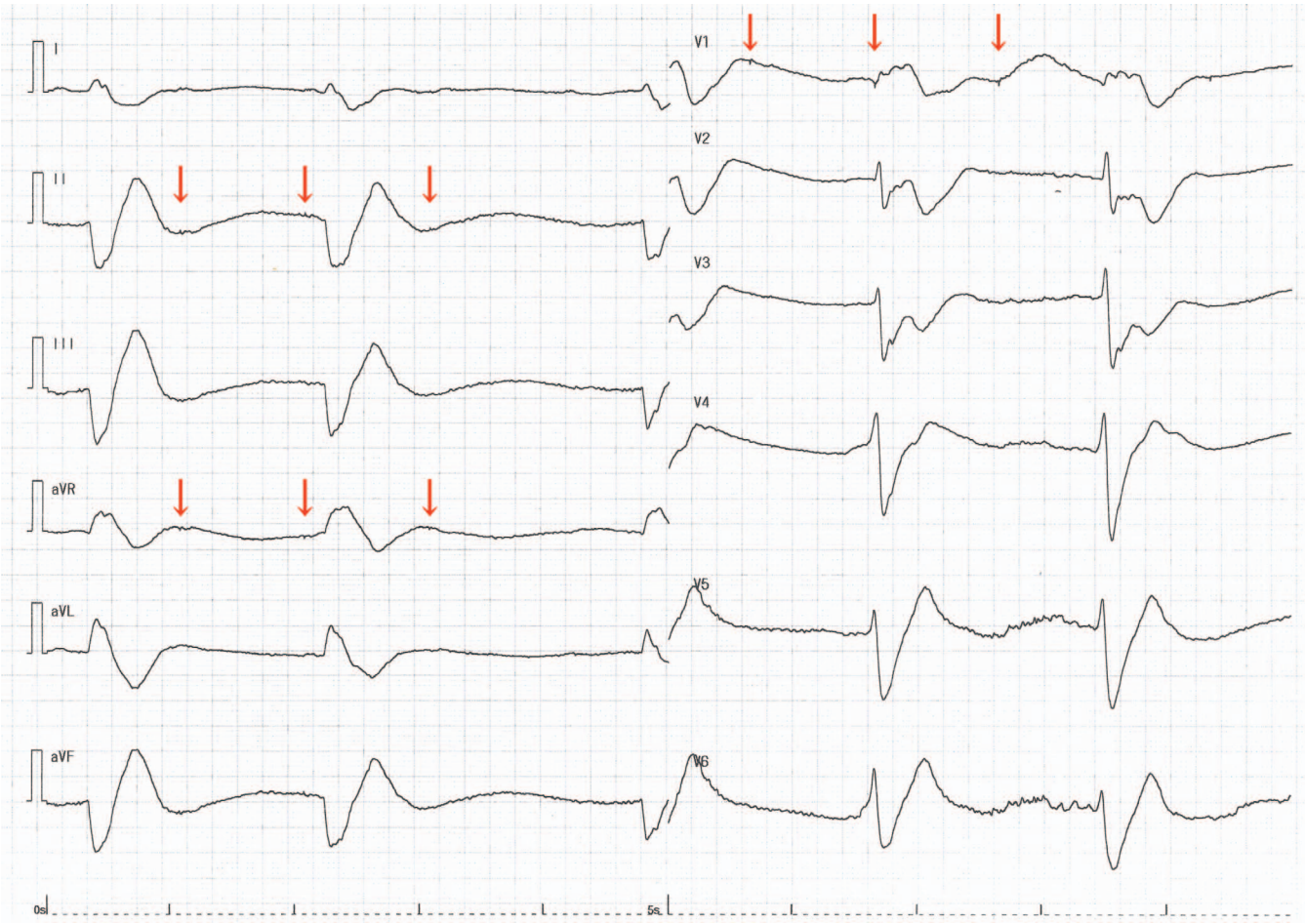
Figure. A 12-lead electrocardiogram (ECG) obtained soon after the patient's condition initially deteriorated.



Idioventricular pattern noted on the ECG along with pacing failure. Heart rate was approximately 30 beats/min. Regularly spaced red arrows indicate pacemaker spikes that were occurring despite lack of capture.

a permanent pacemaker was implanted. Two months prior to the dental treatment, AV node ablation was performed because of junctional tachycardia causing cardiac symptoms and impaired exercise tolerance. Post–AV node ablation, the patient was otherwise stable. The pacemaker was programmed as follows: mode, DDDR; lower rate, 60 beats/min; upper rate, 140 beats/min; atrial pacing threshold, 1.0 V (pulse width 0.5 milliseconds); ventricular pacing threshold, 0.3 V (pulse width 0.5 milliseconds); and output, 3.5 V (pulse width 0.4 milliseconds).

The developed plan for her dental care included restorative treatment for dental caries under local anesthesia while she was monitored using a sphygmomanometer, pulse oximeter, and electrocardiogram (ECG) because of the potential for intraoperative vital sign fluctuations. On the day of dental treatment, the patient's condition deteriorated immediately after her arrival on the premises, and she collapsed before undergoing any dental treatment. Although she was conscious, she had facial pallor and difficulty walking independently. Therefore, she was immediately transferred to the internal medicine department attached to our dental institution, where a sphygmomanometer, pulse oximeter, and ECG were quickly applied. At that time, she exhibited a heart rate of approximately 30 beats/min and pacing failure (Figure). The ECG demonstrated an idioventricular rhythm, with the absence of a QRS complex noted after a pacing impulse (red arrows in Figure). The patient's Glasgow Coma Scale score at this time was 13 points (E3V4M6). Her blood pressure was 67/38 mm Hg, and her radial artery pulse was imperceptible because of low blood pressure. A 22G indwelling catheter was placed in her forearm to secure venous access, and Ringer acetate solution was administered. The patient's oxygen saturation as measured by pulse oximetry (SpO_2) was 83% on room air; therefore, supplemental oxygen at 2 L/min was admin-

istered via an oxygen mask, after which her SpO_2 recovered to 99%.

Because her pacing failure persisted, we did not provide dental treatment and instead requested emergency transportation to a medical institution where a cardiologist and clinical engineers were on staff. However, the patient repeatedly lost and regained consciousness while she was being transported. Prior to her arrival at the medical hospital approximately 20 minutes later, she lost consciousness, and her radial artery pulse again became imperceptible. Clonic convulsions and ventricular tachycardia were observed upon her arrival to the medical facility. Immediately, cardiopulmonary resuscitation, fluid infusion, defibrillation, and administration of intravenous epinephrine and amiodarone were performed. Possible antiarrhythmic drug poisoning was suspected based on the persistent cardiac arrest and ECG findings of an idioventricular rhythm before the cardiac arrest. Large-volume infusion and percutaneous cardiopulmonary support (PCPS) were performed, which quickly elicited a pacing response and successful resuscitation of the patient. Additionally, no device abnormality was found during evaluation of the patient's pacemaker, which was performed after the start of PCPS.

The day after resuscitation, blood levels of several antiarrhythmic drug possibilities were measured. The concentration of pilsicainide in her blood was found to be as high as 1.46 μg/mL (therapeutic range is 0.2-0.9 μg/mL), suggesting pilsicainide poisoning. After resuscitation, temperature modulation using therapeutic hypothermia was performed for 48 hours to prevent brain damage, followed by withdrawal from PCPS. The patient remained hospitalized for several days, received treatment including physical rehabilitation mainly performed for disuse syndrome, and was later discharged without sequelae.

DISCUSSION

Pilsicainide is an antiarrhythmic drug classified as Vaughan-Williams class Ic. Because it selectively blocks Na^+ channels and does not affect K^+ and Ca^{2+} channels, it inhibits conduction to the atrial muscles, the conduction system tissues below the His bundle, and the ventricular muscles.[14] Pilsicainide has arrhythmogenic and negative inotropic effects and is indicated for ventricular and supraventricular tachyarrhythmias that are not associated with organic heart disease or decreased cardiac function.[2,10,11,15,16]

During the preoperative examination, our patient indicated that there was no immediate history of any oral medication use. However, pilsicainide serum levels exceeding the therapeutic range were detected in her blood after resuscitation. Upon further investigation, she reported feeling ill on the day of her dental treatment and self-administering oral teprenone. Teprenone increases gastric bicarbonate concentrations and helps heal gastric ulcers. Teprenone and pilsicainide are marketed in different colors; however, both medications are formulated as capsules and are roughly the same size. It is possible that pilsicainide, previously prescribed for the treatment of supraventricular tachycardia and stored by the patient, was mistaken for teprenone and inadvertently ingested.

Some antiarrhythmic agents (eg, procainamide, disopyramide, pilsicainide, and flecainide) raise the pacing threshold and can cause pacing failure.[4,6,17–19] The pacing threshold refers to the minimum voltage required to obtain myocardial excitement after a pacing impulse or "spike." Pacing failure refers to a state in which voltage-mediated myocardial excitement does not occur even if the pacing threshold voltage is reached. Pilsicainide and flecainide, which belong to the antiarrhythmic class Ic, have particularly strong Na^+ channel blocking effects and therefore cause a large increase in pacing threshold.[19] Moreover, even if the blood concentration of these drugs remains within the therapeutic range, the pacing threshold will increase in proportion to any increases in blood concentration.[20] Pacing failure has been reported, primarily outside of Japan, for both pilsicainide and flecainide poisoning. Therefore, the same level of caution is required when using either of these drugs.[21–23]

In the current case, the patient's blood concentration of pilsicainide was 1.46 μg/mL the day after resuscitation, which far exceeds the therapeutic range. When a healthy adult with a creatinine clearance (CCr) ≥80 mL/min is orally administered 50 mg of pilsicainide, the serum half-life is 3.4 hours.[16] Thus, we surmise that when our patient's condition deteriorated, the pilsicainide level was in fact higher than the later-measured value. In previous reports, pacing failure due to pilsicainide poisoning have occurred at blood levels of at least 2.3 to 2.5 μg/mL, and we surmise that our patient's blood levels at the time of deterioration were close to or higher than this.[6,11] Therefore, it appears that although the patient's pacemaker was delivering pacing impulses, voltage-based excitement of the myocardium did not occur.

Treatment for pilsicainide poisoning includes large-volume infusion, hemodialysis, sodium bicarbonate administration, and PCPS induction, plus cardiac pacing to maintain circulation.[3,10–12] Percutaneous cardiopulmonary support consists of a closed-circuit heart-lung machine that uses a centrifugal pump, a membrane oxygenator, monitors, and a heating system

to provide cardiopulmonary support via the femoral arteriovenous system. In this case, pacemaker capture resumed after large-volume infusion and introduction of PCPS after emergency transportation. It is highly possible that pilsicainide poisoning caused a transient increase in the pacing threshold, ultimately leading to pacing failure and cardiac arrest.[16]

Although the patient in this case had no renal dysfunction, there are many reports of renal dysfunction causing pilsicainide poisoning.[3,5,10,11] Oral administration of 50 mg of pilsicainide to patients with impaired renal function with a CCr $\leq$20 mL/min prolongs the serum half-life to 23.7 hours.[16] In patients with impaired renal function, the blood concentration may exceed the therapeutic range and reach toxic levels even if the prescribed dose is taken orally. In addition to concerns about renal dysfunction, caution is warranted for concomitant use of pilsicainide with diuretics and angiotensin receptor blockers, in cases of dehydration, and with elderly patients.[10,13] When the blood concentration of pilsicainide exceeds the therapeutic range and reaches toxic levels, fatal arrhythmias (ie, ventricular tachycardia and ventricular fibrillation) and ECG changes may be observed, as in this case.[7,10,11] Therefore, appropriate dosing and monitoring of drug levels are important considerations for the safe management of patients taking pilsicainide who are undergoing dental treatment.

Causes of pacing failure due to elevated pacing threshold include lead issues, myocardial ischemia, organic changes in the myocardium, metabolic abnormalities, electrolyte abnormalities, and the effects of drugs like antiarrhythmics. Pacing failure due to pacemaker generator or battery insufficiency is rare.[6,18,19,24] In this case, a pacemaker check was performed 12 days before the planned dental treatment and twice after the introduction of PCPS, but no device abnormality was ever observed.

It is difficult for a dentist to identify the causes of pacing failure, given that they are diverse and require specialized knowledge and equipment to identify. In addition, treatments differ depending on the underlying cause of pacing failure. Therefore, it is necessary to verify the relevant medical history, medications, and periodic assessment of the device and its settings prior to treating dental patients with implanted pacemakers.

Although it was difficult to suspect and respond to antiarrhythmic drug poisoning when the patient's condition initially deteriorated, we were able to provide urgent care, applying noninvasive monitors and quickly determining that more definitive medical help was needed. After timely activation of emergency medical services, the patient was expediently transported to a medical hospital, where the likely cause was identified and appropriately managed. This led to the successful resuscitation of the patient. When pacing failure occurs, it is important to judge the degree of urgency from the patient's vital signs, take appropriate emergency measures, and collaborate with other medical colleagues (eg, a cardiologist or clinical engineer) as soon as possible.

CONCLUSION

We experienced a case of pilsicainide poisoning suspected to be the cause of pacing failure that led to cardiac arrest. Pilsicainide poisoning is rare and was attributed to accidental ingestion following a possible medication error at home. The patient was expediently transported to a medical hospital, where the likely cause was identified and appropriately managed, leading to a successful resuscitation and discharge.

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Postoperative Epistaxis Following Dental Treatment With Nitrous Oxide/Oxygen Sedation

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A 12-year-old Caucasian male undergoing a dental extraction for a grossly carious mandibular molar under inhalational sedation with nitrous oxide/oxygen experienced an episode of anterior epistaxis postoperatively that was controlled well with local measures. Epistaxis following inhalational sedation with nitrous oxide/oxygen in the dental setting is a very rare complication but has been previously reported in the literature. This case report provides a review of the existing literature regarding cases of epistaxis associated with inhalational sedation using nitrous oxide/oxygen and discusses the potential etiology of epistaxis associated with inhalational sedation. Patients at higher risk of epistaxis should be properly informed of the risks prior to inhalational sedation with nitrous oxide/oxygen, and dentists should also be familiar with epistaxis management in the dental setting.

Key Words: Epistaxis; Inhalational sedation; Nitrous oxide; Dental extraction, Case report.

Epistaxis is fairly common in adults and children as the blood vessels supplying the nasal mucosa have little anatomic support or inherent protection. The most common causes of epistaxis in children include nasal mucosal dryness, trauma, foreign body, and rhinitis. Other important potential causes that are less common include systemic conditions such as bleeding or inflammatory disorders, medications that impact hemostasis (eg, NSAIDs, anticoagulants) and tumors.[1] Congestion of nasal blood vessels or irritation and drying of the nasal mucosa are also thought to increase the risk of epistaxis.[1]

Although a variety of classification schemes exist, epistaxis is often classified anatomically based on the site of bleeding: anterior or posterior epistaxis. Anterior epistaxis is most common, accounting for more than 95% of cases,[2] and is normally caused by bleeding from Kiesselbach plexus. It is commonly controlled mainly by local measures like compression of the nasal soft tissues or application of hemostatic dressings. Posterior epistaxis is much rarer, accounting for ~5% of all epistaxis cases,[3] and it may be associated with bleeding from Woodruff plexus. It is more commonly associated with increased age and medical comorbidities such as hypertension, thrombocytopenia, atherosclerosis, and clotting disorders. Treatment of posterior epistaxis is also more likely to require medical care and hospitalization.[4] Complications of severe epistaxis may include hypovolemia and anemia, and in posterior epistaxis, there is an increased risk of airway difficulty, aspiration, and death.[5]

Epistaxis may occur during the provision of sedation or general anesthesia for dental care as a result of nasotracheal intubation,[6] insertion of a nasopharyngeal airway,[7] use of a nasal cannula,[8] or as a complication from intranasal drug administration. This case report describes postoperative epistaxis attributed to the use of inhalational sedation with nitrous oxide/oxygen and discusses the likely etiology and potential precautions.

CASE PRESENTATION

A healthy, American Society of Anesthesiologists (ASA) I 12-year-old Caucasian male (height, 62 inches; weight, 53.1 kg; BMI, 21 kg/m^2) was seen at Midlands Partnership University NHS Foundation Trust for the planned extraction of a symptomatic grossly carious mandibular right first molar under inhalational sedation with nitrous oxide/oxygen, following 2 separate unsuccessful attempts with only local anesthesia 1 week prior. He had no known allergies and was not taking any

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medications. The patient had no previous history of sedation or general anesthesia and had difficulty accessing dental care due to the COVID-19 pandemic.

General anesthesia was offered but not preferred by the parent, and consent was confirmed with the patient's mother (who was also a health care professional) to arrange a future appointment 1 week later to attempt extraction under inhalational sedation with nitrous oxide/oxygen. The risks and benefits of dental extraction and inhalational sedation with nitrous oxide/oxygen, which included nausea, vomiting, headaches, and lethargy, were reviewed with the patient and his mother. Preoperative instructions given at that time included restriction to a light nonfatty meal 2 hours prior to the procedure and to contact our clinic if there were any significant changes to his medical history that may affect the provision of inhalational sedation with nitrous oxide/oxygen.

On the day of treatment, the patient presented to the dental clinic where all preoperative checks for inhalational sedation were completed, including obtaining a full medical and pharmacological history to confirm no changes since the last appointment, confirming the time of last oral intake (which was 2 hours prior to the sedation appointment), and ensuring nasal patency. As there were no contraindications for inhalational sedation with nitrous oxide/oxygen noted, we proceeded with the planned dental treatment using our standard technique for inhalational sedation. To start, 100% oxygen at 6 L/min was administered for 1 minute after fitting the nasal hood. The initial flow rate of 6 L/min was determined after assessing the patient's respiratory rate and breathing depth and observing the reservoir bag. Following this, nitrous oxide was concurrently administered in 10% increments up to 20% after which 5% increments were given (ie, 10%, 20%, 25%, 30%, 35%...) until the patient was considered suitably sedated. The patient was given up to 50/50% nitrous oxide/oxygen by titration but did not feel relaxed, so additional nitrous oxide was given. At this point (60/40% nitrous oxide/oxygen), the patient appeared much more relaxed; the patient was giggling and at one point started joking with his mother. However, in retrospect this may have been a sign of oversedation or disinhibition.

The patient permitted administration of local anesthesia consisting of a right lingual and inferior alveolar nerve block with 2.2 mL of 2% lidocaine 1:80,000 epinephrine (44 mg lidocaine with 27.5 μg epinephrine) that produced anesthesia of the tongue and lip. However, the patient was still reporting pain, and therefore additional local anesthesia was given via intrapulpal, intraligamentary, and buccal infiltration injections. A total of 4.4 mL of 4% articaine with 1:100,000 epinephrine was administered: 2.2 mL for the intraligamentary (88 mg articaine with 22 μg epinephrine), 1.1 mL for the intrapulpal (44 mg articaine with 11 μg epinephrine), and 1.1 mL for the buccal infiltration (44 mg articaine with 11 μg epinephrine) injections. The local anesthetic was given ~15 minutes to take effect from the first injection.

Despite this, the patient did not permit the extraction due to the sensation of pressure, and the procedure was subsequently abandoned. The patient was given 5 minutes of 100% oxygen to prevent diffusion hypoxia. Postoperative Eve test (patient instructed to extend their arm and touch the tip of their nose while having their eyes closed) and Romberg checks were satisfactory, and the patient was deemed suitable for discharge. The patient's total treatment time under sedation lasted over 60 minutes (including the 5 minutes of oxygen to prevent diffusion hypoxia).

The patient was then referred to Royal Stoke University Hospital for the planned tooth extraction under general anesthesia. To avoid further delay in treatment, a request for a panoramic radiograph for the preanesthetic and surgical assessment and orthodontic treatment planning was made ~3 to 5 minutes after the patient was deemed fit for discharge. However, the patient reported spontaneous bleeding from the right naris while the panoramic radiograph was being taken. The patient denied any inadvertent trauma to his nose (ie, excessive rubbing of his nose) and gave no previous history of epistaxis. The acute epistaxis episode was treated with local measures (compression of the nasal alae and paper towels) and eventually stopped after ~10 minutes.

The patient reported feeling lightheaded while being treated for epistaxis as he was sitting upright, and therefore, supplemental oxygen was administered through a face mask (avoiding the scavenging nasal hood due to a recent episode of epistaxis). After ~5 minutes, Eve test and Romberg checks were satisfactorily repeated, and the patient was discharged home in the care of his mother. We contacted the patient later that day, and his mother confirmed no further incidences of epistaxis and that the patient was feeling well. He had no history of bleeding issues, and it was his first episode of epistaxis that the patient and mother could recall.

DISCUSSION

The vestibule, the respiratory region, and the olfactory region are the 3 simple divisions of the nasal cavity. The incisive canal also forms a strong association with the nasal cavity. The olfactory, nasopalatine, and nasociliary nerves all provide innervation to the nasal cavity. Both the internal carotid (through the anterior and posterior

Table 1. Epistaxis Cases Associated with Nitrous Oxide Sedation.*

Study	*Patient age (years)*	*ASA class*	*Nitrous oxide concentration (%)*	*Potential etiology/risk factors associated with nitrous oxide/oxygen sedation*
Faulks et al. 2007	3–81†	Study group consisted of "patients with intellectual disability"†	50	Anxiety
Baygin et al. 2010	5–8†	I or II†	40	No explanation given
Mathur et al. 2020	8	I	40	Irritation of nasal cavity Thin nasal lining Previous injury/trauma to nose
This case report	12	I	60	Excessive/aggressive nose breathing Drying and/or irritation of the nasal cavity Self-inflicted trauma (from nasal hood or on removal, nose rubbing etc) White coat syndrome (hypertension)

* Literature review of epistaxis cases associated with inhalational sedation using nitrous oxide/oxygen.
† Specific information for patient with epistaxis not detailed in study.

ethmoidal arteries) and external carotid (through the lateral nasal, greater palatine, sphenopalatine, and superior labial arteries) arteries provide its vascular supply. Furthermore, epistaxis may occur as a result of injury/trauma to Kiesselbach plexus and Woodruff plexus, 2 highly vascular regions in the nasal cavity.

The potential etiology of epistaxis following inhalational sedation with nitrous oxide/oxygen in this case report is still not definitively determined. A literature review using the medical subject headings (MeSH) terms: ((("Anesthesia, Inhalation"[Mesh])) OR "Nitrous Oxide"[Mesh]) AND "Epistaxis"[Mesh] in PubMed and the free terms 'inhalation sedation', 'inhalational sedation', 'nitrous oxide', and 'epistaxis' using Google Scholar and the Cochrane Library was carried out. In addition, the reference lists of identified articles were also assessed and further complemented by an internet free search. Only 3 previous reports regarding epistaxis associated with inhalational sedation with nitrous oxide/oxygen were identified (Table 1).

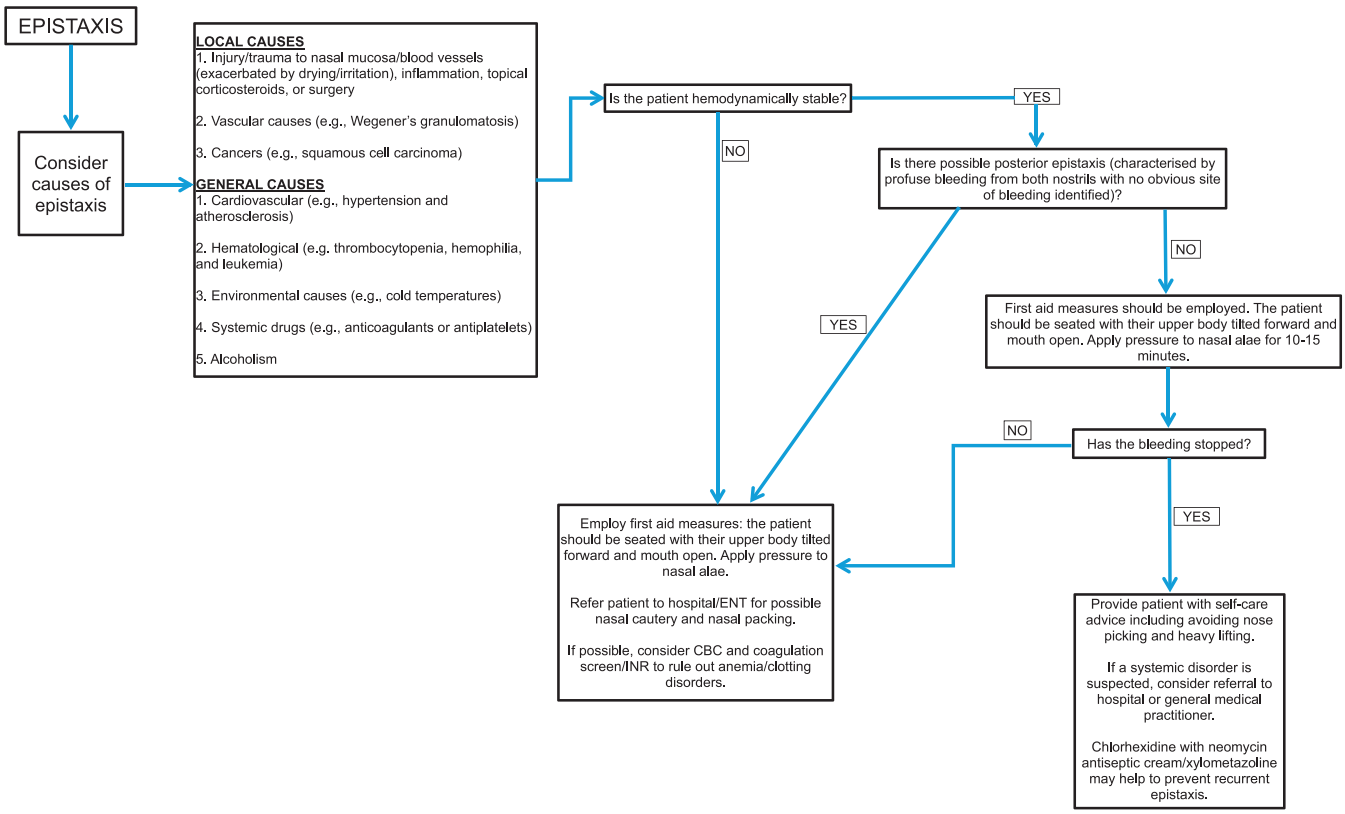
Faulks et al[9] reported 1 case of epistaxis in over 605 sessions of inhalational sedation with 50/50% nitrous oxide/oxygen used alone in patients with intellectual difficulties. The authors concluded that epistaxis was linked to anxiety rather than the use of inhalational sedation. However, this conclusion seems rather unlikely considering virtually all dental patients who receive inhalational sedation have some degree of anxiety, and as such, anxiety-induced epistaxis would be expected to have a much higher incidence. In addition, there is no conclusive evidence of anxiety being a risk factor for epistaxis.[10] It is not clear from this study if any of the patients with intellectual disabilities also had any risk factors for epistaxis.

Baygin et al[11] also reported 1 case of epistaxis following treatment with inhalational sedation with 40/60% nitrous oxide/oxygen. This study involved children between 5 and 8 years of age and ASA I or II, but there was no specific information provided about the patient, and no explanation was given for the potential cause of epistaxis.

Most recently, Mathur et al[12] also reported in 2020 a rare case of epistaxis in an 8-year-old male during dental treatment with 40/60% nitrous oxide/oxygen inhalational sedation. Similar to this case report, that patient had no risk factors for epistaxis and was scheduled for dental extractions, but the epistaxis episode occurred during the administration of inhalational sedation in contrast with this case. Mathur et al[12] suggested the etiology of epistaxis associated with inhalational sedation could be due to irritation of the nasal cavity mucosa, an overly thin nasal mucosal lining, or a pre-existing or previous nasal injury (although this was not proven).

Considering the risk factors for epistaxis, it is likely that the potential causes of epistaxis for the patient in this case report were excessive and overly enthusiastic nasal breathing as the inhalational sedation was being administered, which may have caused some trauma (eg, rupture of vessels), and the prolonged administration of nitrous oxide/oxygen. These factors may have contributed to excessive drying of the nasal mucosa and increased the risk of epistaxis. Although the patient denied rubbing his nose, another potential cause could have been self-inflicted trauma following removal of the nasal hood. Nitrous oxide is not known to cause irritation of mucosal membranes[13]; however, oxygen therapy can cause irritation, this may relate to the duration of exposure or concentrated episodes (ie, high oxygen flow rates as occurs with use of the oxygen flush button). In addition, increased arterial blood pressure at the onset of epistaxis may be associated with white coat syndrome[14] in patients receiving dental sedation. Anxiety is related to a rise in heart rate, blood pressure, and increased respiratory rate, which may explain why it could be considered a risk factor for epistaxis.

Figure. Epistaxis Management Flowchart.



Management of epistaxis in the primary dental care setting (adapted from National Institute for Health and Care Excellence[15]).

Epistaxis prevention primarily involves obtaining a thorough medical history, screening for hypertension, and using moisturizing balm prior to treatment. In patients with bleeding disorders or on anticoagulants and who are therefore at higher risk of epistaxis, preinvestigations (such as coagulation assessments) may help to reduce the risk of epistaxis. Should anterior epistaxis occur, continuous pressure should be applied to the nasal alae. Other measures may include chlorhexidine with neomycin cream, xylometazoline, and nasal packing (Figure). A small amount of moisturizing balm or cream can be applied into each nostril (pointing away from the nasal septum) and spread around interiorly by gently squeezing together the alae of the nose to spread the balm or cream around the nose. Xylometazoline normally comes as a nasal spray and used in each nostril to help prevent recurrent epistaxis. Patients with suspected posterior epistaxis or epistaxis not controlled by local measures may require referral to a hospital setting.

The majority of guidelines and studies reviewed focus on nasal oxygen therapy and how it can dry and irritate the nasal mucosa, along with the possibility that the nasal cannula prongs may directly traumatize the nasal mucosa[8] and increase the risk of epistaxis. The potential increased risk of epistaxis linked to the use of scavenging nasal hoods during inhalational sedation for dental surgery needs to be taken further into account. The risk of epistaxis is probably highest with a nasal cannula (or other equipment or airway devices that directly contact the nasal mucosa), somewhat lower with scavenging nasal hoods, and minimal with full face masks used during general anesthesia.

From the cases in the literature including this case report, epistaxis associated with inhalational sedation was seen in patients receiving nitrous oxide at concentrations of 40% and above, and all 4 cases presented as anterior epistaxis, the most common cause of epistaxis. One of the advantages of inhalational sedation with nitrous oxide/oxygen is that there are few medical contraindications to its use compared with intravenous sedation and general anesthesia. The author suggests that patients taking anticoagulants or those with bleeding disorders, a history of epistaxis, or other medical risk factors for epistaxis should be warned about the possible rare risk of anterior epistaxis with inhalational sedation. Most cases of anterior epistaxis should resolve quickly with local

Table 2. Summary and Recommendations.*

Summary and recommendations for patients at higher risk of epistaxis requiring inhalational sedation
All reported cases in the literature presented with anterior epistaxis and were controlled with local measures.
All patients receiving inhalational sedation should be screened for previous episodes of epistaxis or other episodes of bleeding.
Patients who are at higher risk of epistaxis (eg, previous trauma/epistaxis, inflammation, on anticoagulants, or patients with bleeding disorders) should be informed of risks beforehand.

* Summary of findings and recommendations from a literature review of epistaxis associated with inhalational sedation using nitrous oxide/oxygen.

measures, but in certain cases, such as the higher risk patient groups previously mentioned, epistaxis may require urgent medical care and/or referral to an ear, nose, and throat surgeon. A summary of the findings and recommendations from our literature review of epistaxis associated with inhalational sedation with nitrous oxide/oxygen for dental surgery are presented below (Table 2).

CONCLUSION

Inhalational sedation with nitrous oxide/oxygen is a common form of sedation used for dental treatment, and it has an excellent safety record. However, it can be very rarely associated with anterior epistaxis. Patients at higher risk of epistaxis should be warned prior to treatment to gain informed consent. Simple preventative measures for patients at higher risk of epistaxis who require inhalational sedation may include moisturizing the nasal cavity prior to treatment, screening for hypertension, reducing treatment time under sedation, avoiding direct trauma to the nasal anatomy, and asking patients to avoid aggressive and excessive nasal breathing. It may also be beneficial to assess for hemostatic stability in patients with bleeding issues and those at higher risk of epistaxis prior to treatment. Dentists should also be aware of the management of epistaxis and when to refer patients to a hospital setting.

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Successful Premedication With Sublingual Midazolam Using a Suction Toothbrush

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Premedication is often used to reduce the stress associated with anesthesia-related procedures. However, in some cases, patients may not cooperate with medication delivery because of significant fear and anxiety. We report a case of an uncooperative patient with severe intellectual disabilities who was successfully premedicated with the unique technique of sublingual midazolam administration using a suction toothbrush. The 38-year-old male patient was planned to receive dental treatment under deep intravenous sedation (IVS), but he refused both intravenous cannulation and mask induction. Preanesthetic medication delivery using other routes was attempted but not accepted. As the patient tolerated toothbrushing, we used repeated practice with sublingual water administration through the toothbrush's suction hole to gradually desensitize the patient. Using that same method, sublingual midazolam was administered as a successful premedication to allow placement of a face mask for inhalational induction without distress and completion of the dental treatment under IVS. For patients who refuse other premedication routes, sublingual administration during toothbrushing with a suction toothbrush may provide a successful alternative.

Key Words: Intellectual disability; Developmental disorder; Sublingual administration; Suction toothbrush.

Patients with intellectual disabilities, including developmental disorders and autism, often have difficulty undergoing dental treatment because of poor compliance. Attempts to promote treatment acceptance through desensitization and other means can be made but in many instances are unsuccessful, prompting the use of sedation or general anesthesia for the safe completion of treatment.[1] However, the procedures commonly involved with the delivery of anesthesia services, such as intravenous (IV) cannulation or mask fitting for anesthetic inhalation, can be very stressful. If the patient is unable to cooperate, physical restraint may be necessary, potentially leading to problematic psychological and/or physical insult. Efforts to mitigate these adverse effects can include preanesthetic medications,[2] which can be administered via several methods depending on the degree of patient cooperation and acceptance. Patients who are fearful or overly alert may have difficulty accepting premedication.

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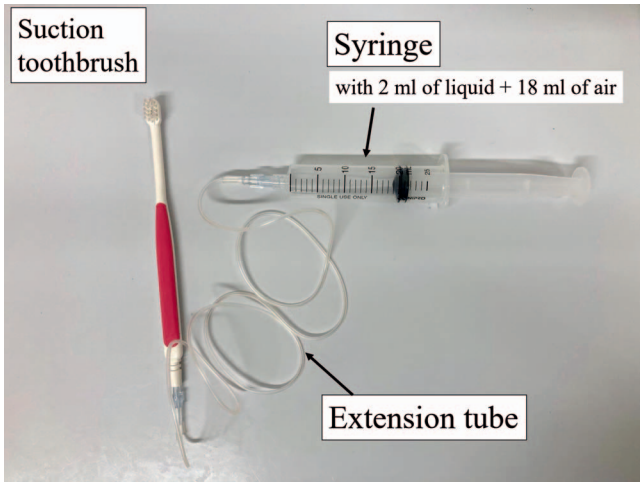
In the present case, we initially planned to use deep IV sedation (IVS) to treat a patient with severe intellectual disability who had difficulty undergoing dental treatment because of noncompliance. However, this was not readily achieved because the patient strongly refused IV cannulation and a face mask for inhalational induction. We attempted premedication administration by intramuscular injection and by the oral route to sedate the patient sufficiently to permit the aforementioned procedures, but neither was successful because of his significant fear and anxiety. Therefore, we administered sublingual midazolam as premedication using a suction toothbrush while brushing the patient's teeth. This approach was successful, as he became sufficiently sedated to accept the face mask for inhalational induction without discomfort, allowing the dental treatment to be successfully completed under IVS.

CASE PRESENTATION

The patient was a 38-year-old male (height 160 cm; weight 38.5 kg; body mass index 15.0 kg/m^2) with severe intellectual disability and dental phobia but no other medical comorbidities, medications, or allergies. He had difficulty speaking, and conversational communication was impossible. At 28 years of age, he made his first visit

Figure 1. Suction toothbrush used for sublingual administration.



Suction toothbrush (Cutect, Always Co, LTD) with an extension tube and injection syringe connected.

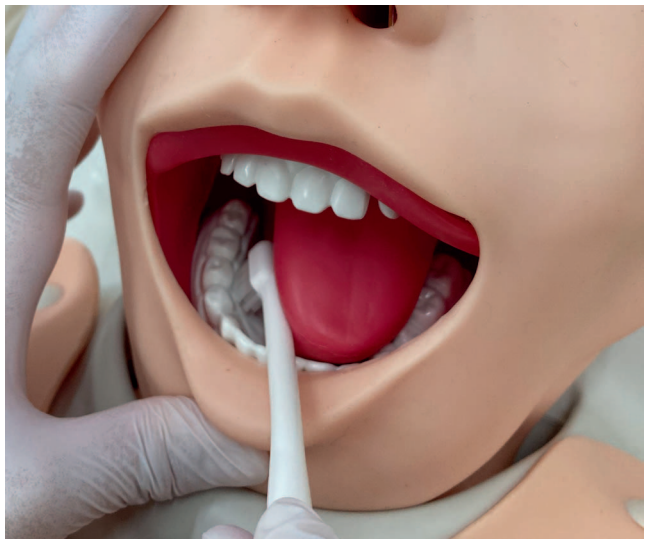
to our dental clinic and was diagnosed after oral examination with chronic periodontitis, necessitating periodontal treatment. The patient demonstrated marked fear and anxiety and was unable to lie supine in the dental chair. He was extremely uncooperative during treatment and only tolerated toothbrushing while sitting upright. Desensitization for treatment was attempted but did not produce adequate results.

Periodontal treatment was then performed under deep IVS; however, the patient had to be restrained by several people while mask induction was performed, which caused significant emotional trauma. Afterwards, he would run out of the room during subsequent dental visits whenever he found the anesthesia mask.

Six years after the initial visit, dental caries requiring treatment were identified. The patient remained remarkably uncooperative and again required IVS with the use of physical restraint during inhalational induction. Subsequently, his cooperation during dental treatment was even lower, and he was no longer able to even enter the anesthesia procedure room and only permitted toothbrushing in the sitting position. Desensitization for dental treatment was continued, but little progress was made.

Nine years after the initial visit, exacerbation of chronic periodontitis was observed, requiring additional periodontal treatment. Because of the patient's uncooperative nature, IVS was once again required. However, the patient became extremely agitated and ran out of the room after seeing the syringe and the anesthesia machine. We were unable to perform IV cannulation while the patient was conscious and could not calm him enough to safely perform mask induction. Oral and

Figure 2. Sublingual administration on a mannequin.



While the teeth were brushed, the tip of the toothbrush was set sublingually, and a sedative was injected.

intramuscular premedication were attempted, but neither was possible because of poor patient compliance. Because the only procedure the patient would accept was toothbrushing, we planned to administer sublingual midazolam for premedication by injecting the drug through the suction hole of a suction toothbrush while brushing his teeth.

The first step was to change the toothbrush used for his oral care to a suction toothbrush (Cutect, Always Co, LTD; Figure 1). The brushing was also performed on a stretcher in the anesthesia recovery room rather than in the dental chair, with the assumption that he would be transferred to the anesthesia treatment room after premedication. After the patient grew to accept the suction toothbrush, brushing was then performed with an extension tube connected to its suction hole. Once that was accepted, brushing was then performed with the suction toothbrush connected to an extension tube and an injectable syringe (filled with 2 mL of water and 18 mL of air) used to eject water sublingually during brushing (Figures 1 and 2). A separate staff member operated the syringe as it was hidden in her pocket (Figure 3). The desensitization steps described above were carried out once a month over approximately 3 months.

On the day of treatment, the patient was instructed not to eat or drink for at least 6 hours. Toothbrushing was initiated using the suction toothbrush with the patient sitting on a stretcher in the anesthesia recovery room as described previously. While his response was monitored, a syringe filled with 2 mL of midazolam (10

Figure 3. Simulated sublingual administration while toothbrushing.

The syringe was concealed in the staff member's pocket and manipulated without being seen by the patient.

mg) and 18 mL of air was used to deliver the premedication sublingually via the suction toothbrush. Minimal amounts of the ejected medication leaked out of his mouth or were observed remaining in his oral cavity. We continued to brush his teeth for approximately 1 minute, during which time he showed no distinct swallowing movements and displayed no disquiet during the injection. We then stopped brushing, turned off the lights, darkened the room, and observed him at rest so as not to stimulate him.

Thirty minutes after administration, he was lying on his side on the stretcher, asleep and unresponsive to voice commands. We attempted to move him into the treatment room; however, stimulation from the move awakened him. He became more alert, refused to lie on the stretcher at that point, and remained in a sitting position.

Fifteen minutes later, we brushed his teeth again with the suction toothbrush and administered an additional dose of sublingual midazolam 5 mg/1 mL in the same manner described above. He fell asleep again approximately 10 minutes later and was easily transported into the anesthesia room without being awakened. At that time, the depth of sedation was 2 on the Modified Observer's Assessment of Alertness/Sedation scale, and his respiratory status was stable.

After entering the room, he tried to get up in a dazed state. The anesthesiologist gently held his head while performing mask induction using nitrous oxide 4 L/min, oxygen 2 L/min, and sevoflurane 5% to safely facilitate IV cannulation. The patient was successfully anesthetized without significant agitation or the need for physical restraint, and the inhalational agents were discontinued once the IV cannula was successfully placed. Blood pressure, oxygen saturation as measured by pulse oximetry (SpO_2), electrocardiographic, and bispectral index (BIS) monitoring were then initiated. Deep IVS was maintained with a continuous infusion of propofol 50 mcg/kg/min to 83 mcg/kg/min along with supplemental oxygen 3 L/min via nasal cannula. No local anesthetic was used for the dental treatment. His intraoperative vital signs were as follows: blood pressure 70 mm Hg to 105 mm Hg/45 mm Hg to 64 mm Hg, heart rate 88 beats/min to 105 beats/min, SpO_2 98% to 100%, and BIS 44 to 70. Significant body movements, airway obstruction, and cough associated with aspiration were not observed during anesthesia, and the periodontal treatment was successfully completed. Operative time was 1 hour and 1 minute, and anesthesia time was 2 hours and 17 minutes.

After the dental treatment ended, the patient was transferred to the recovery room while still in a sleeping state. After we confirmed that SpO_2 was maintained above 98% under room air conditions, the IV catheter was removed, and he opened his eyes approximately 5 minutes later. The patient was briefly agitated but was calmed down within a few minutes with the help of his parents. He remained calm, did not become somnolent, and had a stable respiratory status throughout the recovery period. The patient was discharged home after confirming that he was clearly awake and back to his baseline level of consciousness. We called his mother 6 and 9 hours later for follow-up and confirmed that he was stable with no signs of resedation, was able to eat, had resumed his daily activities without any problems, and had no postanesthetic complications. Of note, he did not refuse to come to our clinic afterwards and continues to receive regular dental treatment.

DISCUSSION

Patients with intellectual disabilities tend to have complex dental needs and poor oral health because they have difficulty accessing preventive dental care and understanding its importance. In addition, when they need dental care, they are often unable to accept treatment because of strong fears and anxiety. It is common practice to treat such patients using sedation or general anesthesia.[1] However, common anesthetic procedures, like use of a face mask or establishing IV access, can be extremely stressful. In the absence of adequate cooperation, physical restraint is often unavoidable, which can easily lead to psychological trauma for the patient. There is also a risk of adverse events like physical injury to patients and/or medical staff when physically restraining an uncooperative patient. Anesthetic premedication is commonly used to help avoid such events.[2]

Midazolam, a short-acting benzodiazepine, is a commonly used agent among the various sedatives used for premedication. Because of its anterograde amnesic effects, it is well suited for patients with fear and anxiety regarding anesthetic procedures, as noted in this case.[3] Midazolam as premedication can be administered intravenously, orally, intramuscularly, sublingually, intranasally, or rectally.[4,5]

Sublingual administration, as used in this case, has the advantages of faster onset, less variation in gastrointestinal absorption, and lower dosage for optimal effects compared to oral administration because the drug enters the systemic circulation directly and avoids first-pass hepatic metabolism.[6,7] In a pharmacokinetic study of midazolam administered sublingually to children, a dose of 0.2 mg/kg was reported to produce blood levels above 70 ng/mL.[8] Another study reported that a sublingual dose of 0.2 mg/kg produced adequate sedation depth that allowed mask fitting without discomfort.[9] Therefore, we set the initial dose at 10 mg (~0.26 mg/kg) to account for potential drug leakage out of his mouth in this case. However, an additional 5-mg dose was administered because adequate sedation was not achieved initially. One possible drawback of this method may be that some of the drug may have been swallowed and migrated into the gastrointestinal tract, making it unclear exactly how much was absorbed sublingually.

Midazolam has a strong bitter taste, so it might be assumed that a patient would spit it out when administered orally or sublingually. However, when administered in a small volume (eg, 2 mL) and in the appropriate area sublingually as in this case, the patient tolerated the midazolam well and did not spit it out. We also recommend that midazolam be administered without dilution so as not to increase the drug solution volume.

In a pharmacokinetic study of midazolam tablets administered sublingually in healthy adults, it was reported that the maximum blood concentration was reached within approximately 15 minutes after sublingual administration of 15 mg, with an elimination half-life of approximately 5.5 hours.[10] In the present case, the patient fell asleep approximately 30 minutes after the first sublingual administration of midazolam. Time until optimal sedative effect may vary depending on a patient's state of mental tension and the surrounding stimuli during administration.

We attempted to reduce his anxiety by continuing desensitization for the procedures involved with this sublingual administration method prior to anesthesia and by keeping the room dark and quiet after drug administration to avoid overstimulation. The patient refused to wear a pulse oximeter or other monitoring devices, so monitoring was not possible until he lost consciousness. After administering sublingual midazolam, we visually monitored his respiratory status and were prepared to respond immediately in case of an emergency. In a study examining the effect of premedication with sublingual midazolam 0.3 mg/kg in children, serious adverse events, such as hypoxemia, were not reported after administration.[11] However, oxygenation monitoring should ideally be performed in anticipation of rapid oversedation, and preparations should be made for emergency airway management.

Because the patient poorly tolerated spending long periods in an unfamiliar space, which would make inpatient management difficult, we opted for ambulatory anesthesia in this case. We telephoned his mother after discharge home to inquire about his condition several times and confirmed that he was progressing without any issues. However, because the sedative effects of midazolam may persist, it may be advisable to consider inpatient management for appropriate patients.

Because the method of premedication used in this case requires patient acceptance and cooperation, it may be difficult to perform on patients who refuse administration because of fear or anxiety. In the present case, we used the time when we brushed his teeth, as that was the only chance we had to easily access his mouth, and used a suction toothbrush to administer the midazolam sublingually through its suction hole. Toothbrushing is a less invasive and rudimentary step in dental care and is often easily accepted by uncooperative patients with intellectual and developmental disabilities. Another possible advantage is that the patient is often preoccupied during toothbrushing, making them less conscious of the stimulation from oral or sublingual drug administration. Although this method requires additional time and practice for both providers and patients, it may be a means of successfully premedicating patients who have difficulty accepting drug administration without significant distress.

CONCLUSION

The use of a suction toothbrush to administer sublingual midazolam during toothbrushing may be an effective method of premedication delivery. This method can be considered for patients who are uncooperative and refuse to easily accept premedication using other methods but do permit toothbrushing. However, this technique may take additional time and practice for success.

Conflict of Interest

The authors declare no conflict of interest.

Consent Approval

The parents of the patient gave permission to use clinical information and photographic material.

Ethical Approval

All procedures involving human participants were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

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Evaluation of Sedation Levels Using SedLine During Intravenous Sedation for Dental Procedures: A Case-Series Study

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The Patient State Index (PSI) is the numerical value of anesthesia depth as measured using a SedLine Sedation Monitor (Masimo Corporation). In this pilot study, we evaluated PSI values captured during intravenous (IV) moderate sedation for dental treatment. During the dental treatment, a dental anesthesiologist maintained the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score at 3 to 4 by adjusting the administration of midazolam and propofol while PSI values were recorded. The mean (SD) and median (25th percentile, 75th percentile) PSI values during dental treatment under IV moderate sedation were 72.7 (13.6) and 75 (65, 85), respectively.

Key Words: Intravenous sedation; Moderate sedation; SedLine; Patient State Index (PSI).

The Patient State Index (PSI) is measured using the SedLine Sedation Monitor (SedLine; Masimo Corporation) proprietary equipment and represents a numerical value of anesthesia depth. However, no study has examined PSI values for moderate sedation. We conducted a case-series study to investigate PSI values during moderate intravenous (IV) sedation for dental treatment.

This pilot study was approved by the ethics committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital (approval No. 2006-047) and was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000042451).

METHODS

Potential subjects included patients scheduled for IV moderate sedation at the Department of Dental Anesthesiology, Okayama University Hospital. Selection criteria included (1) age ≥20 years and (2) American Society of Anesthesiologists physical status classification scores of 1 or 2. Furthermore, we excluded (1) patients requiring deep sedation, (2) patients taking medications acting on the central nervous system (eg, antidepressants, antiepileptic drugs, and/or antipsychotic drugs), (3) patients with contraindications for propofol and/or midazolam, and (4) patients otherwise considered to be ineligible for study participation as determined by the study director or investigators.

IV midazolam (1-3 mg) was administered, followed by a continuous target-controlled infusion of propofol. The propofol rate was adjusted during dental treatment by the dental anesthesiologist to ensure the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score[1] remained at 3 or 4 while the study investigators recorded the PSI values. The dental anesthesiologists remained blinded from the PSI values during treatment. After completion of the dental treatment, the PSI values recorded at 2-second intervals during treatment (from start until completion) were extracted from the SedLine monitor.

To evaluate intraoperative amnestic effects and patient satisfaction with the IV moderate sedation, attending dental anesthesiologists requested patients respond to a postoperative questionnaire survey. The

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questionnaire used a 4- and 5-point scale to evaluate intraoperative amnesia and assess patient satisfaction, respectively.

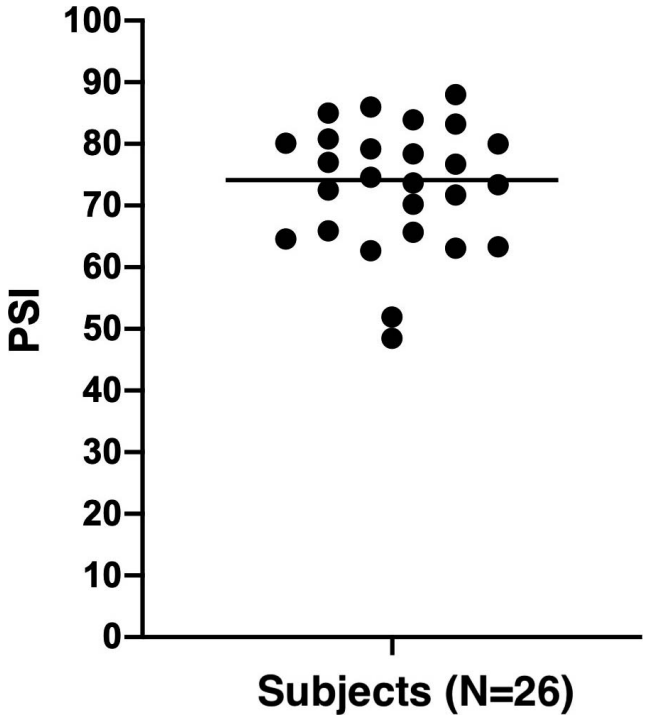
RESULTS

A total of 26 subjects participated in this study and were administered on average 1.5 mg of midazolam and propofol infusions at 3.7 mg/kg/h (61.7 μg/kg/min; Table). The mean (SD) PSI was 72.7 (13.6), and the median (25 percentile, 75 percentile) PSI was 75 (65, 85) for the entire study cohort (Figure). Per the postoperative survey, ~85% reported not remembering much or anything, and 92% reported being "satisfied" with the IV moderate sedation (Table).

DISCUSSION

On both SedLine and bispectral index (BIS) monitors, the depth of anesthesia is calculated as PSI and BIS values, respectively, through electroencephalogram analysis. Previous studies compared the sensitivity and specificity of these 2 monitoring systems for detecting changes in the level of consciousness and indicated that the sensitivity and specificity of SedLine were more favorable than those of a BIS monitor.[2] Furthermore, it was reported that SedLine markedly reduced artifacts

Figure. Scatter plot of mean PSI values during dental treatment.



Each point represents the mean PSI value for an individual subject. The horizontal line represents the mean PSI (72.7) for all subjects. PSI, Patient State Index.

Table. Subject Demographics, Anesthetic Dosing, Treatment Times, and Postoperative Survey Data.

Subject demographics (N = 26)		
Age, mean (SD), y		43.3 (13.3)
Sex, male/female		17/9
Height, mean (SD), cm		159.9 (8.5)
Weight, mean (SD), kg		54.3 (10.3)
Body mass index, mean (SD), kg/m^2		21.2 (3.6)
Anesthetic agents and treatment times		
Midazolam dose, mean (SD), mg		1.5 (0.5)
Propofol dose, mean (SD), mg		154.7 (57.3)
Propofol infusion rate, mean (SD), mg/kg/h		3.7 (0.9)
Propofol infusion rate, mean (SD), mcg/kg/min		61.7 (15)
Treatment time, mean (SD), min		44.0 (16.4)
Postoperative survey		
Amnesia, No. (%)	1. I don't remember it at all	14 (53.8)
	2. I don't remember much	8 (30.8)
	3. I remember most of the procedure	3 (11.5)
	4. I remember it well	1 (3.8)
Satisfaction, No. (%)	1. I was satisfied	24 (92.3)
	2. |	0 (0)
	3. I can't say either way	2 (7.7)
	4. |	0 (0)
	5. I was unsatisfied	0 (0)

during the use of an electric knife in comparison with a BIS monitor.[2]

Soehle et al[3] reported that PSI values during general anesthesia were 10 to 15 points lower than corresponding BIS values. However, no study has compared the 2 values during IV moderate sedation. Sandler and Sparks[4] indicated the relationship between OAA/S scores and BIS values for patients undergoing IV sedation for third molar extraction. According to that study, OAA/S scores of 3 and 4 corresponded to mean BIS values of 81.3 and 87.1, respectively. On the other hand, Drover and Ortega[5] reported the data used for PSI calibration; OAA/S scores of 3 and 4 corresponded to PSI values of ∼67 and ∼73, respectively. These findings are consistent with the data from our study. In comparison with the existing literature, the PSI values observed during IV moderate sedation might be lower than the BIS values.

In conclusion, the mean (SD) and median (25th percentile, 75th percentile) PSI values during IV moderate sedation with MOAA/S score at 3 to 4 were 72.7 (13.6) and 75 (65, 85), respectively.

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Ultrasound-Guided Maxillary Nerve Block and Superficial Cervical Plexus Block During Surgery for Maxillary Malignancy: A Case Report

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We report a case of ultrasound-guided craniocervical nerve blocks performed with ropivacaine for perioperative local/regional anesthesia in a patient who underwent right partial maxillary resection and neck dissection under general anesthesia. The patient was an 85-year-old woman with multiple medical comorbidities in whom analgesia using nonsteroidal anti-inflammatory drugs and opioids was expected to increase the risk of postoperative complications. Bilateral ultrasound-guided maxillary (V2) nerve blocks and a right superficial cervical plexus block were performed, which provided adequate perioperative anesthesia and avoided postoperative complications. The use of ultrasound-guided craniocervical nerve blocks with ropivacaine can be an effective approach for providing prolonged perioperative local anesthesia and analgesia, minimizing the need for other potentially problematic analgesics.

Key Words: Ultrasound guided; Maxillary nerve block; Superficial cervical plexus block; Postoperative analgesia; General anesthesia; Local regional anesthesia.

CASE PRESENTATION

The patient was an 85-year-old woman (height 146 cm; weight 55 kg; body mass index 25 kg/m^2) scheduled for right partial maxillary resection and right neck dissection under general anesthesia as treatment for squamous cell carcinoma of the palate. Her medical history included Alzheimer's disease, diabetes mellitus type 2, hypertension, dyslipidemia, C5-C6 cervical spinal stenosis, gastroesophageal reflux disease, and binocular cataracts. In addition, she also had a decreased forced expiratory volume in the first 1 second/forced vital capacity ratio of 67.3%, indicating moderate obstructive lung disease. Ultrasound-guided maxillary (V2) nerve blocks (UGMNBs) for the maxillary resection and a superficial cervical plexus block (SCPB) for neck dissection were planned to minimize the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Figures 1 and 2 show the affected surgical areas and effective distribution of the right UGMNB and SCPB planned for this case.

General anesthesia was induced using propofol (30 mg) and rocuronium (40 mg), after which the patient was intubated and the nerve blocks performed. A linear probe for the ultrasound imaging system (SonoSite SII, Fujifilm) was used for guidance during the right UGMNB procedure, which was performed by approaching the pterygopalatine fossa transcutaneously from the zygomatic arch.[1] The probe was placed inferior to the zygomatic arch to visualize the maxillary tuberosity and lateral pterygoid plate of the sphenoid bone. The 22-gauge, 80-mm needle (Perican, B. Braun) was inserted at the intersection of the frontal process of the zygomatic bone and zygomatic arch and advanced carefully to avoid damaging the maxillary artery. Normal (0.9%) saline was injected several times during insertion to confirm positioning of the needle tip. When the needle reached the lateral pterygoid plate, 6 mL of 0.375% ropivacaine (22.5 mg) was injected. Because a near-midline incision may be required during tumor resection, a left UGMNB was also performed following the same method.

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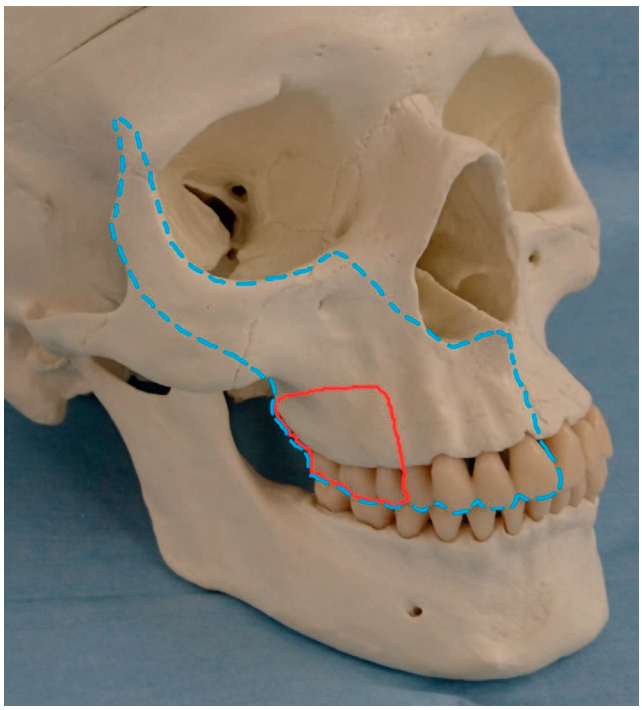
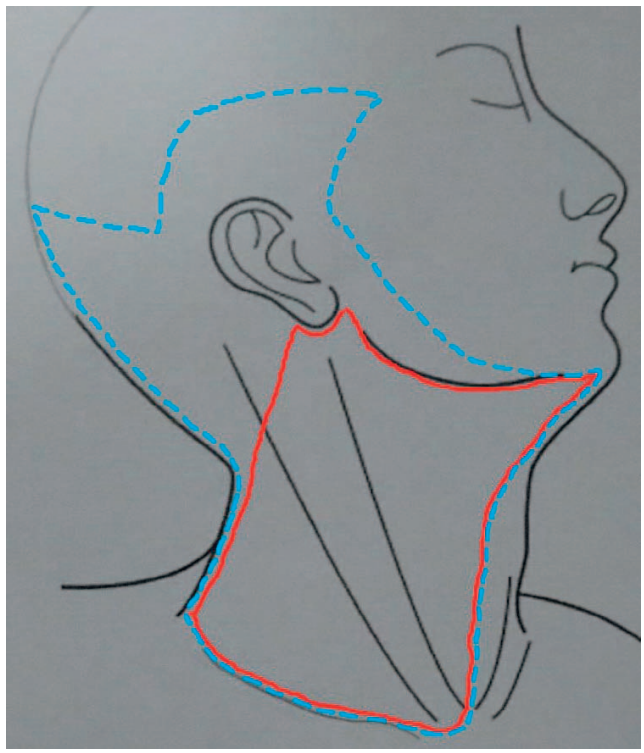
Figure 1. Right Maxillary Partial Resection and Maxillary (V2) Nerve Block.



The red line indicates the anatomic extent of the right maxillary partial resection. The blue dashed line indicates the effective distribution of the right ultrasound-guided maxillary (V2) nerve block.

Figure 2. Right Neck Dissection and Superficial Cervical Plexus Block.



The red line indicates the anatomic extent of the planned right neck dissection. The blue dashed line indicates the effective distribution of the right superficial cervical plexus block.

The right SCPB was performed based on the landmark technique.[2] The patient's head was turned to the left, and a 23-gauge, 25-mm needle (NN-2325N, Terumo) was inserted at the posterior border of the sternocleidomastoid muscle at the level of the second cervical vertebra, and 2 mL of 0.375% ropivacaine (7.5 mg) was then injected subcutaneously.

General anesthesia after intubation was maintained with desflurane (4%), oxygen/air (50/50%; 1-2 L/min), and a remifentanil continuous infusion (0.05 μg/kg/min), and fentanyl (100 μg) was administered only at the end of the surgery in case the nerve blocks were unsuccessful. No significant changes in the patient's vital signs were observed intraoperatively.

Upon emerging from general anesthesia, the patient experienced postoperative shivering for a short period, which resolved. Other postoperative complications associated with general anesthesia, such as delirium, nausea, and vomiting, were not observed during recovery. The patient reported no postoperative pain in her right maxilla and neck, and no other analgesics or antiemetics were used postoperatively.

DISCUSSION

Avoiding or reducing the dose of NSAIDs and opioids helps minimize the risk of associated postoperative complications. Potential problems related to NSAIDs may include gastrointestinal and cardiovascular disorders, impaired platelet function, and renal issues, while opioids can cause nausea/vomiting, constipation, drowsiness, delirium/hallucinations, respiratory depression, and hyperalgesia.[3] Patient recovery from surgery and their prognosis are more favorable in the absence of such complications.

Ropivacaine has 2 major advantages when used for a nerve block: a prolonged analgesic effect (12-24 hours) and less cardiotoxicity than bupivacaine.[4] The ultrasound-guided nerve block techniques used in this case are safe and accurate procedures because they allow real-time visual confirmation of deep anatomical structures and local anesthetic solution delivery as it spreads from the needle tip during injection.[5] These benefits help increase the effectiveness of local anesthetics when used for blocks such as an UGMNB and SCPB. Thus, craniocervical nerve blocks performed with ropivacaine under ultrasound guidance can be effective for providing

perioperative anesthesia for many invasive oral and maxillofacial surgeries.

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Hypotension Without Skin Symptoms at Local Anesthesia in Dental Treatment: Anaphylaxis? Or Vasovagal Reaction?

In 2020, the World Allergy Organization Anaphylaxis (WAOA) Guidance document was published that updated the definition of and amended the criteria for diagnosing anaphylaxis (Table). The WAOA definition now reads as follows: "Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present."[1]

Anaphylaxis is one of the medical emergencies (systemic contingencies) that can occur in dental practice and is a serious, life-threatening allergic reaction.[2,3] It has a rapid onset (minutes to several hours) and includes signs and symptoms such as skin changes, dyspnea (respiratory difficulty), and cardiovascular collapse.[1] Skin changes can include urticaria (hives), erythema, itching, and edema of mucous membranes. Many dentists become convinced that anaphylaxis has occurred upon observing such findings. Although many of these signs and symptoms are typically visible, not all patients experiencing anaphylaxis will have all of them. During anaphylaxis, histamine released from mast cells and/or basophils causes vasodilation, and reflexive tachycardia is generally observed in the early stages as a compensatory reaction.[4] However, bradycardia may also be noted rather than tachycardia.[5]

Vasovagal syncope (VVS) is the most common medical emergency in dentistry (>60%)[6] and is often induced by fear of or pain during the injection of local anesthesia.[7] VVS stems from abrupt changes in autonomic activity: increased parasympathetic activity (ie, increased vagal tone) that leads to bradycardia and decreased sympathetic activity that causes arterial relaxation resulting in hypotension. If the drop in cardiac output and blood pressure (BP) is severe, cerebral blood flow is substantially reduced, and loss of consciousness may occur. Because VVS is a reflex, signs and symptoms are usually observed rapidly (seconds to minutes) following a triggering stimulus. VVS often does not require treatment with medications (eg, atropine), as placing the patient in the Trendelenburg position is usually sufficient. However, administration of atropine may be needed if the VVS episode is severe or unresponsive to patient repositioning. Bradycardia is one of the typical signs noted with VVS, but modest tachycardia may be noted during the prelude to the actual syncopal event. Differentiating between VVS and anaphylaxis may be difficult given that some of the common signs and symptoms may overlap, which may negatively affect diagnosis and treatment.

It has been a point of debate whether dentists should consider nausea and hypotension without skin symptoms after administration of local anesthesia to be anaphylaxis or VVS. Given the low incidence of allergy to local anesthetic agents, particularly amides, and the high incidence of VVS associated with local anesthesia delivery, the likelihood of anaphylaxis remains quite low as compared with VVS. However, dentists following the WAOA Guidance 2020 could erroneously consider such a situation to be anaphylaxis without skin symptoms (Table) and inappropriately administer intramuscular epinephrine. Although epinephrine is first-line treatment for true anaphylaxis, it should ideally be reserved for accurately diagnosed anaphylactic emergencies and carefully administered because of severe systemic side effects such as coronary vasospasm, myocardial infarction, and cardiomyopathy.[8,9]

Key points to consider when differentiating between anaphylaxis and VVS are the differences in heart rate (HR) and BP, the speed of onset and resolution, positioning of the patient, and the likelihood of exposure to offending agents. With VVS, there is often a prelude where the patient becomes quite pale and/or diaphoretic, especially if not in the supine position. Furthermore, the immediate bradycardia and hypotension noted upon loss of consciousness typically resolves relatively quickly following appropriate management (placement into the Trendelenburg position, administration of atropine). Regarding anaphylaxis, patients with cardiovascular involvement would generally be expected to have profound hypotension and tachycardia, even though bradycardia may be seen rarely. In dental patients, exposure to offending agents for anaphylaxis is relatively uncommon outside of known triggers such as antibiotics (eg, penicillin), latex, and neuromuscular blockers. Local anesthetic allergies are so rare they would seem unlikely to fit the definition of a high-risk allergen as presented in the WAOA Guidance 2020 document. Looking at these differences, it appears that the WAOA anaphylaxis recommendations would be inappropriately applied to hypotension in the absence of skin symptoms following

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Table. World Allergy Organization Anaphylaxis Guidance 2020 Amended Criteria for Diagnosing Anaphylaxis[1]

Anaphylaxis is highly likely when any 1 of the following 2 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least 1 of the following: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to nonfood allergens
2. Acute onset of hypotension, bronchospasm, and/or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement

administration of local anesthesia for dental treatment (especially when bradycardia is observed). Therefore, when unsure of the diagnosis (VVS vs anaphylaxis) in these circumstances, dentists should first rule out VVS by appropriately managing it before moving on to anaphylaxis. Once the differential diagnosis shifts from VVS to anaphylaxis, emergency medical services should be immediately activated and preparations made to administer epinephrine. In addition, dental providers must also understand that BP should never be treated without assessing the HR.

Although the WAOA Guidance 2020 document describes hypotension in the absence of skin symptoms after exposure to an allergen as a possible presentation of anaphylaxis, we want to note that hypotension without skin symptoms after local anesthesia in dentistry is more consistent with VVS, not anaphylaxis. All dental providers should be aware of the challenges in how anaphylaxis may present and be able to quickly form a differential diagnosis when a patient experiences signs and symptoms that could be anaphylaxis or VVS.

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Management of Anaphylaxis in Dental Practice

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Anaphylaxis is a potentially fatal systemic complication that can occur as a side effect of dental treatment, oral and intravenous sedation, and general anesthesia. Although anaphylaxis rarely occurs during dental treatment, once it develops, the signs and symptoms progress rapidly and may lead to upper airway obstruction, respiratory distress, cardiovascular collapse, and cardiac arrest; thus, a prompt response is critical for saving lives. When anaphylaxis develops in a dental office, it should be diagnosed and managed immediately. Based on the clinical findings, emergency medical services should be activated and epinephrine administered intramuscularly without hesitation followed by transportation to a hospital facility for further care. It is very important to establish a definitive diagnosis of anaphylaxis after emergent care to identify the causative agent and perform subsequent dental treatment without triggering a recurrence. This review aims to explain the different issues and necessary considerations in managing anaphylaxis in the office-based dental setting based on established guidelines and practical guides for treating anaphylaxis.

Key Words: Anaphylaxis; Basophil activation test; Dental treatment; Epinephrine (adrenaline); Serum tryptase; Skin test.

According to the World Allergy Organization (WAO) Anaphylaxis Guidance 2020, anaphylaxis is defined as "a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death."[1] Severe anaphylaxis is characterized by potentially life-threatening compromise in the airway, breathing, and/or circulation.[1] Moreover, anaphylaxis may occur without typical skin features or cardiovascular shock being present.[1]

The primary pathogenesis of anaphylaxis is an immediate immunoglobulin (Ig) E-mediated allergic reaction. It is impractical to measure IgE during actual clinical diagnosis, and it is difficult to determine an IgE-mediated allergic reaction. For this reason, the term *anaphylactoid reaction* was often used as a broad term encompassing IgE-mediated and non-IgE-mediated reactions. However, the WAO and the European Academy of Allergy and Clinical Immunology (EAACI) have proposed a more comprehensive concept by defining anaphylaxis as "a severe, life-threatening, generalized or systemic hypersensitivity reaction" and suggested that the term *anaphylactoid reaction* should not be used.[2–4] Furthermore, according to the WAO and EAACI, the term *allergic anaphylaxis* should be used for reactions due to immunological mechanisms such as IgE-, IgG-, and immune complex-, complement-, or immune cell-mediated mechanisms, and all other reactions should be known as "nonallergic anaphylaxis."[2–4]

The lifetime prevalence of anaphylaxis is 0.3% to 5.1% worldwide.[1] Although it is a relatively rare reaction, once anaphylaxis develops, its signs and symptoms progress rapidly and can be life threatening; thus, prompt medical attention is required. Anaphylaxis often develops in the perioperative period; however, numerous cases of anaphylaxis caused by various drugs and materials used during dental treatment have been reported.[5–15] Since anaphylaxis is a rare occurrence in the general dental setting, it can be difficult to diagnose quickly and provide appropriate prompt treatment. A previous study reported that knowledge regarding anaphylaxis and the life-saving treatment of anaphylaxis was not significantly different between physicians and dentists ($P = .078$).[16] However, the proportion of dentists who knew the appropriate epinephrine doses for anaphylaxis (14%; 14/98 dentists), administration routes (40%; 39/98 dentists), and proper usage of an epinephrine autoinjector (27%; 26/98 dentists) was significantly lower than that of physicians ($P < .001$).[16] Furthermore, in an assessment

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Table 1. Drugs and Materials That May Cause Anaphylaxis During Dental Treatment.

Product	*Examples*
Drugs	Antibiotics (eg, amoxicillin and penicillin) Analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] and acetaminophen) Antiseptics (eg, chlorhexidine) Sedatives (eg, midazolam, propofol, and dexmedetomidine) Local anesthetics (eg, preservatives [sodium metabisulfite], lidocaine, mepivacaine, prilocaine, and articaine)
Dental materials	Used in endodontics (eg, formaldehyde and sodium hypochlorite) Used in impressions (eg, alginate impression material)
Items with latex	Gloves, bite blocks, prophy polishing cups, dental rubber dams, orthodontic elastics, adhesive tape, anesthetic cartridges, bite wing tabs, impression materials containing latex, masks, and gutta percha

A variety of drugs and materials that can cause anaphylaxis are used in dental office. In particular, antibiotics, latex-containing products, and chlorhexidine are often reported to cause anaphylaxis in dental practice.

of knowledge regarding anaphylaxis involving 286 dentists, only 60% correctly answered "epinephrine" when asked the following question: "Which drug should be used as first-line treatment for anaphylaxis?"[17,18] Thirty-two percent of dentists selected the answers "antihistamines" and "corticosteroids,"[17,18] which are presently not recommended as initial treatment for anaphylaxis.[1,19,20] Furthermore, 40% of dentists did not have epinephrine on hand at their dental offices,[17,18] and only 55% (231/419 dentists) indicated (via self-assessment) that they could manage anaphylactic shock in the dental office themselves.[21] Therefore, it is necessary to ensure dentists have accurate knowledge about anaphylaxis. Hence, this review aims to discuss the necessary considerations and issues in the clinical diagnosis, initial treatment, definitive diagnosis, and identification of the causative agent in cases of anaphylaxis in a general dental office.

ANAPHYLAXIS IN THE DENTAL OFFICE

Epidemiology of Anaphylaxis

Since pain and psychological stress often occur during dental care, it is not uncommon for systemic complications to occur in patients undergoing treatment in a dental office. The most common systemic complications during dental treatment are vasovagal syncope (62%–63%), angina (12%), hypoglycemia (10%), and seizure (7%–10%); as its incidence is only 0.4% to 2.1%, anaphylaxis is considered a rare complication.[21–24] The number of cases of anaphylaxis during dental treatment encountered by a dentist is approximately 0.004 to 0.013 per year, suggesting that a dentist is likely to encounter a case of anaphylaxis once every 77 to 250 years.[23,24] This rate is extremely low compared with that for vasovagal syncope, in which the number of cases likely to be encountered by a dentist is 1.9 per year (i.e., once every 6 months).[23]

Furthermore, some dentists perform intravenous (IV) sedation and general anesthesia in the office-based setting[25]; accordingly, those providers should also know how to manage perioperative anaphylaxis. The incidence of perioperative anaphylaxis varies by region and by study. The most prominent estimated incidence is 0.01% (1 in 10 000 cases of general anesthesia), with a mortality rate of 3.8% to 4.8%, based on studies performed in the United Kingdom and France.[26–28]

Typical Causative Agents of Anaphylaxis in Dental Practice

Various drugs and materials are used in dental practice, many of which can cause anaphylaxis[5–15]; hence, care should be taken when using them (Table 1). Special attention should be observed when using antibiotics such as penicillin, pain medications such as nonsteroidal anti-inflammatory drugs, antiseptics such as chlorhexidine, and latex products in dental practice. Penicillin and amoxicillin are frequently used in dentistry. These antibiotics are classified as β-lactam antibiotics, and cross-reactivity with cephalosporins has been reported, albeit with a low probability of 2%.[29] In addition, Zagursky and Pichichero[30] reported that there is ample evidence to allow for the safe use of all but a few early-generation cephalosporins in patients with penicillin or amoxicillin allergy. They reported that the past belief that penicillin-allergic patients must avoid all cephalosporins should be dismissed as a myth.[30] Therefore, penicillin cross-reactivity may no longer be considered. In the past, performing an intradermal test using a small amount of drug before the IV administration of antibiotics was also recommended. However, this is currently not recommended owing to its poor predictive value for the onset of anaphylaxis.

In a survey of 402 people who visited an allergy clinic due to complaints of allergic reactions associated with local anesthesia, only 0.5% (2 people) had genuine and presumably IgE-mediated allergy to local anesthetics, thus indicating that anaphylaxis related to the use of local anesthetics is extremely rare.[31] It should be noted that

latex-related anaphylaxis is a concern not only for patients but also dental professionals, such as dentists and dental hygienists, who also frequently report occupation-related anaphylaxis due to latex-containing products.[32,33]

Typical Causative Agents of Anaphylaxis During General Anesthesia

A large-scale epidemiological study conducted in France reported that the major causative agents of perioperative anaphylaxis were neuromuscular blocking agents (NMBAs; 58%) used in general anesthesia, latex (20%), and antibiotics (13%).[28] The most common NMBAs that induce anaphylaxis were succinylcholine (33%), rocuronium (30%), atracurium (19%), and vecuronium (10%). Unlike adults, anaphylaxis in children aged 18 years and younger was mainly caused by latex (42%), followed by NMBAs (32%) and antibiotics (9%).[28] The 6th National Audit Project of the Royal College of Anaesthetists (NAP6), a large-scale epidemiological study conducted in the United Kingdom, reported antibiotics (47%), NMBAs (33%), and chlorhexidine (9%) as the primary causes of perioperative anaphylaxis, and the most common NMBAs were rocuronium (42%), atracurium (35%), and succinylcholine (22%).[27] In addition, penicillin antibiotics accounted for half of the antibiotic-induced perioperative anaphylaxis cases that were reported in both the French and NAP6 studies.[27,28] A Japanese survey found that NMBA-reversing sugammadex (28%), rocuronium (22%), cefazolin (17%), and other antibiotics (15%) were the major causative agents of perioperative anaphylaxis.[34] Since 64% of sugammadex-induced anaphylaxis cases are reported from Japan,[35] sugammadex, NMBAs, and antibiotics are considered the major causative agents of perioperative anaphylaxis in Japan. Based on the above findings, the main allergens that induce perioperative anaphylaxis are NMBAs and antibiotics, while latex and sugammadex are also important allergens reported in some regions.

Timing of Anaphylaxis Onset

Anaphylaxis in dental offices is caused mainly by drugs and latex-containing products used during dental treatment. As with anaphylaxis in general, the timing of onset is within several minutes to several hours after exposure to the causative agent. In general, IV administration causes an earlier onset of anaphylaxis and more severe reactions compared with oral administration. Therefore, an observational period of 15 minutes should be used when a drug is administered intravenously, and 2 hours should be used when a drug is administered orally. However, 50% of patients who experience anaphylaxis caused by endodontic disinfectant or sealant (formaldehyde) develop a reaction 2 hours or more (maximum of 12 hours) after treatment; hence, caution should be observed when using this product.[5,6]

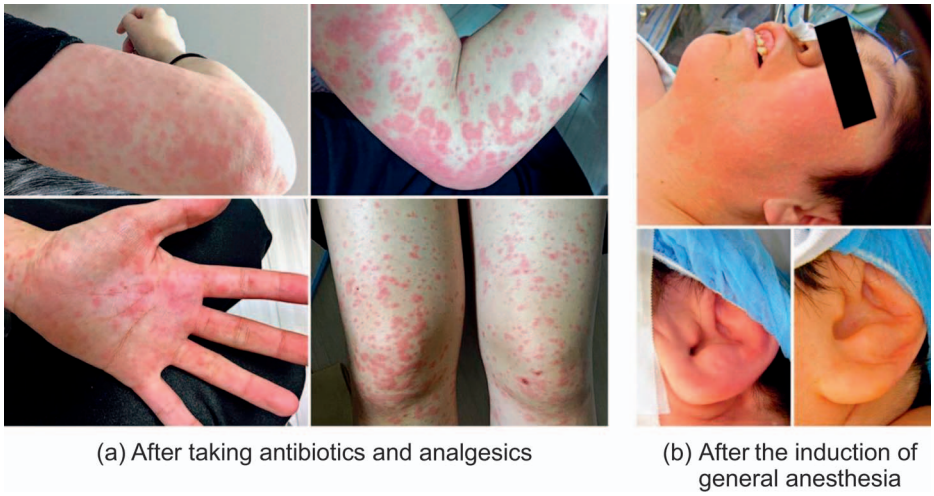
Furthermore, both Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are known as type IV (delayed) hypersensitivity reactions.[36,37] SJS and TEN can be fatal allergic reactions like anaphylaxis that are triggered by the administration of common analgesics, such as acetaminophen and non-steroidal anti-inflammatory drugs, and antibiotics.[36,37] Because SJS and TEN are delayed allergic reactions, they develop hours to days to weeks after drug administration, unlike anaphylaxis.[36] SJS and TEN show early systemic signs and symptoms, including fever, fatigue, a sore throat and mouth, cough, red eyes, and tender, pink skin ~1 to 3 days before a rash develops.[36–38] As the condition worsens, other systemic signs and symptoms include unexplained widespread skin pain, a red or purple rash that spreads, and blisters on the skin, lips, nose, eyes, and genitals. Although SJS and TEN are rare conditions, the mortality rate is 15% to 50% for TEN, 19% to 29% for SJS/TEN overlap, and 5% to 10% for SJS.[36,37] Therefore, SJS and TEN require appropriate diagnosis and management just like anaphylaxis.

Meanwhile, ~81% of perioperative anaphylaxis cases develop after anesthesia induction and before the operation's commencement.[27] This is thought to be due to the increased exposure to NMBAs, antibiotics, and latex-containing products that cause anaphylaxis when anesthesia is induced. In addition, 95% of NMBA-induced anaphylaxis cases occur within 5 minutes after IV administration,[27] 97% of antibiotic-induced anaphylaxis cases occur within 15 minutes after IV administration (74% within 5 minutes, 18% within 6–10 minutes, and 5% within 11–15 minutes),[27] and 72% to 92% of sugammadex-induced anaphylaxis cases develop within 5 minutes after IV administration.[35] Therefore, vital signs should be monitored for at least 5 minutes after the IV administration of NMBAs and sugammadex and at least 15 minutes after the IV administration of antibiotics.

Recognizing Anaphylaxis

During anaphylaxis, signs and symptoms appear throughout the body as the allergen induces the release of large amounts of histamine from mast cells and basophils via various immunological and nonimmunological mechanisms.[1] The main clinical findings of

Figure 1. Skin Involvement and Anaphylaxis



(a) Skin findings developed after the oral administration of antibiotics and analgesics following the extraction of a third molar. (b) Skin findings on the face and ears immediately developed after the induction of general anesthesia. Lower left figure: At the onset of anaphylactic shock. Lower right figure: After treatment of anaphylactic shock.

anaphylaxis are skin or mucosal (Figure 1), respiratory, cardiovascular, gastrointestinal, and central nervous system signs and symptoms (Table 2).[1] The WAO position paper published in 2020 presented the following 2 simplified criteria for diagnosing anaphylaxis[1]:

Diagnostic criterion 1: Acute onset with simultaneous involvement of skin, mucosal tissue, or both (eg, generalized hives; pruritus or flushing; swollen lips, tongue, or uvula) and at least 1 of the following: respiratory compromise, cardiovascular collapse, or severe gastrointestinal symptoms.

Diagnostic criterion 2: Acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

Signs and symptoms were previously thought to develop in multiple organs when anaphylaxis occurred; however, close monitoring should be performed as severe symptoms may appear in only one organ system. It has been reported that skin signs are absent in 10% to 20% of anaphylaxis reactions, which may result in delays recognizing and initially treating anaphylaxis.[1]

Table 2. Typical Signs and Symptoms of Anaphylaxis.

Clinical features	*Frequency (%)*
Skin or mucosa	80–90
Flushing, urticaria (hives), angioedema, rash, erythema, and conjunctival erythema	
Periorbital itching; itching of lips, tongue, palate, external auditory canals, genitalia, palms, and soles	
Edema; swelling of lips, tongue, or uvula	
Respiratory	Up to 70
Nasal: itching, congestion, rhinorrhea, and sneezing	
Throat: itching and tightness, dysphonia, hoarseness, stridor, and dry staccato cough	
Lower airways: chest tightness, deep cough, and wheezing or bronchospasm	
Increased respiratory rate, shortness of breath, and cyanosis; respiratory arrest	
Gastrointestinal	Up to 45
Nausea, vomiting, dysphagia, abdominal pain, and diarrhea	
Cardiovascular system	Up to 45
Chest pain and fainting spells	
Tachycardia, bradycardia (less common), arrhythmias, and palpitations	
Hypotension and shock; cardiac arrest	
Central nervous system	Up to 15
Aura of impending doom, uneasiness, altered mental status, and confusion	
Headache, dizziness, tunnel vision	
Other	Not determined
Urinary or fecal incontinence; metallic taste; cramps and bleeding due to uterine contractions	

Table 3. Considerations When Establishing a Differential Diagnosis of Anaphylaxis.

Difficult-to-differentiate disease and symptoms	*Common symptoms*	*Consideration points*
Vasovagal syncope	Hypotension	Typically relieved by supine positioning; usually associated with pallor and sweating; without urticaria, skin flushing, respiratory or gastrointestinal findings
Anxiety or panic attack	Aura of impending doom, flushing, tachycardia, shortness of breath, and gastrointestinal symptoms	Does not cause urticaria, angioedema, wheeze or stridor, or hypotension
Hyperventilation	Tachycardia, dizziness, and shortness of breath	Does not cause urticaria, angioedema, wheeze or stridor, or hypotension
Acute asthma	Cough, wheezing, shortness of breath, and cyanosis	Does not cause itching, urticarial (hives), angioedema, abdominal pain, or hypotension

When anaphylaxis is differentiated from other conditions, it is easier to make a diagnosis based on skin (eg, itching, rash), respiratory (eg, wheezing, dyspnea), and cardiovascular (eg, hypotension, tachycardia) findings.

In diagnosing anaphylaxis that develops at a dental office, patients should be observed for complaints of anxiety, dizziness, itching, dyspnea, and abdominal pain considering they are often conscious during the early stages of anaphylaxis. In addition, to correctly diagnose anaphylaxis, it should be distinguished from systemic complications that may occur during dental treatment, such as vasovagal syncope, panic or anxiety attacks, and asthma. Table 3 shows the valuable points to consider when developing a differential diagnosis.

The clinical signs and symptoms of anaphylaxis that develop during general anesthesia are not different from those proposed by the WAO, and anaphylaxis is typically diagnosed based on skin and mucosal involvement (eg, flushing; erythema; angioedema; measles-like rash; edema of the lips, tongue, and uvula; palpebral erythema or edema; conjunctival erythema; and palpebral conjunctival hyperemia), respiratory complications (eg, wheezing, bronchospasm, airway narrowing findings on capnography, decreased tidal volume during pressure-controlled ventilation, increased maximum airway pressure during volume-controlled ventilation, and hypoxemia), and cardiovascular complications (eg, rapid drop in blood pressure, tachycardia, bradycardia, arrhythmia, and Kounis syndrome [an acute coronary syndrome, such as coronary spasm and acute myocardial infarction associated with mast cell activation from hypersensitivity including anaphylaxis][39]).[4]

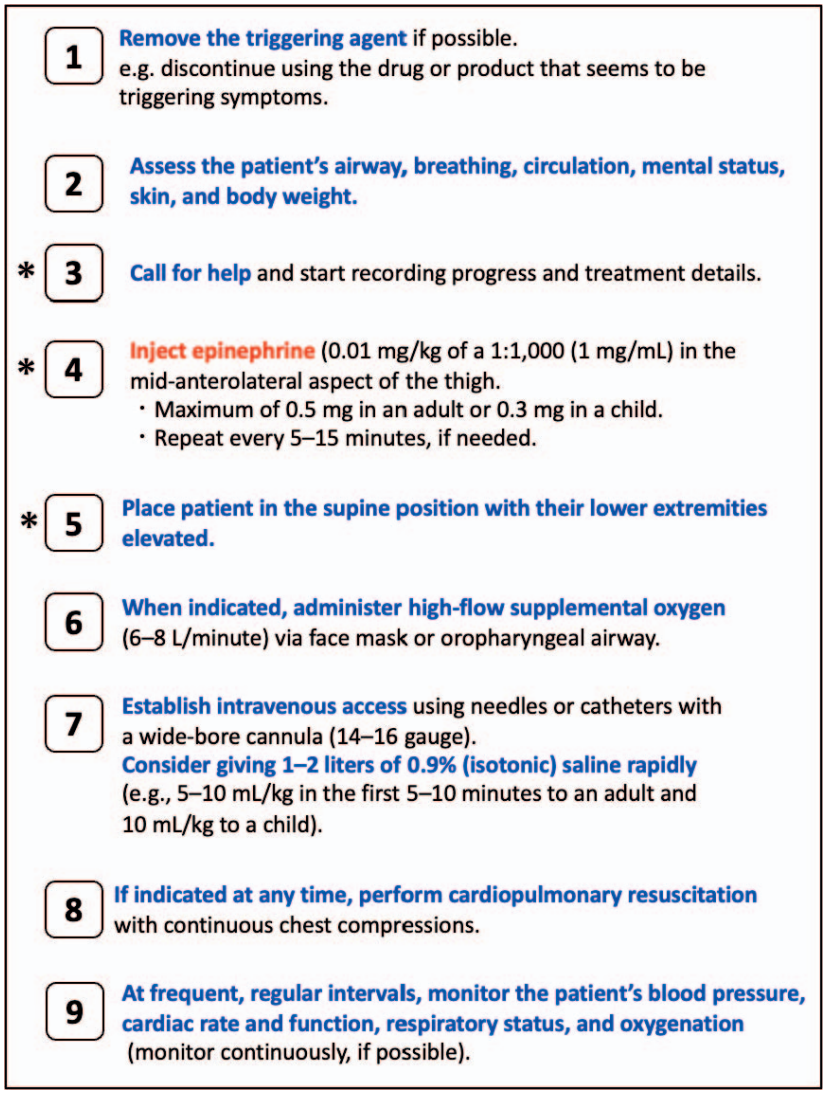
However, caution should be taken, as the early diagnosis of perioperative anaphylaxis during anesthesia can be complicated for the following reasons: (1) the patient may be unconscious and not complain of any symptoms; (2) causative drugs may affect the cardiovascular system during induction, making it difficult to discern whether the cardiovascular complications are due to anaphylaxis or the anesthetic agents; (3) it may be challenging to identify any respiratory complications before the clinical condition worsens because the patient is often intubated and possibly under mechanical ventilation; and (4) skin involvement may not be promptly observed as the patient's body is usually covered with surgical drapes while under anesthesia.

In recent years, skin involvement (flushing or rash), which usually occurs in 90% of patients who experience anaphylaxis, accounted for less than 10% of the initial findings for perioperative anaphylaxis, and rash appeared in only 56% of patients who experienced perioperative anaphylaxis.[27] In a perioperative anaphylactic case that was the first case of anaphylactic shock encountered by the present author within 7 years after becoming a dental/dentist anesthesiologist, epinephrine was administered within only 25 minutes after the onset of anaphylaxis because no skin reactions (a specific symptom of anaphylaxis) were observed, thus preventing the early diagnosis of anaphylaxis.[40] Fortunately, the patient survived the anaphylactic episode, but the delayed initial response was a major reflection point for the present author. Therefore, regardless of the presence or absence of skin symptoms, anaphylaxis should be suspected, and initial treatment for anaphylaxis should be considered and/or initiated when vasopressor-resistant shock occurs, the blood pressure suddenly drops, or airway narrowing or breathing difficulties arise whenever a triggering substance is in use.

Managing Anaphylaxis in the Dental Office

Since the incidence of anaphylaxis in dental offices is extremely low, it is difficult for all dental/dentist anesthesiologists, dental surgeons, and dentists to gain sufficient experience managing this condition. However, once signs and symptoms develop, they progress rapidly, and various treatments should be provided immediately; therefore, emergency protocols that fit each dental practice or institution should be developed and initiated at the time of anaphylaxis onset. In addition, emergency

Figure 2. Management of Anaphylaxis in the Dental Office



Anaphylaxis should be recognized at an early stage, epinephrine should be administered intramuscularly, and the patient should be transported immediately to a hospital.
*Implement steps 3–5 promptly and simultaneously.[1]

simulations should be performed regularly that include anaphylaxis and incorporate team collaboration when managing an emergency.

Initial Treatment of Anaphylaxis.[1] Figure 2 outlines the initial response at the time of anaphylaxis onset. Upon development, anaphylaxis should be promptly recognized. When a patient is diagnosed with anaphylaxis, the first step is to activate emergency medical services (EMS; ie, paramedics and ambulance). Next, potentially triggering substances (eg, drugs, dental materials, equipment or instruments, latex-containing products) should be removed, and the patient's condition should be appropriately evaluated. Assessing a patient's airway, breathing, circulation, mental status, and skin condition is essential for establishing a differential diagnosis of anaphylaxis. The patient should be placed in the supine position, and epinephrine should be administered intramuscularly, ideally in the vastus lateralis (outer thigh), at an early stage. If necessary, the patient should be given high-flow supplemental oxygen via a face mask, IV access should be established using large-bore catheters (ideally 14–16 gauge), and a transfusion of 0.9% saline (5–10 mL/kg for an adult and 10 mL/kg for a child in the first 5–10 min) should be initiated. In addition to these measures, cardiopulmonary resuscitation should be performed if indicated. Preparations should be made to secure the airway for providers capable of doing so. The patient's blood

pressure, heart rate, respiratory status, and oxygenation should be monitored closely, regularly and continuously.

Supplemental medications may include beta-2 adrenergic agonists (eg, albuterol), antihistamines, and glucocorticoids. Antihistamines relieve only skin signs and symptoms and are ineffective against cardiovascular and respiratory involvement.[19] Glucocorticoids may be effective in preventing biphasic reactions; however, they do not alleviate acute anaphylaxis and may even be harmful in younger patients.[1,19] It has been reported that children with anaphylaxis younger than 18 years who received glucocorticoids may be at an increased risk of biphasic reactions.[41] As such, the routine use of glucocorticoids is becoming controversial. Therefore, administering antihistamines and glucocorticoids as initial or primary treatment for anaphylaxis is not recommended. Antihistamines and glucocorticoids can be administered as secondary or tertiary treatment if necessary.[1,19,20,41]

Administration of Epinephrine

In cases of iatrogenic anaphylaxis, the median time from onset to cardiac arrest is 5 minutes.[42] Hence, a prompt diagnosis and timely treatment are critical for saving the patient's life when anaphylaxis occurs. In addition, an absence of skin involvement coupled with the delayed administration of epinephrine leads to fatal anaphylaxis.[43] The incidence of biphasic reactions also increases when the time from the onset of anaphylaxis to epinephrine administration exceeds 30 minutes.[44] Therefore, epinephrine should be administered early when serious cardiovascular and respiratory findings are noted, even in the absence of skin involvement. The proper administration of epinephrine is described below.

Epinephrine in the Dental Office Setting. When a patient develops anaphylaxis in a dental office, epinephrine can be safely administered via intramuscular (IM) injection, which has almost no adverse effects. When epinephrine is administered intramuscularly, it should be injected in the middle of the anterolateral thigh (vastus lateralis). The anatomical landmark for needle insertion is the midpoint of the line connecting the greater trochanter of the femur and the center of the patella with a needle depth well into the muscle tissue. The initial dose of IM epinephrine is 0.01 mg/kg (maximum dose for adults: 0.5 mg; maximum dose for children: 0.3 mg).[1] By age, the recommended doses are 0.01 mg/kg for infants weighing 10 kg or less, 0.15 mg for children aged 1 to 5 years, 0.3 mg for children aged 6 to 12 years, and 0.5 mg for teenagers and adults.[1] The blood concentration of epinephrine peaks within 10 minutes after IM administration and is reduced to half within 40 minutes after administration.[45,46] Korenblat et al[47] reported that 36% (38/105 patients) of patients who developed anaphylaxis required 2 or more doses of epinephrine. Therefore, if epinephrine is administered intramuscularly and the symptoms do not improve, IM injections should be repeated every 5 to 15 minutes.[1,19]

The transient adverse effects of IM epinephrine in adults were reported as pallor (25%; 13/52 injections), tremor (13%; 7/52 injections), heart palpitations (13%; 7/52 injections), headache (6%; 3/52 injections), and shivers and dizziness (2%; 1/52 injections)[5]; those in children included tremor (94%; 16/17 injections), pallor (82%; 14/17 injections), headache (24%; 4/17 injections), tingling of the extremities (18%; 3/17 injections), and nausea (6%; 1/17 injections).[46] However, no serious adverse effects were reported in these studies.[45,46] Therefore, epinephrine should be administered intramuscularly without hesitation. However, IM epinephrine in patients aged 60 years and older increases the incidence of cardiovascular adverse events, especially in those aged 80 years and older (odds ratio: 8.8); hence, elderly patients receiving epinephrine should be thoroughly monitored.[48] If unfamiliar with IM administration using ampule formulations, syringes, and needles, an epinephrine auto-injector (eg, EPIPEN) is recommended. The EPIPEN for adults and children can accurately, quickly, and easily administer 0.3 mg or 0.15 mg of epinephrine, respectively. Therefore, the use of an EPIPEN may eliminate overdose or underdose errors.

Epinephrine in the Perioperative Setting. Epinephrine for the treatment of perioperative anaphylaxis can be administrated intravenously or intramuscularly. The Japanese Society of Anesthesiologists Practical Guidelines recommends IV epinephrine for perioperative anaphylaxis.[4] This is probably because the IV onset of action is quicker than IM and because hemodynamic changes are easy to ascertain while a patient is being thoroughly monitored under general anesthesia. The required doses of IV epinephrine are 0.2 μg/kg at the time of hypotension, 50 to 300 μg at the time of cardiovascular collapse, and continuous IV infusion (0.05–0.1 μg/kg/min) if repeated administration is necessary.[4,49] However, it should be remembered that IV epinephrine is more likely to cause overdose (odds ratio: 61.3) and adverse events (odds ratio: 8.7) than IM epinephrine.[50] When epinephrine is administered intravenously, the present author recommends titrating 10 to 20 μg per dose as relatively safe while monitoring the patient's hemodynamics, although this depends on certain conditions, such as blood pressure. However, if a dentist is not familiar with the use of epinephrine, IM

administration is preferred, even in the perioperative period.

Monitoring After Initial Treatment of Anaphylaxis

After the onset of anaphylaxis, 0.4% to 14.7% of patients may experience biphasic reactions that lead to recurrent anaphylaxis without reexposure to the trigger.[44,51] Patients diagnosed with anaphylaxis should be monitored in a hospital for at least 6 to 8 hours if respiratory symptoms occur and for at least 12 to 24 hours if hypotension occurs.[19] Therefore, if a patient develops anaphylaxis in the dental office, they should be transported emergently to a hospital after initial treatment, regardless of the severity or potential resolution of the allergic reaction.

ANAPHYLAXIS: ESTABLISHING A DEFINITIVE DIAGNOSIS

After the acute management of anaphylaxis, establishing a definitive diagnosis and identifying the trigger are required. Therefore, dental/dentist anesthesiologists should proactively conclude a definitive diagnosis of anaphylaxis and prevent its recurrence. The definitive diagnosis of anaphylaxis has 3 important elements: (1) evaluation of clinical symptoms, (2) measurement of tryptase and histamine levels, and (3) identification of the causative agent by skin tests. Therefore, it is important to reach a definitive diagnosis based on multiple perspectives by combining these factors.[52] The accuracy of identifying causative substances can be improved by combining in vivo and in vitro tests.

The First Piece of Evidence: Assessment of Clinical Signs

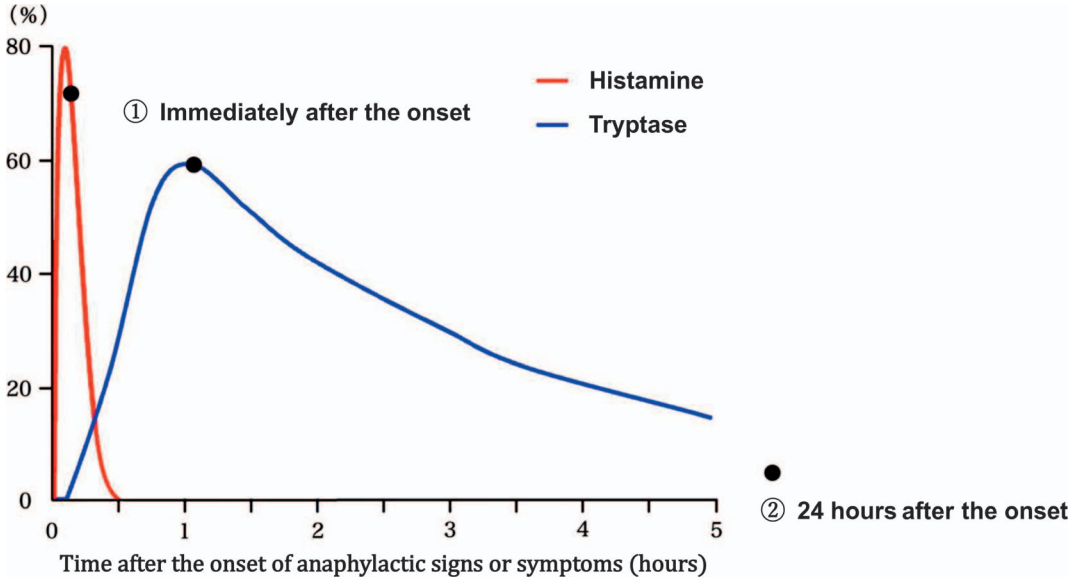
The first piece of evidence in obtaining a definitive diagnosis of anaphylaxis should include the characteristics and severity of clinical findings at the onset of the allergic reaction, the use of suspected allergens (ie, triggers), and the timing of the onset of the allergic reaction. Although various criteria for diagnosing anaphylaxis have already been established based on the clinical presentation, the present article recommends the clinical scoring system for immediate-onset allergic reactions reported by Hopkins et al,[53] which the author frequently uses. This scoring system is specialized for diagnosing perioperative anaphylaxis, and the following 5 categories are assessed: (1) cardiovascular, (2) respiratory, (3) skin or mucosal, (4) combinations, and (5) timing of onset. These categories are scored, and the total score is used to estimate the likelihood of anaphylaxis. Since specialists in immediate-type allergies created this scoring system, it is considered highly reliable and likely to help obtain an objective diagnosis of perioperative anaphylaxis. Anaphylaxis during dental treatment should be evaluated according to the diagnostic criteria proposed by the WAO as previously described.

The Second Piece of Evidence: Serum Tryptase and Histamine Levels

The second piece of evidence is obtained by collecting blood samples after the onset of anaphylaxis and measuring the serum tryptase and histamine levels to confirm the activation of mast cells and basophils. When anaphylaxis occurs, histamine and tryptase are often released from mast cells and basophils into the blood. Therefore, if anaphylaxis is suspected, blood samples should be collected to measure the histamine and tryptase levels when possible.[4] Since tryptase is relatively mast cell selective, an increase in tryptase levels in the blood directly signifies the activation of mast cells. Tryptase levels tend to elevate when anaphylaxis worsens, with median tryptase levels reported as 10.7 μg/L for class III anaphylaxis (cardiovascular collapse, tachycardia or bradycardia, cardiac arrhythmias, or bronchospasm), 66.2 μg/L for class IV (cardiac or respiratory arrest), and 200 μg/L for class V (death).[54]

Histamine levels peak 5 minutes after the onset of anaphylaxis and return to baseline levels 15 to 30 minutes after the onset; hence, blood samples should be taken within 5 to 10 minutes after the onset of anaphylaxis.[4] The WAO position paper recommends blood sampling for histamine levels within 15 to 60 minutes after the onset of anaphylaxis.[55] The plasma concentrations of tryptase increase within 30 minutes after the onset of anaphylaxis and reach a peak within 1 to 2 hours after the onset of anaphylaxis; hence, the optimum timing for blood sampling is 30 to 120 minutes after anaphylaxis onset (Figure 3).[55,56] Blood sampling within 30 minutes or after 180 minutes of onset may not show an increase in the tryptase level; therefore, care should be taken when measuring this parameter.[56] Considering the half-life of histamine, it is easier to measure the tryptase level than the histamine level; therefore, blood sampling should be performed to at least measure the tryptase level. In addition, blood sampling for histamine and tryptase should be performed at the time of anaphylaxis onset and after 24 hours, and the measured values at these 2 times should

Figure 3. Changes in Blood Concentrations of Histamine and Tryptase After the Onset of Anaphylaxis



When anaphylaxis occurs, mast cells and basophils release histamine and tryptase. To diagnose anaphylaxis, blood samples should be collected at 2 times: the onset of anaphylaxis and after 24 hours. Histamine and tryptase levels should be compared.

be compared. The activation of mast cells is indicated when the serum acute tryptase level at the onset of anaphylaxis is higher than the following calculated value [serum baseline tryptase level (value at 24 hours after onset) × 1.2 + 2].[56] This formula has a 94% positive predictive value, 53% negative predictive value, 75% sensitivity, 86% specificity, and a Youden's index value of 0.61.[57] However, anaphylaxis cannot be ruled out even when tryptase levels are not elevated. Since few studies have reported a cutoff value for histamine in diagnosing anaphylaxis, further research is warranted to explore this matter further.

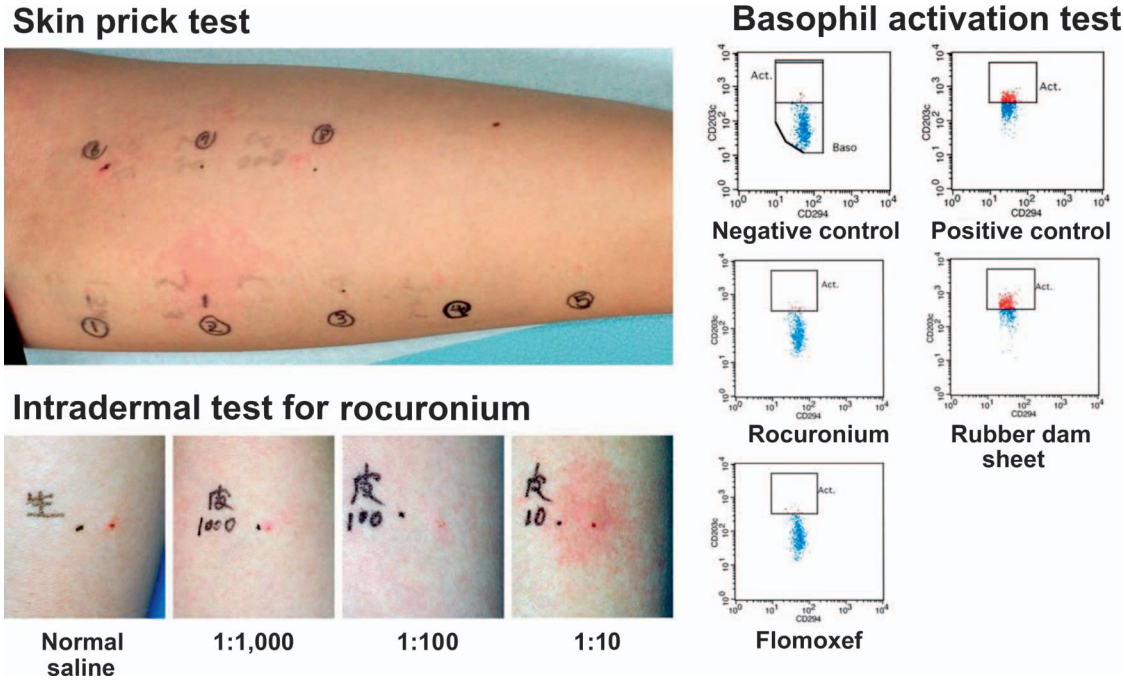
The Third Piece of Evidence: Identification of Causative Agents

The third piece of evidence is obtained using skin and blood tests to identify the causative agent of anaphylaxis (Figure 4). Currently, skin testing performed within 4 to 6 weeks after the onset of anaphylaxis is considered the gold standard for determining the causative agent.[4] However, it should be noted that the diagnostic accuracy of this method is 72.9%; it is not always 100% accurate.[58] The skin prick test (SPT) is initially performed; if the SPT result is negative, an intradermal reaction test is carried out.[4] As anaphylaxis can recur during the skin test, with incidence rates of only 0.4% for SPT and 3.2% for an intradermal test,[59] and because these tests are invasive and cause pain, many parents of pediatric patients are against using these tests. Therefore, performing a combination of in vitro tests (with less risk and burden on the patient) can make it easier to obtain the patient's cooperation in undergoing the tests and improve their diagnostic accuracy. The dilution ratios of reagents used for skin tests are provided in Australian and New Zealand guidelines, which are helpful.[60]

Since drug-induced lymphocyte stimulation testing is used only for determining class IV allergies, it is not a suitable tool for diagnosing anaphylaxis.[4] Most reagents used for allergen-specific IgE tests are foods, plants, animals, and latex, and it is difficult to use muscle relaxants during allergen-specific tests, as they frequently trigger perioperative anaphylaxis.[4] As β-lactam antibiotics do not have high sensitivity and specificity, using these drugs for routine testing is meaningless.[4]

In recent years, the basophil activation test (BAT) has attracted attention as an in vitro test for identifying the causative agent of anaphylaxis.[4,61,62] The BAT does not induce anaphylaxis recurrence, and obtaining the patient's or parent's consent for this test is easy. It is also very versatile, as it can also be tested with the products actually used during dental treatment (rubber dam sheets, etc).[63] Moreover, the BAT has high diagnostic accuracy for rocuronium (sensitivity: 92%, specificity: 100%) and sugammadex (sensitivity: 88%, specificity: 100%), likely triggers for perioperative anaphylaxis.[61,62] Accordingly, this test may be helpful for the identification of triggers of perioperative anaphylaxis. However, because of some disadvantages

Figure 4. Skin Prick and Basophil Activation Tests



Example of a skin prick test: 1. normal saline (negative control), 2. histamine (positive control), 3. fentanyl, 4. remifentanil, 5. atropine, 6. piperacillin, 7. propofol, and 8. rocuronium. All skin prick tests showed negative results. Intradermal skin test for rocuronium showed positive result at 10-fold dilution (15 minutes later, wheal: 5 × 7 mm; erythema: 25 × 22 mm). Basophil activation test showed that rocuronium and flomoxef were negative results, and a rubber dam sheet was a positive result.

of the BAT, such as the need for fresh blood samples, the need to perform the test within the recommended 4 hours after blood collection,[4] the possibility of false-negative or false-positive test results, and the small number of institutions that can perform tests requiring a flow cytometer, the results should be carefully interpreted and the findings of other skin tests should also be considered.

Simulation Training for Anaphylaxis in the Dental Office Setting

Since anaphylaxis rarely occurs during dental treatment, it is important to perform routine simulations that include the initial treatment of anaphylaxis. Kishimoto et al[64] reported that when they simulated anaphylaxis using a software application, the percentage of respondents who answered, "I can treat anaphylaxis adequately" increased from 6% to 42% before and after the simulation training. Tan[65] reported that simulation activity using a human patient simulator is an acceptable and valuable technique to help improve confidence in managing crisis situations that may occur in dental offices. Therefore, to save lives, it is important to create a protocol for anaphylaxis that suits each dental office and conduct regular simulations with all staff.

CONCLUSION

Since the signs and symptoms of anaphylaxis progress rapidly once it develops, prompt diagnosis and timely treatment are necessary in out-of-hospital settings. In such situations, regardless of the presence or absence of skin symptoms, it is important to suspect anaphylaxis, quickly activate EMS, and immediately administer appropriate doses of epinephrine if respiratory or cardiovascular symptoms are present. In addition, a definitive diagnosis of anaphylaxis should be obtained, and the causative agent should be identified after managing the anaphylactic emergency.

AUTHOR NOTE

Written consent was obtained from all patients to publish patient information related to this contribution. There are no organizations with conflicts of interest that should be declared in relation to this contribution.

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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.

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

1) Cutaneous involvement (i.e., signs and symptoms) is not obligatory for diagnosing anaphylaxis.

   a. True
   b. False

2) Which of the following is the drug of choice for the initial treatment of anaphylaxis?

   a. Albuterol
   b. Diphenhydramine
   c. Epinephrine
   d. Prednisone

3) Which of the following sites is most ideal for administering intramuscular (IM) epinephrine?

   a. Masseter muscle
   b. Pectoral muscle
   c. Rectus abdominis muscle
   d. Vastus lateralis muscle

4) Which of the following is necessary for obtaining a definitive diagnosis of anaphylaxis?

   a. Aspartate aminotransferase
   b. Platelet count
   c. Tryptase level
   d. White blood cell count

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

Aziz M, Berkow L. Pro-con debate: videolaryngoscopy should be standard of care for tracheal intubation. Anesth Analg. 2023;136(4):683-688. doi: 10.1213/ANE.0000000000006252.

This debate compares the benefits and limitations of video laryngoscopy (VL). There is compelling evidence that VL improves first-pass success rates, reduces the risk of intubation failure and esophageal intubation, and has benefits in the difficult-airway patient. But VL is not without complications and does not possess a 100% success rate. In the case of failure, it is important to have backup plans for airway management. Although transition of care from direct laryngoscopy (DL) to VL may result in improved airway management outcomes, strict reliance on VL may degrade other important clinical skills when they are needed most. If VL is adapted as the standard of care, airway managers may no longer practice and retain competency in other airway techniques that may be required in the event of VL failure. Although cost is a barrier to broad implementation of VL, those costs are diminishing over time. However, it may still be challenging for institutions to secure purchase of a video laryngoscope as well as backup airway devices for every intubating location. As airway management care increasingly transitions from DL to VL, providers should be aware of the benefits and risks to this practice change.

Comment: It is important to clarify the terms *standard* and *standard of care* as used in this paper. The term *standard* derives from the work of D. M. Eddy,[1,2] who differentiated standards, guidelines, and recommendations in the context of health care practice policies. Standards are meant to be rigidly followed in almost all circumstances, whereas guidelines are recommendations that should be followed but allow flexibility, depending upon a clinician's assessment of the circumstances and clinical judgment. In contrast, *standard of care* is a legal term that defines the expectations for care provided under similar circumstances by an average health care practitioner in the group to which the practitioner belongs.[3] Differentiating these terms is important for understanding both the practical and legal implications of assigning the term "standard of care" to VL.

This pro-con paper debates the question of whether DL should be considered "standard of care" or a "standard." However, both the article and the accompanying editorial[4] frame the debate with circumstances normally encountered in a hospital or ambulatory surgery center. For example, DL and VL are compared in the contexts of managing the known difficult airway, intubating patients with a full stomach, and intubating pregnant women requiring emergency cesarean section. The debate also describes significant shortcomings for VL regarding pediatric intubation, the unanticipated difficult airway, cardiopulmonary resuscitation, and the cost and practical aspects of maintaining proper infection control for routine use of video laryngoscopes. Although recommendations for the office-based setting are not specifically addressed, the debate tends to support a recommendation for having both DL and an appropriate method of VL available, depending upon the experience of the provider and nature of the procedure.

Xiao H, Liu M, Man Y, Wei Y, Ji F. Effect of low-dose propofol combined with dexamethasone on the prevention of postoperative nausea and vomiting in gynaecological day surgery under remimazolam-based general anesthesia. Medicine (Baltimore). 2023;102(10):e33249. doi: 10.1097/MD.0000000000033249.

This study examined the effectiveness of low-dose propofol combined with dexamethasone for preventing postoperative nausea and vomiting (PONV) in women undergoing total intravenous anesthesia for ambulatory gynecologic surgery with remimazolam and alfentanil. Three antiemetic regimens were compared: dexamethasone 5 mg alone, dexamethasone 5 mg combined with droperidol 1 mg, and dexamethasone 5 mg combined with propofol 20 mg. A total of 120 patients were randomized into 3 equal groups receiving one of the described regimens. The primary outcomes were PONV in the postanesthetic care unit (PACU) and PONV reported within 24 hours after surgery. In the PACU, patients in groups receiving either the dexamethasone/droperidol combination or the dexamethasone/propofol combination showed less PONV than those in the dexamethasone only group ($P < .05$). Within 24 hours after operation, there was no significant difference in the incidence of PONV among the 3 groups, but the incidence of vomiting in the groups receiving dexamethasone/droperidol or dexamethasone/propofol was significantly lower than that in the dexamethasone alone group ($P < .05$). The authors concluded that dexamethasone in combination with low-dose propofol was similar to the combination of dexamethasone and

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droperidol for preventing PONV in gynecologic surgery with remimazolam and alfentanil.

Comment: The reported incidence of nausea and vomiting in patients undergoing gynecological surgery is 60% to 83% in the absence of a prophylactic antiemetic. Remimazolam, although displaying several desirable properties for ambulatory anesthesia, has been shown to be inferior to propofol in preventing PONV. Furthermore, the combination of remimazolam and alfentanil for gynecologic surgery has been shown to be associated with a high incidence of PONV. Considering these factors, the efficacy of the dexamethasone/propofol combination demonstrated in this study is impressive and encouraging.

Remimazolam has been suggested as a promising drug for dental office–based sedation and general anesthesia.[5] To date, there is only 1 published randomized clinical trial reporting the use of remimazolam in a dental setting; however, it did not investigate PONV as an outcome, and the depth of anesthesia was not comparable to the depth reported in this study.[6] Several factors need to be considered when trying to determine if this antiemetic strategy could be applied to dental office–based sedation and general anesthesia. The study population in this study by Aziz and colleagues is small; however, looking at the data, the effect is clearly demonstrated and significant, despite having an $n = 40$ for each of the 3 groups. Aziz and colleagues examined anesthetics that used mivacurium, whereas most dental office–based anesthetics do not routinely include muscle relaxants. Dental office–based anesthetics may also involve additional emetogenic factors, such as the perioperative ingestion of blood and the use of ketamine during induction. Further studies that examine the use of remimazolam for dental office–based sedation and general anesthesia are needed.

Dijk H, Hendriks MP, van Eck-Smaling MM, van Wolfswinkel L, van Loon K. Age-stratified propofol dosage for pediatric procedural sedation and analgesia. Anesth Analg. 2023;136(3):551-558. Published online February 17, 2023. doi: 10.1213/ANE.0000000000006196. PMID: 36136079; PMCID: PMC9907688.

Currently, a schedule for age-stratified propofol induction and maintenance dosage for pediatric sedation and analgesia is not available, despite the long-standing need for such information. This retrospective cohort study examined records of children who received procedural sedation at a large tertiary pediatric hospital in the Netherlands. A total of 6438 pediatric procedures were retrieved from Anesthesia Information Management Systems. Of those, 5567 records were available for induction dose analysis, and 5420 records were available for analysis of the maintenance dose. After adjustment for sex, American Society of Anesthesiologists physical status classification, opioid administration, and diagnostic or interventional procedures, the authors obtained a coefficient of –0.11 (95% CI, –0.12 to –0.11) for age (years) from a multivariable linear regression model for propofol induction dosage ($mg \cdot kg^{-1}$) and a coefficient of –0.36 (95% CI, –0.39 to –0.34) for age (years) for propofol maintenance dosage. A noteworthy inverse age effect was discovered on propofol dosage for both induction and maintenance of pediatric procedural sedation. This study also revealed that remarkably higher propofol sedation doses were needed for infants and toddlers than previously expected and reported.

Comment: The package insert provided by Pfizer recommends an induction dose of 2.5 to 3.5 mg/kg for most patients between 3 and 16 years of age, adjusting for physical status and the concomitant use of opioids and/or benzodiazepines. For children less than 3 years of age, larger doses are anticipated but not defined. Similarly, maintenance dosing is not well defined in the insert; however, subsequent publications report an approximate maintenance dose of 9 to 12 mg/kg/h for children ages 1 to 3 years.[7] The linear regression analysis in this study suggests an adjusted dosing formula of 4.45 + age (years) to determine the mg/kg induction dose. An adjusted dosing formula of 17.74 + age (years) was similarly derived to determine the mg/kg/h maintenance dose. Readers are referred to the paper for details on the variance and adjustments for these formulas and a graphical representation of dosing for children up to age 18.

Summaries and comments provided by

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