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Obstructive sleep apnoea in children: perioperative considerations

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Editor's key points

- Obstructive sleep apnoea (OSA) is common in children, and is a source of significant morbidity.
- Adenotonsillar hypertrophy is often associated with OSA, which can lead to perioperative complications.
- Optimal perioperative management of OSA includes preoperative snoring assessment, close respiratory observation and monitoring, and opioid-sparing anaesthetic and analgesic approaches.

Summary. Obstructive sleep apnoea (OSA) has become a major public health concern as its incidence and severity have increased in tandem with the obesity epidemic. In children, OSA is now recognized as a common disorder and can be associated with significant morbidity. OSA belongs to a spectrum of diagnoses known as sleep-related breathing disorders in which the airway is completely (apnoea) or partially (hypopnoea) occluded during sleep despite continued respiratory efforts. This airway obstruction can cause abnormal gas exchange leading to hypoxaemia, hypercapnia, sleep fragmentation, and their attendant physiological and behavioural consequences. The degrees of hypercapnia, hypoxaemia, and upper airway airflow reduction are the primary factors determining the severity of OSA. In young children, adenotonsillar hypertrophy is the most common anatomical abnormality associated with OSA, and adenotonsillectomy is, therefore, the most common surgical intervention. Perioperative complications associated with adenotonsillectomy are more common in children with severe OSA. A thorough understanding of the pathophysiology of OSA, careful and complete preoperative assessment, meticulous intraoperative and postoperative management, and early recognition of potential perioperative complications are essential to optimization of outcomes. The safe anaesthetic management of a child with OSA requires an anaesthetic technique tailored to the underlying aetiology and severity of OSA and the surgical procedure. This review focuses on the epidemiology, pathogenesis, and diagnosis of OSA, and the state-of-the-art and future directions in the perioperative management of children with OSA.

Keywords: adenoidectomy; analgesics, opioid; child; sleep apnoea obstructive; sleep apnoea syndromes; tonsillectomy

Sleep-related breathing disorders (SBD) are a continuum of disorders including primary snoring, upper airway resistance syndrome and obstructive sleep apnoea (OSA). The most severe form of SBD with the highest risk of perioperative complications is OSA.[1] The pathophysiology of paediatric OSA is often multifactorial, with significant contributions from adenotonsillar hypertrophy, obesity, and genetics. Polysomnography is currently the most widely accepted diagnostic modality for OSA, but restricted availability and high cost limit its routine use. Currently, there is no consensus among anaesthetists regarding the best and safest anaesthetic technique for children with significant OSA; there is also a lack of agreement among anaesthetists, surgeons and institutions on specific criteria to identify children with OSA who will benefit from admission to hospital and aggressive postoperative monitoring after surgery. The objectives of this review are to: (i) update anaesthetists with the latest on the epidemiology, pathophysiology, diagnosis, and treatment of OSA, (ii) outline current strategies for the perioperative management of children with OSA, and (iii) analyse current perioperative outcomes in children with OSA undergoing one of the most common surgical procedures in this patient population, adenotonsillectomy.

Epidemiology

In children, the prevalence of OSA is 1–4%; primary snoring is more common, with an incidence as high as 20%.[1] SBD are more common in boys and children who are obese.[2] The incidence of OSA peaks between ages 2 and 8 years and then declines in older children, although a second increase in the incidence of OSA seen in adolescence is associated with obesity.[3 4] This peak corresponds to the age range where adenotonsillar hypertrophy is most commonly observed in children. African-American children have a higher prevalence of OSA.[5 6] Infants whose family history includes OSA or multiple episodes of sudden infant death syndrome are more likely to be diagnosed with OSA than infants from families with no history of OSA

or a single episode of sudden infant death syndrome; this observation suggests a strong association between a family history of OSA and potentially life-threatening infantile OSA.[7]

Pathogenesis

Increased resistance in upper airway during sleep is an essential feature of OSA. Paediatric OSA is often a multifactorial disorder with overlapping contributions from airway narrowing (e.g. adenotonsillar hypertrophy), abnormal airway muscle tone, and genetics predisposing children to obstructed breathing during sleep.[4] Upper airway patency is determined by the interaction between respiratory dynamics, anatomic structures, and neuromotor tone; the degree of patency is determined by the balance between forces acting to collapse the airway (e.g. negative pressure during inspiration; size, shape, and floppiness of pharyngeal structures) and forces acting to maintain airway patency (e.g. pharyngeal dilator muscle tone, stiffness of pharyngeal structures). Suppression of pharyngeal dilator muscle tone is seen during sleep and anaesthesia/sedation; because of the imbalance of forces in the airway, this suppression leads to accentuated airway obstruction in patients with OSA. Therefore, airway obstruction in OSA can be relieved by arousal from sleep, and OSA is characterized by repeated episodes of airway obstruction relieved by arousal, resulting in restless sleep.[8 9] Children with habitual primary snoring often do not have apnoea, hypopnoea, respiratory effort-related arousals, and gas exchange abnormalities because of a compensatory neuromuscular mechanism preventing significant airway obstruction during sleep. The polysomnographic pattern in children with primary snoring shows obstructive hypoventilation and stable increased respiratory effort, but not frank apnoea, hypopnoea, or respiratory arousal.[10] Obstructive events during sleep in children with OSA have an inverse pattern in relation to sleep stage in comparison with that seen in adults with OSA. Eighty per cent of obstructive events in children with OSA occur during rapid eye movement (REM) sleep, whereas 80% of obstructive events in adults with OSA occur during non-REM sleep.[11 12] As a result, obstructive events in children are rare during slow wave sleep.[12] Non-REM obstructive events occur less often in children, but tend to increase in older children, in African-American children, in the lateral position and at low levels of oxyhaemoglobin saturation.[12] Non-REM obstructive episodes leading to arousal occur at higher oxygen saturation than events during REM sleep.[12] Body position during sleep seems to play a role in the degree of obstruction; the supine position is associated with more severe obstruction than the lateral or prone positions. The use of comprehensive respiratory obstruction event profiles may enhance our understanding of the pathophysiology and clinical manifestations, including adverse outcomes, of OSA in children.[12]

Accepted risk factors for OSA in children include adenotonsilar hypertrophy, craniofacial malformations, hypotonia, obesity, midface hypoplasia, macroglossia, retrognathia, micrognathia, and glossoptosis.[13] While adenotonsillar hypertrophy is the major structural factor contributing to the pathogenesis of OSA in younger children, obesity is increasingly recognized as an important contributing factor to OSA in adolescents.[14] The prevalence and severity of OSA are higher in obese children and adolescents, and the severity of OSA parallels the degree of obesity.[15] However, many obese adolescents do not develop OSA, despite having a narrow airway. Recently, Huang and colleagues speculated that obese adolescents without OSA maintain protective upper airway reflexes during adolescent development, whereas those who go on to develop OSA do not.[16] Obese patients experience alterations in respiratory dynamics resulting from reduced functional residual capacity, and also increased tissue mass and pressure in the neck and pharynx leading to airway narrowing. The increased respiratory effort required to initiate inspiration in the face of reduced functional residual capacity and also to overcome upper airway resistance because of narrowing of the pharynx results in a greater degree of negative pressure in the pharynx and upper airway and accentuates airway collapse in the obese patient.

A subgroup of children with OSA associated with Down syndrome, the mucopolysaccharidoses, craniofacial syndromes, and achondroplasia may have obstructions at several levels in the airway.[15 17] Children with craniofacial syndromes, especially those with midfacial hypoplasia, micrognathia, maxillary hypoplasia, or deformation of the cranial base (e.g. Crouzon, Apert and Pfeiffer syndromes), frequently have OSA, often associated with nasal and nasopharyngeal airway obstruction. In patients with Down syndrome, the upper airway obstruction occurs as a result of midface hypoplasia, macroglossia, and muscular hypotonia. In this subgroup of patients, adenotonsillectomy often alleviates obstruction because of adenotonsillar hypertrophy, but may fail to relieve the obstruction at other levels. These patients frequently require more complex and invasive airway surgery such as tongue reduction or lingular tonsillectomy.

Recurrent episodes of abnormal gas exchange resulting in hypoxaemia, hypercapnia, and acidosis in children with moderate and severe OSA can lead to haemodynamic co-morbidities such as pulmonary hypertension and cor pulmonale; these are usually reversible with resolution of OSA. Chronic hypoxaemia is an independent risk factor for left ventricular hypertrophy.[18] These cardiovascular manifestations arise from endothelial dysfunction from an increased sympathetic tone and inflammatory response facilitated by increases in levels of C-reactive protein.[19] In children with OSA, these inflammatory markers seem to be involved with metabolic and neurocognitive/neurobehavioural manifestations of OSA.[20]

Diagnosis

A description of the signs and symptoms of OSA was published in the *British Medical Journal* in the 19th century: 'the stupid-lazy child who frequently suffers from headaches at school, breathes through his mouth instead of his nose, snores and is restless at night, and wakes up with a dry mouth in the morning, is well-worthy of the solicitous attention of the school medical officer'.[21] While our medical and

technological sophistication have vastly progressed since this description was first published, it still applies to paediatric OSA in the 21st century. Technological innovation and advances in research have improved our understanding of OSA in children and have provided better tools for its diagnosis and management.

The diagnosis of SBD in children can be challenging because of the variety of presenting symptoms. Evaluation of children with suspected sleep disorders begins and, to a large extent, ends with a thorough history. The clinical presentation of OSA includes behavioural and neurocognitive disorders, poor school performance, enuresis, headaches, and cardiovascular sequelae, including systemic and pulmonary hypertension. It is important to note that parental reports alone do not distinguish OSA from simple primary snoring. The accuracy of clinical evaluation of paediatric OSA in predicting positive sleep studies is poor, ranging from 30% to 85%.[22 23]

Further diagnostic evaluation of a child with a clinical history suggestive of OSA includes performance of polysomnography, which is considered to be the 'gold standard' for the diagnosis and quantitative description of OSA. Polysomnography continuously monitors physiological variables during different sleep phases and can differentiate primary snoring from OSA and also provide a more complete description of obstructive events occurring during sleep. Children with primary snoring do not have other night-time and daytime symptoms and have normal sleep polysomnography studies. Central sleep apnoea is characterized on polysomnography by the absence of both airway flow and respiratory effort. Some patients, especially those with neuromuscular conditions, may display mixed central and OSA.

Although polysomnography is the definitive diagnostic study to evaluate OSA, it requires significant time and healthcare resources, is expensive, and is not readily available at all medical centres. The role of polysomnography in the diagnosis of SBD in children remains controversial because of a lack of standardized interpretation and diagnostic criteria. Furthermore, it is not known whether outcomes are significantly improved in children evaluated by polysomnography compared with those who are not. Currently, polysomnography is indicated in the evaluation of children with failure to thrive, unexplained polycythaemia, in particular whether the child also snores, or sickle cell disease associated with a clinical history suggestive of OSA or frequent veno-occlusive crises. In addition, patients with morbid obesity, craniofacial abnormalities, neuromuscular disorders, cor pulmonale, and systemic hypertension may benefit from polysomnography.[24] Commonly reported measures from polysomnography include the nadir of oxygen saturation and the respiratory disturbance index (RDI), which is the number of apnoeic/hypopnoeic episodes per hour. Apnoea is defined as a decrease in flow >90% for two breaths or more. Hypopnoea is defined as a decrease in flow >50% coupled with a 3% decrease in oxygen saturation or electroencephalographic evidence of arousal. The RDI does not specifically diagnose OSA as it includes episodes of central apnoea in addition to episodes of obstructive apnoea.[4] Another commonly reported measure from polysomnography, the apnoea/hypopnoea index (AHI), counts the number of hypopnoea/apnoea events secondary to obstructive events during sleep for 60 min; as the AHI does not include episodes of central apnoea, the AHI is a better indicator of the severity of OSA than the RDI.

Daytime nap polysomnography has been used to evaluate children with suspected SBD, although a normal nap study is not sufficient to exclude a diagnosis of OSA in patients with clinical manifestations suggesting OSA. While the validity of portable monitoring modalities in the diagnosis of OSA in children is still unknown, there is increasing interest in their use in place of polysomnography to improve access and lower costs. One example of a portable monitoring modality is nocturnal oximetry, which assesses the severity of OSA by quantifying the number and severity of oxyhaemoglobin desaturations during sleep. Isolated severe desaturation (<80%) or clusters of desaturation (more than three episodes of <90%) are considered abnormal. The positive predictive value for oximetry is 97%.[25] The McGill Oximetry Scoring System further determines the severity by the lowest desaturation measured during nocturnal oximetry (Table 1).[26] This scoring system was developed as a screening tool to assess the severity of OSA and identify children who require urgent intervention. The American Thoracic Society[24] in 1996 and the American Academy of Pediatrics[27] in 2002 produced clinical guidelines or practice parameters outlining indications for polysomnography in children. These guidelines were intended to assist clinicians by providing a framework for diagnostic decision-making, although specific anaesthetic concerns were not addressed. The American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep

Table 1 The McGill Oximetry Scoring System. The severity of OSA is determined by the Sp_{O_2} nadir and by the number of these episodes during nocturnal oximetry. OSA, obstructive sleep apnoea

Oximetry score	OSA classification	Number of events of $Sp_{O_2} < 90\%$	Number of events of $Sp_{O_2} < 85\%$	Number of events of $Sp_{O_2} < 80\%$
1	Normal/inconclusive for OSA	<3	None	None
2	Mild	≥3	≤3	None
3	Moderate	≥3	>3	≤3
4	Severe	≥3	>3	>3

Table 2 OSA severity by polysomnography (PSG) in children and adults as defined by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. OSA, obstructive sleep apnoea; AHI, apnoea/hypopnoea index. Modified from Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea by the American Society of Anesthesiologists

OSA severity	AHI children	AHI adults
None	0	0–5
Mild	1–5	6–20
Moderate	6–10	21–40
Severe	>10	>40

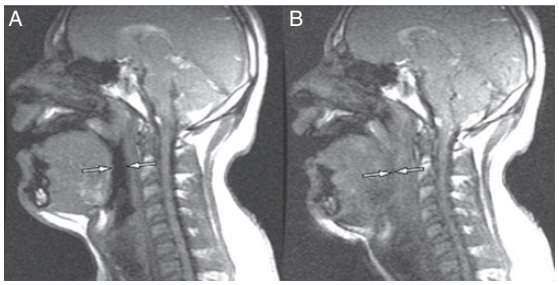

Fig 1 Sagittal midline fast gradient MRI images obtained during expiration (A) and inspiration (B) show intermittent collapse of the retroglossal airway (arrows). At expiration (A), the retroglossal airway (arrows) is patent. During inspiration (B), there is glossoptosis, with the tongue moving posteriorly and obstructing the retroglossal airway (arrows).

Apnea defines the degree of severity of OSA in children according to the AHI (Table 2).[28] These guidelines noted that children with OSA who were obese and younger than 3 years of age had increased perioperative risk associated with adenotonsillectomy.[28] These guidelines did not discuss other issues related specifically to children and the management of infantile OSA.

The challenge in evaluating paediatric OSA does not end with confirmation of a diagnosis of OSA. An equally important issue to be addressed during evaluation is identification of the site(s) of airway obstruction. Examination of patterns of dynamic airway collapse in patients with OSA during sleep identifies anatomic causes of airway obstruction and facilitates planning of interventions to relieve the obstruction. Sites of airway collapse during sleep have been evaluated using differential pharyngeal pressures via catheters placed at various levels in the upper airway, ciné fluoroscopy, video endoscopy, computerized tomography, fibreoptic bronchoscopy, and ciné MRI (Fig. 1). Ciné MRI sleep studies have been reported to detect airway motion abnormalities that are related to OSA.[29] The ideal ciné MRI sleep study would assess the sleeping child's airway anatomy and dynamics free of artificial airways adjuncts. Maintaining upper airway patency during spontaneous respiration in sedated/anaesthetized children with significant OSA can be a challenge. There is no consensus among anaesthesia providers regarding when to interrupt MRI airway imaging because of low oxyhaemoglobin saturation. Lower limits of oxyhaemoglobin saturation may be tolerated in patients who stand to benefit from a complete description of airway obstruction during sleep; such patients might include those who have failed previous surgical interventions for OSA or have severe, multi-level obstructions. It is helpful to review polysomnography reports, noting in particular the severity of oxygen desaturations (nadir and duration) during natural sleep, as a guide to anaesthetic management during imaging studies. Anaesthetic agents impair the ability of pharyngeal muscles to counteract negative pressures during inspiration; this may result in studies that are deceptive, either because the study could not be completed without the use of airway adjuncts or because the anaesthetic precipitated airway obstruction not seen during natural sleep. Anaesthetic agents commonly used for MRI sleep studies include pentobarbital, propofol, benzodiazepines, ketamine, and dexmedetomidine.[30] In contrast to other sedatives, dexmedetomidine possesses properties that mimic non-REM sleep, without significant respiratory depression or airway obstruction. These properties make dexmedetomidine an attractive agent for MRI sleep study evaluation in children with OSA.[31 32]

Perioperative care

The increase in the prevalence of obesity and OSA in childhood, combined with recent evidence suggesting benefits from early surgery over watchful waiting in paediatric OSA,[33 34] makes it likely that increasing numbers of children will present for adenotonsillectomy and other surgical procedures to alleviate OSA. More than 500 000 adenotonsillectomies are performed every year in the USA alone, and more than three-quarters of these include management of OSA symptoms among their indications.[35 36] It is anticipated that approximately one in eight American children will have their tonsils removed.[29] Given the ubiquity of the procedure in the management of OSA, it is appropriate to focus on the perioperative management of children with OSA undergoing adenotonsillectomy in this review. The general principles of perioperative management of a child with OSA presenting for adenotonsillectomy will be applicable to a child with OSA presenting for other surgical procedures. When the surgical procedure permits, regional anaesthesia, including local infiltration, peripheral nerve blocks, and central neuraxial blocks as indicated, should be strongly considered for the child with significant OSA as a means of reducing opioid requirements and opioid-associated respiratory depression and sedation in the perioperative period; the same logic supports the use of intraoperative and postoperative acetaminophen and non-steroidal anti-inflammatory drugs when appropriate to the surgical procedure in order to further reduce opioid requirements.[37]

Preoperative assessment

The components of a successful anaesthetic plan include readily accessible medical records, a thorough medical history with review of systems and careful attention to clinical risk factors, and a targeted physical examination. Preoperative assessment should begin with the history, including any family history of OSA or SIDS. Since primary care providers do not routinely screen patients for OSA, anaesthetists should strive to identify these individuals before surgery by asking about snoring; most children with OSA snore, and the absence of reports of snoring make a diagnosis of OSA much less probable. The anaesthetist must also be attentive to extremes of body habitus, as failure to thrive in infants and children and obesity in children and adolescents are both associated with an increased incidence of OSA. Follow-up questions in patients suspected of OSA should include a review of associated symptoms, including daytime sleepiness, restless sleep, episodes of apnoea, paradoxical breathing, mouth breathing, night-time sweating, sleeping in unusual positions, parasomnias (sleep terrors, sleep walking), secondary nocturnal enuresis, lack of concentration, and neurobehavioural disturbances. If the child carries a diagnosis of OSA, it is important to review its severity and current management, including airway adjuncts such as bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP), home monitoring, supplemental oxygen administration, and positioning during sleep; if airway adjuncts are used, it is important that current settings be reviewed and that the device be available during recovery from anaesthesia. Important findings during the physical examination include the presence of mouth breathing, elongated facies, chest retractions, obesity, failure to thrive, and inspection of tonsil size; although the most common cause of obstruction in children with OSA is adenotonsillar hypertrophy, the magnitude of tonsillar hypertrophy does not correlate with the OSA severity.[38] Other physical characteristics leading to alterations in airway dynamics and OSA may also be identified during the physical examination; these include micrognatia, macroglossia, and midface hypoplasia. Syndromes associated with these anatomical abnormalities include Pierre Robin sequence, Goldenhar syndrome, Treacher Collins syndrome, the mucopolysaccharidoses (including Hunter and Hurler syndromes), and CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality) association.

Although preoperative laboratory testing including polysomnography is rarely performed in patients with OSA presenting for routine tonsillectomy, the presence of a compensatory metabolic alkalosis on a metabolic panel suggests a degree of chronic hypercarbia. Only a minority of children with OSA undergoing adenotonsillectomy have a sleep study performed before operation to assess OSA severity. More commonly, the diagnosis of OSA is based on clinical symptoms, which makes it difficult to know the degree of severity before operation. In the absence of sufficient information, it may not be possible to differentiate primary snoring from OSA. If preoperative polysomnography has been performed, important information to evaluate severity includes not only the AHI, but also the nadir and duration of oxyhaemoglobin desaturation, and also the peak end-tidal carbon dioxide E'_{CO_2} measurement. Patients with nadir episodes of oxygen desaturation reaching 70% during sleep may develop chronic hypercarbia and subsequently increased pulmonary pressures resulting in cor pulmonale. These patients should have an electrocardiogram, echocardiogram, and evaluation by a cardiologist before proceeding with elective surgery. These cardiopulmonary abnormalities are seen less commonly in children compared with adults.[4] At the end of the preoperative evaluation, a risk assessment can be performed based on the presence and severity of symptoms, associated co-morbidities, physical examination, and, if available, the results of polysomnography.[4]

Caution must be exercised with regard to sedative premedication in children with severe OSA, as significant airway obstruction and severe oxygen desaturation can occur; some anaesthetists advocate avoidance of all sedative premedication in children with severe OSA. Children with OSA who do receive sedative premedication must be continuously monitored by clinical observation and, at a minimum, continuous pulse oximetry until transfer to the operating suite is complete. It is important to realize that residual effects of sedative premedication may persist into the recovery period, especially after very short surgical procedures; residual sedatives may exacerbate postoperative respiratory depression and increase the likelihood of complications.[39 40]

Intraoperative management

The administration of sedation or anaesthesia can result in a state that resembles that of natural sleep with increased airway collapse as a result of increased closing pressure,[41] loss of pharyngeal muscular tone,[42] and failure of coordination of phasic activation of upper airway muscles with diaphragmatic activity.[43] There is no current evidence to recommend any specific anaesthetic technique for children with OSA. As such, there is no consensus among anaesthetists regarding the anaesthetic management in children with OSA presenting for adenotonsillectomy. Based on the considerations outlined above, opioid and sedative sparing anaesthesia with careful titration of relatively shorter acting anaesthetic agents appears warranted; while standard monitors are adequate during anaesthesia for adenotonsillectomy in children with OSA, extreme vigilance is called for, as severe airway obstruction can occur even at light levels of anaesthesia.

Indeed, inhalation induction of anaesthesia in children with significant OSA often leads to early, significant airway obstruction related to anaesthetic-induced reductions in pharyngeal muscle tone and increased airway collapsibility. Moreover, the lower lung volumes caused by general anaesthesia cause a cephalad displacement of the mediastinum which decreases longitudinal tension on the upper airway and increases susceptibility to airway collapse.[44 45] Children with severe OSA and craniofacial syndromes can quickly obstruct and experience oxyhaemoglobin desaturation; advanced airway interventions may be necessary to maintain airway patency, oxygenation

and adequate ventilation. Therefore, in this setting, anaesthetists should confirm that appropriate airway management tools, including a variety of sizes of face masks, oral airways, nasopharyngeal airways, tracheal tubes, laryngoscope blades and handles, and laryngeal mask airways (LMAs), are available. If difficult intubation is anticipated, appropriate tools including the fibreoptic bronchoscope, video laryngoscope and difficult airway cart should be available before anaesthetic induction. I.V. access should be achieved as quickly as possible in the setting of severe obstruction; placement of an i.v. catheter before induction is indicated if the past anaesthesia history includes severe obstruction during anaesthesia, especially during induction and emergence. Airway maintenance during adenotonsillectomy using a flexible LMA is not widely accepted and a previous study found that many patients managed with LMA required subsequent placement of a tracheal tube because of difficult ventilation or inadequate surgical visualization.[46] Interestingly, rates of larnygospasm were similar between the flexible LMA and intubation groups.[46]

Respiratory depression, increased pharyngeal collapse, and exacerbation of obstructive apnoea are also seen with benzodiazepines, barbiturates, propofol, and opioids.[47] On the other hand, airway collapse and respiratory depression appear to be relatively less likely after administration of ketamine or dexmedetomidine. Dexmedetomidine produces a sedative state that mimics natural non-REM sleep.[48] Higher doses of dexmedetomidine in healthy children do not cause airway obstruction; it is unknown whether higher doses of dexmedetomidine in children with OSA will lead to airway collapse and obstruction.[49] Ketamine preserves pharyngeal muscle tone and airway reflexes.[50] Co-administration of glycopyrrolate with ketamine can be beneficial by reducing the hypersalivation associated with ketamine alone. A limitation of the use of ketamine in these cases could be its adverse psychotropic effects.

Increased sensitivity to intraoperative and postoperative opioids in children with OSA is well known.[37] Different central and peripheral mechanisms partially explain this increased sensitivity. Severe OSA patients develop an up-regulation of μ-opioid receptors as a result of recurrent episodes of hypoxaemia, leading to an increased risk of respiratory depression with opioid administration.[51] Peripheral mechanisms are also involved, with OSA patients demonstrating a decreased ventilatory response to hypoxaemia. As a result, reduced doses of opioids (typically 50% of usual) with careful titration are recommended for children with significant OSA, accompanied by continuous monitoring including pulse oximetry. Short-acting agents are preferred over long-acting, because they provide faster recovery of pharyngeal tone to avoid postoperative episodes of hypoxoemia and hypercarbia. Given the pharmacokinetic profile of remifentanil, with minimal residual effects, it is an attractive option for intraoperative analgesia in patients with OSA.[52] A previous study found that OSA patients with preoperative nocturnal $Sp_{O_2} < 85\%$ required only half of the opioid dose compared with patients with $Sp_{O_2} > 85\%$.[37] Co-administration of non-opioid analgesics can reduce the dose of opioid analgesics, and thus the risk of respiratory depression. Non-opioid analgesic adjuncts include dexamethasone 0.0625–1 mg kg^{-1}, ketamine 0.1–0.5 mg kg^{-1}, and acetaminophen 10–15 mg kg^{1}.[53 54] A single intraoperative dose of 0.5 μg kg^{-1} of dexmedetomidine administered during adenotonsillectomy can decrease the incidence of emergence delirium and improve pain scores.[55]

Emergence from anaesthesia after tonsillectomy in children with severe OSA can be a challenge. Children with severe OSA or those with co-morbidities should be extubated awake after full recovery of muscle strength. Even under these conditions, frequent episodes of significant airway obstruction and respiratory complications are common. Airway interventions including jaw thrust, placement of an oral or nasal airway, or placement in lateral or even prone position may be necessary to maintain airway patency.

Postoperative care

Residual anaesthetics and opioids administered for postoperative analgesia can lead to changes in airway dynamics resulting in significant airway obstruction. The incidence of respiratory complications in patients with OSA is as high as 27%.[56] These are often seen as recurrent episodes of apnoea, hypopnoea, oxyhaemoglobin desaturation, and hypercarbia similar to episodes on preoperative polysomnography. Abnormal ventilatory responses to hypoxaemia and hypercapnia often persist during the immediate postoperative period.[57 58] Recovery of a normal ventilatory drive responses can take weeks. Postoperative use of positive pressure ventilation (e.g. BiPAP or CPAP) at the preoperative settings might be needed during recovery and postoperative admission. Administration of opioids for postoperative pain management follows the same principles as described above for intraoperative management; continuous monitoring is essential. Use of non-opioid analgesic adjuncts and techniques should be strongly considered in order to reduce the dose of opioid analgesics required, and thus the risk of opioid-related respiratory complications. Although an earlier meta-analysis of non-steroidal anti-inflammatory drugs and adenotonsillectomy suggested an increased risk of bleeding, a subsequent meta-analysis demonstrated no increase in post-tonsillectomy bleeding, except after intraoperative ketorolac.[59 60] Administration of non-steroidal anti-inflammatory drugs after adenotonsillectomy is currently promoted by organizations such as the American Academy of Otolaryngology in its clinical tonsillectomy practice guidelines,[61] and their use has become a routine part of the authors' practice in an effort to minimize opioid-related morbidity.[62 63]

The anaesthetist and surgeon should discuss possible postoperative admission for children with significant OSA at high risk of postoperative respiratory complications (Table 3).[27] Children older than 3 years of age with OSA of unknown severity must be evaluated perioperatively to determine whether postoperative hospital admission is indicated. If significant airway obstruction occurs during the perioperative period, or if the child has significant co-morbidities, postoperative admission and continuous monitoring are strongly recommended (Fig. 2).

Post-adenotonsillectomy monitoring

Given the high risk of postoperative respiratory complications in children with OSA, continuous monitoring of ventilation and oxygenation is critical. Specific standards or guidelines to monitor postoperative respiratory status in children with OSA are not available. The ASA task force on the perioperative management of OSA recommends extended monitoring and observation after anaesthesia and surgery in patients with OSA, although these recommendations are not quantified.[28]

Recovery from anaesthesia can be problematic for children with OSA. Vigilance must continue into the postoperative period, and continued surveillance by experienced medical staff for signs of airway obstruction is important. Postoperative respiratory monitoring of children with OSA should include continuous pulse oximetry to assess oxygenation and clinical observation with measurement of the respiratory rate at frequent intervals as a secondary assessment of the adequacy of ventilation. In children at the highest risk of respiratory complications, continuous monitoring of adequacy of ventilation is highly recommended; early detection of changes in the child's airflow may make it possible to avert life-threatening alterations in ventilation and oxygenation. Unfortunately, at present there is no ideal monitor of ventilation in the non-intubated child; no currently available respiratory monitor is free of limitations or capable of completely avoiding respiratory complications. Options to continuously monitor ventilation include the use of transthoracic impedance (TI) and nasal capnography. TI uses the electrocardiogram signal to detect changes in thoracic impedance with respiration; it is well tolerated and inexpensive, although there is a high incidence of false alarms, which can lead to alarm fatigue on the part of patients, families, and caregivers. An important limitation of TI is that it will continue to record a respiratory rate even with complete airway obstruction, provided there is on-going respiratory effort; this situation is, of course, essentially pathognomonic for OSA. More sensitive forms of monitoring such as nasal capnography are based on the detection of airflow and not on changes in thoracic geometry. Limitations of nasal capnography include poor tolerance of the nasal cannula in young children, dislodgement of the nasal cannula, and undetected airflow in children who are mouth breathers. An alternative secondary monitor of adequacy of ventilation is transcutaneous CO_2 monitoring, which measures

Table 3 Risk factors for postoperative respiratory complications after adenotonsillectomy

Children <3 years old
Severe OSA documented by PSG
Failure to thrive
Obesity
Cardiac involvement (right ventricular hypertrophy)
Down syndrome
History of prematurity
Craniofacial abnormalities
Neuromuscular diseases
Chronic lung disease
Sickle cell disease

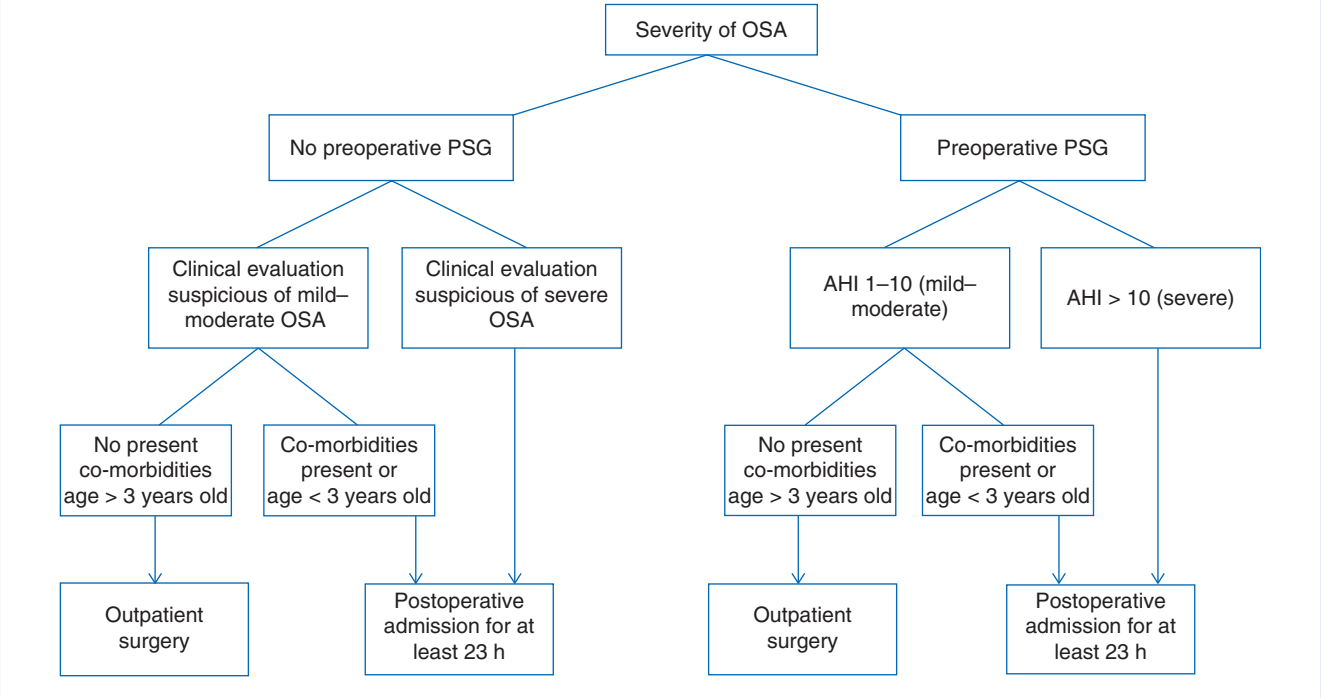

Fig 2 Post-adenotonsillectomy disposition of children with OSA. PSG, polysomnography; AHI, apnoea/hypopnoea index.

Fig 3 Acoustic sensor monitoring with a sensor placed in a child's neck (acoustic respiratory monitoring; Masimo Corporation®, Irvine, CA, USA).

tissue CO_2 rather than airflow itself. Episodes of apnoea or hypopnoea are not detected directly; however, increases in the transcutaneous CO_2 suggest hypoventilation and can prompt evaluation of adequacy of ventilation and degree of airway obstruction. Changes in transcutaneous CO_2 correlate well with changes in Pa_{CO_2}. Limitations of transcutaneous CO_2 monitoring include a complex and time-consuming probe calibration process, delayed detection of inadequate ventilation, and the need for frequent changes in probe location in order to avoid thermal injury from the heated probe.[64]

New forms of respiratory monitoring are needed to improve the postoperative care of patients with OSA. The Masimo Rainbow Acoustic Monitoring® system (Masimo Corporation, Irvine, CA, USA) has been approved by the United States Food and Drug Administration (FDA) for continuous monitoring of ventilation in spontaneously breathing adults and children >10 kg.[65] Acoustic monitoring uses a sensor placed on the patient's neck to detect the acoustic signature of air movement in the upper airway during respiration; the device measures and displays the respiratory rate continuously and will alarm if no air flow is detected, such as during partial or complete airway obstruction (Fig. 3). A recent study in children found that the acoustic sensor was well tolerated and that the monitor was reliable and demonstrated accuracy comparable with capnography.[66] Further studies evaluating the performance of acoustic monitoring in children with OSA are needed in order to define its role in this setting.

Perioperative outcomes

Surgical outcomes

Our understanding of surgical outcomes after adenotonsillectomy has historically been limited because large, robust, and consistent postoperative studies of outcomes were unavailable. A recent multicentre randomized controlled trial (Childhood Adenotonsillectomy Trial – CHAT) examined the outcome of early adenotonsillectomy compared with a conservative approach of watchful waiting without surgical intervention with respect to neurobehavioural symptoms, quality of life, and changes on polysomnography.[33] The study population included 464 school-aged children (5–9 years old) with mild sleep apnoea, moderate OSA, or severe OSA determined by polysomnography. More than 50% of subjects were African-American and nearly 50% were overweight or obese. The primary outcome, attention and executive function on the Developmental Neuropsychological Assessment,[67] did not show any significant difference in the early tonsillectomy group compared with the watchful waiting group.[33] However, compared with the watchful waiting strategy, there was a significant improvement in behaviour, reduction of OSA symptoms, normalization of polysomnography findings, and quality of life (evaluated by the Pediatric Quality of Life Inventory) in children undergoing early adenotonsillectomy.[33] Although the percentage of subjects experiencing normalization of polysomnography after early adenotonsillectomy was higher than that in the watchful waiting group (79.5% *vs* 46.5%), it should be noted that almost half of subjects in the non-surgical intervention group demonstrated normalization of polysomnography at the end of the 7-month follow-up period.[33] This improvement in the non-intervention group was attributed to growth of the developing airway leading to a proportional reduction in airway obstruction because of adenotonsillar hypertrophy.

Anaesthetic, analgesic, and other postoperative outcomes

A recent review of reports of mortality after tonsillectomy revealed that events not related to post-tonsillectomy bleeding, such as opioid-related respiratory depression, account for a significant number of deaths and events leading to significant morbidity, including anoxic brain injury, after adenotonsillectomy in children.[68] The need for additional research to define best practices for the management of children with OSA, including safer pain management strategies, is clear.[69 70]

A review of the LexisNexis 'MEGATM Jury Verdicts and Settlements' database for tonsillectomy-related malpractice claims and jury verdict reports from the USA revealed 248 claims between 1984 and 2012.[71] Claims related to surgery were the most common; however, malpractice claims associated with opioids and anaesthesia had larger monetary awards. Sleep apnoea was documented in 17 fatal and 15 non-fatal malpractice claims related to tonsillectomy, demonstrating a need for improved management of children with OSA undergoing tonsillectomy. Recent data collected from the American Society of Anesthesiologists Closed Claims Project and the Society for Pediatric Anesthesia about serious complications after tonsillectomy found that death or neurological injury were reported secondary to postoperative respiratory events in hospital or at home; a significant fraction of these events were potentially preventable had the child been cared for in a medical setting with an appropriate level of observation and monitoring.[72] Of note, more than half of these children carried a diagnosis of OSA or met criteria for 'at risk of OSA'.[72]

A major limitation of the use of opioids such as morphine or codeine in children with OSA is the development of potentially

life-threatening respiratory depression, especially in unmonitored home settings. Ultra-rapid metabolizers of codeine are at especially high risk of postoperative respiratory depression, potentially leading to death. Clinical doses of opioids markedly depress ventilation, particularly the ventilatory response to hypercapnia, primarily through their binding to μ-opioid receptors. The μ-opioid receptors responsible for analgesia and the ventilatory response to hypercapnia are abundant in the brainstem, especially the medulla.[73 74] In addition to their effects on the ventilatory response to hypercapnia, opioids have profound effects on cortical centres controlling breathing, which potentiates their actions in the brainstem.[75] Children with a history suggestive of sleep apnoea are particularly sensitive to the central respiratory depressive effects of opioids. A previous study recommended halving the usual dose of opioids in children with OSA compared with those with no OSA history.[76] Central serotonin neurones mediate the arousal response to hypercapnia,[77] and central respiratory drive might play a greater role than upper airway tone in adapting to hypercapnia in patients with sleep apnoea.[78] Impairment of this response to hypercapnia might contribute to sudden unexpected death in patients with sleep apnoea.[77]

Based on reports of multiple deaths and respiratory complications resulting in anoxic injuries with the use of codeine for analgesia after adenotonsillectomy in children, the US FDA recently added a Black Box warning against the use of codeine for this indication.[79] Although this warning from the FDA is applicable to all children undergoing tonsillectomy, children with significant OSA and higher CYP 2D6 activity[80 81] (e.g. ultra-rapid and extensive metabolizer status) are at especially high risk of developing serious respiratory complications when given codeine or other opioids significantly metabolized by the CYP 2D6 pathway (Fig. 4).

The effects of race on postoperative pain outcomes in children undergoing tonsillectomy were recently evaluated at our institution; of note, the incidence of OSA was higher in African-American children than in Caucasian children.[6] While African-American children had more frequent reports of inadequate pain control after tonsillectomy, Caucasian children experienced more frequent opioid-related adverse effects, despite comparable perioperative doses of morphine.[6] A history of OSA did not affect pain outcomes in Caucasian children; however, African-American children with OSA were more likely to have inadequate pain control leading to delayed discharge from the recovery room.[6] These results support the practice of reducing morphine doses in Caucasian children with OSA, but suggest a need for more aggressive, opioid sparing pain control in African-American children (Fig. 5).

Future of paediatric tonsillectomy

As noted above, in February 2013 the FDA added a Black Box warning to the package insert for codeine, strongly discouraging its use in children after adenotonsillectomy.[79] Codeine, a morphine pro-drug, depends on the hepatic cytochrome

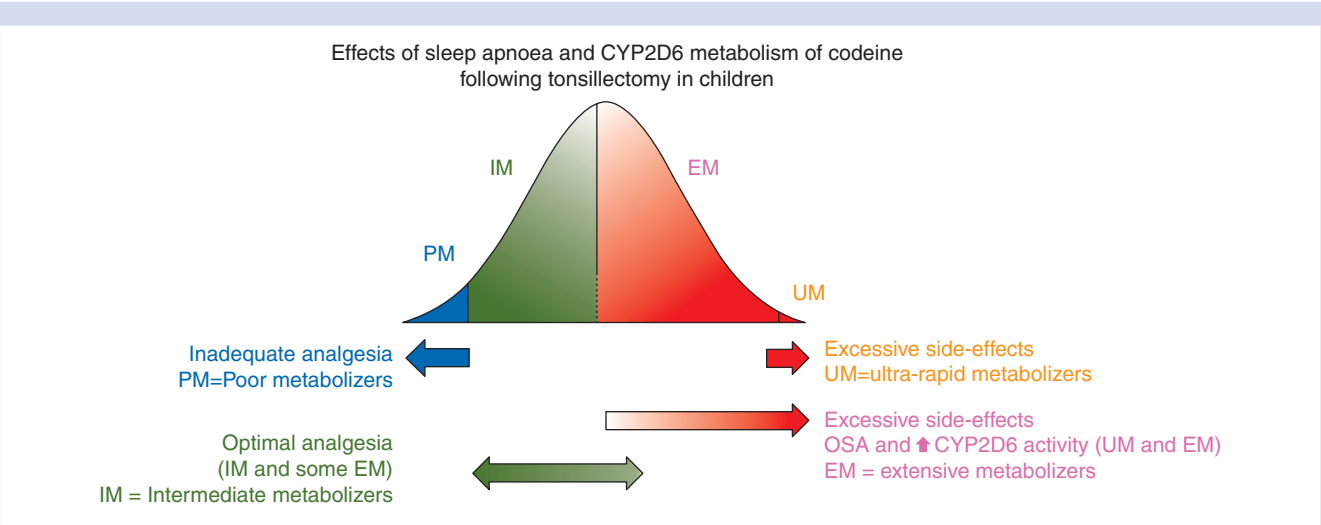

Fig 4 Effects of obstructive sleep apnoea (OSA) and CYP2D6 metabolism on codeine. This figure illustrates the effects of OSA and genotypes of CYP2D6 on codeine's analgesic and adverse effects. CYP2D6, Cytochrome P-450 family enzyme type 2D6; PM, poor metabolizers; IM, intermediate metabolizers; EM, extensive metabolizers; UM, ultrarapid metabolizers. The bell-shaped curve illustrates approximately distributions of CYP2D6 phenotypes, PM, IM, EM and UM in the US population. This distribution may vary depending on the ethnicity (Ethiopians have higher proportions of UMs than the US population). CYP2D6 PMs have inadequate or no pain control from lack or very minimal conversion of codeine (pro-drug) to morphine (blue arrow). UMs are likely to have more codeine adverse effects as they more readily form higher morphine concentrations from a given dose of codeine (solid red arrow). In children with OSA, higher CYP2D6 activity including EM and UM have higher incidence of codeine-related adverse effects because of increased sensitivity of children with OSA to central depressive effects of morphine (red arrow with an increasing gradient). This might be applicable to other opioids metabolized significantly by the CYP2D6 pathway such as tramadol and hydrocodone. Optimal analgesia is a balance of codeine's analgesia and adverse effects, which is more likely achieved in IM and some EM with relatively normal CYP2D6 activity.

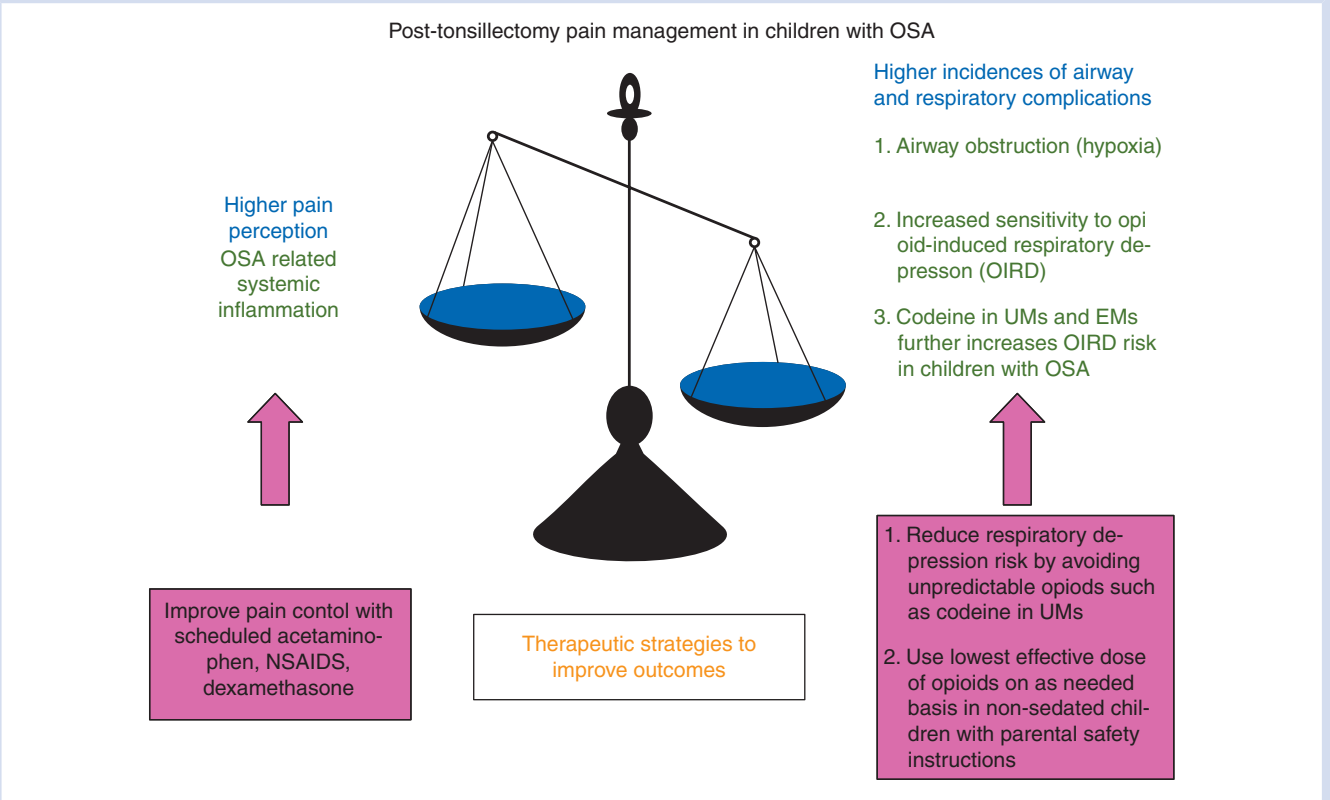

Fig 5 Post-tonsillectomy pain management in children with obstructive sleep apnoea (OSA). Children with OSA have chronic systemic inflammation with increased pain perception, making their postoperative pain control challenging. Children with OSA are at higher risk of upper airway obstruction and opioid-induced respiratory depression (OIRD) because of their higher sensitivity to central depressive effects of opioids, especially in children with Cytochrome P-450 family enzyme type 2D6 (CYP2D6) ultrarapid metabolizer status taking codeine. Scheduled doses of acetaminophen, non-steroid anti-inflammatory drugs (NSAIDs; such as oral ibuprofen 24 h after tonsillectomy) and dexamethasone can help control pain, inflammation, and swelling from tonsillectomy while minimizing the need for opioids. EM, extensive metabolizers; UM, ultrarapid metabolizers.

P450 enzyme CYP 2D6 for transformation to the active metabolite, morphine. Some of the deaths and serious injuries reported to the FDA occurred in children with co-existing OSA who were ultra-rapid or extensive metabolizers based on their CYP 2D6 genotype (Fig. 4).

A recent prospective pharmacogenetic research study of children receiving codeine at home for analgesia after tonsillectomy showed an increase in the incidence of codeine-related adverse effects as CYP 2D6 activity increased, with the highest incidence seen in extensive metabolizers; sedation was most prominent on the evening after tonsillectomy.[80] This study,[80] along with the recent FDA warning,[79] has led us to modify our management of pain after tonsillectomy in children, especially those with OSA or other SBD. Our current practice includes the scheduled administration of opioid-sparing analgesics and adjuncts such as acetaminophen,[82] ibuprofen, and dexamethasone, and also avoidance of scheduled administration of potent opioids, especially those dependent on the CYP 2D6 pathway for their activation (codeine and tramadol). Typically starting on postoperative day 1, the lowest effective doses of non-CYP 2D6-dependent opioids are administered to children >6 years of age on an as-needed basis (Fig. 5).[80] Children presenting for adenotonsillectomy at our institution, especially those with a history of OSA, routinely receive i.v. acetaminophen and dexamethasone in an effort to minimize opioid requirements in the immediate perioperative period. We do not routinely administer i.v. ketorolac or other nonsteroidal anti-inflammatory drugs intraoperatively because of concerns about bleeding; however, we start scheduled ibuprofen 24 h after tonsillectomy (Fig. 5).[61] A better understanding of the mechanisms of OSA-related risks and genetic variability in responses to anaesthesia and opioids in children with OSA or other SBD may help personalize care and improve perioperative outcomes in the future.

Conclusion

OSA is a common diagnosis and anaesthetic challenge in children undergoing surgery. As most children with OSA snore, every child presenting for surgery should be screened for a history of snoring; the absence of snoring makes a diagnosis of OSA much less likely. The most common cause of OSA in children is adenotonsillar hypertrophy, and adenotonsillectomy is the mainstay of therapy for paediatric OSA. As the child with OSA is at risk of potentially life-threatening respiratory complications during and after surgery, optimal perioperative

management of the child with OSA requires cooperation between paediatrician, surgeon, and anaesthetist to ensure adequate preoperative evaluation and preparation, anaesthesia and pain management tailored to the severity of OSA symptoms, and an adequate time for recovery in a setting permitting an appropriate level of monitoring.

Authors' contributions

M.P., S.S., M.M. reviewed the relevant literature, prepared the manuscript, approved the final manuscript, and attested to the integrity of the data reported in this manuscript.

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Declaration of interest

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