Drug-induced Sleep Endoscopy - DISE - Anesthesia and the Upper Airway

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Introduction

It is estimated that between 1% and 4% of children have obstructive sleep apnea (OSA) and first-line therapy is removal of the tonsils and adenoids. However, up to 33% of these children will have persistent disease after adenotonsillectomy.[1] For children with persistent OSA, multiple sites of obstruction have been identified including lingual tonsillar hypertrophy, sleep-state dependent laryngomalacia, recurrent adenoidal growth, glossoptosis and lateral wall collapse. In order to personalize the care of these patients, surgeons often perform drug-induced sleep endoscopy (DISE) in order to determine the individual's sites of obstruction.

DISE is an evaluation of the upper airway that is completed during a "sleep-like" state which is initiated using anesthetic agents. In adults, it has been shown to have good test-retest reliability and inter-rater reliability.[2,3] Propofol is the agent used most commonly to anesthetize adults with OSA undergoing DISE and bispectral analysis(bis) monitoring is typically employed to ensure a relatively consistent level of sedation. However, propofol is known to have a dose-dependent effect on the airway.[4] A recent evaluation of anesthetic use for DISE at pediatric otolaryngology programs, found that there are a number of different anesthetic protocols used and there was no consensus regarding a standard protocol.[5]. As more medical centers establish DISE programs, the need to standardize these protocols is critical in order to compare findings between centers and optimize patient outcomes.

In light of these concerns, we review the literature regarding the effects of common anesthetics and pain medications on the collapsibility of the upper airway.

Upper Airway Effects of Anesthetics

A 2016 English language systematic review of articles pertaining to anesthetic agents effects on the human upper airway by Ehsan *et al.* identified 56 studies involving 8,540 patients which evaluated a myriad of outcomes including imaging results, electromyography (EMG) of the genioglossus muscle, level of obstruction on DISE, polysomnographic (PSG) results, clinical signs of obstruction (e.g., oxygen desaturations) and upper airway closing pressure (Pcrit). This review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) recommendations and included articles indexed in PubMed (from 1950 to June 12, 2014),the Cumulative Index to Nursing and Allied Health Literature (from 1982 to June 12, 2014), Evidence-Based Medicine reviews, and Scopus (from 1996 to June 12, 2014).[3]

Lidocaine is a topical medical with a rapid onset of action between 1 and 5 minutes and a duration of efficacy of 10 to 15 minutes. It is noted to act on muscles that act as significant dilators and tensors of the pharynx and larynx. This review include 10 studies which evaluated the effects of local anesthetics/lidocaine on the upper airway; 3 of these studies reported that upper airway obstruction increased with local anesthetic use while 4 found no significant effect on the airway.[6-12] Two additional studies looked at the effect of local anesthetic medications on PSG parameters; 1 reported that mean apnea duration increased while 1 found no effect of lidocaine on either the duration or frequency of apneas or hypopneas.[9,13] The last study evaluated the plasma levels of anesthetic with upper airway dryness and found that there was a significant correlation between the two parameters. Overall, 5 of the 10 articles found a significant relationship between local anesthetic use and airway obstruction. In light of these findings, the authors suggested that lidocaine likely has an effect on upper airway dynamics.

Propofol is a short-acting intravenous anesthetic agent that is lipophilic. It has a short onset of approximately 30 seconds with quick redistribution, clearance and metabolism, which results in a typical duration of action between 3 and 10 minutes. It is known to result in depression of the central nervous system as a result of activity at the gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors. The 12 studies looking at propofol looked at a number of heterogeneous outcomes. Four of these studies reinforced the dose response characteristics of this medication with decreases in airway cross-sectional area with increasing dosage.[15,16] These studies identified that obstruction was most likely to occur at the base of tongue, primarily in the anterior-posterior direction.[16] Three additional studies demonstrated a decrease in EMG activity with increasing medication dosing.[17-19] A single study looking at sleep staging found that the Pcrit during propofol administration was similar to that seen during stage N2 sleep.[19] Overall, propofol is known to cause dose-dependent effects on the upper airway which make airway collapse more likely with increasing doses.

Dexmedetomidine is an alpha adrenergic agonist with analgesic, sedative and anxiolytic effects. It is often recommended for use when preservation of spontaneous respiration is needed and is available in intravenous and nasal preparations. It requires a 10 minute loading dose followed by a continuous infusion. Four studies have reported on the effects of dexmedetomidine on the upper airway; all 4 have demonstrated that this agent has a minimal effect on the cross-sectional area of the airway. These studies also report that it is less likely to effect upper airway dynamics than propofol.[20-23] A single study evaluated sleep staging with dexmedetomidine sedation and demonstrated that this agent approximates non-rapid eye movement (NREM) sleep without respiratory depression.[24] Overall, dexmedetomidine was found to have a minimal effect on the upper airway.

Midazolam is a benzodiazepine with quick onset of action within 1 to 3 minutes and a duration of 15 to 60 minutes. It works via the GABA receptors and is an anxiolytic and sedative that provides amnesia. It is frequently used prior to the administration of anesthesia, often in the pre-operative setting for children. Six studies have evaluated the effects of midazolam on the upper airway. Two of these

studies evaluated PSG outcomes; the first reported that REM was absent and N3 sleep was reduced in children receiving 4 to 7.5mg of midazolam.[24] The second study, however, used lower medication doses (median dose=2.4 mg), reported that all sleep stages were seen and that Pcrit levels were minimally effected.[25] Two studies looking at airway obstruction reported conflicting results. The first reported that children given both midazolam and nitrous oxide had no worsening of desaturations, upper airway obstruction or hypoventilation.[26] The second reported that children receiving midazolam during adenotonsillectomy had more airway obstruction than those who did not receive this medication.[27] Overall, the data suggests that midazolam may cause upper airway obstruction, but it is unclear if this effect is related to the dose of medication given.

Pentobarbital is a short-acting barbiturate with onset of action within 1 to 5 minutes that is a sedative and hypnotic but does not have amnestic qualities. Its mechanism of action is through binding to the GABA receptor and inhibition of excitatory glutamate receptors. It is given orally and frequently used to assist with induction of sedation or sleep. Two studies have evaluated its effect on the upper airway. The first study reported that Pcrit and genioglossus muscle function were unchanged but the medication was noted to increase time to arousals and genioglossal activation prior to arousals.[28] The second evaluated soft palate obstruction and found that pentobarbital was more likely to result in obstruction in children with developmental delay when compared to those without developmental delay.[29] Both studies suggested that pentobarbital may have some effect on the upper airway but evidence is very limited.

Ketamine is an NMDA receptor agonist which results in dissociative anesthesia with onset of action in 3 to 5 minutes and recovery within 45 to 120 minutes after administration. It is known to increase oral secretions and typically requires co-administration of anti-sialogogues. Three studies have focused on the effect of ketamine on the upper airway.[30-32] These studies focused on laryngospasm and concluded that ketamine is relatively safe and the most common complication noted is mild hypoxemia.

Inhalational anesthetics work through multiple central nervous system neurotransmitter release and result in rapid onset (1-3 minutes) of general anesthesia and rapid recovery. **Agents studied include sevoflurane, desflurane, isoflurane, halothane, the first 2 of which are also known to suppress responses to tracheal stimulation. Eleven studies evaluated the effect of these agents on the upper airway and 6 demonstrated increased upper airway collapse.** One study reported that sevoflurane causes a dose-dependent reduction in cross-sectional area while 2 additional studies suggest that sevoflurane posed little risk for airway obstruction. A study of isoflurane found that airway dilator muscle function correlated with level of respiratory depression while anesthetized.[33]

Opioids interact with one or more opioid receptors present in the central nervous system respiratory control centers as well with mechanosensory receptors in airways. These medications are known to depress the ventilatory and pharyngeal neuromotor drives with resultant reduction in airway patency. Nine animal and human studies reveal that opioids increase upper airway obstruction.[34, 35-42] Six of

these studies reported clinical upper airway obstruction, 2 reported that patients receiving opioids had a decrease in upper airway reflexes[34, 43] and the last reported decreased respiratory compliance with opioid use.[44]

Putting it all together

There is insufficient study of the effect of anesthetics on the upper airway and very few studies that compare the effects of difference anesthetic agents. In addition, the outcomes assessed are numerous making direct comparisons difficult. **Propofol is the medication used most commonly for DISE in adults, As we found in this review, propofol has a dose-dependent effect on upper airway collapse and careful titration of this medication is necessary to assure a uniform depth of sedation in order to evaluate treatment outcomes. Other medication, like dexmedetomidine, have minimal independent effects on respiratory control, and as such, may be effective agents for DISE. Similarly, ketamine has minimal airway compromise and may allow lower doses of dexmedetomidine to be used for DISE.** However, agents such as inhalational anesthetics and opioids were noted to result in exaggerated dynamic airway collapse suggesting that they would not be ideal for use in airway evaluations. Moreover, while local anesthetics are typically used to decrease the risk of laryngospasm, they appear to effect airway reflexes, and we suggest that they only be used when tracheal evaluation is planned as part of the upper airway evaluation.

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