Premedication with salbutamol prior to surgery does not decrease the risk of perioperative respiratory adverse events in school-aged children

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Abstract

Background: Perioperative respiratory adverse events (PRAE) remain the leading cause of morbidity and mortality in the paediatric population. This double-blinded randomized control trial investigated whether inhaled salbutamol premedication decreased the occurrence of PRAE in children identified as being at high risk of PRAE.

Methods: Children with at least two parentally reported risk factors for PRAE undergoing elective surgery were eligible for recruitment. They were randomized to receive either salbutamol (200 μg) or placebo prior to their surgery and PRAE (bronchospasm, laryngospasm, airway obstruction, desaturation, coughing and stridor) were recorded.

Results: Out of 470 children (6–16 yr, 277 males, 59%) recruited, 462 were available for an intention-to-treat analysis. Thirty-two (14%) and 27 (12%) children from the placebo and salbutamol groups experienced PRAE. This difference was not significant [odds ratio (OR): 0.83, 95% confidence interval (CI): 0.48–1.44, P: 0.51]. Oxygen desaturation [14/232 (6%) *vs* 14/230 (6%), OR: 1.01, 95% CI: 0.47–2.17, P: 0.98] and severe coughing [12/232 (5%) *vs* 10/230 (4%), OR: 0.83, 95% CI: 0.35–1.97, P: 0.68] were the most common PRAE, but did not significantly differ between the groups. The occurrence of PRAE was slightly lower in children with respiratory symptoms who received salbutamol compared with placebo [16/134 (12%) *vs* 21/142 (15%), OR: 0.93, 95% CI: 0.38–2.26, P: 0.87], but was not significantly different.

Conclusions: Premedication with salbutamol to children aged between 6 and 16 years and at high risk of PRAE prior to their surgery did not reduce their risk of PRAE.

Trial registration number: ACTRN12612000626864 (www.anzctr.org.au).

Key words: β-2 agonist, salbutamol; perioperative respiratory adverse events; prevention; paediatric population

Editor's key points

- It is not known if inhalation of salbutamol before anaesthesia decreases the incidence of perioperative respiratory complications in children at increased risk of complications.
- Preoperative inhalation of salbutamol did not significantly reduce the incidence of respiratory complications in children aged 6-16 years undergoing elective surgery.

Perioperative respiratory adverse events (PRAE) are the most common complications in paediatric anaesthesia. They can potentially lead to significant neurological harm due to hypoxia.[1] Children with respiratory symptoms linked to airway inflammation and bronchial hyper-reactivity [e.g. respiratory tract infections (RTI) or asthma] are at higher risk of PRAE.[1–5] These symptoms are present in >25% of children presenting for surgery.[5–10] Paediatric anaesthetists thus face the complex task of identifying at-risk children and deciding whether to proceed with anaesthesia or postpone the procedure.[5]

β-2-Adrenergic agonists (e.g. salbutamol) act as bronchodilators in individuals with asthma.[11] While salbutamol effectively prevents an increase in respiratory resistance during intubation, its role in decreasing the incidence of PRAE is controversial.[12–14] Preoperative salbutamol is commonly used, especially in children with RTI,[15] and an observational study from our group showed that preoperative salbutamol in children with a recent moist cough significantly reduced the incidence of perioperative bronchospasm.[10]

The primary objective of this double-blinded randomized control trial was to investigate whether inhaled salbutamol premedication decreased the occurrence of PRAE. We hypothesized that children receiving salbutamol would experience significantly less PRAE compared with children receiving placebo. The secondary outcomes of this study assessed whether the risk of PRAE was reduced in children with at least one respiratory symptom receiving salbutamol compared with placebo and also whether the occurrence of PRAE varied during the different phases of anaesthesia between the placebo and treatment groups.

Methods

Study design

This trial was conducted as a single centre, double-blind, placebo-controlled and parallel-group study at Princess Margaret Hospital for Children in Perth, Western Australia between December, 2012 and February, 2015. Princess Margaret Hospital for Children is the only tertiary paediatric centre in Western Australia and caters for a large heterogeneous population with approximately 15 000 anaesthetics administered every year. Approval for this study was obtained from the Princess Margaret Hospital for Children Ethics Committee (2009/EP) and the University of Western Australia Committee (RA/4/1/5892). The trial was registered with the Australian and New Zealand Clinical Trial Registry (www.anzctr.org.au, ACTRN12612000626864).

Potential participants to the study were first identified from the elective surgery list by a research team member based on their age and type of surgery. The research team member then approached the anaesthetist in charge of the identified patients to determine their suitability for participation to the study. Following the latter's approval, the researcher approached the family to determine final eligibility for the study. This was based on the presence of at least two risk factors for PRAE and the absence of any exclusion criteria (Fig. 1). Written informed voluntary consent was obtained from parents and assent from child, prior to enrolment of the participants in the study. Recruited children were block randomized and assigned to one of the two groups, in a 1:1 ratio to receive either salbutamol or placebo. Any PRAE listed in Table 1 that met the definitions given was recorded by the anaesthetist during the perioperative period and by the post-anaesthesia care unit (PACU) nurse during the recovery period of anaesthesia.

No interim analyses for efficacy or futility were performed and an independent data monitoring committee was in place in case any unexpected reviews of un-blinded data needed to be performed. No changes were made to the initial protocol design between the start and end of the study.

Study population

Children aged between 6 and 16 yr (until end of 16th birthday) with at least two parentally reported risk factors for PRAE, and without any contraindication for salbutamol, undergoing elective surgery were eligible for recruitment into the study. The risk factors for PRAE were previously defined by our group in a large observational trial and detailed in Fig. 1.[1] The exclusion criteria are also summarized in the same figure. Participants were able to voluntarily withdraw consent at any point in time during the study.

Drug administration

Children were randomized to two actuations of either salbutamol (100 μg Ventolin® per actuation, GlaxoSmithKline, UK) or placebo (hydrofluoroalkane propellant, HFA-134a, GlaxoSmithKline, UK) delivered via a disposable spacer (Lite Aire®, Thayer Medical, Tucson, USA) using slow inhalations to near total lung capacity with a 5 s breath hold.

Treatment was administered at least 20 minutes preoperatively to ensure maximal bronchodilation.[16] In cases of unanticipated theatre delays, impacted participants were monitored and readministered the treatment 20 minutes prior to their rescheduled surgery if their waiting time since the initial administration of the drug had exceeded 1 h (half-life of salbutamol: ~2.5 h). The same inhaler attributed through the randomization process was used and the same dose was administered. This ensured that treatment was fully active in all patients over the perioperative period, irrespective of alterations in the timing of surgery.

Anaesthesia management

All children were anaesthetized in accordance with the safety standards of the Australian and New Zealand College of Anaesthetists (ANZCA) and the Department of Anaesthesia and Pain Management of Princess Margaret Hospital for Children using the institutional anaesthesia workstations (Draeger Primus, Luebeck, Germany).[17] Minimal and standardized routine anaesthesia monitoring always included ECG, non-invasive blood pressure measurements, capnography and pulse oximetry.

Anaesthesia induction was performed as deemed appropriate by the attending anaesthetist with either incremental inhalation of sevoflurane (up to 8 vol%) or i.v. propofol (>3 mg kg^{-1}). The method of sevoflurane inhalation and i.v. propofol
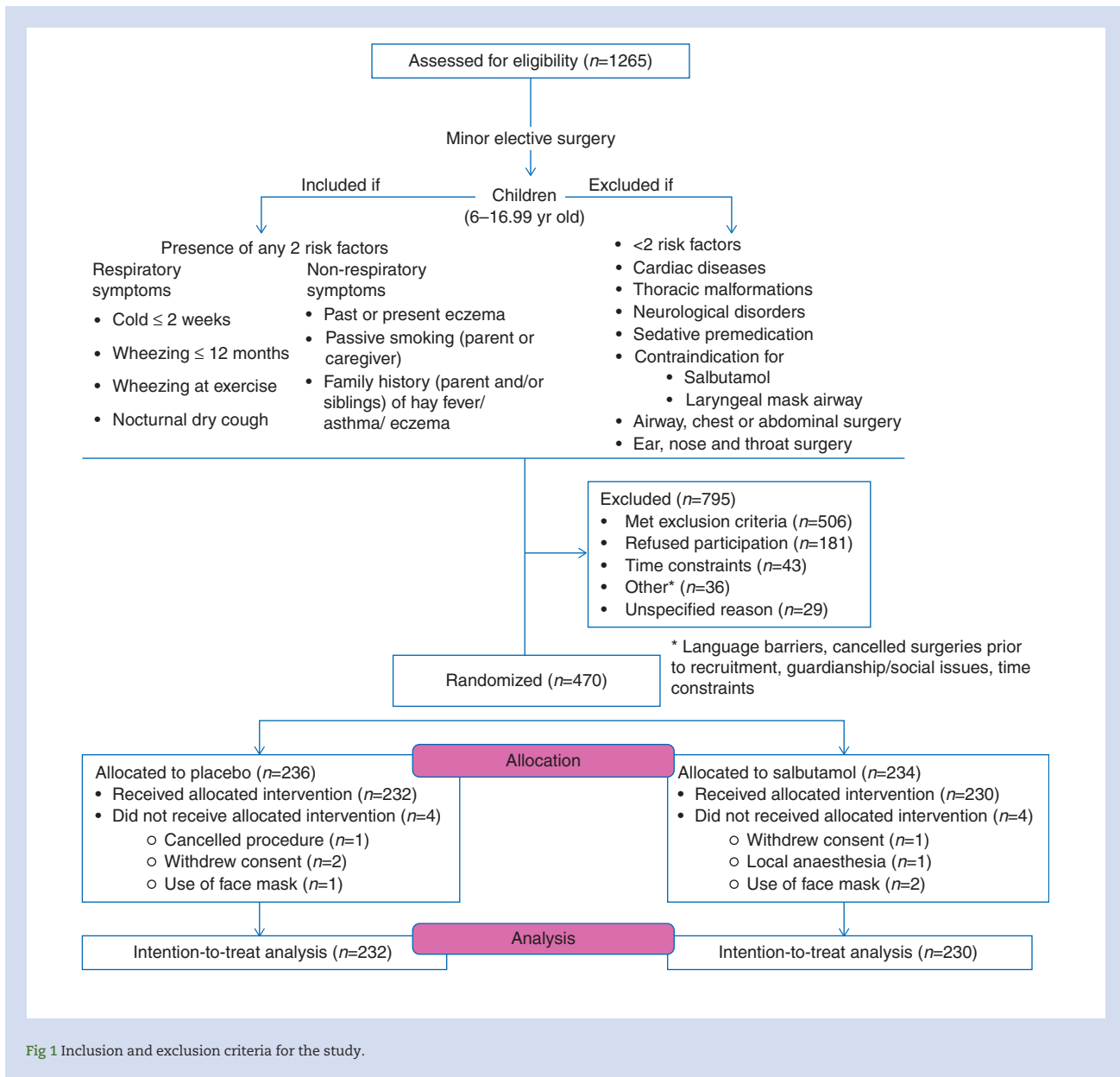
Fig 1 Inclusion and exclusion criteria for the study.

administration was left to the discretion of the anaesthetist to reflect routine practice. As a note, in our institution, sevoflurane induction involved in most cases a gradual increase in its concentration to 8% along with the use of nitrous oxide; a dose of i.v. propofol (1–2 mg kg^{-1}) was also typically administered as soon as i.v. access was secured prior to placing the airway device. As for i.v. induction, pre-oxygenation was not used routinely; to minimize pain with propofol administration, propofol was mixed with lidocaine and injected slowly. Airway management was performed with a laryngeal mask airway (LMA) in all children. The LMA was inserted when the patient was deemed deep enough by not reacting to a bi-manual jaw thrust manoeuvre.[18] Sevoflurane was used for the maintenance of anaesthesia in all children. Typical gas-flow ranged between 6 and 8 litres min^{-1} via a t-piece at induction. Continuous positive airway pressure was also applied as deemed appropriate by the anaesthetist. Analgesia was adjusted to each patient's individual

needs as determined by the attending anaesthetist. The timing of the LMA removal after surgery was left to the discretion of the anaesthetist.

Randomization and masking

Participants were randomly assigned (1:1) to receive either salbutamol or placebo. The randomization process was performed by the clinical trials pharmacy at Princess Margaret Hospital using a computer-generated block randomization algorithm (block size of six). Both salbutamol and placebo were manufactured by the same company (GlaxoSmithKline) and were made visually unidentifiable by the clinical trials pharmacy. Each canister was then placed in a plain white box sealed with a sticker containing the allocated randomized number. These were then transferred to the research team for use in the study. The randomization log was kept by the pharmacy department. All

Table 1 List of perioperative respiratory adverse events (PRAE) monitored in this trial along with the applied definitions

PRAE	Definition
Laryngospasm	Complete airway obstruction with associated muscle rigidity of the abdominal and chest walls
Bronchospasm	Increased respiratory effort, particularly during expiration and wheeze on auscultation
Desaturation <95%	Below 95%. The limit of 95% is chosen in line with institutional guidelines based on post-anaesthesia care unit (PACU) discharge criteria
Airway obstruction	Presence of airway obstruction in combination with a snoring noise and/or respiratory efforts
Severe coughing	A series of pronounced, persistent severe coughs lasting more than 10 s
Postoperative stridor	High pitch sound during breathing in the postoperative period

members directly involved in this study were blinded as to the allocation. Each participant was assigned the next available patient number during the study and received the contents of the corresponding canister prior to surgery. Only after the study was finalized and the data were analysed by the independent statistician (G.Z.) that the randomization log was made available to the research team members involved in the study.

Measured outcomes and monitoring

Primary outcome

Our primary outcome was the difference in the rate of occurrence of PRAE between children having received salbutamol and those having received placebo prior to surgery.

We hypothesized that there would be a significant decrease ($\geq$13%) in the rate of PRAE in children receiving salbutamol compared with placebo. A comprehensive list and definitions of those monitored in this trial are provided in Table 1.[1] All PRAE were monitored from the induction of anaesthesia until discharge from the PACU. The occurrence and rate of each PRAE were recorded by the attending anaesthetist during induction, maintenance and emergence phases of anaesthesia and by specialized nurses during recovery in the PACU.

Secondary outcomes

In addition to the primary outcome, we performed the following *post hoc* exploratory analyses:

i. whether the incidence of PRAE in children with at least one respiratory symptom who received salbutamol was reduced compared with those with at least one respiratory symptom who received a placebo.
ii. whether the occurrence of PRAE varied during the different phases of anaesthesia between the treatment group and the placebo group.

Furthermore, in line with clinical importance, PRAE were also subdivided into two groups: major (bronchospasm and laryngospasm) and minor (all other PRAE). We assessed whether major or minor PRAE differed between treatment groups.

Statistical analysis

In a previous observational study, we identified a difference of 13% in the incidence of overall PRAE between children having received salbutamol prior to surgery compared with those who were not administered any bronchodilator.[10] In this trial, we aimed to ascertain the difference of $\geq$13% in the incidence of overall PRAE between the salbutamol and placebo groups.

A sample size of 210 children in each arm of this trial provided an 80% power at a 0.05 two-sided significance level to detect a difference of at least 13% between the two groups. The null hypothesis applied was that salbutamol was not more effective than placebo in reducing the risk of PRAE. Based on our experience from previous studies and the rate of dropouts (~10%), we recruited a total of 470 children equally split between both groups so that the trial maintained its power to reject the null hypothesis.

Statistical analysis was performed with SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp.). An intention-to-treat (ITT) approach was used to analyse the data.

The primary and secondary outcomes were analysed using binary logistic regression with the occurrence of PRAE and grouped randomization being the dependent and independent variables, respectively. Results are reported as odds ratio (OR) and 95% confidence intervals (CI) along with the associated P-value for statistical significance.

Results

Four-hundred and seventy participants (277 males, 59%) aged between six and less than 17 years of age were recruited into this study. Complete datasets were available from 462 children and young people with exclusions being due to three cancellations, three consent withdrawals and two procedures carried out under local anaesthesia. The full trial profile is provided in Fig. 1. All patient variables were statistically comparable between the two groups. A detailed overview of these variables and airway management is provided in Table 2.

PRAE were observed at least once in 32/232 (14%) and 27/230 (12%) children from the placebo and salbutamol groups, respectively. This difference was not statistically significant (ITT analysis: OR: 0.83, 95% CI: 0.48–1.44, P: 0.51). A summary of these results along with the incidence of PRAE over the different phases of anaesthesia are provided in Table 3.

The occurrence of each individual PRAE was statistically comparable between the groups and is detailed in Table 4. Severe coughing and oxygen desaturation were the most observed PRAE in both groups. No significant differences were observed in the occurrence of these two PRAE between the placebo group and the salbutamol group.

The benefit of salbutamol *vs* placebo in children with respiratory symptoms and those without was also assessed. No significant differences were observed between the two groups in both cases (Table 5).

As a *post hoc* analysis, the amount of time spent in PACU by children was compared based on whether they experienced PRAE

Table 2 Distribution of sex, age, weight, height, ASA status and risk factors for perioperative respiratory adverse events (PRAE) within the placebo and the salbutamol groups. Other surgical procedures include dermatology, dental and oncology procedures. ENT, ear, nose and throat; LMA, laryngeal mask airway; PACU, post-anaesthesia care unit; min, minimum; max, maximum

		Placebo	Salbutamol
n		232	230
Male (%)		131 (57)	141(61)
Mean (min–max)	age (yr)	11.7 (6.1–16.9)	11.7 (6.0–16.9)
	weight (kg)	47.7 (18.7–109.3)	46.3 (17.6–115.7)
	height (cm)	151 (116–192)	150 (113–198)
ASA	I	139 (60%)	142 (62%)
	II	89 (38%)	83 (36%)
	III	4 (2%)	5 (2%)
Respiratory risk factors	cold ≤2 weeks	53 (23%)	60 (26%)
	wheezing ≤12 months	13 (6%)	19 (8%)
	wheezing at exercise	44 (19%)	44 (19%)
	previous asthma (if wheezing negative)	65 (28%)	52 (23%)
	nocturnal dry cough	25 (11%)	17 (7%)
	passive smoke exposure	92 (40%)	97 (42%)
Other risk factors	family history—hay fever	132 (57%)	127 (55%)
	family history—asthma	105 (45%)	102 (44%)
	family history—eczema	59 (25%)	64 (28%)
Timing—LMA removal	deep:awake	27 (12%):201 (88%)	20 (9%):207 (91%)
Anaesthesia duration	mean (min–max) min	56 (9–218)	55 (9–243)
PACU duration		38 (10–117)	35 (14–127)
Type of surgery	general	61 (26%)	44 (19%)
	orthopaedics	62 (27%)	74 (32%)
	plastics	44 (19%)	37 (16%)
	gastroenterology	19 (8%)	27 (12%)
	ENT	12 (5%)	14 (6%)
	ophthalmology	10 (4%)	7 (3%)
	rheumatology	10 (4%)	12 (5%)
	other	14 (6%)	15 (7%)

Table 3 Incidence of perioperative respiratory adverse events (PRAE) during the different phases of anaesthesia in the placebo and salbutamol groups

Phase	Placebo	Salbutamol	Odds ratio	95% CI	P-value
Induction	5 (2%)	9 (4%)	1.85	0.61–5.60	0.28
Maintenance	5 (2%)	1 (0.4%)	0.20	0.02–1.71	0.14
Emergence	11 (5%)	4 (2%)	0.36	0.11–1.13	0.08
Recovery	15 (7%)	17 (7%)	1.16	0.56–2.37	0.70
Overall	32 (14%)	27 (12%)	0.83	0.48–1.44	0.51

or not (Table 6). When no PRAE were experienced, children spent approximately the same amount of time in the PACU, irrespective of treatment allocation (one-way ANOVA: F: 0.122, P: 0.727). However, those who received placebo and experienced PRAE, spent on average 12 more minutes [48 (SD 20) min *vs* 36 (19) min] in PACU compared with those who received salbutamol and experienced PRAE (one-way ANOVA: F: 5.176, P: 0.027). Additionally, within-group comparisons demonstrated that children in the placebo group who experienced PRAE spent significantly more time in PACU than those who did not experience PRAE [48 (20) min *vs* 39 (16) min; one-way ANOVA F: 6.459, P: 0.012]. In the salbutamol group, those who experienced PRAE spent on average 4min less

in the PACU than those who did not experience PRAE (36 vs 40min) and this difference was not statistically or clinically significant when compared with a one-way ANOVA (df: 1, F: 1.410, P: 0.236).

Discussion

Against our hypothesis, our double-blinded randomized controlled trial shows that the administration of inhaled short acting bronchodilators prior to surgery to children older than six years with at least two risk factors for PRAE did not reduce the risk of these events from occurring.

These results are in agreement with those of Elwood and colleagues[13] who performed a similar trial using both anticholinergic and β-2 agonist premedication. They argued that the bronchodilator effect might have been lost among the multitude of other factors contributing to the emergence of PRAE along with the fact that bronchoconstriction may not be a factor in emergence of PRAE. However, in our study, the loss of bronchodilator effect is unlikely because we ensured that salbutamol/placebo was administered 20 min prior to the start of the surgery. In this study, anaesthesia was maintained with sevoflurane, which is known to have a significant bronchodilator effect from a minimum alveolar concentration of one.[19] Coupled to the awareness of the anaesthetist on the high risk of PRAE of these patients, this might explain the low incidence of bronchospasms and laryngospasms observed in our trial. These factors may have

Table 4 Comparison of the incidence of each individual perioperative respiratory adverse event (PRAE) between the two groups over the whole period of anaesthesia for each group

PRAE	Placebo	Salbutamol	Odds ratio	95% CI	P-value
(a) Bronchospasm	3 (1%)	0 (0%)	—	—	—
(b) Laryngospasm	2 (1%)	5 (2%)	2.56	0.49–13.31	0.27
Major PRAE (a and b)	5 (2%)	5 (2%)	1.01	0.29–3.53	0.99
(c) Severe coughing	12 (5%)	10 (4%)	0.83	0.35–1.97	0.68
(d) Oxygen desaturation	14 (6%)	14 (6%)	1.01	0.47–2.17	0.98
(e) Airway obstruction	7 (3%)	5 (2%)	0.71	0.22–2.28	0.57
(f) Stridor	0 (0.0%)	2 (1%)	—	—	—
Minor PRAE (c–f)	33 (14%)	31 (14%)	0.94	0.55–1.59	0.82

Table 5 Comparison of the incidence of perioperative respiratory adverse events (PRAE) in the placebo and salbutamol groups in children with and without respiratory symptoms

Occurrence of PRAE				
Placebo	Salbutamol	Odds ratio	95% CI	P-value
≥1 respiratory symptom present				
21/142 (14.8%)	16/134 (12%)	0.93	0.38–2.26	0.87
No respiratory symptoms present				
11/90 (12.2%)	11/96 (12%)	0·78	0.39–1.57	0.49

Table 6 Comparison of the amount of time spent in the post-anaesthesia care unit (PACU) by children in the placebo group *vs* the salbutamol group categorized by the occurrence of perioperative respiratory adverse events (PRAE) or not

	Placebo		Salbutamol	
Duration	no PRAE (n=200)	PRAE (n=32)	no PRAE (n=203)	PRAE (n=27)
PACU [min (SD)]	39 (16)	48 (20)	40 (17)	36 (19)

masked any potential beneficial effect of the inhaled salbutamol prior to surgery.

Our results are also in contrast with our previous observational findings where children having received salbutamol had a decreased rate of perioperative bronchospasm and severe coughing compared with those who did not receive a premedication with salbutamol.[10] There are characteristic differences between the populations of the two studies which might explain why no beneficial effect of salbutamol was observed in this study; in the observational trial, the children were significantly younger (median of 5 yr younger, 59% <6 yr compared with a median age of 12.0 yr in the current study), which is known to be a risk factor for PRAE (11% increase in PRAE with each year younger).[3] Almost 40% were scheduled for ear, nose and throat (ENT) procedures and had all experienced an RTI with a moist cough within the two weeks prior to surgery. The risk of PRAE is highest in the first two weeks of an RTI due to exacerbated airway inflammation and interaction with the autonomic nervous system consequent to airway hyper-responsiveness.[4 20 21] Additionally, a moist cough has been linked with higher rates of PRAE compared with other RTI symptoms.[1] Comparatively, less than one-quarter of the whole population recruited in this trial had a cold over the last two weeks and ENT procedures were not included in this study. Therefore, it is feasible that we may have introduced a bias in our study population by recruiting children with absence/presence of these symptoms and with varying severity. Additionally, symptoms such as wheezing and dry night cough may be triggered by specific stimuli such as exercise or inhaled triggers such as aeroallergens or air pollution and thus only generate acute episodes of airway inflammation not present at the time of surgery in the recruited children.

All children included in this trial had an LMA during surgery. Those having an endotracheal tube were excluded. While it is well documented that the use of an LMA decreases the risk of PRAE, using an ETT has been shown to play an important role in the increased occurrence of PRAE.[20 22 23] Endotracheal tubes, especially during insertion, cause active mechanical stimulation of the upper airway and the latter can consequently have a reduced calibre.[24 25] This would be particularly exacerbated in children with respiratory symptoms and/or airway hyper-reactivity. As the use of a β-2-adrenergic agonist has been shown to reduce the resistance of the airways following intubation in adults, the benefits of inhaled salbutamol prior to surgery might thus be more prominent in children having an Endotracheal tube for airway management compared with an LMA.[26 27] However, with LMA being increasingly the device of choice in the paediatric population, the results of this study are relevant to current routine paediatric clinical practice across the world.

PRAE in this study occurred mostly in the emergence and recovery phases of anaesthesia with severe coughing and oxygen desaturation (minor PRAE) observed as the most common PRAE in both groups. Awake removal of the LMA, which was the most practiced timing in this trial, is known to be associated with an increased incidence of coughing due to the return of the protective airway reflexes engaging the gag reflex and coughing mechanism.[28] Therefore, these cough events are unlikely to be induced by any underlying respiratory symptoms, and the administration of a bronchodilator such as salbutamol is also unlikely to resolve their occurrence.

The *post hoc* analysis carried out with regards to the amount of time spent in PACU by children in each group showed interesting results, albeit a limited sample size for those experiencing PRAE. Children receiving salbutamol and spending less time

in the PACU when experiencing PRAE compared with those receiving placebo and experiencing PRAE might indicate a protective effect of salbutamol aiding in a faster recovery, especially when minor PRAE are observed. However, it needs to be noted that these results are based on *post hoc* analysis and should be interpreted cautiously due to a limited sample size and the initial design not being based on this outcome.

Our study also has certain limitations. It was carried out as a single-centre study and the results might not be considered generalizable. However, our institution is the only paediatric referral centre in Western Australia where the population is very heterogeneous, therefore, extending the generalizability of the results. With Princess Margaret Hospital being a tertiary centre, registrars and fellows also participated in our study. Though it is known that the risk of PRAE occurring is influenced by the experience of the anaesthetist, all registrars and fellows who participated in the study did so under the direct supervision of a consultant anaesthetist.[12] The core group of the latter at our hospital is composed of paediatric anaesthetists that have been practicing for more than five years within the same hospital. One other main limitation of our study is that PRAE can be a composite outcome and the specificity of each PRAE involves a degree of clinical judgement. We endeavoured to ensure that the strict definitions for all PRAE (Table 1) were used by the anaesthetists and PACU nurses in an attempt to minimize the risk of investigator bias and of selective reporting (e.g. including events of soft tissue obstruction in the laryngospasm group).

Conclusion

The results of this double-blinded randomized controlled trial show that preoperative β-2 agonist administration to school-aged children and adolescents with risk factors for PRAE, having general anaesthesia with an LMA, did not reduce their risk of PRAE. The outcome might be different in younger children with respiratory symptoms more intricately linked to the occurrence of PRAE.

Authors' contributions

Study proposal and design, management, manuscript writing: B.S.v.U.-S.
Study design, management, manuscript writing: G.L.H.
Study proposal and design, statistical oversight: G.Z.
Study design, management, manuscript writing: G.L.H.
Study coordination and management, data entry and database management: L.S.
Data collection and database management: T.F.E.D.-B.
Manuscript preparation and writing: D.S.
Data collection, statistical analysis, interpretation of results and manuscript writing: A.R.

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Declaration of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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