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Association between Intraoperative and Post-Anesthetic Care Unit Respiratory Events among 12,641 Children in Southern Thailand

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Authors' contributions:

This work was carried out in collaboration between all authors. Author MO designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author FAG participated in the study design, undertook the statistical analysis and revised the draft manuscript. Author VC participated in the study design and revised the draft manuscript. Author NP participated in the study design and author KN participated in the study design and coordinated the drafting of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The association between intraoperative respiratory events (IRE) and post-anesthetic care unit respiratory events (PARE) in children as well as the risk factors for PARE have not been described. The objectives of this study were to describe the association between IRE and PARE and to identify the risk factors of PARE in children at a tertiary care hospital in southern Thailand.
Methodology: A historical cohort study based on the surveillance anesthetic database and chart review of children who received surgery at Songklanagarind Hospital during January 2005 to December 2011 was conducted. Demographic, surgery and anesthesia-related data were

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collected. The association between IRE and PARE and other potential risk factors were analyzed using cross tabulation. Multivariate logistic regression was employed to identify independent predictors for PARE, indicated by adjusted odds ratios (aOR) and their 95% confidence intervals (CI).

Results: Overall, perioperative respiratory event (PRE) occurred in 531 out of 14153 children (315 IRE, 348 PARE). The association between PARE and IRE was strong, with adjusted odds ratios ranging from 3.1 (laryngospasm) to 18.5 (desaturation). Anesthesia-related risk factors for PARE were ASA classification 3 (aOR=3.1, 95%CI=1.9-5.0), jet ventilation (aOR=3.4, 95%CI=1.6-7.1), intubation with succinylcholine vs non-depolarizing muscle relaxant (aOR=1.9, 95%CI=1.4-2.5), use of intraoperative morphine vs fentanyl (aOR=2.4, 95%CI=1.7-3.3) and duration of anesthesia ≥ 3 hours (aOR=3.2, 95%CI=2.1-4.9).

Conclusion: The magnitude of association between IRE and PARE was high. Increased vigilance and close monitoring by anesthesia personnel in high risk children and high risk surgery may prevent IRE and therefore also PARE, so that overall PRE can be reduced. Preventable risk factors for PARE such as using succinylcholine and morphine can be managed under discretion of the anesthesiologist.

Keywords: Intraoperative period; post-anesthetic care unit; respiratory events; pediatric anesthesia; tertiary care hospital.

ABBREVIATIONS

ASA=American Society of Anesthesiologists; BMI=Body mass index; IRE=Intraoperative respiratory event; NDMR=Non-depolarizing muscle relaxant; PACU=Post-anesthetic care unit; PARE=Post-anesthetic care unit respiratory event; PICU=Pediatric intensive care unit; PRE=Perioperative respiratory event; ROC= Receiver operating characteristics; UAO=Upper airway obstruction.

1. INTRODUCTION

Perioperative respiratory event (PRE) such as laryngospasm, bronchospasm, and desaturation in pediatric anesthesia is serious. Severe PRE can cause cardiac arrest and death [1,2]. The incidence and risk factors for PRE were described in several studies [3-9]. Known risk factors for PRE are divided into children's risk factors (age less than 6 years, history of upper respiratory tract infection or hyperreactive airway, obesity), surgery risk factors (airway surgery, ear-nose-throat surgery) and anesthesia risk factors (American Society of Anesthesiologists (ASA) physical status 3-5, airway management, desflurane anesthesia) [3-9].

Most studies included under PRE both intraoperative and post-anesthestic care unit (PACU) periods [3-7]. Few studies have examined only intraoperative period or reported incidence and risk factors of intraoperative respiratory event (IRE) [8,9]. Only two studies presented separate incidences of IRE and PACU respiratory events (PARE) [5,7]. The relationship between intraoperative respiratory events (IRE) and post-anesthetic care unit respiratory events (PARE) in children has never been reported. An association between IRE and PARE would increase vigilance for patient safety in pediatric anesthesia. Moreover, isolated risk factors for PARE, which might be different from those for PRE, have not yet been investigated. Therefore, the objectives of this study were to describe the association between IRE and PARE and to identify the risk factors for PARE in children undergoing surgery with general anesthesia.

2. MATERIALS AND METHODS

After approval by the Ethics Committee, Prince of Songkla University (EC 552100813), a historical cohort study was conducted at Songklanagarind Hospital. The second part of the cohort study focusing on PARE was managed after the first part regarding IRE was published [9]. Written informed consent was waived during the study period.

2.1 Participants

The surveillance anesthetic database under quality assurance by nurse anesthetists was used to identify IRE and PARE of children aged < 15 years undergoing general anesthesia with or without other anesthetic procedures between the periods of January 2005 to December 2011. After IRE and PARE were identified, the

researcher rechecked the accuracy of the data by reviewing either paper-based or electronic anesthetic records which were available from 2005 to 2011. The details of anesthetic records are described elsewhere [9]. All anesthetic procedures were done by a certified anesthesiologist with at least one year's experience. Patients were excluded if they were classified as ASA physical status of 4 or 5, had preoperative arterial oxygen saturation at room air < 95%, were endotracheally intubated and/ or mechanically ventilated prior to surgery, or had congenital heart disease with cyanosis. These criteria were meant to exclude hypoxemic children or children who had severe respiratory problems prior to surgery.

2.2 Anesthesia Practice and Standard Operating Procedures

The routine anesthesia practices as well as the standard operating procedures for pediatric anesthesia in Songklanagarind Hospital were described in our previous study [9]. Basic parameters monitored during anesthesia included non-invasive blood pressure, electrocardiogram, oxygen saturation by pulse oximetry and end tidal carbon dioxide. The choices of anesthetic technique including airway devices and anesthetic agents were at the discretion of the attending anesthesiologists. Attending anesthesiologists take responsibility over anesthesia residents and nurse anesthetists for all anesthetized children from the start of anesthesia until discharge from the PACU. Children were sent either to the PACU or pediatric intensive care unit (PICU) depending on the discretion of the surgeon or anesthesiologist after the operation was finished. One hundred percent oxygen is not given routinely during transfer of children to the PACU except for children who develop persistent desaturation (arterial oxygen saturation < 95% with 100% oxygen for more than one minute) intraoperatively.

2.3 Outcome of Interest

IRE and PARE were the outcomes of interest, assessed by the attending anesthesiologist. These comprised laryngospasm, wheezing or bronchospasm, hypoxemia or desaturation (oxygen saturation < 95% for more than 10 seconds) [10], upper airway obstruction (UAO) [9] and re-intubation that occurred in either the intraoperative period or the PACU period or both.

2.4 Potential Confounding Variables

Variables collected and used as potential predictors for PARE included patient-related risk factors (age, sex, body mass index (BMI) [kg/m^2], recent upper respiratory tract infection, pulmonary disease such as asthma or pneumonia, non-cyanotic heart disease and anemia), surgery-related risk factors (type of surgery [elective/emergency], type of patient [inpatient/outpatient], site of operation, position) and anesthesia-related factors (ASA classification, choice of anesthesia, premedication agent, induction anesthetic agent, intubation agent, opiate, airway equipment, inhalation agent, gas mixed with oxygen, use of muscle relaxant, duration of anesthesia and occurrence of IRE) (Table 1). In 1.4% the height variable was missing, and these heights were substituted with the mean height of the same sex and age.

2.5 Statistical Analysis

Descriptive statistics in the PARE and no-PARE group were presented with number and percent. The occurrence of IRE and PARE were recorded. The association between IRE and PARE was analyzed using cross tabulation. Other potential risk factors for PRE related to patient, surgery and anesthesia profiles were included in the univariate analysis for PARE [3-9]. Multivariate logistic regression was employed, in which potential predictors being a *P-value* less than 0.2 in the univariate analysis were initially included, to adjust for confounding and to estimate adjusted odds ratios and their 95% confidence intervals. A backward elimination technique was used to determine the final model based on the lowest value of Akaike's information criterion. The predictive ability of the final logistic regression model was evaluated by calculating the area under the receiver operating characteristics (ROC) curve. The association of each factor with the outcome was considered statistically significant if the likelihood ratio test *P*-value was less than 0.05. Analysis was done using R-software version 14.1.

2.6 Sample Size Considerations

The overall probability of PARE was estimated from the database of 14,153 children to be 2.75%. With a sample of approximately 12,600 children and a prevalence of exposure to a risk factor between 5% and 50%, differences in the

risk of PARE as small as 2.5% to 1% (depending on prevalence) should be detectable as significant at an alpha of 0.05 and a power of 80%. We therefore believed that a sample size of 12,641 would be adequate.

3. RESULTS AND DISCUSSION

3.1 Results

Fig. 1 shows the flow diagram of the study. A total of 2,163 children were excluded owing to ASA physical status 4 or 5 and preoperative arterial oxygen saturation at room air < 95%. Overall, PRE occurred in 531 (3.75%) of the 14,153 study children (315 IRE). There were 1,512 children (10.68%) who bypassed the PACU to PICU owing to their being high risk children or to the expectation of serious postoperative conditions such as having IRE (65 children), hemodynamic instability or major bleeding operation. PARE occurred in 348 (2.75%) of 12,641 children admitted to PACU and 71 of these had already encountered IRE. Among the 348 children who developed PARE, the numbers (%) of desaturation, UAO, wheezing or bronchospasm, reintubation and laryngospasm were 242 (67%), 50 (14%), 44 (12%), 22 (6%) and 4 (1%), respectively. Eight children had more than 1 PARE. The most common cause of desaturation at PACU was hypoventilation (88%). Among children who developed PARE, having desaturation (59) and wheezing (22) intraoperatively were more common than having laryngospasm (4) and reintubation (4). Table 2 shows a comparison of the incidence of PARE among children who developed no, one and two IREs. The incidence of PARE was highest (34.6%) among children who developed only one IRE.

3.1.1 Univariate and multivariate analysis of PARE

Univariate analysis of factors associated with PARE included patient-related factors (6 variables), surgery-related factors (4 variables), anesthesia-related factors (11 variables) and type of IRE (Table 1). Nineteen out of 22 variables having a *P*-value less than 0.2 were initially included in the multivariate logistic regression model (Table 1). All 19 variables except the following eight; anemia, type of patients, patient position, choice of anesthesia, premedication, induction agent, use of neuromuscular blocking agent, and type of gas mixed with oxygen, were statistically significant and retained in the final multivariate logistic regression model. Table 3 shows multivariate logistic regression analysis for PARE. Independent risk factors for PARE were age ≤ 6 years, BMI ≥ 25 kg/m^2, non-cyanotic heart disease, pulmonary disease, airway or intrathoracic surgery, ASA classification 2 or 3 compared to 1, intubation with succinylcholine vs non-depolarizing muscle relaxant (NDMR), using intraoperative morphine vs fentanyl, duration of anesthesia ≥ 3 hours and having intraoperative desaturation, wheezing or laryngospasm. Fig. 2 shows the ROC curve of the final logistic regression model for potential risk factors for PARE. The area under the curve was 0.8 indicating good predictive ability of the model. The sensitivity and specificity of the final model were 73% and 70%, respectively.

Table 4 shows risk factors of different forms of PARE. Age was a significant predictor for UAO and reintubation in PACU; children aged ≤ 6 were more likely to have these PAREs. BMI was a significant predictor for desaturation, UAO and reintubation in PACU; being overweight increased the risk of these PAREs. Having congenital non-cyanotic heart disease was a significant predictor for desaturation and reintubation in PACU, whereas having pulmonary disease was significant predictor for only wheezing in PACU. Jet ventilation comparing to other airway devices was a significant predictor for UAO and reintubation in PACU. Use of succinylcholine for intubation comparing to other agents was a significant predictor for desaturation and UAO in PACU whereas use of intraoperative morphine comparing to fentanyl was a significant predictor for only PACU desaturation. Having intraoperative desaturation was a significant predictor for desaturation, UAO and wheezing in PACU and having intraoperative wheezing was a significant predictor for all PAREs especially wheezing in PACU. Having intraoperative laryngospasm was a significant predictor for only UAO in PACU whereas having intraoperative UAO in combination with reintubation was a significant predictor for only reintubation in PACU.

Table 1. Univariate analysis of patient-related, surgery and anesthesia-related factors for post-anesthetic care unit respiratory events (N = 12,641)

Variable	No-PARE (12293) Number (%)	PARE (348) Number (%)	*P-value*
Patient-related factors			
Age			< 0.001
> 6	4879 (39.7)	116 (33.3)	
1-6	5972 (48.6)	159 (45.7)	
< 1	1442 (11.7)	73 (21.0)	
Sex			0.26
Male	7304 (59.4)	212 (60.9)	
Female	4989 (40.6)	136 (39.1)	
Body mass index (kg/m^2)			< 0.001
5-14.9	5149 (41.9)	157 (45.1)	
15-24.9	6551 (53.3)	154 (44.3)	
25-60	593 (4.8)	37 (10.6)	
Anemia			< 0.001
No	8077 (65.7)	237 (68.1)	
Yes	4216 (34.3)	111 (31.9)	
Non-cyanotic heart disease			< 0.001
No	11655 (94.8)	302 (86.8)	
Yes	638 (5.2)	46 (13.2)	
Respiratory disease			< 0.001
None	10923 (88.8)	281 (80.7)	
Upper respiratory tract infection	685 (5.6)	25 (7.2)	
Pulmonary disease	685 (5.6)	42 (12.1)	
Surgery-related factors			
Type of surgery			0.27
Elective	9951 (80.9)	273 (78.4)	
Emergency	2342 (19.1)	75 (21.6)	
Type of patient			< 0.001
Inpatient	10961 (89.2)	339 (97.4)	
Outpatient	1332 (10.8)	9 (2.6)	
Patient position			0.001
Supine	11073 (90.1)	300 (86.2)	
Lateral	474 (3.9)	28 (8)	
Lithotomy	502 (4.1)	14 (4)	
Prone	244 (2)	6 (1.7)	
Site of operation			< 0.001
Superficial	6850 (55.7)	140 (40.2)	
Airway	1140 (9.3)	48 (13.8)	
Thoracic	155 (1.3)	27 (7.8)	
Abdomen	1137 (9.2)	47 (13.5)	
Spine & extremity	2620 (21.3)	70 (20.1)	
Remote*	391 (3.2)	16 (4.6)	
Anesthesia-related factors			
ASA classification			< 0.001
1	3524 (28.7)	37 (10.6)	
2	7712 (62.7)	233 (67)	
3	1057 (8.6)	78 (22.4)	
Choice of anesthesia			< 0.001
GA only	10905 (88.7)	297 (85.3)	
GA with regional anesthesia	999 (8.1)	46 (13.2)	
GA with peripheral nerve block	389 (3.2)	5 (1.4)	
Premedication agent			0.041
None	3362 (27.3)	100 (28.7)	
Chloral hydrate	3299 (26.8)	99 (28.4)	
Diazepam	2369 (19.3)	46 (13.2)	
Others	3263 (26.5)	103 (29.6)	
Induction agent			< 0.001
Propofol	2645 (21.5)	78 (22.4)	

Variable	No-PARE (12293) Number (%)	PARE (348) Number (%)	*P-value*
Thiopental	5930 (48.2)	205 (58.9)	
Sevoflurane	3379 (27.5)	53 (15.2)	
Others	339 (2.8)	12 (3.4)	
Intubation agent**			< 0.001
NDMR	5694 (46.3)	176 (50.6)	
Succinylcholine	1806 (14.7)	91 (26.1)	
Sevoflurane	374 (31.0)	14 (4.0)	
Inhalation agent***			0.223
Sevoflurane	7949 (64.7)	236 (67.8)	
Isoflurane	3274 (26.6)	91 (26.1)	
Halothane	199 (1.6)	2 (0.6)	
Desflurane	94 (0.8)	4 (1.1)	
Opiate			0.001
Fentanyl	9942 (80.9)	261 (75)	
Morphine	1334 (10.9)	61 (17.5)	
Others	803 (6.5)	22 (6.3)	
None	214 (1.7)	4 (1.1)	
Use of NMBA			< 0.001
No	5889 (47.9)	107 (30.7)	
Yes	6404 (52.1)	241 (69.3)	
Type of gas mixed with oxygen			< 0.001
Air with oxygen	3304 (26.9)	141 (40.5)	
Nitrous oxide with oxygen	8656 (70.4)	197 (56.6)	
100% oxygen	333 (2.7)	10 (2.9)	
Airway device			< 0.001
ETT with controlled ventilation	8919 (72.6)	299 (85.9)	
Jet ventilation with controlled ventilation	150 (1.2)	12 (3.4)	
Facemask with assisted ventilation	1625 (13.2)	11 (3.2)	
Laryngeal mask with assisted ventilation	1552 (12.6)	26 (7.5)	
Spontaneous breathing (oxygen facemask)	47 (0.4)	0 (0)	
Duration of anesthesia (hours)			< 0.001
<1	3198 (26)	53 (15.2)	
1-3	7753 (63.1)	213 (61.2)	
>3	1342 (10.9)	82 (23.6)	
Intraoperative respiratory events			< 0.001
None	12114 (98.5)	277 (79.6)	
Desaturation	49 (0.4)	41 (11.8)	
Wheezing	51 (0.4)	22 (6.3)	
Laryngospasm	69 (0.6)	4 (1.1)	
Upper airway obstruction & reintubation	10 (0.1)	4 (1.1)	

*P-value from Chi-square test, * remote sites include radiology services and cardiac catheterization, ** included only those who received endotracheal tube (N = 8155), *** included only those who were given an inhalation agent (N = 12182); ASA= American Society of Anesthesiologists; ETT= Endotracheal tube; GA=General Anesthesia; NDMR=Non-depolarizing muscle relaxant; NMBA=Neuromuscular blocking agent*

Table 2. Incidence of post-anesthetic care unit respiratory events among children who developed intraoperative respiratory events

Number of IRE	Total	Number of PARE	Incidence of PARE(%)
0	12,391	277	2.2%
1	153	53	34.6%
2	97	18	18.6%

3.2 Discussion

The incidence of PARE between 2005 and 2011 in Songklanagarind Hospital was 2.75%. Despite the low overall rate of PARE, desaturation was the most common and serious complication both in IRE and in PARE, especially in younger children. Having intraoperative desaturation, wheezing and laryngospasm increased the odds of developing PARE 18 times, 16 times and 3 times over not having IRE, respectively. According to Table 2, the overall incidence of PARE would have increased from 2.75% if high risk children (1512), especially those who

developed IRE, had passed PACU. Thus, a strategy to reduce the risk of PARE would be to send the high risk children who developed IRE or had prolonged surgery (> 3 hours) directly to PICU.

When interrogating the association between IRE and different forms of PARE, the independent risk factors of different forms of PARE were quite different. However, we could not identify the independent risk factors for laryngospasm in PACU because of the small incidence of this PARE (4 events).

Hypoventilation was the most common cause of desaturation in PACU in our study because we do not routinely perform oxygen supplementation during the transfer of children to PACU. Having desaturation and wheezing intraoperatively posed increased risks of PACU desaturation of 24-fold and 8-fold, respectively, compared to not

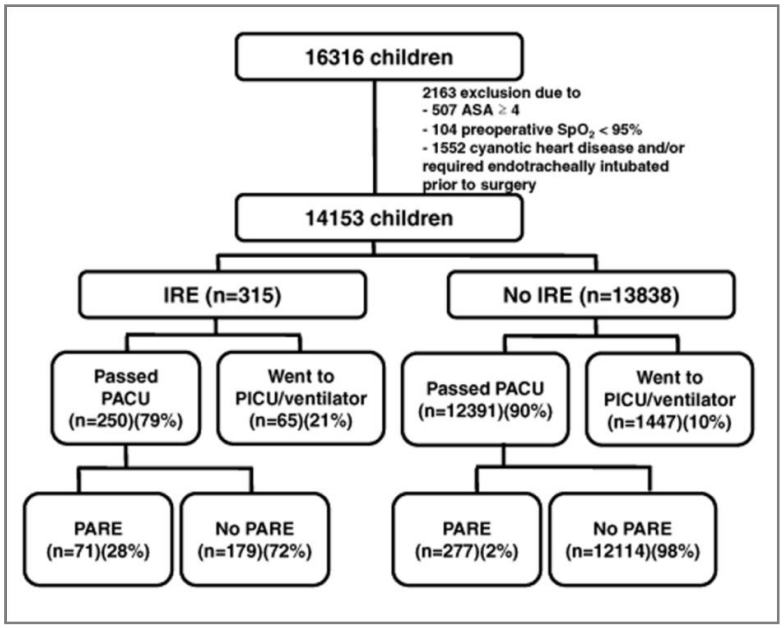

Fig. 1. Flow diagram of the study

IRE=Intraoperative respiratory event; PARE=Post-anesthetic care unit respiratory event

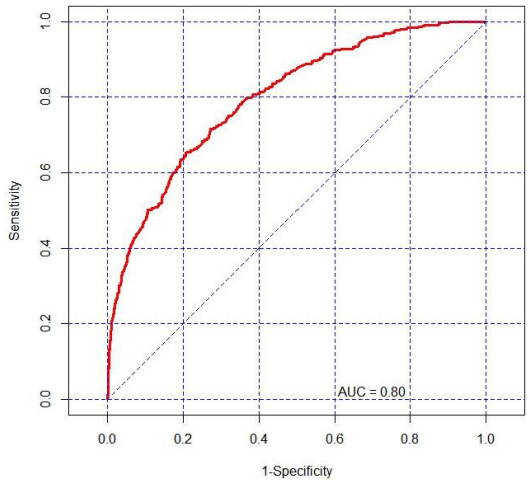

Fig. 2. Receiver operating characteristics (ROC) curve of the final logistic regression model predicting potential risk factors for post-anesthetic care unit respiratory events

AUC=Area under the curve

having IRE. Both obesity (BMI ≥ 25) and having congenital non-cyanotic heart disease were independent patient-related risk factors of PACU desaturation as the limitation of cardiopulmonary reserve in these children would tend to result in hypoventilation. Anesthesia-related risk factors of PACU desaturation were ASA physical status ≥ 2 (*P*<.001), use of succinylcholine for intubation compared to other agents (NDMR, sevoflurane) (*P*<.001) and use of intraoperative morphine compared to fentanyl (*P*<.001) after adjusting for having IRE, BMI and having congenital non-cyanotic heart disease. Obstructive sleep apnea, which can be a complication of obesity, can cause sensitivity to normal doses of morphine intraoperatively and lead to hypoventilation and desaturation in PACU [11,12]. Moreover, morphine administered intraoperatively has been reported to increase the risk of postoperative respiratory events in children with myotonic dystrophy [13].

Table 3. Multivariate logistic regression analysis of post-anesthetic care unit respiratory events (N = 12,641)

Variable	Adjusted odds ratio (95% CI)	*P-value*
Patient-related factors		
Age (Ref:>6)	1 [a]	< 0.001
1-6	1.45 (1.10, 1.96) [b]	
< 1	2.05 (1.42, 2.96) [c b]	
Body mass index (kg/m^2) (Ref: 5-14.9)	1 [a]	0.005
15-24.9	0.95 (0.74, 1.22) [a]	
25-60	1.94 (1.26, 2.97) [b]	
Non-cyanotic heart disease (Ref: No) Yes	1.66 (1.10, 2.49)	0.018
Respiratory disease (Ref: None)	1 [a]	0.036
Upper respiratory tract infection	1.24 (0.79, 1.95) [a b]	
Pulmonary disease	1.65 (1.13, 2.40) [b]	
Surgery-related factors		
Site of operation (Ref: Superficial)	1 [a]	< 0.001
Airway	1.74 (1.12, 2.72) [b c]	
Thoracic	4.03 (2.36, 6.85) [c]	
Abdomen	1.06 (0.73, 1.55) [a]	
Spine & extremity	1.07 (0.77, 1.48) [a]	
Remote*	1.33 (0.73, 2.41) [a b]	
Anesthesia-related factors		
ASA classification (Ref: 1)	1 [a]	< 0.001
2	1.96 (1.36, 2.84) [b]	
3	3.09 (1.92, 4.98) [c]	
Intubation agent (Ref : NDMR)	1 [a]	< 0.001
Succinylcholine	1.88 (1.40, 2.52) [b]	
Sevoflurane	1.31 (0.71, 2.43) [a b]	
Opiate (Ref: Fentanyl)	1 [a]	< 0.001
Morphine	2.40 (1.72, 3.34) [b]	
Others	1.46 (0.90, 2.37) [a b]	
None	0.52 (0.17, 1.61) [a]	
Airway device (Ref: ETT-C)	1 [a]	0.012
Jet ventilation with controlled ventilation	3.36 (1.60, 7.07) [b]	
Facemask with assisted ventilation	0.54 (0.27, 1.12) [a]	
Laryngeal mask with assisted ventilation	0.94 (0.56, 1.60) [a]	
Duration of anesthesia (hours) (Ref: <1)	1 [a]	0.001
1-3	1.29 (0.90, 1.85) [a]	
>3	3.16 (2.05, 4.87) [b]	
Intraoperative respiratory events (Ref: None)	1 [a]	< 0.001
Desaturation	18.47 (11.44, 29.84) [d]	
Wheezing	16.43 (9.46, 28.53) [c d]	
Laryngospasm	3.10 (1.07, 9.01) [b]	
Upper airway obstruction & reintubation	1.88 (0.24, 14.99) [a b c]	

*P-value from likelihood ratio test, * remote sites include radiology services and cardiac catheterization, Odds ratio (ORs) within variables that have no superscript ([a b c]) in common differ significantly at P < .05 (Wald's test). ASA=American Society of Anesthesiologists; CI=Confidence interval; ETT-C=Endotracheal tube with controlled ventilation; NDMR=Non-depolarizing muscle relaxant; Ref= Reference*

Table 4. Multivariate logistic regression analysis of different forms of post-anesthetic care unit respiratory events

Variable	Desaturation (242)	*P-value*	UAO (50)	*P-value*	Wheezing (44)	*P-value*	Re-intubation (22)	*P-value*
	aOR (95% CI)		aOR (95% CI)		aOR (95% CI)		aOR (95% CI)	
Age (Ref:>6)				0.004				0.004
1-6	_		3.3 (1.5, 7.1)		_		3.9 (0.95, 16.2)	
<1			2.9 (1.1, 7.7)				9.9 (2.2, 44.7)	
Body mass index (Ref:<15)		< 0.01		0.030				0.030
15-24.9	0.94 (0.71, 1.3)		0.73 (0.39, 1.4)		_		3.6 (1.3, 9.8)	
25-60	2.0 (1.3, 3.1)		2.9 (1.1, 7.4)				2.9 (0.25, 33.4)	
Non-cyanotic heart disease		0.017	_		_			0.012
(Ref: No) Yes	1.7 (1.1, 2.6)						4.9 (1.4, 16.8)	
Respiratory disease						0.042		
(Ref: No, URI)	_		_				_	
Pulmonary disease					2.8 (1.3, 6.0)			
Site of operation				0.015				
(Ref: Others)	_				_		_	
Airway			3.5 (1.3, 9.8)					
ASA classification (Ref: 1)		< 0.001						0.002
2	2.1 (1.4, 3.3)		_		_		10.1 (1.4, 74.6)	
3	1.9 (1.1, 3.3)						12.5 (1.6, 97.9)	
Intubation agent		< 0.001		0.038				
(Ref: NDMR, sevoflurane)					_		_	
Succinylcholine	1.4 (1.04, 2.0)		2.2 (1.1, 4.5)					
Opiate (Ref: Fentanyl)		< 0.001	_		_		_	
Morphine	2.4 (1.7, 3.4)							
Airway device (Ref: Others)	_			0.002	_			0.038
Jet ventilation			11.7 (3.7, 37.2)				11.4 (2.3, 55.5)	
Duration of anesthesia (hours)				0.032				
(Ref: <1)	_				_		_	
1-3			2.7 (1.1, 7.1)					
>3			4.3 (1.4, 14.0)					
IRE (Ref: None)		< 0.001		0.003		< 0.001		< 0.001
Desaturation	24.0 (15.3, 37.5)		4.9 (1.5, 15.8)		7.3 (2.1, 24.6)		_	
Wheezing	7.9 (4.1, 15.3)		7.3 (2.2, 25.1)		21.6 (9.1, 51.2)		10.3 (1.3, 83.3)	
Laryngospasm	2.6 (0.62, 10.8)		9.0 (1.9, 42.6)		_		_	
UAO & reintubation	2.9 (0.39, 22.2)		_		_		82.2 (18.7, 361)	

P-value from Likelihood ratio test, aOR; Adjusted odds ratio; ASA=American Society of Anesthesiologist; CI=Confidence interval; IRE=Intraoperative respiratory events; NDMR=Non-depolarizing muscle relaxant; Ref= Reference; UAO=Upper airway obstruction; URI=Upper respiratory tract infection

In our institute, the use of succinylcholine for endotracheal tube intubation is for high risk children who need rapid sequence induction or having difficult airway. The effects of succinylcholine on oxygenation in PACU might be from many possibilities [14]. First, histamine release from succinylcholine may cause bronchospasm, airway edema and mucus secretions. Second, the muscarinic effect of succinylcholine may also cause bronchoconstriction and increased secretions. Third, there was a small chance of increased duration of action of succinylcholine associated with deficiency of pseudocholinesterese. Finally, the reasons for using succinylcholine in high risk children may themselves increase the risk of PARE. For example, children who need rapid sequence induction for full stomach might develop hypoventilation and mild desaturation in PACU. Therefore, high risk children or children who develop IRE should be given oxygen supplementation during relocation to PACU.

Among upper airway problems in PACU, partial UAO (14%) from soft tissue obstruction and secretion obstruction was more common than complete UAO from laryngospasm (1%), a result supported by von Ungern-Sternberg et al.[7] The proportion of upper airway obstruction in PACU (15%) was somewhat higher than lower airway obstruction as evidenced by wheezing or bronchospasm (12%), a result also supported by von Ungern-Sternberg' study [7].

Having laryngospasm, wheezing and desaturation intraoperatively increased the odds of UAO in PACU 5- to 9-fold, compared to not having IRE. The other strong risk factors were related to airway surgery (almost 4-fold), jet ventilation (almost 12-fold) and age ≤ 6 years (3-fold) and obesity (3-fold). After adjusting for having IRE, patient-related risk and airway surgery, succinylcholine and duration of anesthesia of at least one hour were anesthesia-related risk factors for UAO. It is postulated that succinylcholine might relate to airway edema either from histamine release or from manipulation of difficult airway which might increase the risk of UAO in PACU. Our result is supported by the studies of Chen et al.,who reported that prolonged surgery or prolonged emergence from anesthesia was an independent risk factor for PRE in airway surgery [15].

The strong risk factors for wheezing or bronchospasm in PACU were having wheezing or bronchospasm (22-fold) and desaturation (7-fold) intraoperatively compared to not having IRE (*P* <.001). There were no surgery-related or anesthesia-related risk factors for PACU wheezing. The only patient-related risk factor was history of pulmonary disease; asthma or pneumonia (*P* =.042), a result supported by Orestes' study [16].

Having wheezing and UAO in combination with reintubation intraoperatively posed an increased risk of reintubation in PACU of 10- to 82-fold compared to not having IRE. The patient-related and surgery-related risk factors for PACU reintubation were quite similar to those for UAO, namely age ≤ 1 year, having congenital non-cyanotic heart and jet ventilation. There were no anesthesia-related risk factors regarding anesthetic agent used or duration of anesthesia except that ASA physical status ≥ 2 was associated with a higher risk of PACU reintubation - 10- to 12- fold compared to ASA physical status 1 (*P* =.002). A previous study of both adults and children in our hospital by Rujirojindakul et al. [17] identified two similar risk factors for PACU reintubation, namely age ≤ 1 years and ASA physical status. Despite the small number (40) of perioperative reintubations, the incidence of reintubation in our study was almost 3 times (28 per 10,000 anesthetics) that reported in a retrospective study by Ing et al. [18].

The risk factors for PARE in our study regarding patient-related, surgery-related and anesthesia-related variables (Table 3) were young age (≤ 6 years), high BMI (≥ 25 kg/m^2), having a history of pulmonary disease, airway surgery, ASA physical status 3 and duration of anesthesia of at least 3 hours, which were quite similar to those reported in other studies [3-6,15,17,19,20].

However, there was no previous study reporting the relationship between IRE and PARE in children or the distribution of different forms of IRE related to PARE. The magnitude of association between IRE and PARE can vary from 3- to 82-fold depending on the form of IRE. Thus, the strategy to prevent the occurrence of IRE in children is far more important than to prevent PARE occurrence. However, if IRE occurs, the anesthesiologist should try to minimize the risk of PARE by sending high risk children to a high care pediatric facility such as PICU as was done in our study.

3.2.1 Strengths and limitations

The strengths of this study are as follows. First, its use of multiple logistic regression analysis

takes into account the adjustment for potential confounding factors. Second, the final logistic model shows a high predictive ability with an area under the ROC curve of 0.8 as well as the fairly high sensitivity and specificity of the final model. Third, the large sample size and the low proportion of missing data affirm the power of the study.

The low incidence of PRE (3.75%) compared to other studies (1.5-15%) could be explained as follows [3,7]. Firstly, high risk children were sent directly to ICU and were not included in the analysis of PARE. Secondly, retrospective studies often encounter information bias [16], for example; under-recording of mild UAO and very brief periods of desaturation, which could underestimate the true incidence. The prospective study of both adults and children of Uakritdathikarn et al. [21] showed a 2- fold higher incidence of intraoperative desaturation in children in Songklanagarind Hospital in 2005 (4.7%, 14 of 297 children). Thirdly, different criteria for PRE have been used in different studies [3-7,21].However, the association between IRE and PARE and risk factors for PARE can be detectable despite the low incidence.

According to the strengths of the study, the internal validity was quite high in spite of the low incidence. Moreover, external validity to other child populations especially in university and other tertiary-level hospitals should be convincing due to high internal validity and the variety of pediatric cases.

4. CONCLUSION

The magnitude of association between IRE and PARE was very high (3- to 82-fold) depending on the form of IRE. The common risk factors for PARE related to patient, surgery and anesthesia in our study were quite similar to the risk factors for PRE identified in other studies except that we also found that use of succinylcholine for intubation and use of intraoperative morphine were anesthesia-related risk factors for PARE. Because of the strong association between IRE and PARE, increased vigilance and close monitoring by anesthesia personnel in high risk children and high risk surgery may prevent IRE and therefore also PARE, so that overall PRE can be reduced. Preventable risk factor of PARE such as using succinylcholine and morphine can be managed under the discretion of the anesthesiologist.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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