Pediatric Emergence Delirium is Linked to Increased Early Postoperative Negative Behavior within Two Weeks After Adenotomy

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Abstract

Background: The aim of this prospective multicenter observational study was to measure the incidence of postoperative pediatric emergence delirium (ED) and to investigate the occurrence of early postoperative negative behavior (ePONB) within two weeks after outpatient adenotomy in preschool children.

Methods: The study comprised n=222 patients between 1 and 7 years of age. Premedication was performed orally with Midazolam (0.3-0.5mg/kg). All children received a multimodal anesthesia based on total intravenous anesthesia with Propofol and Remifentanyl in combination with preemptive Dipidolor [Piritramid] (0.1mg/kg), Ibuprofen (10mg/kg), Dexamethasone (0.15mg/kg) and Ketanest S (0.1mg/kg). Applying intravenous Clonidine (2µg/kg) intraoperatively was left to the discretion of the anesthesiologist. We evaluated ED and pain using the PAED-scale and the FLACC-score at different predefined time points during the recovery period. ED was defined as a PAED score ≥ 9 for the first 3 criteria. Additionally, we defined ePONB to be present when at least 5 of 27 criteria of the questionnaire were positive.

Results: The incidence of postoperative delirium following our multimodal anesthetic approach was 25%. The postoperative incidence of ePONB was significantly higher among patients with ED (24% vs. 11%, p=0.04).

Conclusion: Despite the multimodal pharmacological approach, the incidence of ED after adenotomy remains high. ED not only plays a role immediately after surgery but is also linked to ePONB within two weeks after outpatient adenotomy. Parents should be informed that ePONB may occur in 1 out of 4 patients if ED was present postoperatively.

Keywords: Emergence delirium (ED); Early Postoperative Negative Behavior (ePONB); Pediatric; Multi-Modal Anesthesia; Adenotomy

Introduction

Postoperative emergence delirium (ED) following anesthesia remains an unsolved problem [1,2]. Several risk factors have been identified for example pain [3] surgical procedures such as ear, nose, and throat surgery (ENT) [4,5] and age [5,6]. In combination with certain anesthetic concepts, the incidence of ED can reach up to 80% [5,7]. Nevertheless, several clinical studies have shown that opioids [8,9] total intravenous anesthesia (TIVA) [10], Ketamine [9], and Dexamethason [11] can reduce the risk of ED. Risk reduction (RR) for Sevofluran-anesthesia was measured as 37% for opioids (in particular fentanyl), 35% for Propofol, and 30% for Ketamine. However, to the best of our knowledge, no study has yet investigated the incidence of ED following a multimodal anesthetic concept combining Propofol, Ketamine, Dexamethason, and opioids after outpatient adenotomy for 1 to 7 year old children. We therefore aimed to prospectively perform a multicenter observational study in children investigating the incidence of ED following a multimodal anesthetic regime in elective outpatient adenotomy. Several scales and scores have been published previously to measure ED objectively. The PAED-Score, being the “gold standard” [12] in the past, has been recently adjusted by Locatelli et al. [13]. He modified the scale by focusing only on the first three criteria thus increasing the specificity of this scale. Locatelli disregarded criteria 4 and 5 for defining ED as they – more or less – describe agitation. In our present study we therefore defined ED as proposed by Locatelli.

As ED is an acute disorder that occurs immediately after recovery from anesthesia, it is unknown whether long term sequelasmayalsooccurpostoperatively.Kainetal.describedthe incidence of ePONB (early postoperative negative behavior) after outpatient surgical interventions being as high as 50% [14]. Risk factors for ePONB were identified as increased anxiety of the child in the preoperative holding area [14-16]. Further risk factors linked to ePONB were identified such as child's age, number of siblings, and baseline temperament [14]. Summarized, the aim of this study was to investigate the incidence of postoperative emergence delirium and early postoperative negative behavior in patients following a multimodal anesthetic regime. We therefore performed prospectively a multicenter observational study in children undergoing elective outpatient adenotomy.

Methods

Following Ethics Committee approval (University Clinic Bonn, Germany) and parental written informed consent, we

consecutively enrolled 222 (166 patients in Bonn, 56 patients in Moenchengladbach) children between 1 and 7 years of age scheduled for elective outpatient adenotomy with or without myringotomy. Exclusion criteria were ASA classification ≥ 3 , critical illness with hemodynamic instability, active bleeding or mental retardation. Premedication was performed orally with Midazolam (0.3-0.5mg/kg) 30 to 60 min prior to induction of anesthesia. Anesthesia was preferably induced intravenously with Propofol (2-4 mg/kg) or alternatively via face mask with 4 to 8% Sevoflurane and 100% oxygen. Thereafter the anesthesia regime was switched to a TIVA (total intravenous anesthesia) and the airway was secured by a laryngeal mask. Standard monitoring included ECG, EtCO₂, pulse oximetry and non-invasive blood pressure. After surgery was completed and spontaneous breathing restored, the laryngeal mask was removed and patients were subsequently transferred to the PACU to reunite with their parents. All children received a multimodal anesthesia based on TIVA (Propofol and Remifentanyl), Piritramid (0,1 mg/kg), Ibuprofen (10 mg/kg), Dexamethason (0,15 mg/kg) and Ketanest S (0,1 mg/kg). Applying intravenous Clonidin (2µg/kg) intraoperatively was left to the discretion of the anesthesiologist. After recovery from anesthesia the occurrence of ED (postoperative emergence delirium) was monitored by applying the PAED-Score (Pediatric Anesthesia Emergence Delirium-Score) (Table 1).

ED was defined according to Locatelli, et al. [13] as a so called ED I score of ≥ 9 (0 to 12 possible points) for the first 3 criteria of the PAED-Score (eye contact, purposeful movement, aware of surrounding). We additionally evaluated pain in the PACU applying the FLACC-Score (Table 2) to differentiate between pain related agitation and postoperative delirium. Pain was defined as a FLACC score of ≥ 4 . Score guided assessment started right after awakening (Time 1) and was reevaluated after 20 minutes (Time 2) and prior to discharge from the PACU (Time 3). In addition, reevaluation was performed in case of obvious strange behavior, reawakening or after an intervention by the anesthesiologist following a previously diagnosed ED. 14 days postoperatively, patients' parents were interviewed (via phonecall) using a questionnaire for possible postoperative negative behavior (ePONB) (Table 3) that was handed out towards the parents before discharged home from the ambulatory. We defined ePONB to be present when at least ≥ 5 of 27 questions of this questionnaire were answered positively. The questionnaire was published by Buehrer et al. [17] and is a German translation of the PHBQ (Post-Hospitalization Behavioral Questionnaire) questionnaire from Vernon, et al. [18] published in 1966.

	Criteria	The Child...	Not At All	Just A Little	Quite A Bit	Very Much	Extremely
Delire criteria(ED I score)	1	keeps eye contact	4	3	2	1	0
	2	... shows purposefull movements	4	3	2	1	0
	3	.. Is aware of surrounding	4	3	2	1	0
Agitation Criteria (ED II) Score	4	... is restless	0	1	2	3	4
	5	...is inconsolable	0	1	2	3	4

Table 1: PAED (pediatric anesthesia emergence delirium) scale based on Delir-criteria (EDI) and Agitation-criteria (ED II) according to Locatelli et.al [13].

Observation	Assessment	Points
Cry	No cry (awake or asleep)	0
	Moans or whimpers, occasional complaint	1
	Crying steadily, screams or sobs, frequent complaints	2
Face	No particular expression/Smiling	0
	Occasional grimace or frown, withdrawn, uninterested	1
	Frequent to constant quivering chin, clenched jaw	2
Consolability	Content, relaxed	0
	Reassured by occaisional touching, hugging or being talked to, distractible	1
	Difficult to console or comfort	2
Legs	Normal position or relaxed	0
	Uneasy, restless, tense	1
	Kicking or legs drawn up	2
Activity	Lying quietly, normal position, moves easily	0
	Squirming, shifting, back and forth, tense	1
	Arched, rigid or jerking	2
Number of points		

Table 2: FLACC-Scale.

Number	Questions	Answers		
		less then before	same as before	more than before
1	Does your child make a fuss about going to bed at night?			
2	Does your child make a fuss about eating?			
3	Does your child spend time just sitting or lying and doing nothing?			
4	Does your child need a pacifer?			
5	Does your child seem to be afraid of leaving the house with you?			
6	Is your child uninterested in what goes on around him (or her)?			
7	Does your child wet the bed at night?			
8	Does your child bite his (or her) finger nails?			

9	Does your child get upset when you leave him (or her) alone for a few minutes?		
10	Does your child need a lot of help doing things?		
11	Is it difficult to get your child interested in doing things (like playing games with toys)?		
12	Does your child seem to be avoid or be afraid of new things?		
13	Does your child have difficulty making up his (or her) mind?		
14	Does your child have temper tantrums?		
15	Is it difficult to get your child to talk to you?		
16	Does your child seem to get upset when someone mentions doctors or hospitals?		
17	Does your child follow you everywhere around the house?		
18	Does your child spend time trying to get or hold your attention?		
19	Is your child afraid of the dark?		
20	Does your child have bad dreams at night or wake up and cry?		
21	Does your child have irregular bowel movements?		
22	Does your child have trouble getting to sleep at night?		
23	Does your child seem to be shy around strangers?		
24	Does your child have a poor appetite?		
25	Does your child tend to disobey you?		
26	Does your child break toys or other objects?		
27	Does your child suck his (or her) fingers or thumbs?		

Table 3: German version of the Post-Hospitalization Behavioral Questionnaire (PHBQ) by Buehrer et al. [17].

Statistics

Statistical analysis was performed using Microsoft Excel 2016. Further analysis was performed using Gnu Regression (gretl), Econometrics and Time-series Library 2016d (Allin Cottrell and Riccardo Lucchetti). Statistical significance was evaluated with Fisher exact Test. $P < 0.05$ was considered statistically significant.

Results

Written informed consent was given by 234 care-givers. Of these 234 patients 12 had to be discarded from further analysis due to the following reasons: 8 patients only received a myringotomy and 4 patients additionally received a tonsillectomy, resulting in 222 children being included in the study and completing final statistical analysis. Screening for ePONB two weeks after surgery was successful in 178 patients (80.2%). Due to a false phone number ($n=9$), unavailability despite several phone call attempts ($n=23$), and language barrier ($n=12$) 44 patients in total (19.8%) could not be interviewed two weeks after surgery. Demographic data between the two sites (Bonn and Moenchengladbach) were comparable [data not shown]. The incidence of ED in this observational study was 25%. The occurrence of ePONB

within the observed period of time (two weeks) was 14% ($n=25$ of 178 patients). ED was positively correlated with the occurrence of ePONB with an incidence of 24% in patients developing ED versus an incidence of only 11% for patients without ED, $p=0.04$, (Table 2). An increase of postoperative sleep duration of 15 min resulted in a reduction of ED of approximately 50%, $p=0.0002$ (Figure 1). Furthermore, age correlated with the incidence of ED (Figure 2). Older children had a lower risk for ED than younger children. Unexpectedly, the incidence of ED was significantly higher in male patients compared to female patients (29% vs. 15%, $p=0.02$). However, boys were significantly younger at the time point of surgery (3 ± 1.2 years) compared to girls (4 ± 1.6 years) ($p < 0.001$) (Table 3). Further analysis of ePONB revealed that postoperative negative behavioral changes mostly arose in the categories "sleep disturbance" and "separation anxiety" (Figure 5). When investigating the 27 items of the PHBQ questionnaire in all patients tested positive for ePONB we could reveal certain questions to be of a higher relevance than others. 84% of patients with ePONB answered positively on either of the two questions: "did you detect a higher incidence of nightmares in your child" or "did you detect more sleeping disturbances". 76% of positively tested patients answered that "their child became anxious when it was left alone for a few minutes".

Figure 1: ED according to sleep duration at PACU.

Figure 2: Prevalence of ED according to the patient's age.

Figure 3: Arithmetic average of questions answered with “more than before” within particular categories; Category 1 = separation anxiety; Category 2 = apathy; Category 3 = sleep disturbance; Category 4 = general anxiety and regression; Category 5 = withdrawal; Category 6 = eating disturbance

	ePONB	no ePONB	total
ED	10	32	42
no ED	15	121	136
total	25	153	178
Fisher's exact test: p-Value: 0,044867			

Table 4: Correlation of ED (emergence delirium defined as ED I ≥ 9) and ePONB (early postoperative negative behavior defined as ≥ 5 of 27 criteria of the questionnaire being positive).

	Male	Female	P-Value
Age [years]	3 $\pm$ 1.21	4 $\pm$ 1.62	<0.001
ASA (I:II)	96:21	74:11	0.436
Anesthesia Duration [min]	37 $\pm$ 14	35 $\pm$ 14	0.36
Sleep Duration [min]	50 $\pm$ 32	47 $\pm$ 28	0.43
ED I ≥ 9 (Y:N) [%]	29:71	15:18	0.024
ED I (Time 1)	4 $\pm$ 4.27	2 $\pm$ 3.70	0.04
ED I (Time 2)	2 $\pm$ 3.70	1 $\pm$ 2.86	0.2
ED I (Time 3)	1 $\pm$ 2.20	0 $\pm$ 1.06	0.27
FLACC (Time 1)	2 $\pm$ 2.60	1 $\pm$ 2.36	0.5
FLACC (Time 2)	1 $\pm$ 2.53	1 $\pm$ 2.07	0.12
FLACC (Time 3)	0 $\pm$ 1.37	0 $\pm$ 0.71	0.25
FLACC Total	1 $\pm$ 2.30	1 $\pm$ 1.90	0.17
Induction Quality (calm:restless)	91:37:00	67:21:00	0.44
Induction Quality (calm:restless) [%]	71:29:00	76:24:00	0.44

Table 5: Clinical data for male and female patients, data are given as mean $\pm$ standard deviation.

Discussion

Our investigation revealed a high incidence of ED of 25% following adenotomy in preschool children despite a multimodal anesthetic concept. Interestingly, ED seems to be linked to the incidence of ePONB within two weeks after outpatient adenotomy. Incidences of ED published in the literature alter significantly depending on risk factors such as age and type of surgery as well as the applied anesthetic concept. Pieters, et al. described an incidence of ED of 53% [19]. The comparability of these two studies is difficult due to different definitions of ED (≥ 16 points in all criteria of the PAED-Score vs. ≥ 9 points for criteria 1-3 of the PAED-Score), different pain-Scores applied (CHEOPS vs. FLACC-Score) and different surgical interventions investigated (tonsillectomy vs. adenotomy). Despite these limitations that become apparent when comparing incidences of different studies, we believe that the “low” incidence of ED in our study may be attributed to the multimodal anesthetic concept. The highest incidence of ED published by Grundmann et al. after Desflurane anesthesia and “ENT” (e.g. adenotomy with bilateral myringotomy and insertion of tubes and/or tonsillectomy) surgery was 80%. [7]. Chandler, et al. [20] could show that the mere change from a volatile anesthetic to a Propofol based anesthesia reduced ED by nearly 50% from an incidence of 38.3% to 14.9% after “strabismus surgery” [20].

The reported incidence of ED in our study is therefore in line with previously published data despite the discrepancy of comparing the underlying methodological differences. Aono and colleagues have previously shown that preschool children reveal a higher incidence of ED after sevoflurane anesthesia compared to school children [6]. However, a difference in the incidence of ED between boys and girls has not been reported previously [21]. The higher incidence of ED in male patients in our study could not be explained by “higher excitement” levels during induction of anesthesia or higher FLACC scores after adenotomy (Table 3). On the other hand, we detected a significant difference in age between male and female patients. This difference in lower age may have contributed to the detected increased incidence of ED in boys. Early postoperative negative behavior (ePONB) was diagnosed applying the German version of the PHBQ questionnaire [17]. The questions were grouped in 6 categories: “separation anxiety”, “apathy”, “sleep disturbance”, “general anxiety and regression”, “withdrawal”, and “eating disturbance” [17]. Incidences of ePONB differ considerably within the published literature [14,15,21]. Comparing these incidences is difficult due to different definitions of ePONB. Kain, et al. defined ePONB as at least one positive answered question of the PHBQ [14] while Faulk, et al. [21] defined that at least seven questions must be answered positively. This might explain why the incidence reported by Faulk

(8,8%) was lower compared to Kain’s investigations (54% and 78,4%). In contrast to Kain, et al. reported incidences of ePONB within two weeks after outpatient surgery [14,15] the incidence of ePONB for our patients was comparatively low with 14% (Table 2). It is tempting to speculate that this “lower” incidence of ePONB in our study may be attributed to the performed multimodal anesthetic concept resulting in a lower incidence of ED of 25%. In fact, Kain, et al. previously described that the incidence of ED is correlated with the incidence of ePONB [15]. Our results of ED being positively correlated with ePONB (24% vs. 11%, $p=0.04$) are therefore in line with Kain’s finding. On the other hand, Faulk’s published incidence of ePONB of 8,8% [21] is lower compared to our measured incidence of 14%. An explanation might be seen in the different definition of ePONB (7 positive items [21] of the PHBQ questionnaire versus 5 items applied in our investigation). Furthermore, we believe that type of surgery (dental procedure versus adenotomy) and age (1 to 12 years versus 1 to 7 years) have an impact on the incidence of ePONB. It becomes evident that out of the six defined categories within the PHBQ, “sleep disturbance” and “separation anxiety” (Figure 3) were found to be the most frequent postoperative changes in our investigated patients. Kain et al. also described a higher prevalence of “separation anxiety”, while “sleep disturbance” was not found to be one of the most common behavioral changes [14]. The difference may be explained by the fact, that the children in our study were younger. Furthermore, Kain, et al. used the PHBQ in the Version of Vernon [18] while we used the German Version of the PHBQ from Buehrer, et al. [17]. An essential difference between these two questionnaires is the different assignment of specific questions to the 6 mentioned categories. While Vernon’s version assigns “having bad dreams or waking up at night crying” and “get upset when you leave him (or her) alone for a few minutes” to the category “separation anxiety”, Buehrer’s version assigns these questions to the category “sleep disturbance”. When breaking down our results to single questions, our study was in line with Kains [14] results showing that the questions “having bad dreams or waking up at night crying” and “getting upset when left alone for a few minutes” were the most frequently positively answered questions.

Conclusion

Despite a multimodal pharmacological approach, the incidence of ED after outpatient adenotomy remained as high as 25% in our investigation. ED not only plays a role immediately after surgery but was linked to ePONB within two weeks after adenotomy. In summary, ED affects one of four preschool children following adenotomy and could not be prevented in all cases. Basically, it seems advisable to explain ED to parents ahead of surgery and inform on ePONB that may occur after discharge.

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