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Pediatric emergence delirium is linked to increased early postoperative negative behavior within two weeks after adenoidectomy: an observational study

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Abstract

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

Methods: The study comprised 222 patients (1–7 years of age). All children received a multimodal anesthesia based on total intravenous anesthesia with propofol and remifentanil in combination with piritramid (0.1 mg.kg^{-1}), ibuprofen (10 mg.kg^{-1}), dexamethason (0.15 mg.kg^{-1}) and ketanest S (0.1 mg.kg^{-1}). We evaluated emergence delirium using the Pediatric Anesthesia Emergence Delirium Scale (PAED) at different predefined time points during the recovery period. Emergence delirium was defined as a PAED score ≥ 9 for the first three criteria. Additionally, we defined early postoperative negative behavior to be present when at least 5 of 27 criteria of the post hospitalization behavior questionnaire were positive.

Results: The incidence of emergence delirium following our anesthetic regime was 23%. The incidence of early postoperative negative behavior was significantly higher among patients with emergence delirium (24% vs. 11%, p = 0.04). The two categories, “sleep disturbance” and

"separation anxiety", tested within the questionnaire for early postoperative negative behavior were identified as the most common postoperative negative behavioral changes.

Conclusion: Emergence delirium not only plays a role immediately after surgery but is also linked to early postoperative negative behavior within two weeks after outpatient adenoidectomy. Parents should be informed that early postoperative negative behavior may occur in 1 out of 4 patients if emergence delirium was present postoperatively.

Trial Registration: DRKS – German Clinical Trial Register ID: DRKS00013121

KEYWORDS: Adenoidectomy; Behavior; Emergence delirium; Anesthesia; Child; Preschool

Introduction

Emergence Delirium (ED) following anesthesia remains an unsolved problem.[1,2] Affected children are unaware of their surrounding and show un purposeful movements. They are unable to focus or get in touch with their trusted caregivers. Crying and weeping increases to a point where neither caregivers nor trained professionals are able to calm them down. These children are prone to injure themselves by dislocating catheters, undo bandages, and thereby compromise surgical outcome. Several risk factors have been identified for example pain,[3] surgical procedures such as ear, nose and throat surgery,[4,5] and preschool age versus school age.[5,6] In addition to certain anesthetic regimes, such as desflurane-N20-anesthesia, the incidence of ED is described as high as 80%.[7] Nevertheless, several clinical studies have shown that opioids,[8,9] total intravenous anesthesia,[10] ketamine,[9] and dexamethason[11] can reduce the risk of ED. Risk reduction for sevoflurane-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 an anesthetic concept combining propofol, ketamine, dexamethasone, and opioids after outpatient adenoidectomy for 1- to 7-year-old children.

Several scales and scores have been published previously to measure ED objectively. The Pediatric Anaesthesia Emergence Delirium Score (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. The PAED-Score originally has 5 criteria being: the child keeps eye contact, shows purposeful movements, is aware of surrounding, is restless, and is inconsolable (Table 1). Locatelli disregarded criteria 4 and 5 for defining ED as they – more or less – describe agitation. In our present study, we defined ED as proposed by Locatelli with ≥ 9 points out of 12 defining ED.

As ED is an acute disorder that occurs immediately after recovery from anesthesia, it is unknown whether long term changes may also occur postoperatively. Kain et al. described the

incidence of early Postoperative Negative Behavior (ePONB) 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] the child's age, number of siblings, and baseline temperament.[14]

The aim of this study was to investigate the incidence of emergence delirium and earlypostoperative negative behavior in patients following a multimodal anesthetic regime.

Methods

Following Ethics Committee approval (University Hospital Bonn, Germany) and parental written informed consent, we consecutively enrolled 222 (166 patients in Bonn, 56 patients in Moenchengladbach) children – from June 2015 till March 2016 – between 1 and 7 years of age scheduled for elective outpatient adenoidectomy with or without myringotomy in a prospective multicenter observational study.

Exclusion criteria were American Society of Anesthesiologists (ASA) physical status ≥3, critical illness with hemodynamic instability, active bleeding, or intellectual disability.
Premedication was performed orally with Midazolam (0.3–0.5 $mg.kg^{-1}$) 30 to 60 minutes prior to induction of anesthesia. Induction quality was monitored and documented by a 4-point scale ranging from "sleeping" over "calm and awake" to "anxious and cooperative" and "crying and uncooperative". We subsumed the first two states as being "calm" whereas the last two states were subsumed as being "restless". Anesthesia was preferably induced intravenously with propofol (2–4 $mg.kg^{-1}$) or alternatively via face mask with 4%–8% Sevoflurane and 100% oxygen. Thereafter the anesthesia regime was switched to a total intravenous anesthesia and the airway was secured by a laryngeal mask.

Standard monitoring included ECG, $EtCO_2$, pulse oximetry and noninvasive 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 total intravenous anesthesia (propofol and remifentanil), piritramid (0.1 $mg.kg^{-1}$), ibuprofen (10 $mg.kg^{-1}$), dexamethason (0.15 $mg.kg^{-1}$) and ketanest S (0.1 $mg.kg^{-1}$). Applying intravenous Clonidine (2 $\mu g.kg^{-1}$) intraoperatively was leftto the discretion of the anesthesiologist.

After recovery from anesthesia sleep, duration in the PACU and the occurrence of ED was monitored applying the PAED-Score (Table 1). ED was monitored and 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 Face-Legs-Activity-Cry-Consolability-Score (FLACC-Score) 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. Patients' parents were interviewed (via phone call) 14-days following the operation using a questionnaire for possible postoperative negative behavior (Table 2) that was handed out to the parents before discharged home. The interviewer was blinded to the occurrence of ED of the interviewed parent's child. We defined ePONB to be present when at least ≥ 5 of 27 questions of this questionnaire were answered positively. The questionnaire wasvalidated in a German speaking pediatric population published by Buehrer et al.[17] using a German translation of the PHBQ (Post-Hospitalization Behavioral Questionnaire) from Vernon et al.[18] published in 1966.

Statistics

Statistical analysis was performed using Microsoft Excel 2016. Further analysis was performed using Gnu Regression (gretl), Econometrics and Time-series Library 2016 (Allin Cottrell and Riccardo Lucchetti). Power analyses were undertaken by using G*Power (Heinrich-Heine University, Düsseldorf, Germany).

Descriptive statistics and demographic data between male and female patients are presented as mean ± standard deviation. Differences between groups as described in Table 3 were examined using Fisher's exact Test for categorial variables and Student's *t*-test for continuous variables. Repeated analyses of Fisher's exact test were used to compare variables such as sleep duration and ED. Comparisons were considered statistically significant for $p < 0.05$.

The sample size of the study was calculated to investigate the dependency of early postoperative negative behavior following emergence delirium in children. Assuming an α-error of 0.05, an effect size of 0.3 and a power of 95%, a sample size of 145 was calculated for our investigation. To allow for a considerable amount of dropouts of around 30% due to protocol deviations, language barriers, false phone numbers, or unavailability despite several phone call attempts we calculated a sample size of 200 patients.

Results

Written informed consent was given by 234 caregivers. 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 twoweeks 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. Theincidence of ED in this observational study was 23% (n = 52 of 222 patients). The occurrence

of ePONB within the observed period of time (2-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 4).

An increase of postoperative sleep duration (defined as sleep in the PACU immediately after surgery) of 15 minutes resulted in a reduction of ED of approximately 50%, $p = 0.0002$. We detecteda significant difference in sleep duration between children with or without intraoperative clonidine (55 ± 32 min vs. 42 ± 29 min, $p = 0.002$). Age correlated with the incidence of ED (Fig. 1). 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" (Fig. 2). 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. Out of all patients with ePONB 84% 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?". From all positively tested patients 76% answeredthat their child "became anxious when it was left alone for a few minutes".

Discussion

Our investigation revealed a high incidence of ED of 23% following adenoidectomy inpreschool children despite a multimodal anesthetic concept. Interestingly, ED seems to be linked to the incidence of ePONB within two weeks after outpatient adenoidectomy. Basically, it seems advisable to explain ED to parents ahead of surgery and inform on ePONB that may occur after discharge.

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] Comparing their results with our study 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. adenoidectomy). 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., adenoidectomy with bilateral myringotomy and insertion of tubes and/or tonsillectomy) surgery was 80%.[7] Chandler et al. 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 in line with the published data of Chandler et al. despite the discrepancy in defining ED as a PAED score of ≥10 out of 20 in their study.

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 adenoidectomy (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 inboys.

Early Postoperative Negative Behavior (ePONB) was diagnosed applying the German version of the PHBQ questionnaire.[17] The questions were grouped in six 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.'s 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 4). It is tempting to speculate that this "lower" incidence of ePONB in our study may be attributed to the performed multimodal anesthetic regime resulting in a lower incidence of ED of 23%. 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 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 idems, Faulk et al.[21]) of the PHBQ questionnaire vs. 5-items applied in our investigation). We believe that type of surgery (dental procedure vs. adenoidectomy) and age (1- to 12-years vs. 1- to 7-years) also 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" (Fig. 2) 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. 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'sversion 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.

There are limitations of our study that have to be taken into account. The PAED and FLACC- Score always leave room for subjective interpretation and scoring known as inter-rater variability. The same limitation is true for the PHBQ where answers were dependent on the objectivity of the parents being interviewed as well as the objectivity of the interviewer. Since all parents were interviewed by the same interviewer being blinded to the occurrence of postoperative ED of all investigated patients, we believe that a possible bias of the interviewer was made impossible at this point.

Despite a multimodal anesthetic regime, the incidence of ED after outpatient adenoidectomy remained as high as 23% in our investigation. ED not only plays a role immediately after surgery but was linked to ePONB within two weeks after adenoidectomy.

Conflicts of interest

The authors declare no conflicts of interest.

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Figure 1 Prevalence of ED according to the patient´s age.

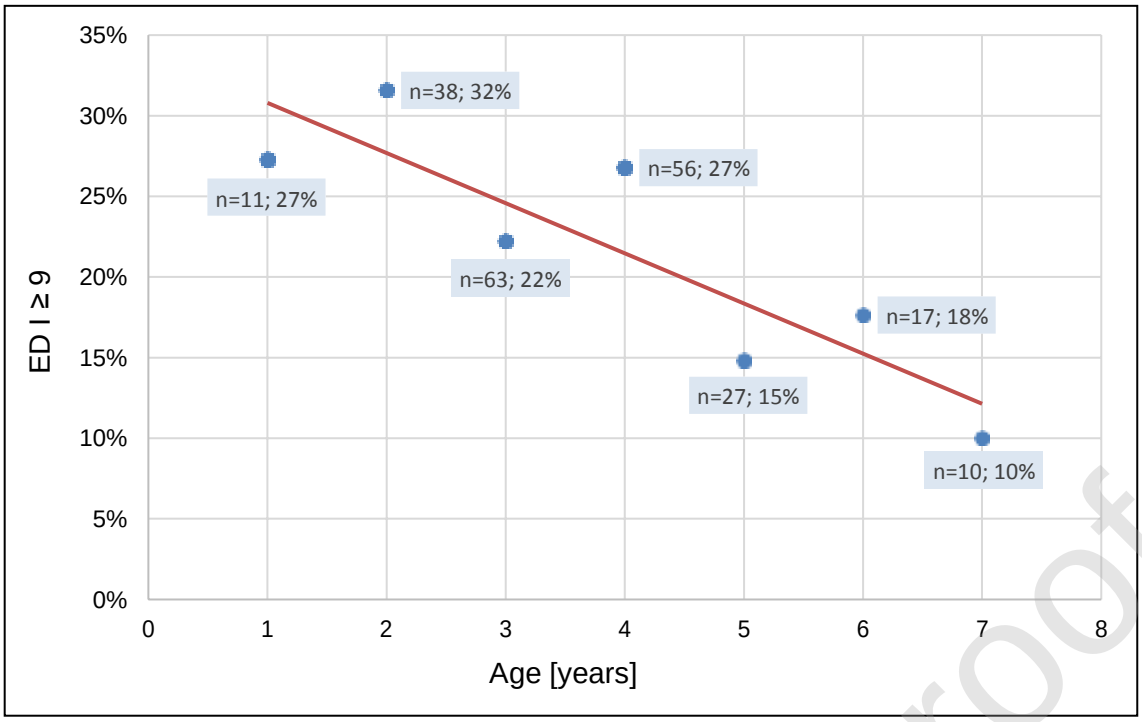

Figure 2 Questions answered with "more than before" in % within particular categories; separation anxiety = Category 1; apathy = Category 2; sleep disturbance = Category 3; general anxiety and regression = Category 4; withdrawal = Category 5; eating disturbance = Category 6.

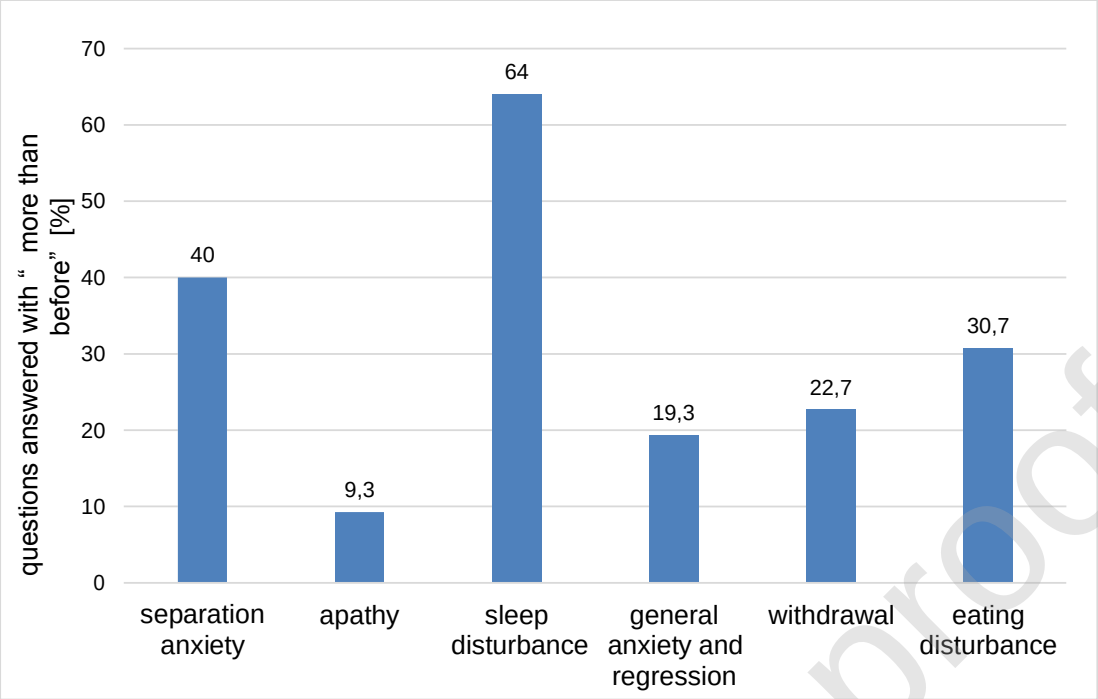

Table 1 PAED (Pediatric Anesthesia Emergence Delirium) scale based on Delir-criteria (EDI) and Agitation-criteria (ED II) according to Locatelli et.al.[13]

	Criteria	The child	Not at all	Just a little	Quite a bit	Very much	Extremely
Delir-criteria (ED I Score)	1	… keeps eye contact	4	3	2	1	0
	2	… shows purposeful 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 2 German version of the Post-Hospitalization Behavioral Questionnaire (PHBQ) by Buehrer et al.[17]

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) fingernails?			
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 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 Clinical data for male and female patients, data are given as mean ± standard deviation.

	Male	**Female**	***p*-value**
Age	3±1.21	4±1.62	< 0.001
ASA (I:II)	96:21	74:11	0.436
Anesthesia duration (min)	37±14	35±14	0.36
Sleep duration (min)	50±32	47±28	0.43
ED I ≥ 9 (Y:N) (%)	29:71	15:85	0.024
Time 1 ED I	4±4.27	2±3.70	0.04
Time 2 ED I	2±3.70	1±2.86	0.2
Time 3 ED I	1±2.20	0±1.06	0.27
Time 1 FLACC	2±2.60	1±2.36	0.5
Time 2 FLACC	1±2.53	1±2.07	0.12
Time 3 FLACC	0±1.37	0±0.71	0.25
FLACC total	1±2.30	1±1.90	0.17
Induction quality (Calm:Restless) (%)	71:29	76:24	0.44

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).

	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.