

## ORIGINAL ARTICLE

# A multicenter, randomized, double-blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy

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## Keywords

pain; NSAIDs; ibuprofen; tonsillectomy; pediatric

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## Summary

**Background:** Tonsillectomy is one of the most common pediatric procedures in the United States. An optimal perioperative pain control regimen remains a challenge. Intravenous ibuprofen administered at induction of anesthesia may be a safe and efficacious option for postoperative tonsillectomy pain.

**Objectives:** To determine whether preoperative administration of intravenous ibuprofen (IV-ibuprofen) can significantly decrease the number of doses of postoperative fentanyl when compared with placebo in pediatric tonsillectomy surgical patients.

**Methods:** This was a multicenter, randomized, double-blind placebo-controlled trial conducted at six hospitals in the United States. A total of 161 pediatric patients aged 6–17 years undergoing tonsillectomy were randomized to receive either a single preoperative dose of 10 mg·kg<sup>-1</sup> IV-ibuprofen or placebo (normal saline). Postoperative pain was managed with intravenous fentanyl (0.5 µg·kg<sup>-1</sup>) on an as needed basis when the visual analog scale (VAS) was >30 mm and deemed appropriate by recovery room nurse/physician. The primary endpoint was the number of doses and amount of postoperative fentanyl administered postoperatively for rescue analgesia.

**Results:** There was a significant reduction in the number of postoperative doses and the amount of fentanyl administered after surgery in the IV-ibuprofen group compared with the placebo group ( $P = 0.021$ ). There were no differences in the time to first analgesia request or the number of patients who required postoperative analgesia. There were no significant differences in the incidence of serious adverse events, surgical blood loss ( $P = 0.662$ ), incidence of postoperative bleeding, or a need for surgical re-exploration between the treatment groups.

**Conclusion:** Administration of IV-ibuprofen, 10 mg·kg<sup>-1</sup>, significantly reduced fentanyl use in pediatric tonsillectomy patients.

## Introduction

With more than 530 000 surgeries annually in children, tonsillectomy is one of the most common surgical procedures performed in the United States (1). Although

tonsillectomies offer numerous benefits, many children suffer from significant postoperative pain for some days after the procedure and attaining optimum perioperative pain control remains a challenge (2,3). Management of posttonsillectomy pain usually entails a combination of

opioids and/or nonsteroidal antiinflammatory drugs (NSAIDs). While opioid analgesics are traditionally considered first line agents for perioperative pain control, their associated side effects such as emesis, excessive sedation, and respiratory depression limit their overall utility (4). The variability in the metabolism of codeine has led to a recent FDA black box warning on the use of this drug in children following tonsillectomy or adenoidectomy (5). A systematic review of local anesthetic infiltration for tonsillectomy did not show it was effective in decreasing opioid requirements or reducing postoperative pain (6). Nonopioid analgesics such as acetaminophen can be of benefit, but often fails to provide adequate analgesia when used as the sole agent (1).

Many otolaryngologists are hesitant to use NSAIDs in procedures with the potential for hemorrhage, such as tonsillectomies. Specific NSAIDs such as ibuprofen and ketorolac have been used in patients undergoing tonsillectomy because of their analgesic and opioid sparing effects; however, ketorolac has been associated with a 4.4–18% posttonsillectomy hemorrhage rate (1,7–9). A recent Cochrane review assessed the effects of NSAIDs on bleeding with pediatric tonsillectomy and concluded that NSAIDs did not cause any increase in bleeding that required surgical intervention (10). Recently, The American Academy of Otolaryngology-Head and Neck Surgery specifically recommended ibuprofen as a safe method to control postoperative pain in children undergoing tonsillectomy (1).

This multicenter, double-blind study was designed to evaluate the efficacy and safety of IV-ibuprofen administered at the induction of anesthesia in the treatment of pain in pediatric patients undergoing tonsillectomy.

## Methods

This study was approved by site specific Institutional Review Boards and has been performed according to the Declaration of Helsinki. Written informed consent from the parent or legal guardian (and assent from the child as required for specific sites) was obtained for all patients prior to study inclusion. Children ages 6–17 years scheduled for tonsillectomy were eligible for study inclusion. Exclusion criteria were inadequate intravenous access, patients with significant cognitive impairment, active (clinically significant) asthma, history of allergy or hypersensitivity to any component of IV-ibuprofen (or related products) or fentanyl, history of congenital bleeding diathesis or any active clinically significant bleeding, or any child with obstructive sleep apnea (Apnea Hyperpnea Index  $\geq$  to 5.0). Patients were excluded from enrollment if they had taken acetaminophen, NSAIDs, narcotics, local anesthetics, or any other

analgesic less than 4 h prior to study drug administration.

A prospective, double-blind, placebo-controlled study design was used, and patients were randomly assigned to receive a single dose of either 10 mg·kg<sup>-1</sup> (not to exceed 600 mg) IV-ibuprofen or normal saline at induction of anesthesia each infused over 10 min. The choice of the dose of IV-ibuprofen was based on previous studies including a pediatric study that showed peak levels of IV-ibuprofen were attained in the cerebro-spinal fluid 30–40 min after IV injection of this dose and were higher than blood levels associated with analgesia (11,12). Investigators, patients, and care providers were blinded to intervention assignment. Only the study pharmacist was unblinded.

Patients underwent induction of anesthesia with 8% sevoflurane/70% N<sub>2</sub>O/30% and O<sub>2</sub> via face mask. A peripheral IV was started, and a single dose of study medication prepared by a pharmacist and labeled as 'Study Drug' was administered over 10 min. Tracheal intubation was facilitated with propofol 3 mg·kg<sup>-1</sup> IV and anesthesia was maintained with sevoflurane in air/oxygen. Glycopyrrolate was given after induction. Analgesia was provided by Fentanyl 1.0 µg·kg<sup>-1</sup> (titrated to maintain spontaneous ventilation). In addition, dexamethasone 0.5 mg·kg<sup>-1</sup> IV was administered. Tonsils were removed using only electrocautery, and adenoids were removed per surgeon preference. At the end of surgery, ondansetron 0.1 mg·kg<sup>-1</sup> IV was administered for postoperative nausea and vomiting prevention. Deep extubation was achieved with either a nasal trumpet or oral airway in place.

In the postAnesthetic Care unit, patients who rated their pain as >30 mm on the visual analog scale received analgesic rescue with intravenous fentanyl (0.5 µg·kg<sup>-1</sup> IV) and repeated in 10 min if required. Patients were discharged with a prescription for hydrocodone/acetaminophen for postdischarge pain management and were allowed to use acetaminophen and oral ibuprofen as needed. Parents were instructed to complete a diary to record analgesic use, incidence of nausea, vomiting, and any adverse event during the 48 h after discharge. They were asked to complete a satisfaction survey and return the survey and diary to the study site. Of the 161 subjects, only 130 subjects returned a completed diary.

## Efficacy assessments

The primary objective of the study was to determine the efficacy of IV-ibuprofen compared to placebo when administered as a single dose, at the time of induction of anesthesia, on reducing the number of doses of

postoperative fentanyl ( $0.5 \mu\text{g}\cdot\text{kg}^{-1}$  IV) prior to discharge. Additional endpoints included the amount of weight-based fentanyl used in the postoperative period prior to discharge, patient reported pain scores, time to discharge, first swallow, time to first dose of analgesic rescue medication, incidence of postoperative nausea and vomiting, amount of postdischarge analgesic use, and parent satisfaction survey.

### Safety assessments

The safety profile using  $10 \text{ mg}\cdot\text{kg}^{-1}$  of IV-ibuprofen was evaluated through comparison of treatment-emergent adverse events. Additionally, blood loss during surgery was captured through a closed-suction system before wound irrigation and measured. Adverse event monitoring continued through study hour 48.

### Statistical analysis

Continuous data were summarized in tables listing the mean, standard deviation or standard error, median, minimum, maximum, and number of patients in each treatment group. Categorical data were summarized in tables listing the frequency and the percentage of patients in each treatment group. Treatment group summaries were constructed across all study sites. All data were listed by patients.

All statistical computations were performed, and data appendices were created using the SAS<sup>®</sup> system version 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical tests were 2-sided, with significance considered for *P*-values less than or equal to 0.05. The number of doses of postoperative IV fentanyl was compared between treatment groups using the Wilcoxon rank-sum test.

### Sample size calculation

A sample size of 154 subjects in the intent-to-treat (ITT) population, randomized in a 1 : 1 ratio into two treatment groups, was calculated to provide at least 80% power to detect a 0.75 dose reduction (>20% reduction in rescue analgesia) in the mean number of doses of postoperative fentanyl between patients receiving IV-ibuprofen and those receiving placebo using a two-sided Wilcoxon rank-sum test assuming the mean number of doses in the placebo group is 3.5 at the significance level  $\alpha = 0.05$  and a standard deviation of 1.6 [based on reference (13) and Moss JR, Cofer S, Hersey S, Goudy S, Werkhaven J, Swanson E, Mantle C, Stowell N, Byrne D, Wang L, Labadie R, unpublished data].

**Table 1** Demographics

	Placebo, <i>N</i> = 79	IV-ibuprofen, <i>N</i> = 82
Age (years)		
Mean (sd)	9 (3.0)	10 (3.41)
<i>P</i> -value		0.739
Gender		
Male	31 (39%)	31 (38%)
Female	48 (61%)	51 (62%)
<i>P</i> -value		0.873
Race		
Caucasian	68 (86%)	69 (84%)
Black	10 (13%)	8 (10%)
Hispanic	13 (16%)	14 (17%)
Asian	0	3 (4%)
Other	1 (1%)	2 (2%)
<i>P</i> -value		0.320
Weight (kg)		
Mean (sd)	40.5 (19.25)	42.1 (19.73)
<i>P</i> -value		0.605

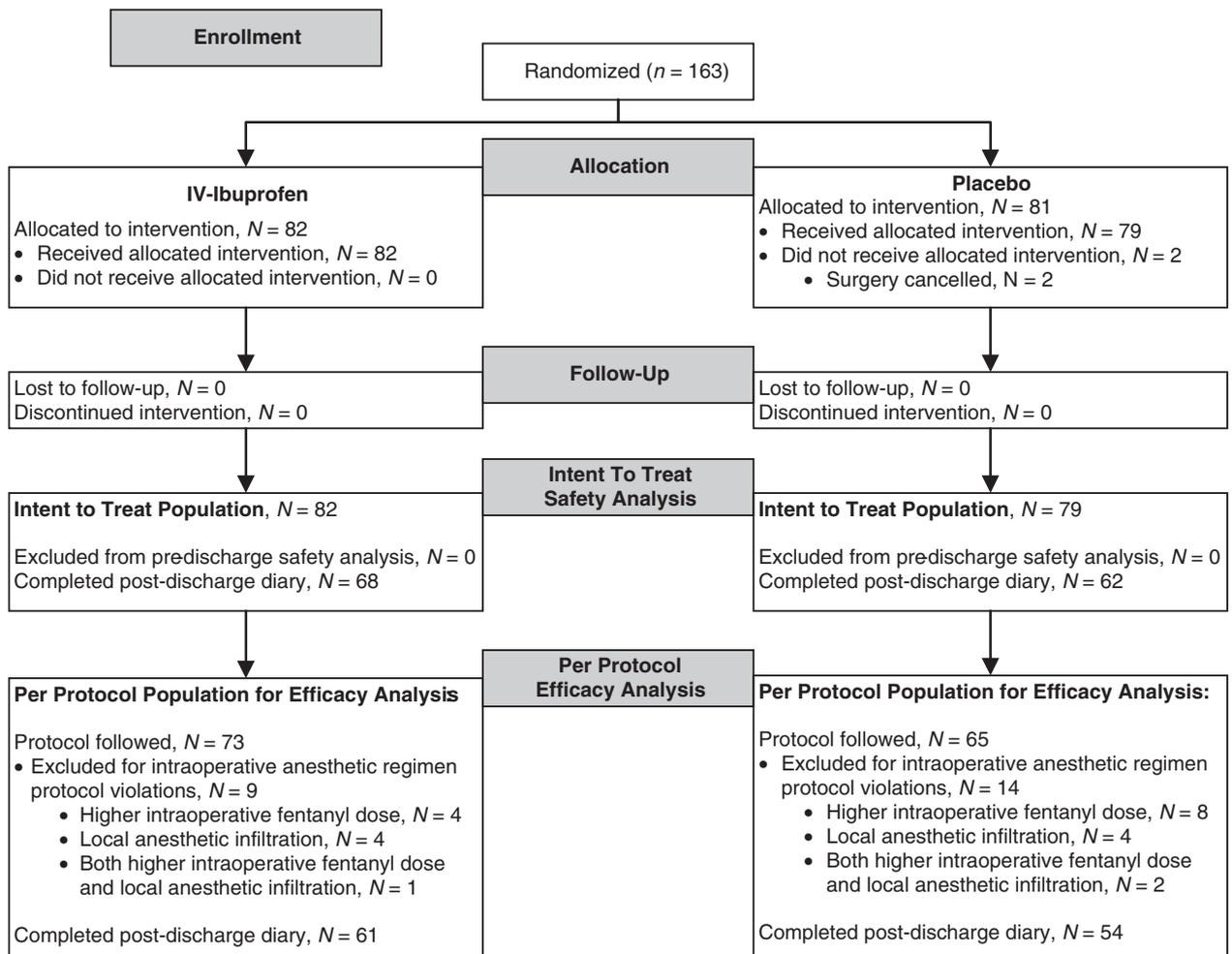
### Results

One hundred and sixty-one patients were enrolled at six US clinical centers. Demographics are shown in Table 1. The distribution of demographic factors was not significantly different between the two groups, and there were no differences in baseline physical examinations.

### Efficacy

Of the 161 patients, 138 patients were eligible for efficacy analysis (73 in the IV-ibuprofen and 65 in the placebo group). Patients were excluded from the efficacy analysis if the intraoperative anesthetic protocol was violated. The reasons for exclusion are listed in Figure 1 and included patients receiving a significantly higher intraoperative dose of fentanyl (Placebo *n* = 10, IV-ibuprofen *n* = 5) and/or administration of local anesthetic (placebo *n* = 6, IV-ibuprofen *n* = 5). **In the efficacy analysis, patients who received a single dose of IV-ibuprofen at induction required significantly fewer doses and amount of postoperative fentanyl compared with those receiving placebo (Table 2). Further, significantly fewer patients in the IV-ibuprofen group required more than 1 dose of postoperative rescue fentanyl in the IV-ibuprofen compared with the placebo group (31 of 73 [42%] vs 40 of 65 [62%], respectively, *P* = 0.028).**

While not significant, consistent trends were seen in the secondary endpoints including pain scores (Figure 2), analgesic use, and time to first rescue. No differences were observed between groups in the time to swallow or time to discharge.



**Figure 1** Consort diagram.

### Safety analysis

All 161 patients who received the study drug were included in the safety analysis. Adverse events (AEs) were reported in 30 of the 161 (19%) patients. In the IV-ibuprofen group, 14 of 82 (17%) patients experienced treatment-emergent adverse events. Of the patients in the placebo group, 16 of 79 (20%) patients experienced treatment-emergent adverse events. The most common adverse events included vomiting 5 (3%) and agitation 4 (2%; Table 3). There was no difference in surgical blood loss ( $P = 0.662$ ), incidence of postoperative bleeding, or a need for surgical re-exploration between the treatment groups.

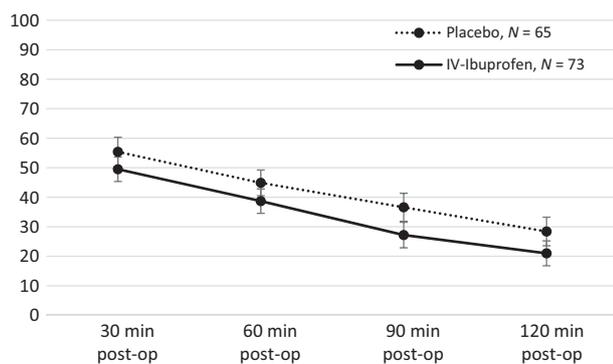
A total of three patients experienced tonsillar fossa hemorrhage (placebo 1, IV-ibuprofen 2), with only one requiring surgical re-exploration (IV-ibuprofen group).

This patient experienced an episode of coughing and spitting up of approximately 3 tablespoons of blood. The patient was brought to the emergency room for evaluation, and examination of all systems was negative except for the throat, where bilateral eschar with no active bleeding was seen. After an evaluation from an ENT (ear nose and throat) specialist, the patient was taken to the operating room for exploration of the throat. After a clot was removed, two vessels in the mid- and inferior pole for the left tonsillar fossa began bleeding. The site of bleeding was cauterized, and hemostasis was achieved.

All subjects returned to their ENT surgeon for a follow-up, but only 130 submitted a completed diary. In these patients, there was a significant reduction in the number of subjects experiencing emesis in the 0–48 and 24–48 h period following discharge (Table 4).

**Table 2** Postoperative analgesic requirements

	Intent to treat		Efficacy evaluable	
	Placebo N = 79	IV-ibuprofen N = 82	Placebo N = 65	IV-ibuprofen N = 73
Number (%) of patients who received rescue fentanyl in the PACU	68 (86%)	68 (83%)	61 (94%)	61 (84%)
<i>P</i> -value		0.666		<b>0.068</b>
Number of rescue analgesic doses of fentanyl in the PACU				
Mean (sd)	1.7 (1.12)	1.5 (1.32)	1.9 (1.06)	1.6 (1.30)
Median	2.0	1.0	2.0	1.0
<i>P</i> -value		0.110		<b>0.021</b>
Postoperative fentanyl ( $\mu\text{g}\cdot\text{kg}^{-1}$ )				
Mean (sd)	0.8 (0.54)	0.7 (0.59)	0.9 (0.52)	0.8 (0.61)
Median	0.9	0.5	1.0	0.5
<i>P</i> -value		0.192		<b>0.037</b>
Number (%) of patients who received				
$\leq 1$ Dose fentanyl	35 (44%)	49 (60%)	25 (38%)	42 (58%)
More than 1 dose fentanyl	44 (56%)	33 (40%)	40 (62%)	31 (42%)
<i>P</i> -value		0.059		<b>0.028</b>
Time to first rescue analgesia (h)				
Median	0.6 (0.06)	0.6 (0.05)	0.5 (0.06)	0.6 (0.05)
<i>P</i> -value		0.554		0.150

**Figure 2** Postoperative pain reduction over time. The patient self-reported pain scores during the 2 h postsurgery period were plotted for the IV-ibuprofen and placebo treatment groups.

## Discussion

The optimal pain regimen for tonsillectomy pediatric patients continues to be a challenge. NSAIDs are a promising option for the treatment of postoperative pain in children.

This was the first clinical study evaluating the safety and efficacy of IV-ibuprofen ( $10 \text{ mg}\cdot\text{kg}^{-1}$  IV) in pediatric patients undergoing tonsillectomy. The primary endpoint was to determine if the number of postoperative doses of fentanyl decreases after a single dose of  $10 \text{ mg}\cdot\text{kg}^{-1}$  IV-ibuprofen administered at the time of induction of anesthesia prior to pediatric tonsillectomy.

A significant reduction in the number of postoperative doses of fentanyl was observed in the IV-ibuprofen group compared with the placebo group indicating a significant opioid sparing effect. Similarly, there was a significant reduction in the weight-based postoperative fentanyl use in the IV-ibuprofen group compared with the placebo group. The number of patients experiencing postoperative vomiting was also significantly reduced in the IV-ibuprofen group in both the 24–48 h and 0–48 h time periods.

The findings in this study add to the growing body of literature supporting use of NSAIDs for postoperative pain in children. The opioid sparing effect observed in this study was consistent with previous trials (10,12). Reduction in the amount of opioid use may lead to less opioid-related complications, including respiratory issues and emesis.

Safety findings in this trial also remain consistent with previous NSAIDs pediatric studies found in the literature including a systematic review from the Cochrane Collaboration of perioperative bleeding after tonsillectomy (10). In this review of over 900 children from 13 randomized controlled trials, there was no significant difference in postoperative bleeding in children who received NSAIDs compared with placebo or other analgesics (odds ratio, 1.46; 95% CI, 0.49–4.40) (1). Additionally, in a subgroup analysis involving 567 children in seven trials, the odds ratio for bleeding requiring re-operation was 0.91 (CI, 0.22–3.71) when

**Table 3** Adverse events, prior to discharge

	Placebo (N = 79) No. of events	IV-Ibuprofen (N = 82) No. of events
Vomiting	2	3
Agitation	3	1
Infusion site pain	0	3
Nausea	1	2
Hemorrhage*	1	2
Restlessness	2	0
Rash erythematous	2	0
Bronchospasm	2	0
Urticaria	0	2
Headache	1	0
Epistaxis	1	0
Pyrexia	1	0
Erythema	1	0
Swelling Face	1	0
Infusion site discomfort	0	1
Cough	0	1
Hypoxia	0	1
Irritability	0	1
Hematemesis*	0	1

\*Three patients experienced four bleeding-related adverse events. One patient receiving placebo experienced posttonsillectomy bleeding (hemorrhage); one patient receiving IV-ibuprofen experienced posttonsillectomy bleeding (hemorrhage); one patient receiving ibuprofen experienced hematemesis and a clot filling the right tonsillar fossa (hemorrhage).

ketorolac was excluded, suggesting no significant impact (1,14). Our findings (no significant increase in intra- or postoperative bleeding in the IV-ibuprofen group) further support these data suggesting that NSAIDs, ketorolac excluded, can be safely used for the treatment of pain following tonsillectomy.

Ibuprofen, unlike other nonopioid IV analgesics such as acetaminophen, has antiinflammatory properties that have the potential to limit the inflammatory cascade from surgical trauma and reduce the development of postoperative pain after this procedure. When IV-ibuprofen is administered before the start of surgery, therapeutic blood and CSF levels are achieved by the time a patient arrives in PACU after this short procedure (15). Studies need to be performed comparing IV-Ibuprofen to other nonopioid/non-NSAID drugs as a foundation for any tonsillectomy pain management regimen. IV-Ibuprofen also allows for a smooth transition from an intravenous to oral formulation providing easy administration for parents. However, there may be risk with continued long-term dosing as ibuprofen metabolism may be affected by genetic factors with lower clearance occurring in subjects with CYP2C8 and CYP2C9 polymorphisms (16).

The main limitation of the study involved the conservative anesthesia regimen that allowed fentanyl use during surgery which may have affected the ability to detect a greater opioid sparing effect of IV-ibuprofen. This conservative anesthesia approach was used in order to ensure that the pediatric population was not exposed to unnecessary pain; therefore, the utility and true effect of the drug may have been greater than observed in the study. Previous adult surgery studies that used a less conservative anesthesia regimen and did not include an opioid during surgery demonstrated a 31% reduction in opioid sparing effect over the first 28 h (12). An additional limitation of the study involved the lack of statistical power regarding the secondary endpoints, as the study was powered for the primary endpoint of number of doses of postoperative fentanyl. A larger sample size may have elucidated key additional efficacy differences

**Table 4** Postdischarge emesis

	Intent to treat		Efficacy evaluable	
	Placebo N = 79	IV-Ibuprofen N = 82	Placebo N = 65	IV-Ibuprofen N = 73
Subjects experiencing postoperative emesis				
Number with 48 h follow-up data	62	68	54	61
0–24 h following discharge				
Yes	13 (21%)	8 (12%)	13 (24%)	7 (11%)
No	49 (79%)	60 (88%)	41 (76%)	54 (61%)
P-value		0.232		0.089
24–48 h following discharge				
Yes	8 (13%)	5 (7%)	8 (15%)	2 (3%)
No	54 (87%)	63 (93%)	46 (85%)	59 (97%)
P-value		0.384		<b>0.044</b>
0–48 h following discharge				
Yes	18 (29%)	10 (15%)	18 (33%)	7 (11%)
No	44 (71%)	58 (85%)	36 (67%)	54 (89%)
P-value		0.056		<b>0.006</b>

between IV-ibuprofen and placebo. Other limitations of this study pertained to the maximum IV-ibuprofen dose of 600 mg. Twenty-five patients were > 60 kg, so when patients received the protocol specified amount of 10 mg·kg<sup>-1</sup>, these patients may not have received a therapeutic dose of IV-ibuprofen to elicit a full analgesic effect. Lastly, dexamethasone was administered in this study as it is recommended and routinely used in pediatric tonsillectomies. Additional studies may be required in children undergoing other surgical procedures where corticosteroids are not routinely used.

## Conclusions

These findings indicate that administration of 10 mg·kg<sup>-1</sup> IV-ibuprofen administered at induction of anesthesia for the management of postoperative pain has a significant narcotic sparing effect and is a safe option in pediatric tonsillectomy patients. IV-ibuprofen continues to be an important component of the

multimodal pain approach. These results are timely considering the recent boxed warning and contraindication released by the FDA recommending against the use of codeine in children undergoing tonsillectomy. IV-ibuprofen should be considered a foundation for any tonsillectomy pain management regimen.

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## Conflict of interest

No conflicts of interest declared.

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