Inhalational versus intravenous induction of anesthesia in children with a high risk of perioperative respiratory adverse events – a randomized controlled trial.

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Abstract

Background: Limited evidence suggests that children have a lower incidence of perioperative respiratory adverse events when intravenous propofol is used compared with inhalational sevoflurane for the anesthesia induction. Limiting these events can improve recovery time as well as decreasing surgery waitlists and health care costs. This single center open-label randomized controlled trial assessed the impact of the anesthesia induction technique on the occurrence of perioperative respiratory adverse events in children at high risk of those events.

Methods: Children (n=300, 0-8 years) with at least two clinically relevant risk factors for perioperative respiratory adverse events and deemed suitable for either technique of anesthesia induction were recruited and randomized to either inhalational sevoflurane or intravenous propofol. The primary outcome was the difference in the rate of occurrence of perioperative respiratory adverse events between children receiving intravenous induction and those receiving inhalation induction of anesthesia.

Results: Children receiving inhalational sevoflurane were significantly more likely to experience perioperative respiratory adverse events compared with those who received intravenous propofol after adjusting for age, sex, ASA and weight (Perioperative respiratory adverse event: 39/149 (26%) vs. 64/149 (10.7%), relative risk (RR): 1.7, 95% confidence interval (CI): 1.2 - 2.3, p-value: 0.002), respiratory adverse events at induction: 47/149 (31.5%) vs. 16/149 (10.7%), RR: 3.06, 95% CI: 1.81 to 5.16, p-value < 0.001).

Conclusion: Where clinically appropriate, anesthesiologists should consider using an intravenous propofol induction technique in children who are at high risk of experiencing perioperative respiratory adverse events.

Introduction

Perioperative respiratory adverse events are experienced by approximately 15% of children undergoing anesthesia with rates as high as 50% reported during some common surgical procedures.[1] The incidence of perioperative respiratory adverse events is associated with increased airway reactivity and this association is strongest in individuals with asthma, eczema, a recent upper respiratory tract infection (URTI) or passive smoke exposure.[1–5]

Perioperative respiratory adverse events are associated with an increased probability of prolonged hospital admissions and impact adversely on the patients and their families, surgery waitlists as well as lead to higher health care costs[6]. In cases where these events are not detected and treated early, they can lead to significant harm including death through hypoxia.[2,3,7–9]

While inhalational induction was traditionally the preferred induction technique in children, intravenous induction is becoming increasingly popular.[10,11] The causal relationship between the type of anesthesia induction and the risk of perioperative respiratory adverse events is poorly understood. A 2014 Cochrane review highlighted the paucity of evidence supporting either inhalational or intravenous induction and called for "high-quality studies … to compare the different types of anesthesia in … children undergoing ambulatory surgery".[11] In an observational study we reported that children with a positive respiratory history receiving an intravenous (IV) induction were at a significantly lower risk of perioperative respiratory adverse events compared with children receiving an inhalational induction.[1]

The aim of this single center open-label randomized controlled trial was to assess whether IV induction with propofol or inhalation induction with sevoflurane influenced the likelihood of perioperative respiratory adverse events in high-risk infants and children undergoing minor elective surgery.

Methods

Study design and participants:

This single center open-label randomized controlled trial (parallel groups) was carried out by the Department of Anesthesia and Pain Management at Princess Margaret Hospital for Children in Perth, Western Australia.

Ethics approval was received from the Princess Margaret Hospital for Children Ethics Committee (1787/EP) and the University of Western Australia Ethics Committee (RA/4/1/5808). The trial was registered with the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au, ACTRN12610000252011).

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 anesthesiologist in charge of the identified patients to determine their suitability for participation in the study. Following the latter's approval, the researcher approached the family to determine final eligibility for the study. Parents/guardians were provided with a detailed explanation of what the trial and their participation entailed as well as the way the randomization process worked. They were informed that their treating anesthesiologist would be blinded to the induction technique until the randomization envelope was unsealed immediately prior to induction. Finally, written consent was provided by the parents/guardians and child assent was sought when applicable.

Infants and children aged up to eight years, with at least two parentally reported risk factors for perioperative respiratory adverse events (figure 1) and scheduled for elective surgery were eligible for recruitment.[1]

Table 1 provides an overview of the different definitions applied to each of the risk factors with detailed definitions found elsewhere[1]. The perioperative respiratory adverse events recorded in this study are defined in table 2. The full inclusion and exclusion criteria are summarized in figure 1. An independent data monitoring committee was in place for this trial.

Randomization and masking

The randomization process was carried out by an independent statistician and the sealed envelopes handed to the research team. No team member was aware of randomization until the anesthesiologist opened the envelope prior to surgery. Computer generated block randomization was used to assign (1:1) participants randomly to either intravenous propofol ("IV" group) or inhalational sevoflurane ("inhalational" group) for anesthesia induction. The randomization envelope was only opened by the attending anesthesiologist immediately prior to anesthesia induction.

Procedures

Participants requiring sedative premedication (e.g. midazolam or clonidine) were excluded from the trial (figure 1) as we have previously shown that premedication increases the risk of perioperative respiratory adverse events.[1] General anesthesia was induced either by the consultant anesthesiologist or under direct consultant supervision and according to the randomized method. At our pediatric hospital, intravenous induction is routinely performed while using effective distraction techniques (e.g. verbal and/or visual distractions) when required. Topical anesthesia (Eutectic Mixture of Local Anesthetic- EMLA) was also used to reduce the discomfort of inserting the cannula. EMLA is provided to all patients at our institution on admission, generally before the anesthesiologist sees the patient and is therefore independent of the type of anesthesia induction performed. In cases where children felt uncomfortable or distressed with either technique of induction, cross-overs to the other group were allowed as a reflection of daily occurrences in pediatric anesthesia.

Inhalation induction was carried out with sevoflurane and nitrous oxide. At our institution, inhalation induction with sevoflurane is achieved by giving the child up to 66% nitrous oxide in oxygen for 20 to 30 seconds, then 8% sevoflurane.[12] Bar one participant receiving inhalation induction, every other participant in that group received nitrous oxide. The ratio of nitrous oxide to oxygen used was 0.5 (median) with the minimum and maximum value being 0.5 and 0.66 respectively. In line with standard clinical practice, the anesthesiologist in charge of the patient was free to administer a dose of intravenous propofol as soon as intravenous access was secured prior to placing the laryngeal mask airway (LMA). Intravenous induction was achieved with propofol (3-5 mg/kg) mixed with lidocaine and manually injected slowly to minimize pain. The injection process was not timed. Pre-oxygenation was not routinely used. Airway management was performed with an LMA in all children and inserted when the patient did not react to a bi-manual jaw thrust maneuver. Sevoflurane was used for the maintenance of anesthesia in all children. Typical gas-flow ranged between 6-8 L/min via a t-piece at induction of anesthesia. Continuous positive airway pressure (CPAP) was also applied as deemed appropriate by the anesthesiologist. All patients were ventilated using a Draeger Primus anesthesia workstation (Draegerwerk AG & Co. KGaA, Luebeck, Germany). Analgesia (including regional/local analgesia) was administered by the attending anesthesiologist as deemed clinically appropriate. Administration of opioids (fentanyl, morphine, alfentanyl, pethidine, tramadol and remifentanil) was left to the discretion of the anesthetist. Routine anesthesia monitoring included electrocardiography, non-invasive blood pressure measurements, capnography and pulse oximetry.

The occurrence and rate of each respiratory adverse event were recorded by the attending anesthesiologist during induction, maintenance and emergence of anesthesia, and by specialized nurses during recovery in the post anesthesia care unit.

Outcomes

Primary outcome

The primary outcome was the difference in the rate of occurrence of perioperative respiratory adverse events between children receiving intravenous induction and those receiving inhalation induction of anesthesia. We hypothesized that the occurrence of these events would be significantly higher with inhalation induction of anesthesia compared with intravenous induction.

Secondary outcomes

Secondary outcomes were:

(i) Frequency of the individual respiratory adverse events. Furthermore, in line with clinical importance, these perioperative respiratory adverse events were clustered into two groups; serious (bronchospasm and laryngospasm) and minor (all other respiratory adverse events) respiratory adverse events.

(ii) Occurrence of respiratory adverse events during the different phases of anesthesia with a particular interest for the induction phase.

Based on trends observed concurrently in other studies from our group, the following additional outcome (not listed on the clinical trial registry) was included in our analysis plan prior to conducting the statistical analysis:[13–15]

The difference in the occurrence of respiratory adverse events between the two types of induction groups in children with and without respiratory symptoms (figure 1).

Finally, as part of the review process we were requested to conduct a post-hoc analysis of the potential impact of a bolus delivery of IV propofol compared to an additional small bolus of propofol within the inhalation group prior to the insertion of the laryngeal mask airway. This secondary, post-hoc analysis was not outlined in the clinical trial protocol nor in the trial analytical plan.

Statistical analysis:

Sample size calculations were based on the reported difference in the incidence of perioperative respiratory adverse events between children receiving an inhalation induction (38%) and an intravenous induction (22%) in our previous observational trial.[1] A sample size of 128 per group using a two group chi square analysis, at a 0.05 two sided significance level provided an 80% power to detect a difference in the rate of perioperative respiratory adverse events between the two groups of at least 16% overall. After allowing for 15% data loss due to unusable or missing data, we aimed to recruit 150 participants in each group.

Statistical analysis was performed with SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22·0. Armonk, NY: IBM Corp.) and STATA (Version 13, StataCorp LLC, Texas, USA). An intention to treat (ITT) and an as per protocol (APP) analysis were performed.

As per the ethics approval requirements, an interim analysis was performed after data from 150 patients was collected. Statistical significance was adjusted according to the Haybittle-Peto method for group sequential testing and fixed at 0.0027 for the interim analysis. Final analysis was performed with statistical significance set at 0.05. The outcomes are presented as binary variables and both primary and secondary outcomes were analyzed using Fisher's exact test. The relative risk (RR) and 95% confidence intervals (CI) reported were calculated according to Altman.[16] For the primary outcome the adjusted and un-adjusted relative risks were presented and for secondary outcomes variables un-adjusted relative risks were reported. Age, gender, ASA and weight were adjusted for using generalized linear models.

Results

Patients

Three hundred children (63% (n=189) male) were recruited (06/08/10 - 20/11/13) into the study and were aged between 0.7 and eight years. Two procedures were cancelled leading to 149 complete datasets being available in each group for the ITT analysis. A further 30 children were excluded from the APP analysis due to study violations (figure 1). Study progress through the phases of recruitment along with the exclusions are shown in figure 1. The distribution of risk factors for perioperative respiratory adverse events between the IV and inhalation induction groups is depicted in figure 2. The demographic characteristics of each group are outlined in Table 3 and the number of participants per group for each surgical specialty is listed in table 4. The interim analysis carried out did not meet the stopping rule (Haybittle Peto, $p<0.0027$) to cease the trail and was therefore continued until the full sample size (300) was reached.

Children in the IV group received an average (± sd) of 4.6 ± 0.9 mg/kg of propofol. In the inhalation group, 69/142 (49%) received a bolus of propofol (mean ± sd: 1.34 ± 0.61 mg/kg) following inhalation induction. The reviewer requested post-hoc analysis did not reveal any significant difference in perioperative respiratory adverse events between those received a propofol bolus and those who did not in the inhalational group (34/69, 49% vs. 28/73, 39%, RR: 1.3, 95% CI: 0.9 – 1.9, p-value: 0.190).

Primary results

Details of the occurrence of perioperative respiratory adverse events are provided in table 5. Inhalational induction was associated with an increased likelihood of perioperative respiratory adverse events compared with intravenous induction and this difference remained significant after adjusting for age, sex, ASA and weight (table 5).

Secondary results

(i) Frequency of each perioperative respiratory adverse events

Table 5 details the rate of occurrence of the different respiratory adverse events recorded over the perioperative period. Minor perioperative respiratory adverse events (severe cough, oxygen desaturation and airway obstruction) were associated with a higher likelihood when inhalation induction was used compared with IV induction for both the intention to treat and as per protocol analysis (table 5). Similarly, IV induction was associated with a significantly lower incidence of serious perioperative respiratory adverse events compared to inhalational induction (table 5; $p<0.01$)

Eight cases of serious perioperative respiratory adverse events (5.4%) were recorded in the inhalation group during induction of anesthesia while none was recorded in the intravenous group (exploratory analysis, table 6).

(ii) Respiratory adverse events over induction phase of anesthesia

Table 6 details the occurrence of individual respiratory adverse events during the induction phase of anesthesia. Children in the inhalation group were significantly more likely to experience a respiratory adverse event during induction than those receiving an intravenous induction of anesthesia. The relative risk of respiratory adverse events was not different between induction groups in children who did not report any respiratory symptoms.

Discussion

The results of this trial show that children with at least two risk factors for perioperative respiratory adverse events having an inhalational induction of anesthesia with sevoflurane were significantly more likely to experience perioperative respiratory adverse events than when intravenous propofol was used. The secondary outcomes showed that both serious and minor perioperative respiratory adverse events were more likely to occur over the perioperative period with an inhalational induction rather than an intravenous induction. Moreover, while the likelihood of perioperative respiratory adverse events was independent of the type of anesthesia induction in children without respiratory symptoms, they were more likely to occur with an inhalational induction than an intravenous induction in those with respiratory symptoms.

Several factors may be influencing the disparity in the rate of perioperative respiratory adverse events observed between the two groups. Compared with sevoflurane, propofol is more potent at blunting the reflex bronchoconstriction commonly occurring during mechanical stimulation of the airway, e.g. during airway management at induction of anesthesia.[17,18] Furthermore, propofol has been demonstrated to be superior in suppressing laryngeal reflex responses in comparison to sevoflurane which is also known to maintain the airway in an excitement phase over a longer period of time.[19,20] Conversely, it is known that sevoflurane is a potent bronchodilator via a reduction in parasympathetic nervous tone and an inhibition of the voltage-dependent calcium, potassium and chloride channels of the bronchial smooth muscle and therefore should be protective of perioperative respiratory adverse events.[17,18] However, propofol also has bronchodilatory effects via the reduction in parasympathetic nervous tone although they are inferior to those of sevoflurane. Furthermore, propofol acts via a reduction in serotonin 5-hydroxytryptamine receptor activity on bronchial smooth muscle cell and an inhibition of adenosine triphosphate induced contraction.[17,18] The fact that both agents are bronchodilators may be reflected in the low incidence of bronchospasm. However, the more potent blunting effect of propofol is probably the most important factor in the lower incidence of perioperative respiratory adverse events such as laryngospasm, cough and oxygen desaturation observed in our study.

The choice of a pediatric population with at least two risk factors for perioperative respiratory adverse events including a range of respiratory symptoms highlights the importance of the pharmaco-chemical properties of sevoflurane and propofol. Common practice at our hospital involves administration of sevoflurane with nitrous oxide. The combination of sevoflurane and nitrous oxide induces an inflammatory response and suppresses the anti-inflammatory response in the local milieu of the airway.[21] In children with the selected risk factors there is a

high likelihood of airway inflammation being present and the combination of sevoflurane with nitrous oxide for anesthesia induction may exacerbate the inflammation leading to the higher rate of perioperative respiratory adverse events observed in the inhalation compared with the IV group. This is supported by further increased incidence of perioperative respiratory adverse events in children with at least one respiratory symptom, a group most likely to have airway inflammation and/or bronchial hyper-responsiveness.

The laryngeal mask airway (LMA), the most commonly used airway device in pediatric anesthesia, was the standardized airway device used in this study. It could be postulated that the difference between intravenous and inhalational induction of anesthesia may have been even greater when using an endotracheal tube, since mechanical stimulation of the airway is greater with an endotracheal tube and therefore increases the risk for laryngeal and bronchial reflex responses.[1,17,18] It could be argued, that the higher incidence of respiratory adverse events in the inhalational group is caused by a generally longer duration of an inhalational induction (not specifically assessed in this trial) compared with an IV induction. While this is possible, we would like to highlight the experience of the anesthesiologists involved in this trial who all had extensive experience in pediatric airway management.

The results obtained should be interpreted while keeping the limitations of this study in mind. In line with routine clinical practice, we relied on parental reporting to assess the presence of risk factors for perioperative respiratory adverse events. Due to the qualitative nature of this information there is a possibility of misclassifying a child as being high risk and including them in the trial. However parental reporting is used in routine clinical practice by anesthesiologists to assess the presence of risk factors for perioperative respiratory adverse events prior to surgery.[13,22]

It must be noted that we focused on children with risk factors for perioperative respiratory adverse events compared to other studies with a broader, unselected population. However, these children, particularly those with respiratory symptoms, represent a large proportion of children undergoing anesthesia and those most at risk of adverse events. Over a quarter of our children scheduled for surgery present with symptoms of an upper respiratory tract infection during the two weeks prior to surgery, while more than 15% have experienced several episodes of wheezing over the last 12 months.[1] Similar numbers have commonly been reported across the literature for children with a recent (2-4 weeks) respiratory tract infections presenting for surgery.[23–26] In the majority of cases, anesthesiologists will still proceed with anesthesia even in the presence of an upper respiratory tract infection as delaying surgery may not necessarily reduce the risk of perioperative respiratory adverse events.[24,25,27,28] It is, therefore, critical that the anesthesia management strategies chosen are personalized to the individual child's needs in order to minimize the risk of perioperative respiratory adverse events. To our knowledge, in this high risk pediatric population, there are no existing studies

that provide adequate evidence with regard to the measures required to limit the risk of perioperative respiratory adverse events.

Limitations of the trial: The major limitation of this trial was an inability to have a double blinded study design. Once the randomization envelope was opened by the anesthesiologist, he/she was no longer blinded to the treatment arm. This may lead to investigator bias in which those diagnosing the outcome are aware of the group allocation and/or the study hypothesis. However, it is important to note that none of the anesthesiologists who participated in this study were aware of the study hypothesis therefore reducing this risk of bias. Complete blinding may also have been achieved by allowing for a different anesthesiologist unaware of the induction technique to assess for perioperative respiratory adverse events or using patient video reviews after the procedure. However, this was an impractical solution in the context of routine clinical practice and experienced anesthesiologists would easily be able to differentiate between the different induction techniques just by simple patient behavior. We therefore opted for the treating anesthesiologist to identify and report any perioperative respiratory adverse events that occurred using well standardized perioperative respiratory adverse event definitions. Since in routine practice perioperative respiratory adverse events are a composite outcome that requires a degree of clinical judgement, we endeavored to ensure that the strict definitions were used by the anesthesiologist and PACU nurses to record any perioperative respiratory adverse events in our study. By doing so, we have minimized the risk of investigator bias and of selective reporting (e.g. including events of soft tissue obstruction in the laryngospasm group). Lastly, analgesia was left to the discretion of the anesthesiologist in both groups. Perioperative pain depends on many patient and surgery specific factors and standardization could lead to suboptimal care that we deemed unethical. It is well documented that analgesia such as fentanyl and morphine do not impact the risk of major perioperative respiratory adverse events (e.g. laryngospasm) and therefore we do not believe analgesia choice will have impacted on the study outcomes.[29]

As a single-center study in a tertiary teaching hospital environment, registrars and fellows were involved in anesthetic care in this study. We recognize that the occurrence of perioperative respiratory adverse events is dependent on the experience of the anesthesiologist, however, all registrars and fellows who participated in the study did so under the direct supervision of a consultant anesthesiologist. The latter is composed of a stable group of pediatric anesthesiologists with significant experience in the pediatric field and at our hospital and therefore likely to be generalizable to wide clinical practice within tertiary pediatric centers.

Furthermore, this clinical trial was carried out in a single-center. We are however confident that our results are generalizable to the majority of pediatric anesthesia practice as Princess Margaret Hospital is the only referral tertiary hospital for the large heterogeneous population that composes Western Australia and therefore has a case load broadly representative of that seen in international practice. Finally, while the duration of this clinical trial might suggest limited suitability of patients, the actual limiting factor in recruitment was budgetary and thus limited availability of staff. In the later years of the trial, recruitment saw a sharp increase when full time and more staff became available.

Acceptability of IV induction

The distress and anxiety generated in children receiving an IV induction and the subsequent emotional consequences has been the subject of much debate.[10] In our study, acceptability of both types of inductions was very high (> 95%) amongst participants. However, only children deemed suitable for both induction methods by the anesthesiologist in charge were recruited. We did not formally assess preference or acceptability in a general surgical population. Treatment cross-over did occur, with 15 participants changing from the IV to the inhalational group. However, IV induction was deemed unethical and not attempted in eight of these patients due to the local anesthetic cream not being applied for a sufficient time span. Therefore, IV induction was attempted and failed in seven patients who crossed over either because of refusal or due to technical difficulties. Surprisingly, six patients in the inhalational group refused the mask at the time of induction and requested an IV induction. This highlights the high feasibility of IV inductions in non-premedicated children without distress.

Conclusion

The results of this trial should not be interpreted as supporting exclusive use of IV induction of anesthesia. While the results favor intravenous induction in children at an increased risk of perioperative respiratory adverse events, there are patient groups who will still benefit from an inhalational induction, e.g. those with needle phobia or with a history of difficult IV access. However, a careful approach, involving meticulous history taking and evidence-based practice, should be the main pillars in tailoring the anesthetic to the individual patient particularly in the children at high risk for respiratory adverse events.

There are currently no evidenced-based guidelines or recommendations that would enable pediatric anesthesiologists to make informed, evidence based choices on the type of anesthesia induction technique required to reduce or prevent perioperative respiratory adverse events. Our results provide initial evidence as to the benefits of using an intravenous induction with propofol to minimize the occurrence of perioperative respiratory adverse

events in high risk children, especially in those with respiratory symptoms when compared with inhalational induction with sevoflurane.

Author contribution

B v U-S, GLH, MH and GZ were responsible for the original proposal, securing funding for the trial, and drafting the original protocol. B v U-S as a chief investigator had the overall responsibility for the management of the study. She also participated in data interpretation and manuscript writing. GLH was involved in data interpretation and manuscript writing. GZ provided statistical oversight for this study and participated in data analysis. MH was involved in the literature review prior to securing funding and was involved in reviewing the manuscript prior to submission. AR analyzed and interpreted the data, produced the figures and tables and wrote the manuscript.

Conflict of interest disclosures:

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest (www.icmje.org/coi_disclosure.pdf) and none were reported for the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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Figure 1. Inclusion and exclusion criteria for this trial along with the recruitment profile. The exclusion criteria for both the intention to treat and the as per protocol analyses are provided for each group of randomization.

Risk factors	Brief definition applied in this study
Cold ≤2 weeks	Signs of runny nose, cough and/or fever (>38ºC) but deemed fit for anesthesia by independent consultant anesthesiologist
Wheezing ≤ 12 months	More than 3 episodes of wheezing experienced during the past year
Wheezing at exercise	Parentally reported wheezing during exercise
Nocturnal dry cough	A persistent dry night cough observed
Past/Present eczema	Persistent eczema observed in past or currently
Passive smoking	Child exposed to parents/caretakers smoking independent of location, e.g., inside or outside of house
Family history of hay fever/asthma/eczema	At least 2 family members (any two of parents/siblings/grandparents) with a history of either hay fever or asthma or eczema.

Table 1. Brief definition of the risk factors used as inclusion criteria in this trial.

Perioperative respiratory adverse events	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 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 10s.
Postoperative stridor	high pitched sound during breathing in the postoperative period

Table 2. Definition used for respiratory complications recorded.

Figure 2. Number of patients in each group who presented with 2,3,4 and 5/5+ risk factors and were included in this trial.

	Type of Analysis			
	Intention to treat (ITT)		As per protocol (APP)	
	IV	Inhalation	IV	Inhalation
	(N=149)	(N=149)	(N=130)	(N=140)
Male, %	92, 62%	96, 64%	79, 61%	91, 65%
Median age years (min-max)	4.5 (0.9 to 8·9)	4.3 (0.7 to 8.8)	4.8 (1.1 to 8.9)	4.4 (0.7 to 8.8)
Age group				
0.0 – 3.0	28 (19%)	39 (26%)	23 (17%)	36 (26%)
3.1 – 5.0	52 (35%)	54 (36%)	44 (34%)	51 (36%)
5.1 – 7.0	40 (27%)	37 (24%)	36 (28%)	35 (25%)
7.1 – 8. 9	28 (19%)	19 (12%)	26 (20%	18 (13%)
Median weight Kg (min-max)	18.4 (6.8 to 40.0)	17.3 (7.8 to 44.3)	18.7 (6.8 to 40.0)	17.6 (7.8 to 44.3)
ASA 1	98(66%)	109(73%)	88(68%)	101(72%)
2	47(32%)	38(26%)	39(30%)	37(26%)
3	4(3%)	2(1%)	3(2%)	2(1%)
Cold ≤2 weeks	49 (33%)	55 (37%)	45 (35%)	51 (36%)
Wheezing 3+ times ≤ 1 yr	27 (18.1%)	22 (15%)	21 (16%)	21 (15%)
Wheezing at exercise	13 (9%)	13 (9%)	12 (9%)	13 (9%)
Nocturnal dry cough	44 (30%)	31 (21%)	40 (31%)	30 (21%)
Past/Present eczema	71 (48%)	56 (38%)	63 (49%)	53 (38%)
Passive smoking	71 (48%)	63 (42%)	63 (49%)	60 (43%)
Family history of hay fever	88 (59%)	97 (65%)	75 (58%)	90 (64%)
Family history of asthma	71 (48%)	82 (55%)	59 (45%)	77 (55%)
Family history of eczema	61 (41%)	55 (37%)	50 (39%)	50 (36%)

Table 3. Demographic data for the study cohort for each group and according to the type of statistical analysis carried out.

Type of surgery	Intention to treat (ITT)		As per protocol (APP)	
	IV (N=149)	Inhalation (N=149)	IV (N=130)	Inhalation (N=140)
Dental	27 (18%)	18 (12%)	26 (20%)	16 (11%)
ENT	29 (20%)	20 (13%)	24 (19%)	17 (12%)
General	40 (27%)	48 (32%)	36 (28%)	46 (33%)
Plastic	25 (17%)	37 (25%)	18 (14%)	36 (26%)
Other	28 (19%)	26 (17%)	26 (20%)	25 (18%)

Table 4. The types of surgery carried out and the number of participants recruited off each list.

	ITT analysis				
perioperative respiratory adverse events	**IV (n=149)**	**Inhalation (n=149)**	**RR**	**95% CI**	**p-value**
Any – unadjusted	39 (26%)	64 (43.0%)	1.64	1.18 to 2.27	0.003
Any – adjusted			1.68	1.21 to 2.33	0.002
I. Bronchospasm	0 (0%)	2 (1%)	-	-	-
II. Laryngospasm	3 (2%)	15 (10%)	5·00	1.48 to 16.91	0·01
Serious (I & II)	3 (2%)	16 (11%)	5.33	1.59 to 17.92	0·007
III. Coughing	17 (11%)	36 (24%)	2.12	1.25 to 3.60	0·006
IV. Desaturation	26 (17%)	38 (26%)	1.46	0.94 to 2.28	0·094
V. Airway obstruction	7 (5%)	25 (17%)	3.57	1.59 to 8.00	0·002
VI. Stridor (recovery)	2 (1%)	4 (3%)	2.00	0.37 to 10.75	0·419
Minor (III-VI)	37 (25%)	63 (42%)	1.70	1.22 to 2.38	0·002
	As Per Protocol analysis				
	(n=130)	**(n=140)**	**RR**	**95% CI**	**p-value**
Any (unadjusted)	34 (26%)	60 (43%)	1.64	1.16 to 2.32	0.005
Any – adjusted			1.67	1.18 to 2.36	0.004
I. Bronchospasm	0 (0%)	2 (1%)	-	-	-
II. Laryngospasm	1 (1%)	15 (11%)	13.93	1.87 to 104.00	0.010
Serious (I & II)	1 (1%)	16 (11%)	14.86	2.00 to 110.50	0.008
III. Coughing	14 (11%)	34 (24%)	2.26	1.27 to 4.01	0.006
IV. Desaturation	23 (18%)	37 (26%)	1.49	0.94 to 2.37	0.089
V. Airway obstruction	7 (5%)	24 (17%)	3.18	1.42 to 7.14	0.005
VI. Stridor (recovery)	2 (2%)	3 (2%)	1.39	0.24 to 8.20	0.714
Minor (III-VI)	33 (25%)	59 (42%)	1.66	1.17 to 2.36	0.005

Table 5. Perioperative respiratory adverse events observed over the perioperative period (from induction of anesthesia to discharge from PACU) and the associated relative risks (RR), 95% CI and p-values for each type of analysis carried out. Adjusted values are for age, sex, ASA and weight.

Respiratory adverse events at induction	Intention to treat analysis IV (n=149)	Inhalation (n=149)	RR	95% CI	p-value
Any - unadjusted	16 (11%)	47 (32%)	2.94	1.75 to 4.94	<0.001
Any –adjusted			3.06	1.81 to 5.16	<0.001
I. Bronchospasm	0 (0%)	2 (1%)	-	-	-
II. Laryngospasm	0 (0%)	7 (5%)	-	-	-
Serious (I & II)	0 (0%)	8 (5%)	-	-	-
III. Coughing	5 (3%)	23 (15%)	4.60	1.80 to 11.78	0·002
IV. Desaturation	13 (9%)	23 (15%)	1·77	0.93 to 3.36	0·081
V. Airway obstruction	1 (1%)	18 (12%)	18.00	2.43 to 133.11	0·005
Minor (III-V)	16 (11%)	45 (30%)	2.81	1.67 to 4.75	<0·001
	≥ 1 respiratory symptom present				
	n = 84	**n = 83**	**RR**	**95% CI**	**p-value**
Any* respiratory adverse events *at induction	8 (10%)	30 (36%)	3.80	1.85 to 7.79	<0·001
	No respiratory symptoms present				
	n = 65	**n = 66**	**RR**	**95% CI**	**p-value**
	8 (12%)	17 (26%)	2.09	0.97 to 4.51	0.059
	As Per Protocol analysis				
	IV (n=130)	**Inhalation (n=140)**	**RR**	**95% CI**	**p-value**
Any - unadjusted	14 (11%)	45 (32%)	2.98	1.72 to 5.17	<0.001
Any –adjusted			3.13	1.81 to 5.43	<0.001
I. Bronchospasm	0 (0%)	2 (1%)			-
II. Laryngospasm	0 (0%)	7 (5%)			-
Serious (I & II)	0 (0%)	8 (6%)			-
III. Coughing	5 (4%)	22 (16%)	4.09	1.59 to 10.47	0.003
IV. Desaturation	11 (9%)	23 (16%)	1.94	0.99 to 3.82	0.055
V. Airway obstruction	1 (1%)	17 (12%)	15.79	2.13 to 116.95	0.007
Minor (III-V)	14 (11%)	43 (31%)	2.85	1.64 to 4.96	<0.001
	≥ 1 respiratory symptom present				
	n = 72	**n = 78**	**RR**	**95% CI**	**p-value**
Any respiratory adverse events at induction	7 (10%)	29 (36%)	3·82	1.79 to 8.18	<0.001
	No respiratory symptoms present				

	n = 58	n = 62	RR	95% CI	p-value
	7 (12%)	16 (26%)	2.14	0.95 to 4.82	0.067

Table 6. Respiratory adverse events observed over the induction period and the associated relative risks (RR), 95% CI and p-values for each type of analysis carried out. Adjusted values are for age, sex, ASA and weight.