Anesthesiological considerations for children with obstructive sleep apnea

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Purpose of review
To summarize recent evidence-based data regarding outcomes associated with children who have obstructive sleep apnea (OSA).

Recent findings
Internet surveys conducted by pediatric otolaryngologists and pediatric anesthesiologists have reported a disturbing number of deaths within 24 h of tonsillectomy attributed to postsurgical/anesthesia apnea. Several occurred in the post anesthesia care unit after routine monitors had been removed. In addition, a number of deaths also have been attributed to children who have duplicated cytochromes allowing the rapid conversion of codeine to morphine, thus producing a relative drug overdose. Finally, there is some human and animal evidence suggesting that repeated episodes of hypoxemia result in altered opioid receptors causing relative opioid sensitivity. These factors have important clinical implications.

Summary
Perioperative deaths in children with OSA occur at a low frequency. Hypoxia-induced opioid sensitivity combined with an approximate 1–2% incidence of rapid conversion of codeine to morphine suggest the need for new approaches for providing preoperative assessment of risk, extended postoperative observation and the need for alternative opioids to codeine. Additionally, new less painful surgical approaches may help to reduce postoperative opioid requirements and therefore perhaps less risk for opiate-induced apnea in this vulnerable population.

Keywords
adverse events, obstructive sleep apnea, opioid sensitivity, OSA, perioperative

INTRODUCTION

Tonsillectomy and or tonsillectomy combined with adenoidectomy is one of the most common surgical procedures performed in children in the USA (approximately 500 000 per year). Recent studies have reported a distressing number of children who have died within 24 h of their surgical procedure and these deaths have occurred in the post anesthesia care unit (PACU), on the ward, and at home [1▪▪,2▪▪]. This review will examine the multiple factors that contribute to these disturbing outcomes.

OVERVIEW

Children may suffer an adverse outcome following tonsillectomy because of their underlying associated medical conditions (e.g., congenital heart disease), surgical complications (hemorrhage), and anesthesia mismanagement (inadequate securing of the airway, anesthetic overdose, among others). Complications directly related to surgery and anesthesia will not be part of this discussion. Rather this review will summarize patient-related factors, data regarding opioid-induced sensitivity, genomic information concerning duplicated cytochromes resulting in minimal or ultra-rapid conversion of codeine to morphine or hydrocodone to hydromorphone thus placing children with obstructive sleep apnea (OSA) at particular risk, and recent recommendations regarding perioperative assessment of

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Curr Opin Anesthesiol 2015, 28:327–332
DOI:10.1097/ACO.0000000000000187

KEY POINTS

- Obesity and ethnicity are specific independent risk factors for OSA.
- Cytochrome variations inability to convert codeine to morphine and hydrocodone to hydromorphone may result in slow metabolism (minimal conversion to active metabolite therefore minimal analgesia) or ultra rapid metabolism (resulting in higher blood levels and possible overdose); similarly, cytochrome variations in the metabolism of tramadol may lead to drug accumulation or reduced duration of analgesia.
- Chronic hypoxemia alters mu receptors resulting in patients being analgesic at lower blood levels of opioid than those who do not have chronic hypoxemia, thus all doses of opioids should be reduced to one-third or half of that used for children undergoing tonsillectomy who do not have OSA.
- A careful history and physical examination is warranted in all children undergoing tonsillectomy so as to assess those who may be at risk for OSA; guidelines from the AAP, the Otolaryngology Association, and the ASA all help to provide assistance with this evaluation and assessment.
- Patients determined to be at risk should be admitted and appropriately monitored following tonsillectomy unless opioids can be omitted from their postsurgical pain management regimen.

children potentially at risk for OSA as well as possible new surgical approaches that may minimize the need for postoperative opioids.

Obesity

In pediatric patients, obesity appears to be the major risk factor associated with OSA [3–5]. Although BMI is frequently used to characterize the extent of obesity in adults, in the pediatric population, a weight exceeding the 95th percentile for age and gender is considered obese. Numerous studies have shown that obesity is a major cause of OSA and that unfortunately obesity has become pandemic in the USA with marked changes in obesity demographics during the past 25 years [3,4]. There is some suggestion that obesity and OSA are linked to metabolic syndrome, that is, hypertension, dyslipidemia, proinflammatory states, insulin resistance, and other features [3]. It has also been shown that tonsillectomy with adenoidectomy is able to reduce OSA by approximately 70% [6,7]. However that implies that 30% of children are not cured and that other measures are needed such as encouraged weight loss, surgical procedures such as uvulopalatopharyngoplasty, mandibular advancement, tongue base reduction, and others. Constant positive airway pressure, bilevel positive airway pressure, and variable positive airway pressure have also been utilized with varying success [8▪].

Clinical signs and symptoms

Loud snoring, gasps, pauses in respirations, night terrors, sleeping in odd positions such as the neck hyperextended, enuresis (after 6 months of continence), cyanosis, morning headaches, daytime somnolence, and poor school performance (learning problems, attention deficit disorder or hyperactivity disorder) are all associated with OSA [9▪]. Physical examination may reveal either failure to thrive (underweight) or obesity. Tonsillar hypertrophy, adenoidal facies, micrognathia, high arched palate, reactive airway disease, and hypertension have all been associated with OSA [9▪]. A careful preoperative history must elucidate these factors and to help clarify which children may be at risk for OSA. The gold standard however is a formal sleep study (polysomnogram) and assessment of the apnea/hypopnea index (the number of pauses in breathing for 10 s or longer or partial obstructions to breathing per hour) (Table 1). However, it is the minority of children that have had these studies and therefore it is exceedingly important for the clinician to ask appropriate specific historical questions described above so that appropriate perioperative pain management and monitoring can be prospectively organized. The American Society of Anesthesiologists (ASA) has recently published an updated guideline for the perioperative assessment and management of such patients (see below) [10▪▪]. An alternative screening tool is overnight pulse oximetry, the McGill oximetry score (Table 2) [11▪▪]. Severity of the desaturation during sleep determines the score. Episodes of desaturation below 80% are considered to be consistent with severe OSA. The pattern of desaturation events

Table 1. Assessing severity of OSA with polysomnography with the apnea/hypopnea index

OSA severity	Number of apneas[a]/hypopneas[b] per hour[c]
None	0
Mild	1–5
Moderate	5–10
Severe	>10

OSA, obstructive sleep apnea.
[a]Apnea is defined as a cessation of breathing for 10 s or longer.
[b]Hypopnea is defined as a partial airway obstruction.
[c]Each polysomnography facility may have a similar but different scoring system.

Table 2. The McGill Oximetry score for assessing obstructive sleep apnea

Score	Severity of nocturnal desaturation events[a]
1 = No risk	No desaturations <90%
2 = mild risk	Desaturations <90%
3 = moderate risk	Desaturations <85%
4 = severe risk	Desaturations <80%

[a]Note that this most often takes a 'saw tooth' pattern correlating with obstruction/apnea/desaturation followed by arousal and resaturation.

is usually 'saw tooth' in nature corresponding to obstruction/apnea/desaturation followed by arousal, relief of obstruction, and re-saturation. The assessment of severe OSA has now been added to the guidelines from the American Academy of Pediatrics (AAP) [9▪], the ASA, and that of the pediatric otolaryngologists [12] (see further).

Ethnicity

Several studies have confirmed greater risk for OSA in African-American and Hispanic children compared with Caucasians [13–16]. One study has shown that Hispanic children with excessive daytime somnolence were three times more likely to have frequent snoring and nearly six times more likely to have witnessed apnea events during sleep [17]. African-American children may have independent genetic factors predisposing to both obesity and OSA; reactive airway disease, and low socioeconomic status are other associated factors [18,19].

Analgesia

The following subsections will review new information regarding the nuances of providing postoperative analgesia to children with OSA following tonsillectomy.

Opioid sensitivity

There is increasing evidence that repeated episodes of desaturation result in altered mu receptors with the net effect of analgesia occurring at lower blood concentrations of opioids than in patients or animal models who have not experienced repeated episodes of desaturation [20▪▪,21–23]. Thus, in children with severe OSA, it would seem that at least some of them would be analgesic with much lower doses of opioids compared with children undergoing the same procedure but for the indication of recurrent tonsillitis; this has been demonstrated in children with OSA who underwent tonsillectomy [20▪▪,24▪▪]. Thus, the standard dose of opioid may in fact be a relative overdose in children with OSA. It is therefore recommended that the initial dose of opioid be one-third to half that of the standard dose. A possible means for assessing this risk that I have used but is not scientifically validated with a randomized trial may be the administration of low-dose opioid during anesthesia with spontaneous respirations and then observation for resulting effects on respiratory rate. If a low dose of opioid results in a significant reduction in respiratory rate, then this is suggestive of potential opioid sensitivity.

Cytochrome snippets, codeine, hydrocodone, and risk

In the last several years, increasing evidence has demonstrated marked ethnic variations in the cytochromes responsible for drug metabolism. In particular, the defect in a specific cytochrome (CYP 2D6) has been shown to result in a fairly high percentage of children being unable to convert codeine to morphine (approximately 8–10%); in these children, virtually no analgesia results from the administration of codeine. Conversely, on average 0.5–2.0% of children may have a duplication of the cytochrome snippet responsible for this conversion, thus resulting in rapid conversion of codeine to morphine and thus producing a much higher blood level than in children with normal cytochromes. Thus, in these children, a relative overdose is possible and when combined with the child who has OSA could and has resulted in fatalities [25,26,27▪▪]. This tragic interaction cannot be diagnosed at present preoperatively and thus the Food and Drug Administration has published a warning admonishing against the use of codeine, particularly 'around the clock' rather than 'as needed' in children following tonsillectomy. The incidence of such duplicated cytochromes is quite variable and definitely ethnically related, for example, as high at 29% African/Ethiopian, 3.4–6.5% African-American, and 1–2% Northern Europeans (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm315627.htm). Similarly, data suggest that hydrocodone is also subject to marked variability in conversion to the active opioid metabolite hydromorphone and also likely to result in minimal analgesia for those with poor conversion, whereas ultra-rapid metabolism will result in up to an eight-fold greater plasma concentration [28].

Alternative approaches to analgesia

Alternative approaches to provide analgesia would be to use oral opioids, which are less subject to

variable metabolism such as oxycodone or hydromorphone [29,30], the use of lower than normal opioid dosing in children with OSA (1/3–1/2 the usual dose), or avoidance of opioids altogether. Some practitioners advocate alternating oral acetaminophen with oral ibuprofen on an 'around-the-clock' basis. A randomized double-blind trial using this approach in children concluded that such an approach was more effective than monotherapy alone for the treatment of childhood fever, but no controlled trials have examined this practice for postoperative analgesia [31]. It should be noted that tramadol is also subject to variable metabolism and that slow metabolizers could theoretically encounter drug accumulation in those with poor CYP2D6 activity and shortened or reduced analgesia in those that are rapid metabolizers [32].

Surgical considerations

It has been shown that the degree postoperative pain relates in part to the surgical approach for tonsillectomy, for example, radiofrequency versus dissection versus guillotine versus microdebrider [33–38] with extensive use of electrocautery resulting in the most postoperative pain. A recent suggestion has been to perform partial tonsillectomy to reduce airway obstruction while avoiding complete tonsillectomy and thus significantly reducing postoperative pain and therefore reducing the need for postoperative opioids [36,39]. It is unclear whether using this approach will later result in regrowth of tonsillar tissue and therefore recurrence of OSA. It should also be noted that airway obstruction may become worse during the first postoperative night despite the fact that the enlarged tonsils have been removed [40]. Thus, the apparent reduction in the cause of airway obstruction may not result in a clear airway.

GUIDELINES

A number of guidelines have been published regarding the evaluation and management of children at risk for OSA. The AAP issued a practice guideline for the diagnosis and management of such children with a review of over 3000 articles [9▪]. They recommended that all children should be screened for snoring, polysomnography should be performed in children with signs and symptoms of OSA, recommended tonsillectomy as a first-line treatment, stated that 'high risk' patients should be monitored as in-patients postoperatively, and then re-evaluated to determine whether additional treatment is needed. They defined high-risk patients as those younger than 3 years, those having severe OSA documented by polysomnography (oxygen saturations <80% during polysomnography or postsurgery or apnea/hypopnea index >24 per hour), those having cardiac complications related to OSA (right ventricular hypertrophy, pulmonary hypertension), those having significant hypercapnia during polysomnography ($PECO_2$ ≥60 mmHg), and those with failure to thrive or obesity, craniofacial anomalies, neuromuscular disorders and current respiratory infection [9▪]. It is unclear to me how the AAP committee chose an apnea/hypopnea index of greater than 24 as being at high risk when most laboratories define risk as having an apnea/hypopnea index of greater than 10 as being at high risk. This emphasizes the importance of knowing the parameters used by the evaluating facility.

The American Academy of Otolaryngology Head and Neck Surgery Foundation has issued a practice guideline regarding the indications for polysomnography prior to tonsillectomy in children [12]. They made the following recommendations for preoperative polysomnography: children with obesity, Down syndrome, craniofacial abnormalities, muscular disorders, sickle-cell disease, and those with mucopolysaccharidoses. They also recommended polysomnography in children without the above-mentioned conditions wherein there is discordance between tonsil size and the severity of reported sleep disordered breathing. They further stated that clinicians should report the results of such studies to the anesthesiologist prior to the induction of anesthesia, that clinicians should admit children with polysomnogram documented OSA if they are younger than 3 years or have severe OSA (an apnea-hypopnea index of ≥10 or oxygen saturation <80% or both). They further clarified that in children for whom polysomnography is indicated; these laboratory-based studies should be conducted preoperatively.

The ASA recently updated their guideline for the assessment and management of patients with OSA [10▪▪]. In that guideline, there are two key tables. Table 1 in that guideline helps the clinician to assess the signs and symptoms that may indicate that the patient is at risk for OSA (both adults and children). Table 2 in that guideline assesses the invasiveness of the surgical procedure (e.g., body cavity), the nature of the surgical procedure (peripheral versus central), the type of anesthesia administered (general versus regional), involvement of the airway (e.g., tonsillectomy), and the need for postoperative opioids on an extended basis; a score of 5–6 indicates likely OSA and the need for appropriate perioperative management [10▪▪]. Although these risk assessment tables have not been systematically validated, when placed in perspective with the guidelines from the AAP and

the otolaryngologists, it would seem that the ASA guideline is quite useful in estimating potential for OSA and perioperative risk (see also below).

RECENT SURVEYS

Two recent surveys (Otolaryngology and Anesthesiology) warrant discussion:

(1) The Patient Safety and Quality Improvement Committee of the American Academic of Otolaryngology–Head & Neck Surgery [2▪▪] in a 32-question survey reported 40 pediatric deaths: six were attributed to bleeding, nine to 'med-narcotic', and 16 described as 'unexplained cause'. Of these, one was in hospital and the remaining 15 occurred 'out of hospital' [2▪▪]. The otolaryngology survey implicated opioid overdose as the cause in eight deaths. Most importantly 10 deaths occurred in children labeled as having OSA and these deaths were unrelated to hemorrhage.

(2) I conducted a similar Internet-based 42-question survey to all 2377 members of the Society for Pediatric Anesthesia (SPA), which was sent out three times at 2-month intervals; approximately, 30% of the surveys were returned [1▪▪]. In addition, we queried the ASA Closed Claims Project database for otolaryngology cases involving children. Out of the 731 surveys returned and in the 45 possible cases from the Closed Claims Project, 111 reports comprised the final database. We used the ASA-OSA guideline criteria [10▪▪] (ASA guideline Tables 1 and 2) to assess those children who might have been at risk for OSA. Those children assessed to be at risk for OSA were more likely to be obese ($P < 0.001$), to have a higher ASA physical status ($P < 0.001$), and as previously reported [41] to be highly related to ethnicity (African-American, Hispanic versus Caucasian) ($P < 0.001$). There was a statistically significantly higher incidence of morbidity and mortality related to hemorrhage in the children assessed to be not at risk for OSA ($P = 0.006$), whereas a greater fraction of the children described as at risk for OSA had the event attributed to apnea ($P = 0.016$). What was most disturbing about our survey is that 10 deaths occurred at home, three in a hospital ward after discharge from PACU, and two in the PACU after monitors were removed (one child felt to be 'asleep' on his father's lap and the other 'asleep' on the stretcher alongside her mother). It was astonishing that two children died while still in the PACU, thus illustrating the insidious way that apnea may occur in children with OSA following tonsillectomy. All of these deaths were attributed to apnea and likely were preventable [42,43].

CONCLUSION

Obesity has become pandemic in the USA and with this a rising increase in the incidence of children at risk for OSA. With the institution of the Affordable Care Act, there will be increasing pressure on hospitals and clinicians to provide care more efficiently and at lower cost. Thus, there will be great pressure on clinicians to avoid postsurgical hospital admissions. This in fact may create the 'perfect storm' in the sense that it will be easy to overlook or to not take adequate time to obtain a complete detailed history to determine which children require postsurgical/anesthesia admission to the safety net of medical supervision. Unfortunately, even when admitted, without continuous monitoring and observation, these events may still occur; simple admission without proper safeguards may result in a false sense of security. It is unacceptable for children to die or become neurologically injured following an elective surgical procedure particularly when we have the tools to help predict those who are at risk and to protect those who are determined to be at risk. Therefore, despite the pressure to reduce costs, both surgeons and anesthesiologists are obligated to improve screening procedures, perhaps develop alternate surgical approaches, and to provide adequate postoperative analgesia, which is least likely to add to risk [42,43].

Acknowledgements

None.

Financial support and sponsorship

The author has not had any funding for the past 2 years.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

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These two articles were surveys sent to otolaryngologists and anesthesiologists assessing the risks and types of post tonsillectomy complications. Both articles reported a disturbing number of children who died within the first 24 h of anesthesia likely because of apnea induced by opioid sensitivity or opioid sensitivity combined with rapid conversion of codeine to morphine.

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