Effect of Albuterol Premedication vs Placebo on the Occurrence of Respiratory Adverse Events in Children Undergoing Tonsillectomies
The REACT Randomized Clinical Trial

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IMPORTANCE Tonsillectomy is a common pediatric procedure for the treatment of sleep-disordered breathing and chronic tonsillitis. Up to half of children having this procedure experience a perioperative respiratory adverse event.

OBJECTIVE To determine whether inhaled albuterol sulfate (salbutamol sulfate) premedication decreases the risk of perioperative respiratory adverse events in children undergoing anesthesia for tonsillectomy.

DESIGN, SETTING, AND PARTICIPANTS A randomized, triple-blind, placebo-controlled trial (the Reducing Anesthetic Complications in Children Undergoing Tonsillectomies [REACT] trial) was conducted at Perth Children's Hospital (formerly Princess Margaret Hospital for Children), the only tertiary pediatric hospital in Western Australia. Participants included 484 children aged 0 to 8 years who were undergoing anesthesia for tonsillectomy. The study was conducted between July 15, 2014, and May 18, 2017.

INTERVENTIONS Participants were randomized to receive either albuterol (2 actuations, 200 μg) or placebo before their surgery.

MAIN OUTCOMES AND MEASURES Occurrence of perioperative respiratory adverse events (bronchospasm, laryngospasm, airway obstruction, desaturation, coughing, and stridor) until discharge from the postanesthesia care unit.

RESULTS Of 484 randomized children (median [range] age, 5.6 [1.6-8.9] years; 285 [58.9%] boys), 479 data sets were available for intention-to-treat analysis. Perioperative respiratory adverse events occurred in 67 of 241 children (27.8%) receiving albuterol and 114 of 238 children (47.9%) receiving placebo. After adjusting for age, type of airway device, and severity of obstructive sleep apnea in a binary logistic regression model, the likelihood of perioperative respiratory adverse events remained significantly higher in the placebo group compared with the albuterol group (odds ratio, 2.8; 95% CI, 1.9-4.2; P < .001). Significant differences were seen in children receiving placebo vs albuterol in laryngospasm (28 [11.8%] vs 12 [5.0%]; P = .009), coughing (79 [33.2%] vs 27 [11.2%]; P < .001), and oxygen desaturation (54 [22.7%] vs 36 [14.9%]; P = .03).

CONCLUSIONS AND RELEVANCE Albuterol premedication administered before tonsillectomy under general anesthesia in young children resulted in a clinically significant reduction in rates of perioperative respiratory adverse events compared with the rates in children who received placebo. Premedication with albuterol should be considered for children undergoing tonsillectomy.

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onsillectomy is among the most frequently performed surgical procedures in children, with half a million tonsillectomies performed in the United States each year. Referral patterns for tonsillectomies have changed over the past decade with most children now presenting with sleep-disordered breathing.1-3

Although the safety of pediatric anesthesia is constantly improving, a substantial proportion of children undergoing tonsillectomies experience perioperative respiratory adverse events, with a prevalence of up to 50% in children with at least 1 risk factor.4 Both minor adverse events, such as oxygen desaturation or upper airway obstruction, and major events, such as laryngospasm or bronchospasm, occur more commonly in children undergoing tonsillectomy compared with other non-airway surgery.5 Risk factors for perioperative respiratory adverse events include younger age, obesity, and recurrent or recent respiratory tract infection—all of which are common in children undergoing tonsillectomy.6

A variety of approaches is available to optimize anesthetic management and minimize adverse events in high-risk children, including the use of a laryngeal mask and the intravenous induction of anesthesia.7,8 Although the use of β2-adrenergic agonists (eg, albuterol sulfate [salbutamol sulfate]) prevents an increase in respiratory resistance during intubation,9 existing evidence has not demonstrated a reduction of respiratory adverse events in the general populations receiving preoperative inhaled albuterol.10,11 Albuterol may, however, be beneficial in higher-risk groups, such as children with asthma and related symptoms or a recent respiratory tract infection.12,13

The aim of this triple-blind randomized clinical trial was to investigate the influence of preoperative inhaled albuterol on the incidence of perioperative respiratory adverse events in young children undergoing tonsillectomy. We hypothesized that children receiving albuterol before tonsillectomy would have 50% fewer perioperative respiratory adverse events than children receiving placebo.

Methods

Study Design

This study was conducted at Princess Margaret Hospital for Children (now Perth Children’s Hospital) in Perth, Western Australia, between July 15, 2014, and May 18, 2017. This study was approved by the Princess Margaret Hospital for Children Ethics Committee and recognized by the University of Western Australia Ethics Committee. Written informed parental consent and child assent (where appropriate) were sought prior to enrollment in the study. There was no financial compensation. The protocol is available in Supplement 1.

The CONSORT flowchart is shown in the Figure. Children 0 to 8 years old were eligible for inclusion if they were undergoing elective tonsillectomy with or without adenoidectomy, grommets, cautery of inferior turbinate, or examination of the ear under general anesthesia with use of laryngeal mask airway (ages 3-8 years) or endotracheal tubes (ages 0-6 years). We stopped stratification by administration method because of a change of practice toward preferring laryngeal mask airways in most children regardless of age shortly after the start of the trial. Children receiving sedating premedication (eg, midazolam) were excluded owing to the increased risk of respiratory adverse events seen with midazolam.14 Other exclusion criteria were known cardiopulmonary disease (mainly). Following identification of potential participants, the consultant anesthetist responsible for their care was consulted to verify the suitability and request permission for the patient to participate in the study. A member of the research team then approached the family for voluntary informed participation in

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the study. No participant was concurrently enrolled into another study.

During the preoperative assessment, patients were evaluated for the presence and absence of obstructive sleep apnea (OSA), as well as common risk factors for perioperative respiratory adverse events: respiratory tract infection within the past 2 weeks, wheezing 3 or more times in past 12 months, wheezing during exercise, previous asthma (if wheeze-negative), persistent nocturnal dry cough, hay fever, current or past eczema, exposure to passive smoking, and family history of asthma, eczema, or hay fever (≥2 family members including parents or siblings).14,15

Randomization and Masking
Computer-generated block randomization with randomly selected block sizes was performed by an independent person to avoid selection bias. Following recruitment, each participant was assigned the next available unique identifier for the study duration. Visually identical albuterol and placebo inhalers were prepared by our institution’s clinical trials pharmacy. Each canister was packaged in a plain white box sealed with a numbered sticker that corresponded with each participant’s unique identifier. All researchers directly involved in the study were blinded to the group allocation. The treating team and the participants were also blinded to the group allocation. The clinical trials pharmacy maintained the randomization log that was made available to the researchers once the study results had been analyzed at the end of the trial. This study was therefore a triple-blind randomized clinical trial.

Drug Administration
Both albuterol (Ventolin) and placebo (hydrofluoroalkane propellant, HFA-134a) were from the same company (GlaxoSmithKline, United Kingdom) and delivered via a pressurized metered-dose inhaler (100 μg/actuation). In accordance with hospital guidelines, each child received 2 actuations via a spacer (total albuterol, 200 μg, or placebo). The spacers used were e-chamber La Petite (antistatic, single-valved; Bird Healthcare, Australia) and LiteAire (disposable paperboard design, dual valved; Thayer Medical, United States). Children who were already familiar with one of the spacers were given that device. Otherwise, we used the La Petite spacer for children aged 1 to 3 years and LiteAire for older children. The La Petite spacer was attached to a disposable mask (PRO-Breathe Anesthetic Mask; PROACT Medical, United Kingdom). The mask was positioned over the straight-seated child’s nose and mouth. The inhaler was actuated, and the child was instructed to take 3 deep inspirations. The process was repeated for the second actuation. Children using the LiteAire spacer were asked to seal their lips around the mouthpiece directly. Following 2 tidal breaths, the inhaler was actuated, and the child was instructed to breathe in deeply and hold their breath for 5 seconds, followed by a tidal breath; the process was repeated for the second actuation.

We aimed to administer the study drug at least 20 minutes preoperatively to ensure maximal bronchodilation.16 In cases of preoperative delays, patients who received the study drug more than 1 hour before their rescheduled surgical time received the treatment again approximately 20 minutes before surgery (half-life of albuterol, approximately 2.5 hours) to ensure the drug’s full effect regardless of surgical delays.

Anesthesia and Airway Management
The anesthetist in charge induced anesthesia in line with institutional clinical practice with either incremental inhalation of sevoflurane (up to 8% volume) or intravenous propofol (≥3 mg/kg−1). In our institution, an inhalational induction with sevoflurane usually involves gradually increasing sevoflurane concentration up to 8% along with nitrous oxide, and administration of intravenous propofol (1-2 mg/kg−1) once intravenous access is secured and before airway device insertion. For intravenous induction, our standard practice does not include preoxygenation, and propofol is mixed with lidocaine and injected slowly to minimize pain.

Airway management was at the discretion of the anesthetist with the airway device (laryngeal mask airway or endotracheal tube). Anesthesia was maintained using sevoflurane for all participants. Routine physiological monitoring included electrocardiography, noninvasive blood pressure, capnography, and pulse oximetry. The anesthesia workstations used were Primus (Dräger; Germany).

Removal of endotracheal tubes occurred in the operating room (deep levels of anesthesia or awake), while laryngeal mask airways were either removed in the operating room (deep levels of anesthesia or awake) or in the postanesthesia care unit (PACU) (only awake) at the discretion of the anesthetist.

Surgical Technique
All procedures were performed by or under the supervision of a consultant pediatric ear, nose, and throat surgeon. We did not attempt to control any aspect of the surgical technique or postoperative surgical management. Usual practice involved a coagulation technique including the use of local anesthetic infiltration.

Primary Outcome
The primary outcome was the incidence of perioperative respiratory adverse events (Box). Events were reported by the attending anesthetist or PACU nurse on a dedicated data collection sheet and were recorded against the phase of anesthesia (induction, maintenance, emergency, or recovery) during which the event occurred.

Secondary Post Hoc Outcomes
We performed post hoc exploratory analyses for differences in the incidence of each respiratory adverse event between treatment groups, as well as the effect of the presence and severity of obstructive sleep apnea on the incidence of adverse events. The severity of OSA was assessed on the day of surgery by the attending anesthetist.

Harm and Adverse Outcomes
Albuterol is a safe medication with a well-known risk profile, available as salbutamol in Australia without prescription. For this reason, we did not seek to assess harm caused by albuterol and placebo. Unexpected adverse and serious
adverse events were reported and reviewed by an independent anesthetist.

Sample Size Calculation
Subgroup analysis of a previously reported investigation of albuterol premedication in children yielded a perioperative respiratory adverse event rate of 48.2% in children (ages 3-8 years) undergoing adenotonsillectomy or tonsillectomy. With the aim of reducing the prevalence of these events by 50%, we conservatively selected the upper limit of targeted incidence of 29.1% (24.1% ± 5%) for our power and sample size calculation. To detect this difference at a power of 0.8 and a 0.05 two-sided significance level, a sample size of 440 participants was required, split equally between treatment groups. We determined from previous experience that a 10% dropout rate should be accounted for, giving a total sample size of 484 children.

Statistical Analysis
An intention-to-treat approach was used to analyze this superiority trial. The primary outcome along with the post hoc outcomes were assessed using binary logistic regression. A forward, stepwise multivariate logistic regression was used to identify significant confounding factors from the following variables: age, weight, height, OSA severity, American Society of Anesthesiologists status, anesthesia induction, airway device, and number of risk factors.

Odds ratios (ORs) and 95% CIs were calculated for each result. The efficacy of the intervention was also expressed as the number of patients who needed to be treated to prevent 1 additional perioperative respiratory adverse event (number needed to treat [NNT] along with 95% CIs (adjusted and unadjusted). Findings were considered significant at \( P < .05 \). Statistical analysis was performed with SPSS, version 22 (IBM Corp).

Results
Four hundred eighty-four children (median [range] age, 5.6 [1.6-8.9] years; 285 boys [58.9%]) were recruited (Figure). Five participants were excluded from analysis owing to 2 cancelled procedures and 3 cases were excluded in which sedating premedication was prescribed following recruitment but before administration of the study drug. Complete data sets were available from the remaining 479 participants (albuterol, 241; placebo, 238) and were analyzed. Eight participants (4 in each group) were included in the analysis who received the study drug via their airway device during the induction of anesthesia. The analysis was not sensitive to exclusion of these 8 participants. In addition, there were 10 children who received a second dose of the study drug (4 albuterol, 6 placebo) owing to surgical delay. Table 1 provides a detailed overview of participant demographics and general clinical history, which were similar between groups.

One or more respiratory adverse events were recorded in 67 children (27.8%) in the albuterol group and 114 children (47.9%) in the placebo group. Table 2 details the incidence of adverse events overall and by phase of anesthesia and event type. Children in the placebo group had 2.4 times greater odds of experiencing a respiratory adverse event compared with children receiving albuterol before an adenotonsillectomy or tonsillectomy (OR, 2.4; 95% CI, 1.6-3.5; \( P < .001 \)). Statistically significant differences were present between the placebo and albuterol groups in the prevalence of laryngospasm (28 [11.8%] vs 12 [5.0%; \( P = .009 \)), coughing (79 [33.2%] vs 27 [11.2%]; \( P < .001 \)), and oxygen desaturation (54 [22.7%] vs 36 [14.9%]; \( P = .03 \)). For every 5 children undergoing adenotonsillectomy treated with albuterol, 1 additional case of respiratory adverse events was prevented (NTT, 4.8; 95% CI, 8.6-3.5). On analysis for confounding factors, we found that age, weight, height, ASA status, anesthesia induction, and number of risk factors were not significantly associated with the respiratory adverse events. Increased OSA severity and use of endotracheal tubes were associated with significantly increased risk of adverse events. Adjustment for OSA severity and type of airway device, however, did not greatly alter the reduction in respiratory complications in children receiving albuterol compared with those receiving placebo (adjusted OR, 2.8; 95% CI, 1.9-4.2; \( P < .001 \)), while there was a small improvement in the adjusted NNT (4.2; 95% CI, 6.4-3.2). Children in the placebo group with moderate and severe OSA had 3 and 5 times, respectively, greater odds of experiencing a respiratory adverse event than those who received albuterol (Table 3).

Time in the PACU was similar between groups, with a median (range) stay of 42 (14-116) minutes for albuterol and 43 (14-114) minutes for placebo. Nine children had an extended hospital admission (3 albuterol, 6 placebo), and 9 readmissions occurred (5 albuterol, 4 placebo). No unexpected adverse or serious adverse events were reported.
Discussion

This triple-blind randomized clinical trial demonstrated a significant reduction in the incidence of perioperative respiratory adverse events in young children receiving albuterol premedication prior to their adenotonsillectomy or tonsillectomy. Children receiving placebo had 2.8 times greater odds of experiencing respiratory adverse events after adjustment for appropriate confounders (OSA severity, type of airway device). Our exploratory analyses demonstrated that laryngospasm, coughing, and oxygen desaturation were the adverse events most significantly reduced in children receiving albuterol compared with placebo, and the benefits of albuterol were more pronounced in children with moderate to severe OSA. Given the global pediatric tonsillectomy caseload and the high prevalence of respiratory adverse events in this surgical cohort, the clinical implications of these findings are significant.

Tonsillectomy is the second most common elective surgery performed on children in Australia, representing 724 admissions per 100,000 people aged 17 years or younger, and up to half of these children experience respiratory adverse events that can cause significant harm.18-21 Although most of these events are minor, such as easily managed airway obstruction and mild oxygen desaturation, other, more serious adverse events can have long-term sequelae. Fatal respiratory adverse events following tonsillectomy, approximately 1 of 100,000 cases, occur twice as frequently in children compared with adults.22

Albuterol is an inexpensive, readily available, and safe treatment option. Our results support its use in children undergoing tonsillectomy to significantly reduce the incidence of respiratory adverse events (adjusted NNT, 4.2). Reducing respiratory adverse events can also benefit health systems, with consequent reduction in unplanned intensive care unit admissions, length of hospital stays, operating room list delays, surgical cancellations, and wait lists likely to result.

Albuterol, a β2-adrenergic agonist, has effects in addition to bronchodilation that may be beneficial during anesthesia. Of previously identified risk factors for respiratory adverse events, many are associated with airway inflammation. There is also an increased prevalence of airway inflammation in children presenting with OSA, and these children are known to be at higher risk for respiratory adverse events during anesthesia.18 Albuterol, acutely, both in vivo and in vitro, inhibits the release of inflammatory mediators from mast cells, and so may also contribute to reduction of perioperative respiratory adverse events via reduced release of inflammatory markers and the suppression of cough receptors and other reflexes.23 Significant risk reduction was observed with albuterol premedication in children with OSA, particularly in those with moderate and severe OSA.

Our findings oppose the results from earlier studies in broader pediatric populations that found no benefits of albuterol for the prevention of respiratory adverse events in children.10,21 Both prior studies, however, were performed in older populations with a lower risk for perioperative respiratory adverse events and did not involve airway-related surgeries. The incidence of respiratory adverse events in children with an upper respiratory tract infection is dependent on current symptoms and timing of the infection.13,14 However, the risk at 4 weeks after an upper respiratory tract infection may even be lower than the risk without the infection, which may explain why no effect was found when children who had had an upper respiratory tract infection 1 to 6 weeks before surgery received albuterol.10

This triple-blind, placebo-controlled, randomized trial represents a significant and sound addition to the evidence for the use of albuterol as a premedication in young children. Our results demonstrate efficacy and are not sensitive to adjustment for OSA severity or airway type. Our low dropout rate also suggested that our intervention is well tolerated and feasible to implement. We are confident that our results are likely to be generalizable to similar centers.
Limitations

Our study is limited by being a single-center trial in a specific cohort. Although this design may limit generalizability to other centers, our institution is the only tertiary pediatric referral center in Western Australia and therefore our population is broad and heterogeneous. Our surgical and anesthetic guidelines are based on Australian guidelines and are similar to those applied across the Australian region.

Because ours is a teaching hospital, anesthetic and surgical registrars and fellows of varying experience were engaged in the clinical care under the direct supervision of consultant pediatric anesthetists. The risk of adverse events is dependent on the experience of the anesthetist and/or surgeon, and although it is unlikely that supervision can fully ameliorate this effect, the supervision reduces the risk of perioperative adverse events. The effect of clinician experience is unlikely to affect differences seen between groups, however, as both groups were exposed to the same group of anesthetists.

Diagnosis of respiratory adverse events is known to be operator dependent owing to the composite aspect of such adverse events and clinical judgment process involved. To limit reporting errors (eg, events of soft-tissue obstruction for laryngospasm), clear definitions (Box) were provided to the anesthetists and PACU nurses. Although reporting errors might have been further avoided by having independent anesthetists assess the occurrence of respiratory adverse events, the substantial resources required to do so made this infeasible. In addition, clear diagnosis (eg, between laryngospasm and airway obstruction) can often be given only within the clinical scenario and is difficult to assess from, for example, video recordings. We acknowledge that OSA status was assessed by an anesthetist from clinical history rather than by polysomnography, which is the standard for diagnosis and quantitative description of OSA. The significant time and economic investment cannot realistically be included in the routine anesthetic workup for all patients. Our approach broadly reflects routine clinical practice for anesthesia for tonsillectomy.

Anesthetists were free to manage anesthesia and administer analgesics as they deemed appropriate for their patient. Patients were not attached to physiological monitoring devices at the time of study drug administration; hence, any immediate physiological response was not known to the treating anesthetist. Given that our groups were comparable for age and weight, with anesthetists blinded to the study randomization and treatment in accordance with the same national and hospital guidelines, it is unlikely that variation in anesthetic care is a major confounder in our study. Full standardization of anesthetic or analgesic dosing does not reflect routine clinical practice and raises significant ethical concerns regarding overdosing or underdosing of analgesic agents.

This study did not directly address harms associated with albuterol (eg, tremor, headache, anxiety). Albuterol at the standard low doses generally used has few adverse effects.

Conclusions

The results of this triple-blind, randomized clinical trial demonstrate significant benefits of administering inhaled albuterol pre-
medication to children up to age 8 years before tonsillectomy with or without adenoidectomy. The significant reduction in the incidence of perioperative respiratory adverse events suggests that anesthetists should consider the use of albuterol in routine practice, particularly in children with moderate to severe OSA. For every 4 to 5 children undergoing tonsillectomy who receive albuterol, 1 additional case of perioperative respiratory tract complications can be prevented.

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