Topical Anesthesia for Endoscopic Office-based Procedures of the Upper Aerodigestive Tract

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Summary: Objective. Over the last two decades, an increase in office-based procedures under topical anesthesia in laryngology and head and neck oncology has occurred. Adequate anesthesia in the nasal cavity, pharynx, and larynx is essential for successful performance of these procedures. Our goal is to provide an objective summary on the available local anesthetics, methods of application, local secondary effects, efficacy, and complications.

Material and Methods. A descriptive review of literature on topical anesthesia for office-based procedures in laryngology and head and neck oncology was performed.

Results. Lidocaine is the most applied and investigated topical anesthetic. Topical anesthesia results in decreased sensory function without impairing motor function of the pharynx and larynx. For the nasal cavity, cotton pledgets soaked in anesthetic spray and decongestant, or anesthetic gel, are effective. For the pharynx, anesthetic spray is the most frequently used and effective method. For the larynx, applying local anesthesia through a catheter through the working channel of the endoscope or anesthetic injection through the cricothyroid membrane is effective. Studies comparing the most effective application methods for each anatomical site are lacking. Complications of topical lidocaine administration are rare.

Conclusions. By properly applying topical anesthesia to the upper aerodigestive tract, several surgical procedures in laryngology and head and neck oncology can be performed in the outpatient clinic under topical anesthesia instead of the operating room under general anesthesia. Lidocaine is the most investigated anesthetic, with adequate efficacy and few complications. Studies that determine the most effective application methods are still wanting.

Key Words: Topical anesthesia—Office-based procedure—Head and neck oncology—Upper aerodigestive tract—Larynx.

INTRODUCTION

The use of topical anesthesia, in combination with the more recent development of flexible transnasal laryngoscopes with a working channel, has led to an increase in performance of so-called office-based procedures in laryngology and head and neck oncology over the past 2 decades.[1,2] Currently, a wide variety of procedures are performed under topical anesthesia, such as flexible endoscopic biopsy, transnasal esophagoscopy, and endoscopic laser surgery.[3,4] To successfully perform office-based procedures, patient cooperation and adequate topical anesthesia are essential.[5]

Cocaine was the first agent used to provide local anesthesia for the upper aerodigestive tract in the late 19th century. The method of action of local anesthetics is based on the blocking of voltage-gated sodium channels that are present on the cell membranes of nerves and muscles. Blocking of these channels prevents initiation or propagation of action potentials thereby achieving local anesthesia.[6] Since the introduction of cocaine as a local anesthetic, a spectrum of new synthetic topical anesthetics have been developed, which are summarized for the upper aerodigestive tract in Table 1.

With the wide variety of local anesthetics available, it remains unclear which local anesthetics and which methods of application are available and provide the best conditions for office-based procedures of the upper aerodigestive tract. Therefore, we conducted a systematic literature search to try to answer these questions in a descriptive review, for office-based procedures of the pharynx and larynx. For each anatomical site, the most frequently used anesthetics, the available methods of application, and local secondary effects are highlighted. Furthermore, efficacy and safety of topical anesthesia of the upper aerodigestive tract are outlined. Our purpose is to provide an objective summary of the available literature, to be used for guidance of physicians who are interested in performing office-based procedures for the pharynx and larynx.

MATERIAL AND METHODS

A literature search was performed in the PubMed (MEDLINE), EMBASE, and Cochrane Library databases. Keywords and MeSH terms include, among others, "local anesthesia," "topical anesthesia," "infiltration anesthesia," "outpatients," and "ambulatory surgical procedures." These terms were combined with "pharynx," "larynx," and "esophagus." Inclusion criteria were articles reporting on topical anesthesia or office-based procedures for the pharynx, larynx, and proximal esophagus (ie, biopsy, laser surgery, vocal cord injection, transnasal esophagoscopy, esophagus balloon dilatation,

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TABLE 1.
Local Anesthetics in Laryngology and Head and Neck Oncology

	Lidocaine	Cocaine	Tetracaine	Prilocaine	Ropivacaine	Bupivacaine	Benzocaine
Concentration	2% (20 mg/mL) 2.5% (25 mg/mL)	4% (40 mg/mL)	0.25% (2.5 mg/mL)	1% (10 mg/mL)	0.2% (2 mg/mL)	0.25%	14% (140 mL/mL)
	4% (40 mg/mL)	10% (100 mg/mL)	0.5% (5 mg/mL)	2% (20 mg/mL)	0.75% (7.5 mg/mL)	(2.5 mg/mL)	20% (200 mg/mL)
	5% (50 mg/mL) 10% (100 mg/mL)		1% (10 mg/mL)		1% (10 mg/mL)	0.5% (5 mg/mL)	
Type	Amide	Ester	Ester	Amide	Amide	Amide	Ester
Administration	Solution Aerosol Ointment Jelly Viscous	Solution	Solution	Infiltration	Infiltration	Infiltration	Spray
Maximum dosage	200–600 mg (solution) 600 mg (jelly) 300 mg (viscous)	1–3 mg/kg	100–200 mg	500 mg	Unknown*	75 mg	Unknown*
Onset	2–5 min	1–5 min	3–8 min	2 min	10 min	1–15 min	0.5 min
Effective duration	15–60 min	30–60 min	30–60 min	2–3 h	0.5–6 h	1–12 h	10–15 min
Complication	Unknown*	More systemic side effects, more toxic in combination with epinephrine	Possible cardiac toxicity	Unknown*	Possible cardiac and central nervous system toxicity	Possible cardiac and central nervous system toxicity	Possible methemoglobinemia

*Not mentioned or found in the included literature.

secondary tracheal-esophageal puncture, esophagus sphincter injection, and foreign body removal). Furthermore, articles had to be in English or Dutch, and full text had to be available. Exclusion criteria were articles reporting on surgery procedures other than the abovementioned, procedures performed under sedation, general anesthesia, or which did not mention the type of anesthesia used, and other languages besides English and Dutch. The included studies were published without a date limitation. Figure 1 shows the search strategy in a diagram.

The initial search was conducted in April 2016, which identified 4790 articles. Duplicate articles were removed, leaving 3715 articles. Four hundred and seventy-six articles were included; full text articles were obtained using the stated databases, Google Scholar, and the institutional medical library. Five articles could not be obtained through the medical library and were thus excluded.

After reading all of the full texts, 72 articles were included. Three articles were added after searching through the references of the included articles. This resulted in a total of 75 articles included for this review.

RESULTS

Topical anesthesia of the nasal cavity

For the nose, a combination of a local anesthetic with a vasoconstricting and decongesting component (eg, oxymetazoline or epinephrine) can be used in spray or drained in cotton pledgets.[7−12] Although no studies were found that investigated the most effective duration of leaving cotton pledgets in the nasal cavity, up to 15 minutes has been reported.[10] The included studies did not mention the maximum dosage of topical anesthesia that can be safely applied in the nasal cavity. Anesthetic gel is an alternative to spray or gauze pledgets.[13] Table 2 provides an overview of included studies that investigated topical anesthesia for the nasal cavity.[12−15]

Gauze pledgets soaked in local anesthesia or anesthetic gel seem to provide more adequate nasal anesthesia compared with anesthetic spray, when a wide diameter transnasal endoscope (eg, transnasal laryngoscope with working channel or esophagoscope) is used.[12,13] Although transnasal laryngoscopes usually have a smaller outer diameter compared with transnasal laryngoscopes with working channel or transnasal esophagoscopes, Özkiriş et al still found that topical nasal anesthesia with gauze pledgets resulted in less nasal pain (measured with visual analogue score) during endoscope insertion compared with a saline solution, for a transnasal laryngoscope with a 4.2-mm diameter. The authors did not investigate the effect of topical anesthesia for the pharynx or larynx. The results of the study by Frosh et al showed, that when an even smaller transnasal laryngoscope (ie, 3.7-mm diameter) is used, topical anesthetic spray is no longer beneficial for nasal pain reduction upon endoscope insertion.[15]

Topical anesthesia of the pharynx

Studies investigating the anesthetic effect of topical anesthesia on the pharynx during transoral endoscopy are summarized in Table 3.[16−27] Spraying of the pharynx is one of the oldest and most used methods of topical anesthesia. By spraying the oral cavity first, the patient gets acquired to the bitter taste and effect of the anesthetic.[9,11] Afterward, spraying in the oropharynx while letting the patient inhale deeply often results in coughing and thus spreading of the anesthetic in the pharynx and larynx.[9] Alternative methods for topical anesthesia of the pharynx are anesthetic lozenges[26] or gargling of a viscous anesthetic solution, which should not be swallowed for at least 5 minutes.[8,24,25] After all pharyngeal and laryngeal anesthesia administration, patients should be advised to remain nil per os for 60 minutes after application to prevent aspiration.[5,7] Studies that compared different application methods found anesthetic spray to result in more adequate pharyngeal anesthesia, compared with alternative application methods.

Different types of topical anesthetics used and compared with sedation, placebo, or a control group are summarized in Table 3. Overall, lidocaine was the most investigated topical anesthetic. Lidocaine resulted in less discomfort for patients during endoscopy, and endoscopists found the procedure easier to perform, compared with placebo or no anesthesia. When sedation was used, patients experienced less discomfort compared with topical anesthesia, although again endoscopists found the procedure better to perform under topical anesthesia.

Several studies investigated the effect of topical anesthesia on sensory and motor function of the pharynx. Ertekin et al investigated the effect of 220−240 mg lidocaine spray on swallowing function in 12 healthy volunteers.[28] The participants received sips of water ranging from 3 to 20 mL. Laryngeal movements were measured using a piezoelectric (ie, electricity resulting from pressure) device. Five volunteers showed early-stage aspiration and only one volunteer swallowed 20 mL of water, after which dysphagia occurred. The effect of anesthesia lasted 3−6 minutes. Chee et al investigated the effect of topical anesthesia on pharyngeal swallowing and sensation.[29] Twenty participants randomly received placebo, 10 mg, 20 mg, and 40 mg of lidocaine spray once, each on different days. Afterward they underwent swallowing and sensation tests. Sensation was significantly affected for the 20-mg and 40-mg doses, but not for the 10-mg dose. The 40-mg dose lasted for 60 minutes, whereas the 20-mg dose lasted 30 minutes, which significantly differed. Although swallowing capacity was not significantly affected, the swallowing speed was significantly reduced in all groups and mostly with 40 mg of lidocaine. Mansson and Sandberg compared topical anesthesia with placebo for oropharyngeal sensitivity and oropharyngeal dry swallowing (ie, saliva).[30] Participants who received topical anesthesia had significant increase in swallowing time, with an average increase of 67%. Additionally, the same authors found unchanged proximal esophageal swallowing function after topical anesthesia with lidocaine.[31] However, when higher doses of lidocaine were administered, contraction of the pharynx was significantly prolonged and relaxation of the proximal esophageal sphincter was significantly shortened.

Topical anesthesia of the larynx

The results of studies investigating the anesthetic effect of topical anesthesia on the larynx are summarized in Table 4.[33−41]

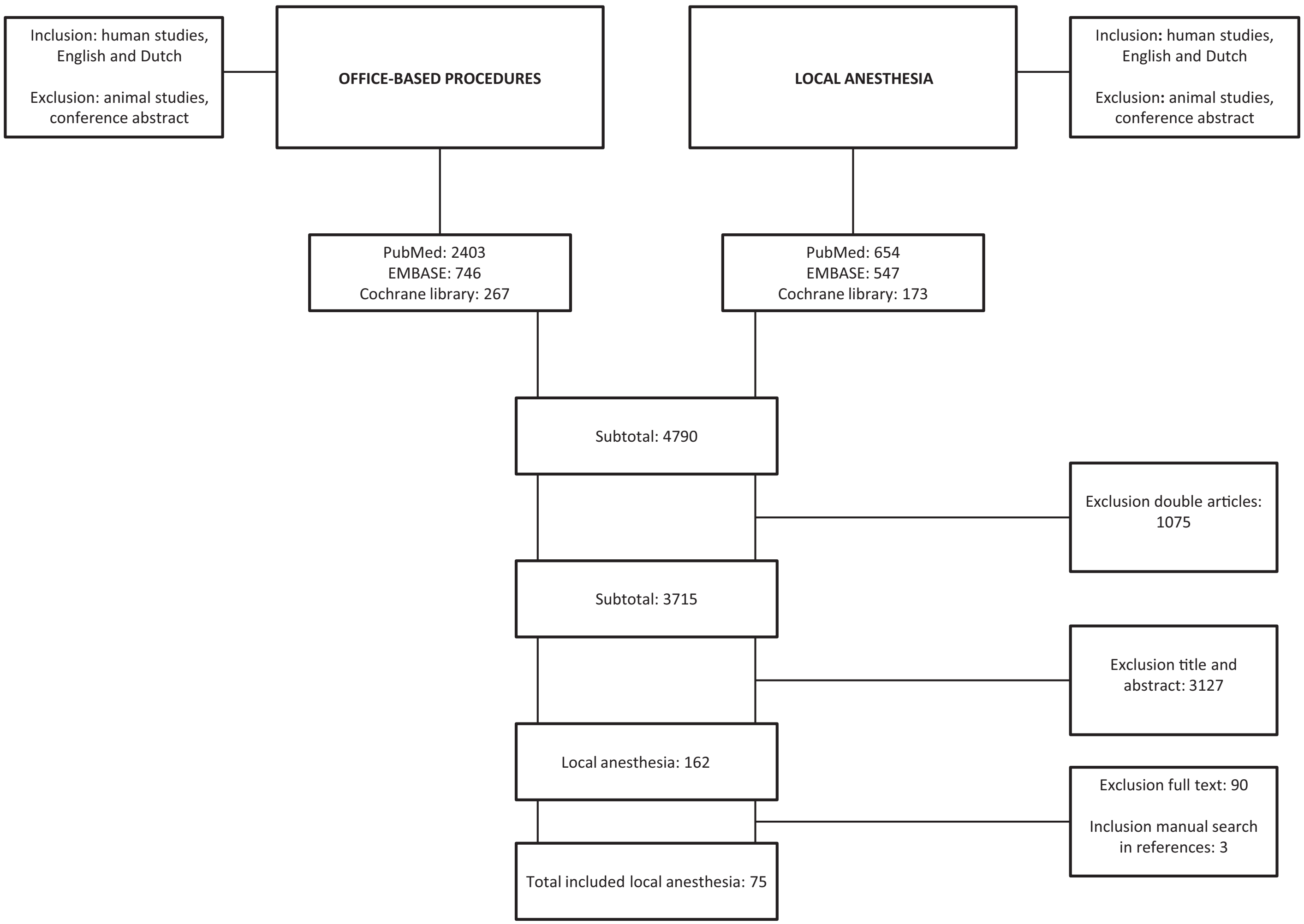

FIGURE 1. Search strategy.

TABLE 2.
Topical Anesthesia for the Nasal Cavity

Author (Study Method)	Type of Endoscopy (Diameter)	Study Population	Topical Anesthetic (Dosage)	Application Method	Effect
Hu 2010[12] (randomized controlled study)	Transnasal esophagogastroduodenoscopy (5.9 mm)	240	4% Lidocaine (2 mL) + 1:1000 epinephrine	Aerosol	Nasal anesthesia: gauze pledgets > aerosol
			2% Lidocaine + 4% lidocaine (dosage unknown)	Gauze pledgets	
Zainudin et al 1993[13] (randomized study)	Fiberoptic bronchoscope (unknown)	25	10% Lidocaine (100 mg)	Spray	Nasal anesthesia: gel > spray
		30	2% Lidocaine (100 mg)	Gel	
Özkiriş et al 2014[14] (randomized placebo-controlled study)	Fiberoptic transnasal laryngoscopy (4.2 mm)	40	10% Lidocaine (0.3 mL)	Gauze pledgets	Nasal anesthesia: lidocaine and prilocaine > ropivacaine and bupivacaine > saline solution
		40	2% Prilocaine (dosage unknown)	Gauze pledgets	
		40	0.2% Ropivacaine (dosage unknown)	Gauze pledgets	
		40	0.25% Bupivacaine (dosage unknown)	Gauze pledgets	
		40	Saline solution	Gauze pledgets	
Frosh et al 1998[15] (double-blinded randomized controlled study)	Fiberoptic transnasal laryngoscopy (3.7 mm)	82	10% Lidocaine (20 mg)	Spray	Nasal pain insertion endoscope: lidocaine < saline solution < no drug
			Saline solution	Spray	
			No drug		

>Better compared with.
<Worse compared with.

TABLE 3.
Topical Anesthesia for the Pharynx

Author (Study Method)	Type of Endoscopy (Diameter)	Study Population	Topical Anesthetic (Dosage)	Application Method	Effect
Smith et al 1985[16] (randomized study)	Transoral gastroscopy (11.33 mm)	14 9	Cetacaine (2 s continuous) Hurricaine (2 s continuous) 10% Lidocaine (20–40 mg) 2% Lidocaine (30 mL for 30 s) 2 Solutions 2% lidocaine with different mouthwash (30 mL for 30 s)	Spray Gargle	Oropharyngeal anesthesia: Cetacaine > Hurricaine, 2% lidocaine, lidocaine + mouthwash Taste: 10% lidocaine > Cetacaine Overall preference: spray > gargle
Hedenbro et al 1992[17] (randomized double-blinded placebo-controlled study)	Transoral endoscopy (unknown)	167	Lidocaine (80–120 mg) Placebo	Spray	Patient discomfort: lidocaine > placebo Endoscopist difficulty: lidocaine > placebo
Campo et al 1995[18] (randomized double-blinded study)	Transoral gastroscopy (9.8 mm)	252	Topicaina (benzocaine 55 mg, butoforme 24 mg, ametocaine 8 mg, butacaine 4 mg) Placebo	Spray	Patient discomfort: Topicaina > placebo Endoscopist difficulty: Topicaina > placebo
Mulcahy et al 1996[19] (randomized double-blinded study)	Transoral gastroscopy (9.8 mm)	97	10% Lidocaine (30 mg and 100 mg)	Spray	Discomfort swallowing: 100 mg > 30 mg Discomfort procedure: 100 mg > 30 mg
Martin et al 1996[20] (prospective study)	Transoral endoscopy (unknown)	500	Lidocaine (4 sprays, dosage unknown) Sedation	Spray	Anxious: topical anesthesia > sedation Patient discomfort: sedation > topical anesthesia
Dhir et al 1997[21] (randomized double-blinded placebo-controlled study)	Transoral endoscopy (9.8 mm)	150	4% Lidocaine (80 mg) Placebo	Spray	Patient discomfort: no significant difference
Soma et al 2001[22] (randomized double-blinded placebo-controlled study)	Transoral endoscopy (11.2 and 10.5 mm)	201	Lidocaine (100 mg) Placebo	Spray	Patient discomfort: lidocaine > placebo

(*Continued*)

TABLE 3. (*Continued*)

Author (Study Method)	Type of Endoscopy (Diameter)	Study Population	Topical Anesthetic (Dosage)	Application Method	Effect
Ristikankare et al 2004[23] (randomized double-blinded placebo-controlled study)	Transoral endoscopy (9.8 mm)	252	10% Lidocaine (100 mg) Midazolam (0.5 mg/kg) Placebo No drug	Spray Intravenous Intravenous	Patient discomfort: midazolam > lidocaine > placebo > control Endoscopist difficulty: lidocaine > midazolam < control
Sohmer et al 2004[24] (retrospective cohort study)	Transoral bronchoscopy (unknown)	57	EMLA (100 mg lidocaine and 100 mg prilocaine)	Gargle	Patient experience: 96.5% "excellent", 3.5% "good"
Amornyotin et al 2009[25] (double-blinded randomized controlled study)	Transoral esophagogastroduodenoscopy (8.8 mm)	930	2% Lidocaine (100 mg)	Gargle	Procedure successfully completed: spray > gargle
		934	10% Lidocaine (50 mg)	Spray	Ease intubation: spray > gargle Patient tolerance: spray > gargle Patient experience: spray > gargle Endoscopist experience: spray > gargle
Chan et al 2010[26] (randomized placebo-controlled study)	Transoral esophagogastroduodenoscopy (unknown)	97	Lidocaine (20 mg)	Lozenge	Pharyngeal numbness: spray > lozenge
		94	10% Lidocaine (60 mg)	Spray	Taste: spray < lozenge Suppression gag reflex: spray = lozenge Discomfort intubation: spray = lozenge
Ibis et al 2015[27] (randomized prospective study)	Transoral endoscopy (unknown)	118	10% Lidocaine (40 mg), benzydamine (1 mg) 10% Lidocaine (20 mg) + benzydamine (0.5 mg)	Spray	Taste: lidocaine < benzydamine Pharyngeal anesthesia: lidocaine > benzydamine Coughing/gagging: lidocaine > benzydamine Discomfort intubation: lidocaine > benzydamine

>Better compared with.
<Worse compared with.
=Equal compared with.

TABLE 4.
Topical Anesthesia for the Larynx

Author (Study Method)	Type of Endoscopy (Diameter)	Study Population	Topical Anesthetic (Dosage)	Application Method	Effect
Clark et al 1954[32] (prospective study)	Rigid transoral laryngoscope (unknown)	60 60	1% Cyclaine (unknown) 2.5% Cyclaine (unknown) 5% Cyclaine (unknown) 0.25% Pontocaine (unknown) 0.5% Pontocaine (unknown) 1% Pontocaine (unknown)	Spray	Vocal cord adduction: higher percentage anesthetic resulted in longer effect for both types
Artru and Strumwasser 1985[33] (randomized controlled study)	Laryngoscopy and intubation (unknown)	45	Etidocaine (50 mg) Etidocaine (75 mg)	Spray Spray	Coughing intubation: etidocaine > control
Mahajan et al 1994[34] (prospective controlled study)	Fiberoptic transnasal laryngoscopy (unknown)	10	10% Lidocaine (100 mg)	Spray	Laryngeal anesthesia: effective Vocal cord movement: no influence of cough peak flow and peak velocity time
Yang and Chen 2005[35] (prospective controlled study)	Transoral laryngeal videostroboscopy (unknown)	30	4% Lidocaine (8 mg)	Spray	Vocal cord movement: no significant effect compared witho no topical anesthesia
Zemlin 1969[36] (prospective controlled study)	Ultra-high speed laryngeal photography	4	5% Cyclaine (dosage unknown)	Aerosol	Vocal cord movement: no significant effect compared with no topical anesthesia
Rubin et al 2009[37] (prospective blinded-controlled study)	Flexible laryngeal videostroboscopy (unknown)	10	20% Benzocaine (2-s application)	Spray	Vocal cord movement: no significant effect compared with no topical anesthesia
Maxwell et al 2012[38] (randomized double-blinded placebo-controlled study)	Fiberoptic transnasal laryngoscopy (3.6 mm)	20	2% Lidocaine (15 mL 5 min) 4% Lidocaine (15 mL 5 min) Placebo (15 mL 5 min)	Gargle	Voice quality: no significant differences between lidocaine and placebo
Raphael et al 1996[39] (prospective study)	Fiberoptic transnasal laryngoscope (4.0 mm)	8	Benzocaine (20 mg) 4% Lidocaine (160 mg, 100 mg)	Lozenge Aerosol, spray	Upper airway reflexes: ammonia vapor stimulation was significantly higher in spray
Walsh et al 2006[40] (prospective double-blinded placebo-controlled study)	Transoral laryngeal videostroboscopy (unknown)	20	Cetacaine (2-s spray) Placebo	Spray	Vocal cord secretion "balling" and "pooling": no significant effect compared with placebo

>Better compared with.
<Worse compared with.

No studies were found comparing different application methods for topical anesthesia to the larynx. In this paragraph, we therefore summarize the most applied methods. An effective method of anesthetizing the larynx is inserting the anesthetic through the working channel of the endoscope.[8,42–44] The endoscope is inserted transnasally and positioned above the vocal cords. The local anesthetic, in a syringe, is released in the working channel of the endoscope and thus directly applied into the larynx and on the vocal cords. Alternatively, the syringe is placed on a small diameter catheter (eg, epidural catheter), which is directed through the working channel of the endoscope and placed above the vocal cords. Another widely used application method for the larynx and upper trachea is performed with an injection through the cricothyroid membrane. After inserting the needle through the membrane, the syringe is drawn back to check if air bubbles arise, which confirms adequate localization in the larynx and safe injection of the anesthetic solution. After injection, the syringe should be removed quickly, as the patient vigorously coughs because of irritation of the larynx.[5,7,9,42,45] If a patient has a tracheostoma, the cannula can be removed and the anesthetic can be applied through the tracheostoma.[5,45] Some authors used a syringe with curved cannula to transorally apply the anesthetic to the larynx and upper trachea under direct vision of an endoscope.[5,7,43,45] A superior laryngeal nerve block is another possible method of locally anesthetizing the larynx for office-based procedures. The location of the injection is where the internal branch of the superior laryngeal nerve crosses the thyrohyoid membrane. This is in the thyrohyoid space, halfway between the hyoid bone and the superior border of the thyroid cartilage and halfway between the anterior midline and the superior cornu of the thyroid cartilage.[7,42] Again, when inserting the needle, the syringe is drawn back to confirm that the tip is not inserted in an artery or the larynx. Local anesthesia, with or without a vasoconstricting agent, can be used. This procedure is repeated at the opposite side. It is essential not to penetrate the thyrohyoid membrane, in contrast to the cricothyroid membrane approach, to prevent endangering the airway. Sensation returns after approximately 3 hours, although the effective time to perform the procedure is shorter.[42] As seen for pharyngeal anesthesia, less frequently described topical anesthesia methods for the larynx are also available. Several authors soaked cotton pledgets in local anesthesia and used a sponge holder to apply this directly to the larynx.[11,46] Erickson described the use of nebulizing the local anesthetic, which requires the nebulizer to produce droplets of the same size that the upper respiratory mucosa can uptake.[9] In practice, this was found to be more difficult as it resulted in inadequate dosage to the specific anatomical site. A squeeze bulb nebulizer is often used for this purpose.[47] Christoforidis et al described the use of an ultrasonic nebulizer, which offers the advantages of self-administration by patients, even distribution of the anesthetic, and control of particle size.[48] The authors noticed no complications in 273 patients. Thawley et al used a face mask covering the nose and mouth to apply topical anesthesia via a nebulizer.[49] For the abovementioned alternative anesthesia methods for the larynx, no information regarding efficacy was mentioned.

Topical anesthesia applied on the upper airway was found to have minimal impact on breathing pattern.[41] Furthermore, minimal effect is seen on bronchus dilatation and constriction. The cough reflex is suppressed because the anesthetic blocks the afferent nerve endings. Other motor functions, such as vocal cord adduction or capability of coughing, are also not influenced after topical anesthesia administration to the larynx.[33–40]

Efficacy of topical anesthesia

Sufficient topical anesthesia will blunt autonomic reflexes such as hypertension, tachycardia, and coughing. Blunting of these reflexes can therefore be used to assess efficacy of the achieved topical anesthesia. Studies investigating the efficacy of topical anesthesia to the upper aerodigestive tract are summarized in Table 5.[25,33,50–54]

Most studies investigated the effect of topical anesthesia to the upper aerodigestive tract during transoral endoscopy or surgery under general anesthesia. When topical anesthesia was used during manipulation in the upper aerodigestive tract (eg, laryngoscopy, intubation, or extubation), blood pressure and heart rate were usually less increased, compared with a control group.[33,51,52] However, Ristikankare et al found contradicting results in a randomized study comparing sedation, topical anesthesia, placebo, and no drug, which showed no significant changes between all groups.[54] When two different topical anesthetics were used, no significant changes in cardiovascular parameters were found during extubation.[50]

Complications of local anesthetics

Systemic toxicity

Systemic toxicity of local anesthetics is caused by the alteration of the functioning of the cardiac conductivity system and the functioning of the central nervous system. Toxicity of the latter usually begins with lightheadedness, dizziness, visual and auditory impairment, and disorientation. Twitching, tremors, and convulsions can follow. With increasing systemic concentrations, central nervous system depression will progress, resulting in respiratory depression or arrest. For the cardiovascular system, direct cardiac effects of toxicity can result in blocking of the cardiac contractibility (ie, cardiac depression) and conduction (eg, bradycardia). Direct vascular effects are either vasodilatation, possible in high doses of synthetic anesthetics, or vasoconstriction, which can be seen in low concentrations of synthetic anesthetics and cocaine.[6]

Several studies investigated the systemic concentrations of local anesthetics after topical administration to the pharynx and larynx. Dosages of topical anesthesia administered ranged from 100 to 800 mg, using spray, gel, or solution.[50,51,53,55–62] Although most studies investigated the effect of lidocaine, some authors studied cocaine[50] or prilocaine.[61] Almost all studies showed venous blood concentrations that were below the maximum dosage of lidocaine and thus did not exceed a plasma concentration of 5 μg/mL. Reasoner et al compared topical lidocaine spray with laryngeal nerve block and found, shortly after administration, significantly higher venous blood

TABLE 5.
Efficacy of Topical Anesthesia

Author (Study Method)	Procedure	Study Population	Topical Anesthetic (Dosage)	Application Method	Effect
Artru and Strumwasser 1985[33] (randomized controlled study)	Laryngoscopy and intubation	15 15 15	Etidocaine (50 mg) Etidocaine (75 mg) No drug	Spray Spray	Blood pressure: etidocaine < no drug Heart rate: etidocaine < no drug Coughing: etidocaine < no drug
Davies et al 1992[50] (double-blinded randomized study)	Extubation	60	Lidocaine (120 mg) Cocaine (150 mg)	Spray Spray	Blood pressure: lidocaine = cocaine Heart rate: lidocaine = cocaine Venous blood concentration: lidocaine = cocaine
Altintas et al 2000[51] (randomized controlled study)	Extubation	36 34	10% Lidocaine (max. 500 mg) Saline	Solution in endotracheal tube	Mean arterial blood pressure (surgery): lidocaine = saline Heart rate (surgery): lidocaine = saline Mean arterial blood pressure (extubation): lidocaine < saline Heart rate (extubation): lidocaine < saline
Hamaya and Dohi 2000[52] (randomized controlled study)	Laryngeal mask, tracheal intubation, bronchial intubation, and bronchoscopy	60	4% Lidocaine (200 mg) Lidocaine (1 mg/kg)	Spray Intravenous Control	Systolic blood pressure: anesthesia < control Heart rate: anesthesia < control
Amornyotin et al 2009[25] (double-blinded randomized controlled study)	Transoral esophagogastroduodenoscopy	930 934	2% Lidocaine (100 mg) 10% Lidocaine (50 mg)	Gargle Spray	Tachycardia: spray < gargle
Jenkins and Marshall 2000[53] (prospective study)	Transnasal intubation	10	2% Lidocaine	Solution	No oxygen desaturation
Ristikankare et al 2006[54] (randomized placebo-controlled study)	Transoral gastroscopy	62 62 64 64	Midazolam (0.05 mg/kg) 10% Lidocaine (100 mg) Saline No drug	Intravenous Spray Intravenous	Blood pressure: no difference Heart rate: no difference Arrhythmia: no difference Oxygen saturation: midazolam < lidocaine, saline and no drug

>Higher compared with.
<Lower compared with.
=Equal compared with.

concentrations in the laryngeal nerve block group.[62] After 10 minutes, this difference disappeared. Applying topical anesthesia to the trachea resulted in higher blood concentration compared with the application of the same amount of anesthesia in the larynx and thus has greater chance of exceeding the maximum dosage.[55,56] The duration of reaching peak plasma concentrations for lidocaine varied from 5 to 60 minutes,[50,53,55,56,58,59,61] although Altintas et al showed highest concentrations 90 minutes after they administered lidocaine solution in the cuff of the endotracheal tube in order to diffuse to the trachea.[51] For cocaine, the peak plasma concentration was reached after 12 minutes and for prilocaine between 10 and 60 minutes.[50,61] Viegas and Stoelting investigated the arterial plasma concentration after topical anesthesia with lidocaine.[63] Ten patients received lidocaine spray to the larynx and trachea, and of these 10 patients, 4 additionally received viscous lidocaine on the intubation tube. After 9−15 minutes, mean lidocaine concentration was lower in the nonviscous group compared with the viscous group. Hamaya and Dohi also compared lidocaine spray and intravenous lidocaine on arterial blood concentrations.[52] Serum concentration of lidocaine was significantly higher in the bronchial spray group compared with the trachea and larynx groups. Complications after topical anesthesia administration to the upper aerodigestive tract are usually caused by overdosage. In Table 6, cases of overdosage due to topical anesthesia administration are summarized.[9,42,60,65,67]

Anaphylactic reaction

Anaphylactic reactions to local anesthetics are rare and account for less than 1% of local anesthetic complications.[1] Daily mentioned that most reactions are responses to ester-type local anesthetics, because breakdown of this type of anesthetic produces para-aminobenzoic acid, which often results in cross-reactions.[1] Several case reports have been published that concern patients who developed a systemic overreaction after topical anesthesia to the larynx, which are summarized in Table 6.[64,66,68]

Methemoglobinemia

Methemoglobinemia is a disorder in which high levels of methemoglobin are present in blood plasma concentration, which is normally below 1%−3%.[69−74] Methemoglobinemia is known to be frequently caused by benzocaine, an ester-type anesthetic. A 10-year retrospective case-control study showed a prevalence of 0.035%.[74] Although less frequently reported, lidocaine, prilocaine, and tetracaine are also capable of causing methemoglobinemia.[70,73,75] Benzocaine is 3.7 times more likely to cause methemoglobinemia, compared with anesthetics not containing benzocaine.[74] Methemoglobin is a form of hemoglobin that contains ferric iron (Fe^{3+}), which has less potential of binding oxygen compared with ferrous iron (Fe^{2+}), and could lead to hypoxia.[70−78] Amounts varying from 15 to 25 mg/kg of benzocaine can induce methemoglobinemia.[76] Clinical signs are dyspnea, cyanosis, changing of mental status, headache, and fatigue.[69] A diagnosis is made by obtaining an arterial blood gas sample, which reveals a brown color and an elevated methemoglobin level. Furthermore, persisting cyanosis unresponsive to 100% oxygen administration can confirm the diagnosis.[69,71,75,78,79] Methemoglobin concentrations between 10% and 25% often result in cyanosis, as levels of 35%−40% cause the abovementioned clinical signs. When 60% of methemoglobin is found, lethargy can occur and concentrations above 70% probably result in death,[7,69,70,72,78,79] although some authors reported lethality above 50%.[74] Several studies mentioned signs of methemoglobinemia using 20% benzocaine doses varying from 20 to 80 mg, or from 1 to 5 seconds of spraying.[69,70,72,75,79] The dosage used for cetacaine was not mentioned.[76] Treatment options are administration of oral ascorbic acid in case of less severe complaints or intravenous administration of methylene blue in case of severe complaints.[7,69−71,73−79] In case of no response to methylene blue, blood transfusion or hyperbaric oxygen therapy are alternative therapies.[73,78]

DISCUSSION

Lidocaine is the most investigated local anesthetic for office-based procedures for the upper aerodigestive tract. For nasal anesthesia, all included studies investigated the effectiveness of lidocaine, with one study comparing lidocaine with several alternatives, and all studies concluded that lidocaine is an effective topical anesthetic for the nasal cavity.[14] The most effective method of application is not extensively compared and investigated, but cotton pledgets soaked in a local anesthetic and decongestant seems most effective.[12] No information was available on the ideal duration upon which the cotton pledgets should be left in the nasal cavity. Anesthetic gel applied in the nasal cavity is an alternative.[13] Studies comparing lidocaine with cocaine or tetracaine were not found, although specific qualities are reported. Cocaine has a stronger anesthetic effect and causes vasoconstriction, compared with lidocaine, but is also more toxic with more systemic side effects.[10] Tetracaine has a longer anesthetic effect compared with lidocaine, although the side effects are also reported to be more severe.[14]

Anesthetizing the pharynx is possible in several ways, with spraying as the most investigated method. Again, lidocaine was the most used anesthetic that showed good sensory suppression.[16−23,27] By administrating topical anesthesia to the pharynx, pharyngeal swallowing is temporarily changed.[28,29] For the larynx, no studies were found that compared topical anesthesia administration techniques for effectiveness during endoscopy. Administration of local anesthesia through the working channel of the endoscope was used in several studies and resulted in adequate anesthesia, although a cricothyroid membrane injection or a laryngeal nerve block showed comparable results.[7−9,42−45] Administrating topical anesthesia to the larynx also showed adequate sensory suppression without impairing motor function.[33−41] Increasing concentrations of anesthesia resulted in longer duration of the anesthetic effect.[29,32]

Secondary effects of topical anesthesia administration on the pharynx and larynx are usually decreased rise in blood pressure

TABLE 6.
Complications of Topical Anesthesia for the Upper Aerodigestive Tract

Author (Study Method)	Procedure	Study Population	Topical Anesthetic (Dosage)	Application Method	Effect
Hesch 1960[64] (case report)	No procedure; lozenge for throat pain	1	Benzocaine (10 mg)	Lozenge	Anaphylactic reaction and died
Erickson 1964[9] (review)	Laryngeal surgery under topical anesthesia	Unknown	Unknown	Cricothyroid membrane injection	Hematoma
Parish et al 1985[65] (case report)	Transoral esophagogastroduodenoscopy	1	4% Lidocaine (1200 mg)	Solution	Two tonic-clonic seizures, apnea; blood concentration lidocaine 7.8 μg/mL
	Bronchoscopy	1	4% Lidocaine (800 mg), 2% lidocaine (unknown dosage) and cetacaine (2 sprays)	Solution, spray, and spray	Tonic-clonic seizure; blood concentration lidocaine 7.7 μg/mL
Patel et al 1989[66] (case report)	Transoral esophagogastroduodenoscopy	1	0.5% Tetracaine (20 mg)	Solution	Grand-mal seizure, cardiopulmonary arrest and died
		1	0.5% Tetracaine (20–25 mg)	Solution	Tonic-clonic seizure
		1	0.5% Tetracaine (20 mg)	Solution	Dizziness, slurred speech, and unresponsive to verbal signs
Kotaki et al 1996[60] (case report)	Transnasal laryngoscopy and vocal cord injection	1	2% Lidocaine (440–600 mg) and 4% lidocaine (120–200 mg)	Solution	Seizure; blood concentration lidocaine 11.6 μg/mL after 30 min and 9.0 μg/mL after 150 min
Sulica and Blitzer 2000[42] (case report)	Laryngeal surgery under topical anesthesia	1	Unknown	Superior laryngeal nerve block	Vasovagal reaction
Wong and McGuire 2000[67] (case report)	Awake intubation	1	2% and 4% Lidocaine (unknown dosage)	Solution and cricothyroid membrane injection	Subcutaneous emphysema
Caron 2007[68] (case report)	Infiltration for back pain	1	Bupivacaine and lidocaine (dosage unknown)	Injection	Allergic reaction to several topical anesthetics

and heart rate, compared with administrating placebo or nothing.[33,51] These secondary effects of topical anesthesia might indicate that appliance of a local anesthetic results in less stress to the body when a patients is intubated or examined with an endoscope.

For the pharynx and larynx, lidocaine is the most used and investigated topical anesthetic. Although the maximum amount of lidocaine that can be safely administered varies in literature from 200 to 600 mg, the toxic blood concentration of 5 μg/mL was never exceeded.[62] A systemic overreaction due to lidocaine administration to the pharynx and larynx is rare,[16] although administration to the trachea and bronchus should be performed with caution, as more rapid and higher systemic uptake is seen for these anatomical sites.[55,56] Several alternative topical anesthetics are available, each with different qualities, but large randomized studies that compare these with lidocaine for effectiveness and possible complications during endoscopy or office-based procedures are still wanting. We did not find any studies reporting on the incidence and treatment of laryngospasm.

Our goal was to provide an objective summary on topical anesthesia for endoscopic office-based procedures for the pharynx and larynx, and thus guidance for physicians who are interested in starting with these procedures. The current literature search lacked adequate studies comparing different application methods for topical anesthesia, and thus, this descriptive review is the only information at hand. Based on these studies, and our experience in office-based procedures under topical anesthesia,[3,4,80] we offer our current expert opinion on topical anesthesia use for office-based procedures. Adequate patient instruction is essential for a successful procedure, and beforehand we explain the procedure and anesthesia techniques. Applying cotton pledgets in the nose is sensitive upon insertion and could lead to sneezing and excessive watering of the eyes. For the nose, we insert two to three cotton pledgets soaked in 10% lidocaine and 0.1% xylometazoline in each nasal cavity, and leave these *in situ* for a minimum of 10 minutes. Although the exact amount of both solutions varies, around four sprays of 10% lidocaine and 1 mL of 0.1% xylometazoline is used for each cotton pledget. For the pharynx, between 8 and 14 sprays of 10% lidocaine are used. We explain to the patient that spraying results in coughing, numbness of the tongue and throat, the formation of excessive saliva, and difficulty in swallowing. First, several sprays are applied to the oral cavity and thereafter to the pharynx, while letting the patient deeply inhale. For laryngeal anesthesia, patients are informed on similar effects to pharyngeal anesthesia, plus the short feeling of dyspnea when topical anesthesia is applied on the vocal cords. A small epidural catheter is passed through the working channel of the laryngoscope and positioned above the vocal cords. Thereafter, the patient is asked to perform a persisting *"i"* tone, and 2.5 mL of 4.3% lidocaine is applied on the vocal cords in several stages. Lidocaine with a lower percentage is used, because of less viscosity compared with 10% lidocaine, which cannot pass through the catheter. When both percentages of lidocaine were directly inserted through the working channel of the laryngoscope, we experienced blurring of the camera and therefore reduced vision. In the past, we have extensively performed laryngeal anesthesia with an injection through the cricothyroid membrane using 1.0 mL of 10% lidocaine, but experienced less laryngeal anesthesia and a more traumatic patient experience. All patients are advised not to eat or drink for 60 minutes after laryngopharyngeal anesthesia is performed.

This descriptive review has systematically searched and included all available articles on this subject. The possibility exists that articles that are in the scope of this review were missed in the literature search. Furthermore, a methodological analysis was not performed because of the descriptive nature of this review, which could have resulted in more thorough conclusions.

In conclusion, by applying adequate topical anesthesia to the upper aerodigestive tract, several surgical procedures in laryngology and head and neck oncology can be performed in the outpatient clinic, instead of the operating room under general anesthesia. Lidocaine is the most investigated anesthetic, with adequate efficacy and few complications.

REFERENCES

1. Daily WW. Local anesthesia of the head and neck. *Ear Nose Throat J*. 1981;60:19–24.
2. Zeitels SM, Blitzer A, Hillman RE, et al. Foresight in laryngology and laryngeal surgery: a 2020 vision. *Ann Otol Rhinol Laryngol Suppl*. 2007;198:2–16.
3. Wellenstein DJ, Schutte HW, Marres HAM, et al. Office-based procedures for diagnosis and treatment of esophageal pathology. *Head Neck*. 2017;39:1910–1919.
4. Wellenstein DJ, de Witt JK, Schutte HW, et al. Safety of flexible endoscopic biopsy of the pharynx and larynx under topical anesthesia. *Eur Arch Otorhinolaryngol*. 2017;274:3471–3476.
5. Rosen CA, Amin MR, Sulica L, et al. Advances in office-based diagnosis and treatment in laryngology. *Laryngoscope*. 2009;119(suppl 2):S185–S212.
6. Miller RD. *Miller's Anesthesia*. 7th ed Philadelphia, PA: Churchill Livingstone/Elsevier; 2010.
7. Simpson CB, Amin MR, Postma GN. Topical anesthesia of the airway and esophagus. *Ear Nose Throat J*. 2004;83(7 suppl 2):2–5.
8. Jourdy DN, Kacker A. Regional anesthesia for office-based procedures in otorhinolaryngology. *Anesthesiol Clin*. 2010;28:457–468.
9. Erickson 3rd JC. Surface anesthesia of the airway and larynx. *Int Anesthesiol Clin*. 1964;2:709–724.
10. Bernal-Sprekelsen M, Schmelzer A. Local anesthesia of the head and neck. *Anesth Pain Control Dent*. 1992;1:81–84.
11. Woo P. Office-based laryngeal procedures. *Otolaryngol Clin North Am*. 2006;39:111–133.
12. Hu CT. Gauze pledgetting versus endoscopic-guided aerosolized spray for nasal anesthesia before transnasal EGD: a prospective, randomized study. *Gastrointest Endosc*. 2010;71:11–20.
13. Zainudin BM, Rafia MH, Sufarlan AW. Topical nasal anaesthesia for fibreoptic bronchoscopy: lignocaine spray or gel? *Singapore Med J*. 1993;34:148–149.
14. Ozkiris M, Aydin R, Gencer ZK, et al. Comparison of topical anesthetic effects of lidocaine, prilocaine, ropivacaine, and bupivacaine in transnasal fiberoptic nasopharyngolaryngoscopy. *Am J Rhinol Allergy*. 2014;28:e141–e143.
15. Frosh AC, Jayaraj S, Porter G, et al. Is local anaesthesia actually beneficial in flexible fibreoptic nasendoscopy? *Clin Otolaryngol Allied Sci*. 1998;23:259–262.
16. Smith JL, Opekun A, Graham DY. Controlled comparison of topical anesthetic agents in flexible upper gastrointestinal endoscopy. *Gastrointest Endosc*. 1985;31:255–258.

17. Hedenbro JL, Ekelund M, Jansson O, et al. A randomized, double-blind, placebo-controlled study to evaluate topical anaesthesia of the pharynx in upper gastrointestinal endoscopy. *Endoscopy*. 1992;24:585–587.
18. Campo R, Brullet E, Montserrat A, et al. Topical pharyngeal anesthesia improves tolerance of upper gastrointestinal endoscopy: a randomized double-blind study. *Endoscopy*. 1995;27:659–664.
19. Mulcahy HE, Greaves RR, Ballinger A, et al. A double-blind randomized trial of low-dose versus high-dose topical anaesthesia in unsedated upper gastrointestinal endoscopy. *Aliment Pharmacol Ther*. 1996;10:975–979.
20. Martin JP, Arlett PA, Holdstock G. Development of a sedation policy for upper GI endoscopy based on an audit of patients' perception of the procedure. *Eur J Gastroenterol Hepatol*. 1996;8:355–357.
21. Dhir V, Swaroop VS, Vazifdar KF, et al. Topical pharyngeal anesthesia without intravenous sedation during upper gastrointestinal endoscopy. *Indian J Gastroenterol*. 1997;16:10–11.
22. Soma Y, Saito H, Kishibe T, et al. Evaluation of topical pharyngeal anesthesia for upper endoscopy including factors associated with patient tolerance. *Gastrointest Endosc*. 2001;53:14–18.
23. Ristikankare M, Hartikainen J, Heikkinen M, et al. Is routine sedation or topical pharyngeal anesthesia beneficial during upper endoscopy? *Gastrointest Endosc*. 2004;60:686–694.
24. Sohmer B, Bryson GL, Bencze S, et al. EMLA cream is an effective topical anesthetic for bronchoscopy. *Can Respir J*. 2004;11:587–588.
25. Amornyotin S, Srikureja W, Chalayonnavin W, et al. Topical viscous lidocaine solution versus lidocaine spray for pharyngeal anesthesia in unsedated esophagogastroduodenoscopy. *Endoscopy*. 2009;41:581–586.
26. Chan CKO, Fok KL, Poon CM. Flavored anesthetic lozenge versus Xylocaine spray used as topical pharyngeal anesthesia for unsedated esophagogastroduodenoscopy: a randomized placebo-controlled trial. *Surg Endosc*. 2010;24:897–901. https://doi.org/10.1007/s00464-009-0687-9.
27. Ibis M, Arhan M, Ibis T, et al. Lidocaine versus lidocaine plus benzydamine as a topical anesthesia regimen for unsedated upper gastrointestinal endoscopy: a comparison study. *Turk J Gastroenterol*. 2015;26:224–227.
28. Ertekin C, Kiylioglu N, Tarlaci S, et al. Effect of mucosal anaesthesia on oropharyngeal swallowing. *Neurogastroenterol Motil*. 2000;12:567–572.
29. Chee C, Arshad S, Singh S, et al. The influence of chemical gustatory stimuli and oral anaesthesia on healthy human pharyngeal swallowing. *Chem Senses*. 2005;30:393–400.
30. Mansson I, Sandberg N. Oro-pharyngeal sensitivity and elicitation of swallowing in man. *Acta Otolaryngol*. 1975;79:140–145.
31. Mansson I, Sandberg N. Effects of surface anesthesia on deglutition in man. *Laryngoscope*. 1974;84:427–437.
32. Clark RE, Orkin LR, Rovenstine EA. An objective method of evaluating topical anesthesia in man utilizing the laryngeal reflex; the effect of methylcellulose, triton A-20, and hyaluronidase as determined thereby. *Anesthesiology*. 1954;15:161–173.
33. Artru AA, Strumwasser TA. Intratracheal aerosolized etidocaine to attenuate cardiovascular and cough responses to laryngoscopy and intubation. *Ann Emerg Med*. 1985;14:1069–1073.
34. Mahajan RP, Murty GE, Singh P, et al. Effect of topical anaesthesia on the motor performance of vocal cords as assessed by tussometry. *Anaesthesia*. 1994;49:1028–1030.
35. Yang CC, Chen SH. Impact of topical anesthesia on acoustic characteristics of voice during laryngeal telescopic examination. *Otolaryngol Head Neck Surg*. 2005;132:110–114.
36. Zemlin WR. The effect of topical anesthesia on internal laryngeal behavior. *Acta Otolaryngol*. 1969;68:168–176.
37. Rubin AD, Shah A, Moyer CA, et al. The effect of topical anesthesia on vocal fold motion. *J Voice*. 2009;23:128–131.
38. Maxwell MJ, English JD, Moppett IK, et al. Vocalization assessed by electrolaryngography is unaffected by topical lidocaine anesthesia: a prospective, crossover, randomized, double-blind placebo-controlled study. *Anesth Analg*. 2012;114:785–790.
39. Raphael JH, Stanley GD, Langton JA. Effects of topical benzocaine and lignocaine on upper airway reflex sensitivity. *Anaesthesia*. 1996;51:114–118.
40. Walsh J, Branski RC, Verdolini K. Double-blind study on the effects of topical anesthesia on laryngeal secretions. *J Voice*. 2006;20:282–290.
41. Karlsson JA. Airway anaesthesia and the cough reflex. *Bull Eur Physiopathol Respir*. 1987;23(suppl 10):29s–36s.
42. Sulica L, Blitzer A. Anesthesia for laryngeal surgery in the office. *Laryngoscope*. 2000;110(10 pt 1):1777–1779.
43. Zeitels SM, Franco Jr RA, Dailey SH, et al. Office-based treatment of glottal dysplasia and papillomatosis with the 585-nm pulsed dye laser and local anesthesia. *Ann Otol Rhinol Laryngol*. 2004;113:265–276.
44. Zeitels SM, Akst LM, Burns JA, et al. Office-based 532-nm pulsed KTP laser treatment of glottal papillomatosis and dysplasia. *Ann Otol Rhinol Laryngol*. 2006;115:679–685.
45. Hogikyan ND. Transnasal endoscopic examination of the subglottis and trachea using topical anesthesia in the otolaryngology clinic. *Laryngoscope*. 1999;109(7 pt 1):1170–1173.
46. Colman MF, Reynolds R. The use of topical cocaine to prevent laryngospasm after general anesthesia on endoscopy procedures. *Laryngoscope*. 1985;95:474.
47. Vale R. A laryngeal spray. *Anaesthesia*. 1967;22:314–315.
48. Christoforidis AJ, Tomashefski JF, Mitchell RI. Use of an ultrasonic nebulizer for the application of oropharyngeal, laryngeal and tracheobronchial anesthesia. *Chest*. 1971;59:629–633.
49. Thawley SE. Head and neck and plastic surgery: nebulized anesthesia for the nose, pharynx, larynx, and trachea. *Laryngoscope*. 1987;97:499–500.
50. Davies DW, Moylan SL, O'Sullivan G. Topical anaesthesia of the larynx: cocaine or lignocaine? *Eur J Anaesthesiol*. 1992;9:393–397.
51. Altintas F, Bozkurt P, Kaya G, et al. Lidocaine 10% in the endotracheal tube cuff: blood concentrations, haemodynamic and clinical effects. *Eur J Anaesthesiol*. 2000;17:436–442.
52. Hamaya Y, Dohi S. Differences in cardiovascular response to airway stimulation at different sites and blockade of the responses by lidocaine. *Anesthesiology*. 2000;93:95–103.
53. Jenkins SA, Marshall CF. Awake intubation made easy and acceptable. *Anaesth Intensive Care*. 2000;28:556–561.
54. Ristikankare M, Julkunen R, Heikkinen M, et al. Sedation, topical pharyngeal anesthesia and cardiorespiratory safety during gastroscopy. *J Clin Gastroenterol*. 2006;40:899–905.
55. Curran J, Hamilton C, Taylor T. Topical analgesia before tracheal intubation. *Anaesthesia*. 1975;30:765–768.
56. Rosenberg PH, Heinonen J, Takasaki M. Lidocaine concentration in blood after topical anaesthesia of the upper respiratory tract. *Acta Anaesthesiol Scand*. 1980;24:125–128.
57. Nydahl PA, Axelsson K. Venous blood concentration of lidocaine after nasopharyngeal application of 2% lidocaine gel. *Acta Anaesthesiol Scand*. 1988;32:135–139.
58. Soda K, Shimanuki K, Yoshida Y, et al. Serum lidocaine and MEGX concentrations after pharyngeal anesthesia for gastroscopy. *Endoscopy*. 1994;26:347–351.
59. Scott DB, Littlewood DG, Vocino BG, et al. Plasma lignocaine concentrations following endotracheal spraying with an aerosol. *Br J Anaesth*. 1976;48:899–902.
60. Kotaki H, Tayama N, Ito K, et al. Safe and effective topical application dose of lidocaine for surgery with laryngomicroscopy. *Clin Pharmacol Ther*. 1996;60:229–235.
61. Larijani GE, Cypel D, Gratz I, et al. The efficacy and safety of EMLA cream for awake fiberoptic endotracheal intubation. *Anesth Analg*. 2000;91:1024–1026.
62. Reasoner DK, Warner DS, Todd MM, et al. A comparison of anesthetic techniques for awake intubation in neurosurgical patients. *J Neurosurg Anesthesiol*. 1995;7:94–99.
63. Viegas O, Stoelting RK. Lidocaine in arterial blood after laryngotracheal administration. *Anesthesiology*. 1975;43:491–493.
64. Hesch DJ. Anaphylactic death from use of a throat lozenge. *J Am Med Assoc*. 1960;172:12–15.
65. Parish RC, Moore RT, Gotz VP. Seizures following oral lidocaine for esophageal anesthesia. *Drug Intell Clin Pharm*. 1985;19:199–201.
66. Patel D, Chopra S, Berman MD. Serious systemic toxicity resulting from use of tetracaine for pharyngeal anesthesia in upper endoscopic procedures. *Dig Dis Sci*. 1989;34:882–884.

67. Wong DT, McGuire GP. Subcutaneous emphysema following trans-cricothyroid membrane injection of local anesthetic. *Can J Anaesth*. 2000;47:165–168.
68. Caron AB. Allergy to multiple local anesthetics. *Allergy Asthma Proc*. 2007;28:600–601.
69. Linares LA, Peretz TY, Chin J. Methemoglobinemia induced by topical anesthetic (benzocaine). *Radiother Oncol*. 1990;18:267–269.
70. Cooper HA. Methemoglobinemia caused by benzocaine topical spray. *South Med J*. 1997;90:946–948.
71. Haynes JM. Acquired methemoglobinemia following benzocaine anesthesia of the pharynx. *Am J Crit Care*. 2000;9:199–201.
72. Kuschner WG, Chitkara RK, Canfield Jr J, et al. Benzocaine-associated methemoglobinemia following bronchoscopy in a healthy research participant. *Respir Care*. 2000;45:953–956.
73. Lavergne S, Darmon M, Levy V, et al. Methemoglobinemia and acute hemolysis after tetracaine lozenge use. *J Crit Care*. 2006;21:112–114.
74. Chowdhary S, Bukoye B, Bhansali AM, et al. Risk of topical anesthetic-induced methemoglobinemia: a 10-year retrospective case-control study. *JAMA Intern Med*. 2013;173:771–776.
75. Marinella MA. When brown and blue make red: a case of acquired methemoglobinemia. *Heart Lung*. 2006;35:205–206.
76. Seibert RW, Seibert JJ. Infantile methemoglobinemia induced by a topical anesthetic, cetacaine. *Laryngoscope*. 1984;94:816–817.
77. Aepfelbacher FC, Breen P, Manning WJ. Methemoglobinemia and topical pharyngeal anesthesia. *N Engl J Med*. 2003;348:85–86.
78. Moos DD, Cuddeford JD. Methemoglobinemia and benzocaine. *Gastroenterol Nurs*. 2007;30:342–345 quiz 346-7.
79. Malhotra S, Kolda M, Nanda NC. Local anesthetic-induced methemoglobinemia during transesophageal echocardiography. *Echocardiography*. 1998;15:165–168.
80. Wellenstein DJ, Schutte HW, Takes RP, et al. Office-based procedures for the diagnosis and treatment of laryngeal pathology. *J Voice*. 2017. https://doi.org/10.1016/j.jvoice.2017.07.018.