Morphine or Ibuprofen for Post-Tonsillectomy Analgesia: A Randomized Trial

Lauren E. Kelly, PhD[a,b], Doron D. Sommer, MD[c], Jayant Ramakrishna, MD[c], Stephanie Hoffbauer, BHSc[c], Sadaf Arbab-tafti, BHSc[c], Diane Reid, MD[c], Jonathan Maclean, MD[c], Gideon Koren, MD[a,b,d]

abstract

BACKGROUND: Pediatric sleep disordered breathing is often caused by hypertrophy of the tonsils and is commonly managed by tonsillectomy. There is controversy regarding which postsurgical analgesic agents are safe and efficacious.

METHODS: This prospective randomized clinical trial recruited children who had sleep disordered breathing who were scheduled for tonsillectomy +/− adenoid removal. Parents were provided with a pulse oximeter to measure oxygen saturation and apnea events the night before and the night after surgery. Children were randomized to receive acetaminophen with either 0.2–0.5 mg/kg oral morphine or 10 mg/kg of oral ibuprofen. The Objective Pain Scale and Faces Scale were used to assess effectiveness on postoperative day 1 and day 5. The primary endpoint was changes in respiratory parameters during sleep.

RESULTS: A total of 91 children aged 1 to 10 years were randomized. On the first postoperative night, with respect to oxygen desaturations, 86% of children did not show improvement in the morphine group, whereas 68% of ibuprofen patients did show improvement (14% vs 68%; $P < .01$). The number of desaturation events increased substantially in the morphine group, with an average increase of 11.17 ± 15.02 desaturation events per hour ($P < .01$). There were no differences seen in analgesic effectiveness, tonsillar bleeding, or adverse drug reactions.

CONCLUSIONS: Ibuprofen in combination with acetaminophen provides safe and effective analgesia in children undergoing tonsillectomy. Post-tonsillectomy morphine use should be limited, as it may be unsafe in certain children.

[a]*Department of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, and* [b]*Ivey Chair in Molecular Toxicology, Western University, London, Ontario, Canada;* [c]*Head & Neck Surgery Division, Department of Surgery-Otolaryngology, McMaster University Medical Centre, Hamilton, Ontario, Canada; and* [d]*Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*

Dr Kelly wrote the first draft of the manuscript and was responsible for study design, data analysis, and interpretation; Drs Sommer and Maclean were responsible for study design and implementation (surgeries, data collection, and patient follow-up), as well as writing and revising the manuscript; Drs Ramakrishna and Reid were responsible for data collection, surgeries, and patient follow-up; Ms Hoffbauer and Ms Arbabtafti were responsible for patient recruitment data collection and data entry; and Dr Koren was responsible for study design, obtaining funding, study oversight, data interpretation, manuscript revisions, and formatting.

This trial has been registered at www.clinicaltrials.gov (identifier NCT01680939).

www.pediatrics.org/cgi/doi/10.1542/peds.2014-1906

DOI: 10.1542/peds.2014-1906

Accepted for publication Nov 5, 2014

WHAT'S KNOWN ON THIS SUBJECT: Sleep apnea is a common condition in childhood, mainly managed by tonsillectomy. Codeine was recently contraindicated for pain management after surgery. Controversy exists regarding the safety and effectiveness of alternative medications, morphine, and ibuprofen.

WHAT THIS STUDY ADDS: Our findings suggest that ibuprofen does not increase tonsillar bleeding and in combination with acetaminophen is effective for pain management after tonsillectomy. Furthermore, standard morphine doses increased postoperative respiratory events and were not safe in all children.

Sleep disordered breathing (SDB) is characterized by a disruption in ventilation and breathing patterns during sleep. SDB ranges in severity from snoring to obstructive sleep apnea (OSA).[1] During sleep, children who have SDB have recurrent episodes of full or partial airway obstruction resulting in hypoxemia, hypercarbia, and sleep disruption.[2] In children, SDB is often caused by hypertrophy of the tonsils and/or adenoids and is commonly managed by tonsillectomy with or without adenoidectomy.[3] The pain associated with this procedure is moderate to severe and more than 500 000 tonsillectomies are performed on children in the United States every year.[1,4] Clinical practice guidelines for post-tonsillectomy pain management recommend educating parents on assessing pain in their children, maintaining proper hydration, and maintaining adequate analgesia, especially in the first few postoperative days.[1]

Until recently, codeine was commonly prescribed for postoperative pain management in many North American centers. However, on August 15, 2012, after the publication of 3 codeine-related fatalities post-tonsillectomy, the US Federal Drug Administration issued a Drug Safety communication advising practitioners that codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare but life-threatening respiratory failure and death. Further investigation revealed 13 cases of death or life-threatening overdose in children receiving standard, appropriate codeine doses and the majority of these cases (8/13) were related to tonsillectomy patients.[5]

Although the Boxed Warning suggests avoiding codeine for post-tonsillectomy pain management, no recommendations have been made as to safe and effective alternate analgesic in pediatric patients. Owing to a fear of increased bleeding, many surgeons have been hesitant to prescribe nonsteroidal antiinflammatory drugs. Our recent meta-analysis, including more than 1700 children, did not detect an increased risk for bleeding after post-tonsillectomy nonsteroidal antiinflammatory drug use.[6] The contraindication of codeine for post-tonsillectomy analgesia has resulted in a shift to oral morphine. Presently, the safety and effectiveness of both ibuprofen and morphine in this population is unclear. The objective of this randomized clinical trial is to assess the safety and effectiveness of post-tonsillectomy analgesia with morphine and ibuprofen in children who have SDB.

METHODS

After approval by McMaster University, The Hospital for Sick Children, and The University of Western Ontario Research Ethics Boards, families were invited to participate in a randomized controlled trial in which their children would receive oral acetaminophen and either morphine or ibuprofen for pain management after tonsillectomy +/− adenoid removal. Recruitment occurred at the McMaster University Medical Centre in Hamilton, Ontario with an allocation ratio of 1:1 run in parallel. This trial was registered with ClinicalTrials.gov (NCT01680939). The inclusion criteria consisted of children who had SDB aged 1 to 10 years, scheduled for tonsillectomy, with or without adenoidectomy. SDB diagnosis was based on parental history, physical examination, and preoperative sleep oximetry. In addition to parental consent, children above the age of 7 years completed an assent form, acknowledging their willingness to participate. Children were excluded if they had previously undergone (adeno)tonsillectomy, or had asthma, obesity (BMI >30), craniofacial/neuromuscular/hematologic/cardiac abnormalities, or contraindications to general anesthesia.

At the preoperative appointment, parents were provided with a pulse oximeter (Nellcor-Boulder N-600) including Oximax Max-p sensors to take home. The research team instructed parents on how to properly apply the oximeter to the child the night before surgery. The oximeter was used to monitor respiratory parameters (O_2 saturation and the number of apnea events per night) during sleep. Parents were also instructed to repeat these measurements the night after surgery. The primary outcome measure was changes in respiratory parameters (O_2 saturation and number of apnea events per hour) after surgery. No changes were made to the primary outcome variables or protocol after the commencement of the trial.

During surgery, anesthesia was delivered to all participants via inhalation induction with air/nitrous oxide and sevoflurane, intravenous supplementation with propofol and/or fentanyl 1 to 2 μg/kg, antiemetic prophylaxis with dexamethasone 150 μg/kg and ondansetron 50 μg/kg, acetaminophen suppository 40 mg/kg, and morphine intravenous 100 μg/kg.

Randomization to morphine or ibuprofen was achieved by using a computer-generated algorithm created by the study coordinator. To maintain allocation concealment the research associate who assigned patients had no knowledge of the randomization sequence. The study clinicians and parents were not blinded, as they were required to write and fill their child's prescription. Parents were instructed to give the children acetaminophen (10–15 mg/kg per dose every 4 hours) and age-appropriate doses of morphine (0.2–0.5 mg/kg per dose every 4 hours) or ibuprofen (10 mg/kg per dose every 6 hours) as needed, as indicated in McMaster Children's Hospital and The Hospital for Sick Children.[7,8] On discontinuation of analgesia, the monitors were returned for data extraction. For both groups,

all adverse events were monitored and recorded by the parents. This included any signs of significant oral or nasal bleeding, in which case they were instructed to return to the hospital emergency department for appropriate assessment and management. Pamphlets describing the signs of serious postsurgical bleeding requiring medical examination were provided to the parents. Secondary outcome variables included pain, adverse drug reactions, and tonsillar bleeding.

Analgesic effectiveness was assessed on postoperative Day 1 and Day 5 using the validated Objective Pain Scale,[9,10] which was recorded by the study researchers in the hospital, and then by the parents at home. The Objective Pain Scale is a validated tool that has been extensively used to compare different analgesic modalities in children (Table 1).[11] In addition, on Day 1 and Day 5, the child completed a modified Faces Scale, a validated tool (ages 1–14 years), which is also commonly used for pain measurement after adenotonsillectomy.[12] Parents were trained by the research staff on how to complete both pain scales. The number of days for a child to return to preoperative diet and the dosing schedule were returned to the research team, after cessation of analgesia.

An independent Data Safety Monitoring Board was set up before trial commencement. The board was commissioned with performing 1 interim analysis halfway through patient recruitment. Pre- and post-tonsillectomy values were compared between the groups by Student's t test or χ^2 test as appropriate. Univariate correlations between the number of morphine doses and the preoperative tonsil size with respiratory parameters were obtained by using nonlinear regression analysis.

RESULTS

From September 2012 to January 2014, a total of 91 children were consented to participate in this study (Fig 1). Demographic characteristics of the cohort can be seen in Table 2. In January 2014 we conducted an interim analysis, as planned in the original protocol, and the Drug Safety Monitoring Board was convened. Morphine and ibuprofen were used for a mean of 4 postoperative days (4.64 ± 1.87 days on ibuprofen; 4.04 ± 1.92 days on morphine). The majority of children (65%) received morphine doses of 0.2 mg/kg and 26% received between 0.25 and 0.35 mg/kg. The remaining 2 children received doses equivalent to 0.1 mg/kg. Acetaminophen was used for 4.46 ± 1.41 days by those randomized to receive ibuprofen and 4.86 ± 1.62 days in the morphine group. On the first postoperative night, with respect to oxygen desaturations, 86% of children did not show improvement in the morphine group, whereas 68% of ibuprofen patients did show improvement (Table 3). The number of desaturation events per hour (preoperative to postoperative) was reduced by a mean of 1.79 ± 7.57 in the ibuprofen group compared with an average increase of 11.17 ± 15.02 in the morphine group with an effect size of 0.96 ($P < .01$) (Table 3). Morphine dose on postoperative day 1 did not correlate with the total number of postoperative desaturation events measured that night (R^2 = 0.10). There were no significant differences in the change in lowest O_2 saturation or the mean O_2 saturation after surgery between the 2 groups (Table 3). Tonsil size did not correlate with the change in desaturation event rates in either group (r = −0.07; P = .74, ibuprofen; r = −0.20; P = .31, morphine).

Pain scale scores on Day 1 and on Day 5 are presented in Table 4. Further secondary outcomes measured in both groups included bleeding rates and adverse drug reactions. Tonsillar bleeding was reported in 3 children who received ibuprofen and 2 children who received morphine. One of the children who bled in the ibuprofen group required hospitalization, as did both of the children who bled in the morphine group. Adverse drug events were reported at similar rates by parents in the 2 groups.

One of the children randomized to the morphine group suffered from a severe adverse drug reaction related to O_2 desaturation. She was a 10-year-old (31-kg) child diagnosed with OSA. Her preoperative desaturation rate was 2.22 events/h and her tonsils were grade 4/4. She returned to the hospital the morning after her tonsillectomy after three 6-mg doses of morphine owing to prolonged vomiting, which the parents reported contained blood. She was given intravenous morphine (3 mg) in the hospital and discharged

TABLE 1 The Objective Pain Scale[10]

	Criteria	Points
Blood pressure	±10% preoperative value	0
	>20% preoperative value	1
	>30% preoperative value	2
Crying	Not crying	0
	Crying but responds to loving care	1
	Crying and does not respond to loving care	2
Movement	None	0
	Restless	1
	Thrashing	2
Agitation	Asleep or calm	0
	Mild	1
	Hysterical	2
Posture	No special posture	0
	Flexing legs and thighs	1
	Holding hands to the neck	2

Postoperative blood pressure was collected in the hospital by the research team and parents were instructed to monitor crying, movement, agitation, and posture every 4 to 6 hours on postoperative Day 1 and Day 5.

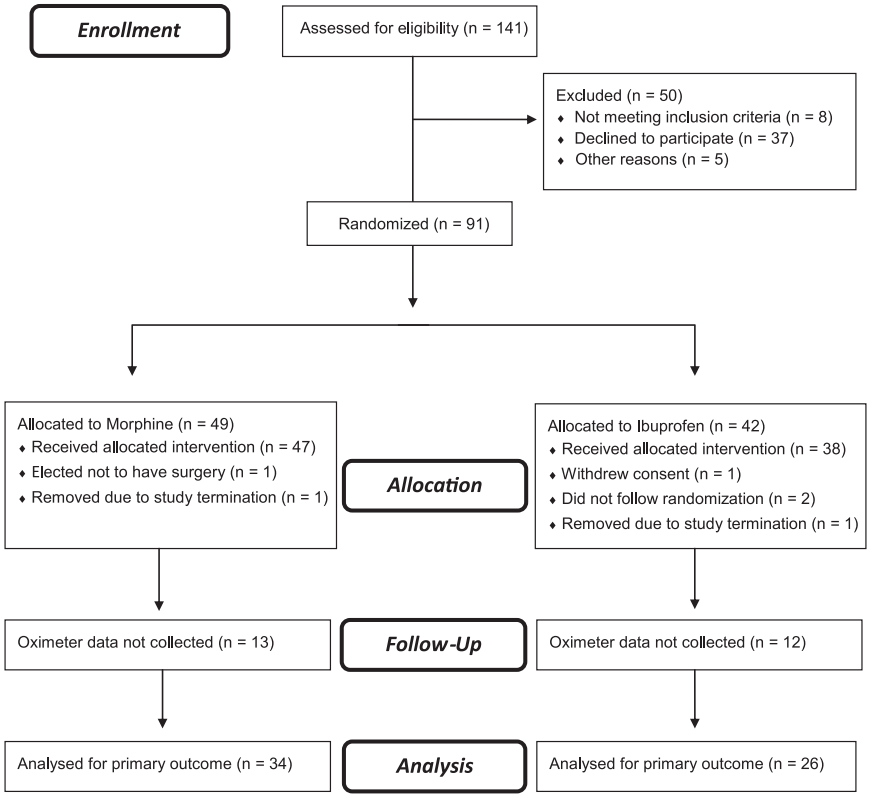

FIGURE 1
Recruitment flow diagram created using the CONSORT guidelines.[38] Other reasons for approached patients not being randomized include language barriers and parents asking specifically for morphine (not wanting to be randomized). Patients who did not follow randomization did not take the medication they were randomized to receive. All patients who were allocated to either morphine or ibuprofen were included in the intent-to-treat analysis. Only those who had oximeter data available were included in the primary outcome analysis.

that evening. Three hours after her 2-AM morphine dose, her parents noticed her lips were blue and she had a slow heart rate and was unresponsive, and returned her to the emergency department. Her O_2 saturation on arrival was 76% and she was promptly administered 0.05 mg intravenous naloxone and supplemental O_2. She was admitted into the PICU and morphine was discontinued. While admitted, chest radiographs revealed right lobe infiltrate, hyperaeration, and air space disease, which was treated with 1500 mg ceftriaxone. After PICU discharge on postoperative day 4, she returned to the hospital 5 days later with a viral upper respiratory tract infection. She has made a full recovery. As a result of the interim analysis, the Data Safety Monitoring Board instructed the research team to discontinue the study on January 31, 2014 and to inform the respective research ethics boards and Health Canada that there were significantly increased desaturations in the morphine group.

TABLE 2 Patient Demographics in the Morphine and Ibuprofen Groups

Demographics	Morphine (N = 46)	Ibuprofen (N = 38)
Age, y	5.07 (2.45)	5.14 (2.25)
Weight, kg	27.36 (8.78)	22.38 (9.59)
BMI	17.31 (3.00)	18.29 (4.56)
Gender, female	50% (23)	54% (22)
Preoperative tonsil size	2.80 (0.61)	3.05 (0.58)
Total number of desaturation events (preoperative)	3.55 (3.63)	4.51 (8.48)
Diagnosis		
SDB	57% (26)	48% (19)
Obstructive sleep apnea	32% (15)	45% (18)
SDB with recurrent tonsillitis	11% (5)	7% (3)
Ethnicity		
Caucasian	87% (40)	93% (38)
African American	7% (3)	7% (3)
Middle Eastern	4% (2)	0
South American	2% (1)	0

Data are presented as mean (SD) for continuous variables, and as a percentage for categorical data.

DISCUSSION

Our study reveals that for children undergoing tonsillectomy, the standard dose range of morphine analgesia increases the risk for oxygen desaturation in comparison with ibuprofen. Furthermore, no differences in analgesic effectiveness or rates of post-tonsillar hemorrhage were identified between children receiving morphine and those receiving ibuprofen. In young children, tonsillectomy ± adenoidectomy have been reported to improve SDB, but only in up to 65% of children.[13–15] Perioperative respiratory complications necessitating a medical intervention may occur in more than 10% of children undergoing adenotonsillectomy, with more than 60% of these occurring in the immediate postoperative period.[16–18] Desaturations can continue for an unpredictable period of time and in a substantial number of children, possibly owing to prolonged changes in the threshold of response to hypoxemia. Moreover, children can experience laryngospasm, airway swelling, and pulmonary edema, leading to further desaturation and even to respiratory arrest.[14] In such cases, in which apnea is not improved after surgery, providing opioids to relieve pain has the potential to increase respiratory depression, through the action of μ and κ opioid

TABLE 3 Primary Outcome Variables in the Morphine and Ibuprofen Groups

	Ibuprofen (N = 26)	Morphine (N = 30)	P Value
Lowest O_2 saturation (% nadir)			
Preoperative	85.39 (6.93)	83.97 (7.86)	
Postoperative	81.27 (15.81)	81.63 (12.75)	
Δ Lowest O_2 saturation	3.96 (12.65)	2.38 (12.30)	.64
Mean O_2 saturation (% nadir)			
Preoperative	97.41 (1.02)	97.20 (1.22)	
Postoperative	96.55 (2.07)	95.00 (2.18)	
Δ Mean O_2 saturation	0.79 (2.33)	2.13 (1.42)	.33
Total number of desaturation events/h			
Preoperative	4.52 (7.87)	3.64 (3.71)	
Postoperative	3.04 (3.27)	14.26 (11.85)	
Δ Total desaturation events/h	−1.79 (7.57)	+ 11.17 (15.02)	<.01
Number of children improved	65% (17/26)	13% (4/30)	<.01

Data are presented as mean (SD) unless otherwise noted. The number of children improved is defined as a child having fewer desaturation events per hour after surgery when compared with their preoperative values.

receptor agonists decreasing respiratory drive and response to hypoxemia.

There are several factors contributing to the adverse respiratory effects of morphine and other opioids used post-tonsillectomy in children who have SDB. Respiratory comorbidities including unresolved apnea, craniofacial disorders, bronchopneumonia, asthma, obesity, and respiratory tract infections combined with swelling after surgery can further compound the respiratory effects of opioids. Hypercarbia is commonly seen in children who have SDB resulting from an overall decrease in ventilation. This disturbance can be reversed after surgery; however, the rate of recovery and extent of reversal is not well understood. Residual respiratory acidosis after tonsillectomy may increase the delivery of nonionized morphine to the brain, owing to an increase in cerebral blood flow, and has the potential to increase respiratory compromise.[19] In canine studies, hypercarbia has been shown to increase cerebral morphine concentrations, whereas serum morphine levels remained unchanged.[20] Furthermore, morphine requirements for analgesia have been shown to be considerably variable in children, as much as 15-fold in some studies,[21] occasionally necessitating large doses for adequate pain control, which may lead to respiratory depression. The hypothesis that morphine analgesia may eliminate respiratory complications by obviating the large variability seen in codeine metabolism and provide more predictable pharmacodynamic effect is not supported by the current study showing similar, unacceptable rates of postsurgical oxygen desaturations to codeine and hydrocodone.[22]

TABLE 4 Secondary Outcomes Including Pain Scores, Bleeding Rates, and Adverse Drug Reactions Between the 2 Groups

Secondary Outcomes	Morphine (N = 45)	Ibuprofen (N = 41)	P Value
Faces scale score, mean Day 1	2.96 (1.02)	2.76 (1.33)	
Faces scale score, mean Day 5	2.02 (1.17)	2.33 (1.19)	
Mean change in faces pain score	0.80 (1.41)	0.21 (2.03)	.29
Objective Pain Scale score, mean Day 1	2.05 (1.56)	2.54 (2.17)	
Objective Pain Scale score, mean Day 5	1.42 (1.52)	2.29 (2.02)	
Mean change in Objective Pain Scale score	0.40 (1.26)	0.42 (1.42)	.95
Number of days back to preoperative diet	7.31 (3.82)	7.17 (5.23)	.89
Number of children with tonsillar bleeding events	4% (2/45)	7% (3/41)	.67
Adverse drug reactions			
Sedation	7% (2/30)	15% (5/34)	.43
Constipation	7% (2/30)	9% (3/34)	.34
Nausea and vomiting	13% (4/30)	12% (4/34)	.29
Dizziness and confusion	7% (2/30)	21% (7/34)	.16
Refusing fluids/anorexia	10% (3/30)	3% (1/34)	.33
Agitation	3% (1/30)	3% (1/34)	.51
Night terrors	0	9% (3/34)	.24
Fever	7% (2/30)	0	.22
Diarrhea	3% (1/30)	0	.47

Data are presented as mean (SD) or as percentage and number for categorical data. Analysis was completed by using unpaired nonparametric statistics.

In this study, pain was managed with similar effectiveness by both morphine and ibuprofen. A previous randomized trial assessing ibuprofen and acetaminophen with codeine in 110 children after tonsillectomy found no statistically significant difference in reported pain and satisfactory pain relief, as reported by parents at postoperative follow-up.[23] The primary outcome measure in that study was tonsillar bleeding rates, which, similar to our experience, were also not significantly different between the 2 groups. Given the unpredictable post-tonsillectomy respiratory response to opioids (codeine, morphine, and hydrocodone) and the analgesic effectiveness of ibuprofen, perhaps the time has come to question the postoperative use of all opioids in this population.[24]

Limitations of the current study include missing oximeter data in both treatment groups owing to children refusing to sleep with the oximeter on their finger. Yet the available sample size provided sufficient statistical power to show the CNS-depressing risks of the opioid. As well, complete polysomnographic (PSG) data were not obtained for our patients. Although this may have provided more data, it may not have been well tolerated in the immediate postoperative period by children. Although PSG is considered the gold standard for diagnosis of pediatric OSA, nighttime oximetry, with its high positive predictive value, can also be used.[25–27] In this era of resource-limited

health care resources, preoperative PSG testing is often not available, and alternatives such as oximetry studies offer a viable alternative.[28] Moreover, the majority of otolaryngologists obtain PSG in fewer than 10% of patients presenting with a sleep disturbance, before recommending adenotonsillectomy.[29] This is supported by recent clinical practice guidelines published by The American Academy of Otolaryngology, Head & Neck Surgery, which state that PSG is indicated for children who have Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses, and should be advocated for in otherwise healthy children for whom the need for surgery is uncertain or when there is a discordance between tonsillar size and the reported severity of SDB.[30] Additional previous work has demonstrated that overnight oximetry correlates well with postoperative likelihood of adverse respiratory events,[31,32] and is useful in determining the indications for (adeno)tonsillectomy.[33]

Physiologic factors that have been previously identified as potential contributors to poor post-tonsillectomy outcomes include smaller tonsils, narrow epipharyngeal airspace, and maxillary/mandibular protrusions.[13] In this cohort, tonsil size did not correlate with an improvement in the number of desaturation events; airspace diameter and maxillary/mandibular orientation were not assessed. Finally, although parents were instructed to maintain hydration, fluid intake was not monitored in this cohort. This could potentially have affected pain scores, as inadequate hydration has been shown to increase reported pain after tonsillectomy.[34] As parents were required to fill their prescriptions at their local pharmacy, parental blinding was not included in the study design. This may have introduced bias in parental report of secondary outcomes; however, this would not have an effect on the measurement of the primary outcome. Finally, the reported severe adverse drug reaction is confounded by the administration of intravenous morphine and the comorbid respiratory tract infection.

Preoperative use of diclofenac and gabapentin[35] has been shown to decrease post-tonsillectomy opioid requirements for children older than 10 years of age, and the effectiveness of these medications in young children warrants further investigation. When compared with morphine, tramadol was shown to result in fewer respiratory events post-tonsillectomy[36]; however, further work is required to assess the safety of tramadol as an alternative analgesic. A retrospective review identified a reduction in recurrent hypoxemia after adenotonsillectomy in children who have severe OSA resulting from dexamethasone administration (~2.4 mg/kg) and a reduction opioid dose.[37] Future studies should prospectively corroborate these findings and address genetic variability in opioid response by assessing both genotype and plasma drug levels to better characterize which children may be increasingly sensitive to post-tonsillectomy opioids.

CONCLUSIONS

The use of a standard morphine dose range for post-surgical analgesia was associated with increased risk for oxygen desaturation. There were no differences seen in tonsillar bleeding events or in analgesic effectiveness. The results of this study support effective post-tonsillectomy analgesia in children by using ibuprofen in combination with acetaminophen.

Address correspondence to Gideon Koren, MD, FRCPC, FACMT, Division of Clinical Pharmacology/Toxicology, Department of Pediatrics, The Hospital for Sick Children and The University of Toronto, Toronto, M5G 1X8, Canada. E-mail: gkoren@sickkids.ca

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by a grant from the Canadian Institutes for Health Research Drug Safety and Effectiveness Network (DSEN).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Baugh RF, Archer SM, Mitchell RB, et al. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg*. 2011;144(1 suppl): S1–S30
2. Schwengel DA, Sterni LM, Tunkel DE, Heitmiller ES. Perioperative management of children with obstructive sleep apnea. *Anesth Analg*. 2009;109(1):60–75
3. Chhangani BS, Melgar T, Patel D. Pediatric obstructive sleep apnea. *Indian J Pediatr*. 2010;77(1):81–85
4. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Rep*. 2009; (11):1–25
5. US Food and Drug Administration. Safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy. Available at: www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf. Accessed January 25, 2014

6. Riggin L, Ramakrishna J, Sommer DD, Koren G. A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of nonsteroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. *Clin Otolaryngol*. 2013;38(2):115–129
7. Children THfS. Pain management in children 2009. Available at: https://www.sickkids.ca/pdfs/Pharmacy/24255-morphine%20ed%20sheet%20long_Feb%2009%20(4).pdf. Accessed October 6, 2014
8. McMaster Children's Hospital. Improving the treatment of pain at McMaster Children's Hospital 2011. Available at: www.hdpha.ca/oral%20morphine.pdf. Accessed October 6, 2014
9. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. *Anesthesiology*. 1987;66(6):832–834
10. Broadman LM, Rice LJ, Hannallah RS. Testing the validity of an objective pain scale fob infants and children. *Anesthesiology*. 1988;69(3A):A770
11. Alhashemi JA, Daghistani MF. Effects of intraoperative i.v. acetaminophen vs i.m. meperidine on post-tonsillectomy pain in children. *Br J Anaesth*. 2006;96(6):790–795
12. Hamers JP, Abu-Saad HH. Children's pain at home following (adeno) tonsillectomy. *Eur J Pain*. 2002;6(3):213–219
13. Shintani T, Asakura K, Kataura A. The effect of adenotonsillectomy in children with OSA. *Int J Pediatr Otorhinolaryngol*. 1998;44(1):51–58
14. Blum RH, McGowan FX Jr. Chronic upper airway obstruction and cardiac dysfunction: anatomy, pathophysiology and anesthetic implications. *Paediatr Anaesth*. 2004;14(1):75–83
15. Walker P, Whitehead B, Gulliver T. Polysomnographic outcome of adenotonsillectomy for obstructive sleep apnea in children under 5 years old. *Otolaryngol Head Neck Surg*. 2008;139(1):83–86
16. Liao P, Yegneswaran B, Vairavanathan S, Zilberman P, Chung F. Postoperative complications in patients with obstructive sleep apnea: a retrospective matched cohort study. *Can J Anaesth*. 2009;56(11):819–828
17. Brown KA, Morin I, Hickey C, Manoukian JJ, Nixon GM, Brouillette RT. Urgent adenotonsillectomy: an analysis of risk factors associated with postoperative respiratory morbidity. *Anesthesiology*. 2003;99(3):586–595
18. Wilson K, Lakheeram I, Morielli A, Brouillette R, Brown K. Can assessment for obstructive sleep apnea help predict postadenotonsillectomy respiratory complications? *Anesthesiology*. 2002;96(2):313–322
19. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician*. 2008;11(2 suppl):S133–S153
20. Finck AD, Berkowitz BA, Hempstead J, Ngai SH. Pharmacokinetics of morphine: effects of hypercarbia on serum and brain morphine concentrations in the dog. *Anesthesiology*. 1977;47(5):407–410
21. Teiriä H, Meretoja O. PCA in paediatric orthopaedic patients: influence of a NSAID on morphine requirement. *Paediatr Anaesth*. 1994;4(2):87–91
22. Khetani JD, Madadi P, Sommer DD, et al. Apnea and oxygen desaturations in children treated with opioids after adenotonsillectomy for obstructive sleep apnea syndrome: a prospective pilot study. *Paediatr Drugs*. 2012;14(6):411–415
23. St Charles CS, Matt BH, Hamilton MM, Katz BP. A comparison of ibuprofen versus acetaminophen with codeine in the young tonsillectomy patient. *Otolaryngol Head Neck Surg*. 1997;117(1):76–82
24. Agarwal R. Use of oral opioids during, after tonsillectomy re-evaluated. *AAP News*. 2014;35(8):13
25. Rochat I, Guinand S, Barazzone C, Hafen G. How to investigate sleep related breathing disorders in children? [in French]. *Rev Med Suisse*. 2008;4(146):515, 7–8, 20–22
26. Ishman SL. Evidence-based practice: pediatric obstructive sleep apnea. *Otolaryngol Clin North Am*. 2012;45(5):1055–1069
27. Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. *Pediatrics*. 2000;105(2):405–412
28. Horwood L, Brouillette RT, McGregor CD, Manoukian JJ, Constantin E. Testing for pediatric obstructive sleep apnea when health care resources are rationed. *JAMA Otolaryngol Head Neck Surg*. 2014;140(7):616–623
29. Mitchell RB, Pereira KD, Friedman NR. Sleep-disordered breathing in children: survey of current practice. *Laryngoscope*. 2006;116(6):956–958
30. Roland PS, Rosenfeld RM, Brooks LJ, et al. Clinical practice guideline: polysomnography for sleep-disordered breathing prior to tonsillectomy in children. *Otolaryngol Head Neck Surg*. 2011;145(1 suppl):S1–S15
31. Nixon GM, Kermack AS, Davis GM, Manoukian JJ, Brown KA, Brouillette RT. Planning adenotonsillectomy in children with obstructive sleep apnea: the role of overnight oximetry. *Pediatrics*. 2004;113(1). Available at: www.pediatrics.org/cgi/content/full/113/1/e19
32. Lee TT, Lefebvre CE, Gans NE, Daniel SJ. Quantifying respiratory complications post-adenotonsillectomy in patients with normal or inconclusive overnight oximetry. *J Otolaryngol Head Neck Surg*. 2013;42:50
33. Saito H, Araki K, Ozawa H, et al. Pulse-oximetery is useful in determining the indications for adeno-tonsillectomy in pediatric sleep-disordered breathing. *Int J Pediatr Otorhinolaryngol*. 2007;71(1):1–6
34. Egeli E, Harputluoglu U, Ozturk O, Oghan F, Kocak S. Can post-adenotonsillectomy morbidity be reduced by intravenous 24 h hydration in pediatric patients following adenotonsillectomy? *Int J Pediatr Otorhinolaryngol*. 2004;68(8):1047–1051
35. Yeganeh Mogadam A, Fazel MR, Parviz S. Comparison of analgesic effect between gabapentin and diclofenac on post-operative pain in patients undergoing tonsillectomy. *Arch Trauma Res*. 2012;1(3):108–111
36. Hullett BJ, Chambers NA, Pascoe EM, Johnson C. Tramadol vs morphine during adenotonsillectomy for obstructive sleep apnea in children. *Paediatr Anaesth*. 2006;16(6):648–653
37. Raghavendran S, Bagry H, Detheux G, Zhang X, Brouillette RT, Brown KA. An anesthetic management protocol to decrease respiratory complications after adenotonsillectomy in children with severe sleep apnea. *Anesth Analg*. 2010;110(4):1093–1101
38. Schulz KF, Altman DG, Moher D, Group C; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg*. 2011;9(8):672–677

Morphine or Ibuprofen for Post-Tonsillectomy Analgesia: A Randomized Trial

Lauren E. Kelly, Doron D. Sommer, Jayant Ramakrishna, Stephanie Hoffbauer, Sadaf Arbab-tafti, Diane Reid, Jonathan Maclean and Gideon Koren

Pediatrics 2015;135;307
DOI: 10.1542/peds.2014-1906 originally published online January 26, 2015;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Morphine or Ibuprofen for Post-Tonsillectomy Analgesia: A Randomized Trial

Lauren E. Kelly, Doron D. Sommer, Jayant Ramakrishna, Stephanie Hoffbauer, Sadaf Arbab-tafti, Diane Reid, Jonathan Maclean and Gideon Koren

Pediatrics 2015;135;307
DOI: 10.1542/peds.2014-1906 originally published online January 26, 2015;