Original article

Perioperative adverse respiratory events in children

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Summary

Three quarters of all critical incidents and a third of all perioperative cardiac arrests in paediatric anaesthesia are caused by adverse respiratory events. We screened for risk factors from both the child and their family history, and assessed the usefulness of common markers of allergic sensitization of the airway as surrogates for airway inflammation and increased risk for adverse respiratory events. One hundred children aged up to 16 years with two or more risk factors undergoing elective surgery were included in the study. Eosinophil counts, IgE level, specific IgE for D. Pteronyssinus, cat epithelia and Gx2 (grass pollen) were measured for each child and adverse respiratory events (bronchospasm, laryngospasm, oxygen desaturation <95%, severe persistent coughing, airway obstruction and postoperative stridor) were recorded. Twenty-one patients had an adverse respiratory event but allergic markers were poor predictors. Binary logistic regression showed a lack of predictive value of the eosinophil range and adverse respiratory events (p=0.249). ROC curves for the presence of adverse respiratory events versus level of specific IgE antibody (to Gx2 (AUC 0.614), Cat Epithelia (0.564) and D.Pteronyssinus (0.520)) demonstrated poor predictive values. However, the presence of risk factors was strongly associated with adverse respiratory events (p<0.0001) and a ROC-curve analysis indicated a fair capacity to predict adverse respiratory events (AUC 0.788). There was a significant difference (p=0.001) between the presence of adverse respiratory events in patients with more than four (p= 0.006) compared with less than four (p=0.001) risk factors. We conclude that while risk factors taken from the child (or family) history proved good predictors of adverse respiratory events, immunological markers of allergic sensitization demonstrated low predictive values. We conclude that preoperative identification of children at high risk for an adverse respiratory event should rely on clinical, rather than immunological, assessment.

Introduction

Perioperative adverse respiratory events are one of the major causes of morbidity and mortality in children [1] and the preoperative identification of those children at high risk is challenging. We have previously identified a range of preoperative factors that were associated with an increased risk for adverse respiratory events [2]. Amongst these factors, clinical features that are surrogate indicators of inflammation of the airway, such as a personal or family history of atopy, asthma and respiratory symptoms, were found to be highly correlated with the occurrence of adverse respiratory events. However, a disadvantage of parentally reported history is the level of uncertainty in obtaining accurate information on the relevant risk factors [3, 4]. The identification of these risk factors may increase the accuracy for predicting adverse respiratory events and would enable the anaesthetist to tailor anaesthesia management specifically for the individual child.

Serum markers of allergic sensitization and active airway inflammation that may serve as direct, objective measures for reliable prediction of adverse respiratory events include total, and allergen-specific, IgE and peripheral blood eosinophil count. Since these markers correlate with the presence of bronchial hyper-responsiveness, even in asymptomatic children [5], their preoperative measurements may improve identification of children with airway susceptibility and hence at increased risk for adverse respiratory events.

The aim of our study was to assess whether immunological markers, including total and specific IgE and eosinophil count could be used to improve the prediction of adverse respiratory events in children presenting for elective surgery who are at particularly high risk due to the presence of two or more risk factors [2].

Methods

Following approval by the local Research Ethics Committees, written informed consent was obtained from each parent or guardian, as well as child assent where deemed appropriate. Children aged up to 16 years, of ASA physical status 1-3, with at least two risk factors and undergoing elective surgery, were considered eligible for inclusion in the study. Risk factors were defined as recent upper respiratory tract infection (≤2 weeks), wheezing more than 3 times during the previous 12 months or a previous history of asthma, previous or current eczema, a family history of eczema, asthma or hay fever in two or more relatives, or exposure to passive smoking. Exclusion criteria were known cardiac disease, airway or thoracic malformations or the requirement for sedative premedication. The child was brought to the operating room accompanied by a parent or guardian and induction of anaesthesia was performed with either inhalational sevoflurane in a mixture of oxygen and air or intravenously with 3-5 $mg.kg^{-1}$ propofol. Standard AAGBI monitoring (ECG, oxygen saturation, non-invasive blood pressure and capnography) was applied and anaesthesia maintained with the patient breathing sevoflurane in an oxygen:air mixture through a laryngeal mask airway. Intraoperative analgesia was determined by the individual anaesthetist. Venous blood samples were taken at the time of cannula insertion and the following tests performed; blood eosinophil count, total IgE level and specific IgE antibody values (to D. Pteronyssinus, cat epithelia and Gx2 [grass pollen]). Each value was compared with the age-dependent reference range and classified into one of two groups: normal or high. An adverse respiratory event was defined as one or more of the following; bronchospasm, laryngospasm, severe persistent cough, oxygen desaturation < 95%, airway obstruction or stridor. These were recorded by an independent assessor from the time of anaesthetic induction until discharge from the recovery area. There are no data available on the association between serum immunological markers and adverse respiratory events so we were unable to conduct a formal power calculation before starting the study. We therefore decided to aim for a sample size of 100 patients, based on our experience that the incidence of adverse respiratory events is 24%. Primary outcome measures were adverse respiratory events. Binary logistic regression was carried out using each marker of allergic sensitization as binary predictors of adverse respiratory events. General linear modelling was used to assess any interaction between the different predictors and extract any resulting regression equation. ROC curve analysis was used to compare the predictive capacity of each immunological marker with the presence of risk factors determined from

the history. Statistical analysis was performed using SPSS version 22 software (IBM, Somers, NY, USA) and a p value of <0.05 was considered statistically significant.

Results

One hundred and nineteen children were considered eligible for inclusion in the study and the results of 100 patients were analysed. Nineteen patients were excluded because the parent or guardian did not understand the study, there was parental or child refusal to take part in the study or because the child was a ward of state. Of the 100 children 72 were male and the median (IQR [range]) age was 8.3 (4.3-12.5 [0.3-16.9]) years and weight was 27.6 17.1-46.9 [6.2-107.2]) kg. The ASA physical status was 1 in 50%, 2 in 47% and 3 in 3%. The preoperative risk factors identified from the patient or family history are shown in Table 1. Twenty-one patients had at least one adverse respiratory event during the perioperative period and the occurrence of events increased with the number of risk factors (Table 2). The markers of allergic sensitisation were grouped into normal and high levels and are shown in Table 3. Most adverse respiratory events occurred at induction (where the incidence was 10%) and emergence (where the incidence was 10%) from anaesthesia as compared with the other phases of anaesthesia management (the incidence during maintenance was 4% and in the recovery area was 7%).

Binary logistic regression using each marker of allergic sensitization (Table 4) as an individual predictor of adverse respiratory events, showed that the total IgE (p=0.034) and specific IgE antibodies to Gx2 (p=0.027) were significant independent risk factors. Eosinophil levels and IgE antibodies to D.Pteronyssinus and cat epithelia did not correlate with adverse respiratory events. A general linear model with the five serum markers was applied in an attempt to extract any significant interaction and no statistically significant interactions were found.

ROC analysis was performed to assess the predictive ability of serum markers, compared with risk factors, as predictors for adverse respiratory events. Risk factors were divided into four categories; two, three, four and five or more risk factors. An area under the curve (AUC) of 0.774 is considered an accurate predictor for the occurrence of adverse respiratory events. The AUCs of Eosinophil, total IgE, D.Pteronyssinus, cat epithelia and Gx2 were 0.439,

0.634, 0.534, 0.545 and 0.619 respectively, indicating poor predictive capacity. Figure 1 illustrates the sensitivity of Gx2, total IgE and risk factors for identifying adverse respiratory events.

Discussion

We assessed whether serum markers that reflect allergic sensitization and systemic inflammation predict the occurrence of perioperative adverse respiratory events in children undergoing general anaesthesia. As we have shown previously, parentally reported risk factors provide a fair capacity to predict the occurrence of adverse respiratory events and this was in contrast to the poor value of immunological markers to predict adverse respiratory events. The predictive value of the serum markers of allergic sensitization was low, despite children with abnormal values displaying a tendency to more adverse respiratory events. Total IgE, a non-specific marker, with an odds ratio [95% CI] of 3.3 [1.1-9.8] and IgE antibodies to GX2, with an odds ratio [95% CI] of 3.2 [1.1-9.0], were the only parameters found to be associated with an increased incidence of adverse respiratory events. Although airway sensitivity is a strong predictor for adverse respiratory events [2, 6], the association of serum markers is thought to be associated with a higher risk for airway inflammation has not been assessed before. We have previously shown that eosinophilic cationic protein (in bronchoalveolar lavage fluid), released by activated eosinophils and tryptase and which reflects mast cell degranulation, correlated with increased airway pressures and a higher risk for perioperative bronchospasm in anaesthetised children [6]. In the present study, we assessed sensitization to house dust mites, cat fur and grass pollen, three common allergens with a high prevalence of sensitization in our community. House dust mite (D.Pteronyssinus) exposure is linked to increased cellular inflammation, including eosinophilia and an increased responsiveness or sensitivity to methacholine [7, 8] and plays an important role in the initiation of allergic airway inflammation [9]. In this study elevated IgE antibodies to D.Pteronyssinus did not correlate with the occurrence of adverse respiratory events. Grass pollen has also been associated with airway hyper-reactivity and inflammation [10, 11], and this is probably the reason for the increase in adverse respiratory events observed in children with high values of IgE antibodies to GX2 in our study.

Most children do not require preoperative blood samples to be taken before elective surgery [12, 13] and in many centres children and their families are not seen by the anaesthetic team before the day of surgery, so any preoperative blood tests that are performed should have a significant impact on the child's management in order to be justified. Using risk factors based on the child's, or family, history not only reduces healthcare costs but also eliminates patient discomfort due to blood sampling, as well as the chances of obtaining false positive or false negative results [14, 15].

One limitation of our study is that the sample size is relatively small because it was intended as a pilot to assess the utility of serum markers to predict adverse respiratory events. As a result of the small sample size the power to detect a correlation between total IgE levels or specific IgE antibodies to grass pollen and the presence of adverse respiratory events was 61.2% and 35.2%, respectively. Although it is possible that a larger sample size might find statistically significant associations between serum markers and adverse respiratory events, for serum markers to be useful in routine clinical practice a significant improvement in prediction of adverse respiratory events would be required in order to outweigh the additional cost and discomfort for the patient.

In conclusion, we found that a detailed history of risk factors taken from the child and their family was a good predictor for adverse respiratory events. By contrast, immunological markers of allergic sensitization did not predict adverse respiratory events. This study provides further evidence of the importance of a thorough preoperative clinical assessment to identify children at high risk for adverse respiratory events.

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Figure Legends

Figure 1. ROC curve analysis: Sensitivity of Gx2 (grass pollen), total IgE and risk factors for identifying adverse respiratory events.

● Risk factors ▲ Grass ⬣ pollen Total IgE

Table 1 Preoperative risk factors identified from the patient or their family.

Risk Factor Distribution (n=100)	
Risk factor	**Proportion**
Upper respiratory tract infection (within previous 2 weeks)	39
Current eczema	19
Pevious eczema	32
Wheezing in previous 12 months	33
Asthma in past (if no wheeze in previous 12 months)	45
Dry nocturnal cough	21
Bronchial hyper-reactivity on exercise	14
Family history of asthma	70
Family history of eczema	55
Family history of hay fever	54
Passive smoking	44

Table 2 Association between the number of risk factors in the history and occurrence of adverse respiratory events.

Number of risk factors	Number of patients	Incidence of adverse events	Proportion of adverse events
2	16	0	0.0
3	22	1	4.6
4	19	3	15.8
5 or more	43	17	39.5

Table 3 Children divided into those with normal concentrations of markers and those with high concentrations of markers.

N = 100 Adverse respiratory events = 21	Normal concentration of marker			High concentration of marker		
	Number of children	Number of adverse events	Proportion of adverse events	Number of children	Number of adverse events	Proportion of adverse events
Eosinophil	76	18	23.7	24	3	12.5
Total IgE	45	5	11.1	55	16	29.1
D. Pteronyssinus	72	14	19.4	28	7	25
Cat. Epithelia	88	17	19.3	12	4	33.3
Gx2	76	12	15.8	24	9	37.5

Table 4 Binary logistic regression for each marker of allergic sensitization.

Plasma marker	Nagelkerke's R^2	p value	odds ratio	95% Confidence Interval
Eosinophil	0.023	0.460	0.249	0.123 – 1.724
Total IgE	0.077	0.034	3.283	1.096 – 9.828
D.Pteronyssinus	0.006	0.541	1.381	0.490 – 3.890
Cat. Epithelia	0.018	0.271	2.088	0.562 – 7.753
Gx2 (grass pollen)	0.072	0.027	3.200	1.141 – 8.973