Is Emergence Time Related to Emergence Agitation in Pediatric Patients?

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Abstract

Background: Emergence agitation is one of the unpleasant symptoms after general anesthesia, especially in pediatric patients. This study was designed to evaluate the correlation between emergence time and emergence agitation. The predictors associated with emergence agitation and behavioral changes in children was also determined as specific outcomes.

Methods: This prospective cohort study was conducted in children undergoing anesthesia between 3 to 12 years. The preoperative unit nurse evaluated the child's baseline behaviors preoperatively. From pre to post anesthesia period, nurse anesthetist recorded anesthetic management data and clinical emergence time. Meanwhile, the investigator team recorded the Processed-EEG emergence time. At the Post-Anesthetic Care Unit (PACU), the well trained PACU nurse evaluated clinical emergence time and emergence symptoms. For the behavioral symptoms, the investigator team evaluated any changes by telephone interview at postoperative days 1, 3, and 7. Statistical significance was set at $p < 0.05$.

Results: Ninety-one pediatric patients were enrolled in the study. Preoperative baseline behaviors were not related to emergence agitation or behavioral changes. There were correlations between clinical emergence time and the incidences of emergence agitation and postoperative separation anxiety. There was no relationship found between processed-EEG emergence time and the incidence of emergence agitation. Multivariate logistic regression analysis showed the significant predictors (ASA physical status, clinical emergence time, and pain) to predict Emergence agitation. (AUC=0.92, sensitivity = 0.89, specificity 0.81). Separation anxiety was significantly higher at postoperative days 1,3 and 7 in the children with emergence agitation (p-values = 0.020, 0.020, and 0.017, respectively).

Conclusion: Clinical emergence time significantly related to emergence agitation and postoperative separation anxiety.

Trial registration: ClinicalTrials.gov Identifier: NCT03358069. Registered 18 January 2017 - Retrospectively registered, https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0007IOW&selectaction=Edit&uid=U0001FGB&ts=2&cx=-7ofx36

Background

Emergence agitation (EA) is one of the unpleasant symptoms after general anesthesia, especially in pediatric patients, for whom the incidence is much higher than in adults. A child emerging from anesthesia can be irritable, uncooperative, cry, moan, and exhibit combative behaviors. Sometimes the child may need to be restrained to prevent physical harm. The mechanism of EA is still unknown. However, previous studies have found that EA was related to anesthesia technique, age, race, and child's temperament. [6–9] Kain and colleagues[10] reported that the patient who had marked EA also tended to have postoperative maladaptive behaviors. These maladaptive behaviors such as insomnia, eating disturbance, aggressive behavior, and even developmental regression could persist until as late as one year after the anesthesia. [11,12]

Previous studies [9, 13] have reported that a fast anesthesia emergence time (time from ceasing anesthesia to spontaneous eye-opening) was associated with a high incidence of agitation. However, a study by Cohen IT et al. did not find such an association. [14]

This prospective cohort study was designed to examine whether clinical emergence time and/or processed EEG emergence time (The M-EntropyTM) affected the incidence of EA. The authors use processed electroencephalogram (The M-EntropyTM) to monitor processed-EEG emergence time (the period during which state entropy level over sixty to eighty. This study evaluated the clinical emergence time by the conventional method (the period from ceasing anesthesia to spontaneous movement or eye-opening).

The primary outcome of this study was the correlation between emergence time and emergence agitation. Two specific outcomes were the correlation between EA and postoperative behavioral changes (POBC), and to evaluate the predictors associated with EA and POBC in children.

Methods

After approval from the institution's Ethics Committee, a prospective cohort study (ClinicalTrials.gov Identifier: NCT03358069) was conducted in pediatric patients aged between 3–12 years, ASA physical status I-II and had a schedule for inpatient elective surgery at Songklanagarind hospital, Thailand. The exclusion criteria were including the patients who had a history of receiving antiepileptic medication, postoperative ICU admission plan, underwent emergency/ neurosurgery.

After gaining the consent from the patient's guardian, the well trained preoperative unit nurse, who had already passed the inter-rater reliability test, evaluated each child's baseline temperament and behaviors by using the Emotionality Activity Sociability and Impulsivity (EASI) survey [15] and the Post Hospitalization Behavior Questionnaire (PHBQ) [16]. The nurse determined the child's preoperative anxiety level by using the modified Yale Preoperative Anxiety Scale (mYPAS) [17]. The attending nurse anesthetist recorded the demographic data before starting anesthesia. There was no premedication allowed due to its effect after the patient emerged from the general anesthesia. According to the protocol, All participants received propofol 3 mg/kg for anesthesia induction. Anesthesia maintained using 2.0–3.0% sevoflurane with air/O2 and fentanyl as a pain killer medication. During the operation, if the patient's there was an increase of baseline blood pressure or heart rate more than 20%, 0.5 mcg/kg of fentanyl was given. The attending nurse anesthetist recorded all Anesthetic management techniques, which including airway removal methods, medications, and clinical emergence times. Processed-EEG was measured starting at the maintenance phase by the first investigator who was otherwise blinded to anesthetic management and records.

Upon the patient arrived at the Post-Anesthetic Care Unit (PACU), a well-trained, experience, PACU nurse who did not involve in any intraoperative procedure, evaluated the EA symptoms and clinical emergence time using the Pediatric Anesthesia Emergence Delirium (PAED) scale. [18] EA and severe EA diagnoses were defined as PAED scores > 10 and > 12, respectively. After discharge from PACU, the second investigator who blinded to any medical records did the telephone interview with the child's guardian to evaluate any behavioral changes (defined as a PHBQ sum score/ subcategories change > 10%) by using PHBQ at postoperative day (POD) 1, 3, and 7. Based on the incidence of the previous study in our institution, the incidence of EA among the children age between 1–15 years old was 34%. [(19)] By using the One-sample proportion equation, The sample size of this present study was calculated at the Power of 80% and p < 0.05. Logistic regression analysis and Receiver Operating Characteristic (ROC) curve analysis were performed to evaluate the predictors of EA and POBC.

Results

Ninety-one pediatric patients were enrolled in the study. The consort flow diagram of the study was shown in Fig. 1. Table 1 demonstrated patient characteristics. There was no correlation found between preoperative baseline behaviors and EA or POBC. Clinical emergence time had significant correlations with the incidences of EA and severe EA (p-values 0.018 and 0.026, respectively). There was no relationship found between processed-EEG emergence time and the incidence of EA (Table 2). There were statistically significant association between EA and factors, including age, ASA physical status, clinical emergence time and pain score (p-values = 0.030, 0.043, and < 0.001, respectively). Multivariate logistic regression analysis and the Receiver operating characteristics (ROC) curve showed the significant predictors (ASA physical status, clinical emergence time and pain) to predict EA (Table 3) (AUC = 0.92, sensitivity = 0.89, specificity 0.81) (Fig. 2). The average agitation times in children diagnosed with EA and severe EA were 10.6 (± 12.7) and 11.8 (± 14.1) minutes, respectively. Comparison to a previous study by Kane et al. (10), this study showed no correlation between the severity of EA and POBC. There were, however, associations between POBC and airway device removal technique, agitation time, MAC, and processed-EEG value when stop anesthesia (Table 3). The Univariate analysis of factors for post-operative behavioral changes were shown in Table 4. This study defined the predictors of POBC by using the Multivariate logistic regression analysis. The study results showed that the children who had severe EA also tended to have maladaptive eating behaviors at PODs 1, 3 and 7 (p-values = 0.024, 0.014 and 0.035, respectively, adj.ORs (95% CI) = 22.29 (1.16,427.72), 30.33 (1.45,634.98) and 33.58 (0.68,1656.73), respectively). Separation anxiety was significantly higher at PODs 1,3 and 7 in the children with EA (p-values = 0.020, 0.020, and 0.017, respectively). Regarding POBC subcategories, separation anxiety was correlated with processed-EEG emergence time (state entropy), clinical emergence time, and processed-EEG value when ceasing anesthesia (Table 5).

Discussion

EA is a group of unpleasant symptoms after emerging from GA, Especially in children. A child who has severe EA tends to go on to develop POBC. The incidence of EA ranges up to 80%20 depending on multiple factors. The mechanism of EA is still unknown. Some hypotheses point out that anesthetics agents mainly inhibitory neurological impulse in various brain regions.[21–23] Previous studies have found that multiple factors were associated with EA, including anesthesia technique (short-acting volatile anesthetic agents), age, race, post-operative pain, surgical type, preoperative anxiety, and child’s temperament.[3, 6–9, 19]

Another study reported that some factors such as behavior management, anesthetic techniques (TIVA, GARA), medications such as benzodiazepine, opioids, alpha 2-agonists, clonidine, gabapentin, melatonin, propofol and ketamine, prolonged emergence time and adequate pain control could reduce the incidence of EA.[24]

The correlation between clinical emergence time and the incidence of EA is still controversial. [25–27] This present study in which the average emergence time in the children who had EA and severe EA was significantly shorter than in the children who had no EA. While the clinical emergence time was correlated with EA, the association between processed-EEG emergence time and EA could not be found. The average processed-EEG emergence times in the groups diagnosed as EA and severe EA were 4.5 (± 4.7) minutes and 4.5 (± 5.1) minutes. (p-values = 0.231 and 0.304, respectively). However, the numbers of children diagnosed as EA and severe EA were quite low, which might have affected the statistical analysis. Other factors including age, ASA physical status and pain score were found to be significantly related to EA and severe EA, similar to previous studies.[7–9, 19] ROC curve analysis showed the significant predictors of EA: ASA physical status, clinical emergence time, and pain. Focusing on pain evaluation, pain measurement in small children was focus on the patient's behaviors. Regarding the evaluation of EA and pain, they share the same behavior parameters, such as restlessness, which could affect the outcomes.

The processed-EEG values, state entropy, had no correlation with EA, which could imply that the depth of anesthesia at the time of ceasing anesthesia did not affect EA. This result was compatible with a study by Frederick HJ et al. who found no link between depth of anesthesia and EA.[28] A possible explanation for this result in the current study involves a limitation of the processed-EEG itself that has some delay interpretation compared with the raw EEG.[29–32] So at the point that the investigator recorded the processed-EEG value, the real depth of anesthesia, as indicated by the raw EEG, may have been lighter, which could have affected the study results.

Previous studies reported the effect of parental presence on the day of surgery and during the induction period, which could reduce the child's preoperative anxiety level [33–35]. Regarding the hospital's policy, parents were allowed to stay with their children since arrival at the preoperative holding area until starting induction at the operating room. However, there was no significant correlation found between the child's preoperative anxiety level and EA in this study. This study result was compatible with the study by Arai YC et al., which reported that parental presence without premedication did not show any effect on emergence behaviors.[36]

Interestingly, our study results showed that the child who had shorter EA duration tended to have separation anxiety at POD 1,3 and 7. Multiple factors can precipitate separation anxiety, including environment changes or loss that result in separation. The surgery itself aggravates separation anxiety symptoms.[37] Kain et al. reported that the anxious child who has parental presence during anesthesia induction tended to have a lower anxiety scale compared with the calm patient.[38, 39] The EA management protocol may explain this study's results in our institution. Regarding the protocol, the child who had EA might be treated with IV fentanyl or propofol. Some of them responded well with medication while their parents were still not available at that period. So there may have a possibility that the acute stress from EA without parental presents can cause separation anxiety. Further investigation needed to prove the hypothesis.

A significant correlation was found between the airway device removal technique and maladaptive eating behaviors, whereas there was no correlation found between the airway device removal technique and severe EA. During awake airway removal, a patient can move their head and neck and cough, which can lead to postoperative sore throat (POST).[40] POST, in turn, can affect eating behaviors depending on its severity,[41, 42] while EA usually happens after the patient wakes up from the anesthesia. There were two limitations to this outcome assessment. Firstly, this present study included the type of surgeries that could precipitate POST, dysphagia, and intraoral cavity wound, which could affect the child is eating behaviors. Secondly, in the telephone interview process, the investigator did not explore more rooted in the group of children who had abnormal eating behavior to rule out POST dysphagia and pain.

As mentioned earlier, the main limitation of this study was sample size was too small to determine some factors which could affect the incidence of EA and POBC. Further investigations need to be done. In this present study, Total opioids consumptions were not collected. As we know that opioid can help to reduce EA, this might affect the study results.

Conclusion

Clinical emergence time significantly related to EA and post-operative separation anxiety, whereas process EEG emergence time needs further investigation to determine. Besides clinical emergence, time, age, ASA, and pain were found as the predictors of EA. Patients who developed EA tended to have separation anxiety after surgery.

Abbreviations

ASA
American Society of Anesthesiologists Classification
EA
Emergence agitation
EEG
Electroencephalogram
EASI
Emotionality Activity Sociability and Impulsivity
GARA
General anesthesia combined with regional anesthesia
mYPAS
Modified Yale Preoperative Anxiety Scale
PACU

Post-Anesthetic Care Unit
PAED
Pediatric Anesthesia Emergence Delirium scale
PHBQ
Post Hospitalization Behavior Questionnaire
POBC
Postoperative behavioral changes
POD
Postoperative day
POST
Postoperative sore throat
ROC
Receiver Operating Characteristic
TIVA
Total intravenous anesthesia

Declarations

Ethical approval: Human Research Ethic Committee, Faculty of medicine, Prince of Songkla University. REC: 55-248-08-1-3

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Author's contributions:

NP: Corresponding author, designs of work, data collection, analysis and interpretation, manuscript preparation

OK: Designs of work, data collection and manuscript preparation

SS: Data collection and manuscript preparation

NK: Data collection and manuscript preparation

RR: Designs of work and Data collection

JL: Designs of work and Data collection

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Tables

Table 1

Patient characteristics

Patient characteristics	
Age (year, mean ± SD)	6.27 ± 2.92
Sex (N,%) Male Female	63 (69.2) 28 (30.8)
Body weight (kg, mean ± SD)	21.24 ± 8.73
ASA (N,%) 1 2	34 (37.4) 57 (62.6)
Single parent (N%) Yes	14 (15.4)
Type of procedure (N,%) ENT surgery Urologic surgery Plastic surgery Eye surgery Intraabdominal surgery Orthopedic surgery Cardiac intervention Radiologic intervention GI scope	16 (17.6) 27 (29.7) 10 (11.0) 6 (6.6) 16 (17.6) 10 (11.0) 2 (2.2) 2 (2.2) 2 (2.2)
mYPAS sum score (points, mean ± SD)	34.62 ± 21.81
EASI sum score (points, mean ± SD)	58.06 ± 9.59
PHBQ sum score (points, mean ± SD)	45.86 ± 10.54
Airway removal technique (N,%) Deep Awake	36 (39.6) 55 (60.4)
Anesthetic time (minutes, mean ± SD)	94.88 + 62.74

Table 2

Univariate analysis of factors for EA and severe EA

	EA (PAED > 10)		**P-values**	**Severe EA (PAED > 12)**		**P-values**
	No (N = 73)	Yes (N = 18)		No (N = 77)	Yes (N = 14)	
Age (years, mean ± SD)	6.6 (3)	4.9 (2.1)	0.030*	6.5 (3.0)	4.8 (2.1)	0.038*
ASA (N, %) -I -II	31 (42.0) 42 (58.0)	3 (16.7) 15 (83.3)	0.043*	32(41.6) 45(58.4)	2 (14.3) 12(85.7)	0.053
Baseline Post Hospitalization behavioral questionnaire (PHBQ) (points, mean ± SD)	45.8 (11)	46.3 (8.6)	0.855	45.9 (10.9)	45.6 (8.8)	0.910
Child Temperament EASI score (points, mean ± SD)	58.3 (9.9)	57.1 (8.6)	0.640	58.4 (9.7)	56.4 (9.3	0.490
Modified Yale Preoperative Anxiety Scale (points, mean ± SD)	35.1 (22.7)	32.8 (18.1)	0.692	35.7 (22.6)	28.7 (16.3)	0.273
Airway removal technique -Deep -Awake	49 (67.1) 24 (22.9)	9 (50.0) 9 (50.0)	0.069	52(67.6) 25(32.4)	6(42.8) 8(57.1)	0.244
Processed-EEG emergence time (State entropy) (minutes, mean ± SD)	7.2 (9.2)	4.5 (4.7)	0.231	7.1 (9)	4.5 (5.3)	0.304
Level of state entropy at the time of Anesthesia stopped (mean ± SD)	57.5 (22.4)	63 (24.8)	0.365	57.5 (22.4)	64.9 (25.6)	0.268
Clinical Emergence time (minutes, mean ± SD)	25.6 (15.1)	16.7 (7.5)	0.018*	25.2 (14.9)	16 (7.1)	0.026*
Pain (score, mean ± SD) -1-3 -4-6 > 7	51 (69.9) 6 (8.2) 16 (21.9)	1 (5.6) 3 (16.7) 14 (77.8)	< 0.001*	52 (67.5) 7 (9.1) 18 (23.4)	0 (0) 2 (14.3) 12 (85.7)	< 0.001*
* Statistically significance						

Table 3

Multivariate logistic regression analysis of EA and severe EA

Factors	EA		Severe EA	
	Adj. OR (95% CI)	p-Value	Adj. OR (95% CI)	p-Value
Age	0.779 (0.52,1.165)	0.193	0.673 (0.425,1.067)	0.061
ASA	19.187 (1.166,315.612)	0.015*	15.74 (1,247.749)	0.020*
Clinical emergence time	0.877 (0.776,0.991)	0.014*	0.931 (0.836,1.036)	0.167
Airway removal technique (Deep Vs. Awake)	1.31 (0.026,66.788)	0.893	8.775 (0.202,381.687)	0.251
Processed-EEG emergence time (State entropy)	0.943 (0.831,1.069)	0.338	0.952 (0.831,1.092)	0.473
Pain	2.384 (1.419,4.007)	< 0.001*	2.193 (1.34,3.589)	< 0.001*
* Statistically significance				

Table 4
Univariate analysis of factors for post-operative behavioral changes

Factors	Behavioral changes (PHBQ Sum score)								
	Day 1			Day 3			Day 7		
	=/<10%	>10%	p-Value	=/<10%	>10%	p-Value	=/<10%	>10%	p-Value
Airway device removal Technique (N, %) Awake Deep	15 (26.8) 41 (73.2)	21 (60) 14 (40.0)	0.003*	16 (28.1) 41 (71.9)	20 (58.8) 14 (41.2)	0.007*	17 (29.3) 41 (70.7)	19 (57.6) 14 (42.4)	0.015*
MAC (Mean ± SD)	0.9 (0.4)	0.6 (0.5)	0.004*	0.9 (0.5)	0.6 (0.5)	0.008*	0.9 (0.5)	0.6 (0.5)	0.031*
Clinical emergence time (Mean ± SD)	24.5 (13.8)	22.7 (15.2)	0.556	24.8 (13.8)	22.2 (15.2)	0.411	24.7 (13.7)	22.2 (15.4)	0.433
Level of State entropy at the time of Anesthesia stopped	52.9 (21.9)	67.8 (21.7)	0.002*	53.5 (22.1)	67.2 (21.8)	0.005*	53.9 (22.2)	66.8 (22.0)	0.009*
Process EEG emergence time (Minutes, Mean ± SD) State Entropy	5.9 (8.3)	8 (9)	0.249	6.4 (9.1)	7.2 (7.7)	0.673	6.5 (9)	6.9 (7.9)	0.83
EA Yes No	49 (87.5) 7 (12.5)	24 (68.6) 11 (31.4)	0.053	7 (12.3) 50 (87.7)	11 (32.4) 23 (67.6)	0.04*	8 (13.8) 50 (86.2)	10 (30.3) 23 (69.7)	0.104
Severe EA Yes No	5 (8.9) 51 (91.1)	9 (25.7) 26 (74.3)	0.063	5 (8.8) 52 (91.2)	9 (26.5) 25 (73.5)	0.05	6 (10.3) 52 (89.7)	8 (24.2) 25 (75.8)	0.143

Factors	Behavioral changes (PHBQ Sum score)								
	Day 1			Day 3			Day 7		
	=/<10%	> 10%	p-Value	=/<10%	> 10%	p-Value	=/<10%	> 10%	p-Value
Pain score (Minutes, Mean ± SD)	5.9 (2.7)	7.1 (3.4)	0.059	6 (2.7)	7 (3.4)	0.119	6 (2.7)	7 (3.4)	0.128
* Statistically significance									

Table 5
Multivariate logistic regression analysis of post-operative separation anxiety

Factors	Behavioral changes (Separation anxiety score change > 10%)					
	Day 1		Day 3		Day 7	
	Adj. OR (95% CI)	p-Value	Adj. OR (95% CI)	p-Value	Adj. OR (95% CI)	p-Value
Baseline separation anxiety	1.1 (0.901,1.343)	0.349	1.1 (0.901,1.343)	0.349	1.141 (0.934,1.393)	0.193
mYPAS score	1.024 (0.996,1.053)	0.093	1.024 (0.996,1.053)	0.093	1.021 (0.993,1.05)	0.143
Clinical emergence time	1.047 (0.999,1.098)	0.047*	1.047 (0.999,1.098)	0.047*	1.047 (1,1.098)	0.043*
Processed EEG-emergence time State Entropy	1.047 (0.999,1.098)	0.047*	1.077 (0.995,1.165)	0.048*	1.078 (0.996,1.166)	0.044*
Level of state entropy at the time anesthesia stopped	1.28 (1.099,1.491)	< 0.001*	1.28 (1.099,1.491)	< 0.001*	1.266 (1.087,1.473)	< 0.001*
EA diagnosis	27.293 (1.378,540.665)	0.020*	27.293 (1.378,540.665)	0.020*	30.634 (1.497,626.694)	0.017*
Severe EA diagnosis	12.449 (0.769,201.648)	0.076	12.449 (0.769,201.648)	0.076	11.648 (0.724,187.293)	0.083
Agitation time	0.693 (0.506,0.949)	< 0.001*	0.693 (0.506,0.949)	< 0.001*	0.691 (0.502,0.951)	< 0.001*

* Statistically significance

Figures

Figure 1: Flow diagram of the study

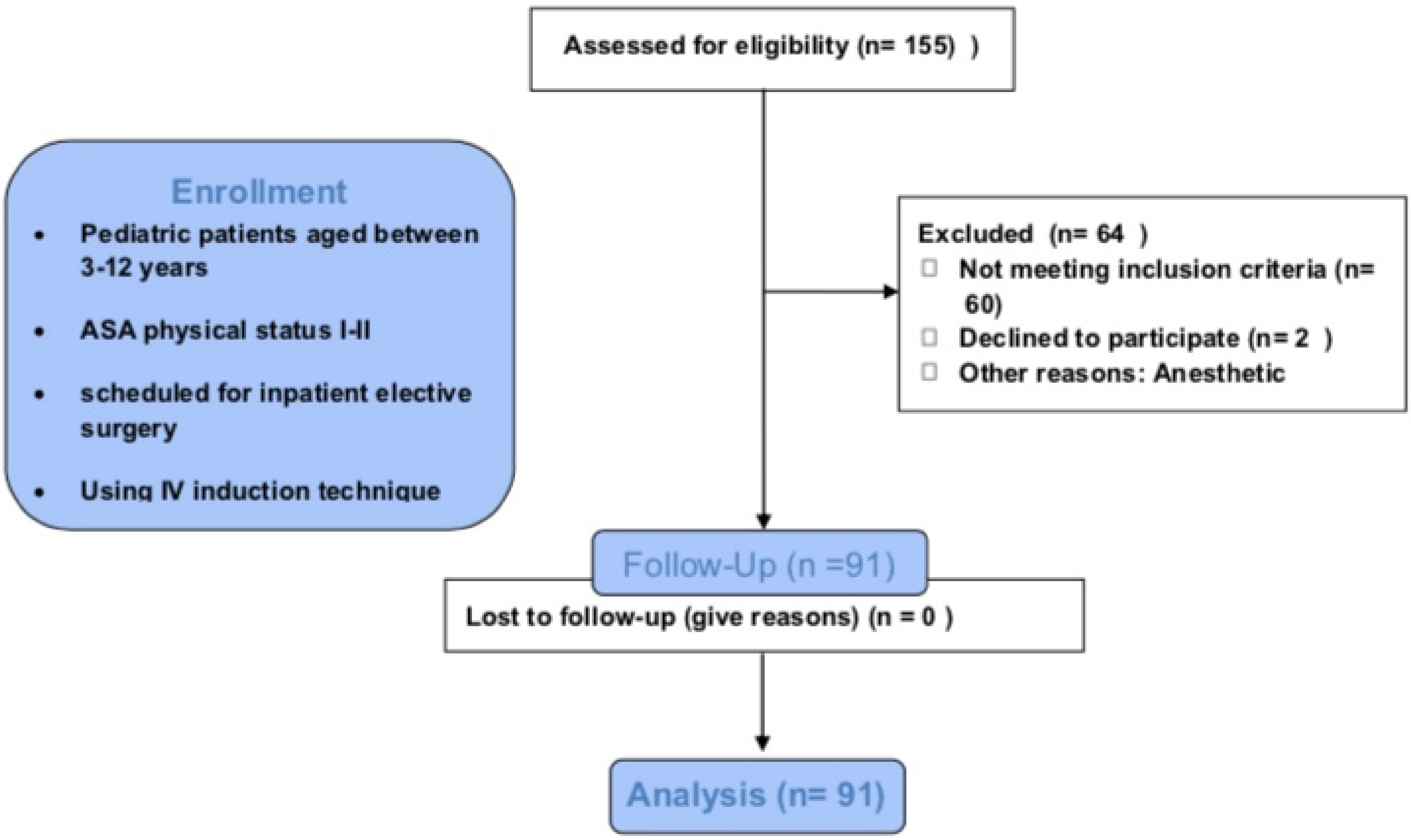

Figure 1

Flow diagram of the study

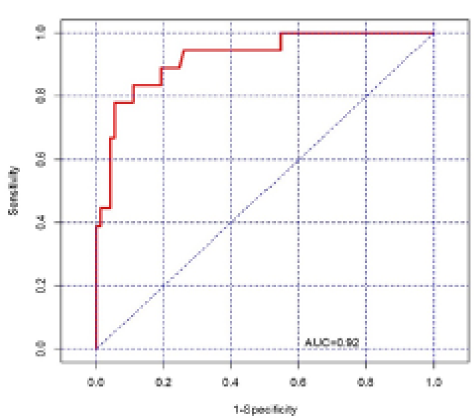

Figure 2

ROC curve for predicting EA

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklistofthestudy.doc