

# Prevention and Therapy of Pediatric Emergence Delirium: A National Survey

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Published online: 28 January 2017  
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## Abstract

**Introduction** Although pediatric emergence delirium (ED) is common, preventive and therapeutic pharmacological treatment is the matter of an international controversial discussion and evidence on different options is partially vague.

**Objective** We therefore examined clinical routine in prevention strategies and postoperative therapy of ED with respect to clinical experience in pediatric anesthesia.

**Methods** A web-based survey was developed investigating routine management (prevention and treatment) of ED, facility structure, and patient population. The link was sent to all enlisted members of the German Society of Anesthesiology.

**Results** We analyzed 1229 questionnaires. Overall, 88% reported ED as a relevant clinical problem; however, only 5% applied assessment scores to define ED. Oral midazolam was reported as standard premedication by 84% of respondents, the second largest group was ‘no premedication’ (5%). The first choice prevention strategy was to perform total intravenous (propofol) anesthesia (63%). The first choice therapeutic pharmacological treatment

depended on clinical experience. Therapeutic propofol was preferentially chosen by more experienced anesthesiologists (5 to >20 patients per week,  $n = 538$ ), while lesser experienced colleagues (<5 patients per week,  $n = 676$ ) preferentially applied opioids. Dexmedetomidine (1%) and non-pharmacological (2%) therapy were rarely stated. The highest satisfaction levels for pharmacological therapy of ED were attributed to propofol.

**Conclusions** Propofol is the preferred choice for pharmacological prevention and treatment of ED among German anesthesiologists. Further therapy options as well as alternatives to a midazolam-centered premedication procedure are underrepresented.

## Key Points

Propofol is the preferred pharmacological choice for prevention and treatment of emergence delirium in children among German anesthesiologists.

Experience in pediatric anesthesiology alters the therapeutic approach in case of ED in favor of propofol.

According to this survey, pharmacological and non-pharmacological alternatives to midazolam premedication seem underrepresented in German pediatric anesthesiology.

A preliminary version of this work was presented as a poster presentation at the European Society of Anesthesiology (ESA), May 30–June 2, 2015, Berlin.

**Electronic supplementary material** The online version of this article (doi:10.1007/s40272-017-0212-x) contains supplementary material, which is available to authorized users.

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## 1 Introduction

The incidence of emergence delirium (ED) varies widely between 18% [1] and 80% [2]. Multiple risk factors have been discussed to contribute to ED [3–5]. These risk factors

include age [1, 6], children's traits and preoperative anxiety [7], anesthetic regimen and premedication drug [8–10], inadequate pain control [11], and type of surgery [1].

We know from our clinical experience and correspondence during the preparation phase of our survey that midazolam is a very popular premedication drug in German anesthesiology. At the same time, it is a risk factor of debate for ED. Some studies have shown that the use of midazolam may decrease the incidence of postoperative emergence delirium [12], whereas others have shown that midazolam increases the incidence of ED [3] and maladaptive postoperative behaviour [13]. Kain et al. could show that preoperative education and training of parents and their children is superior to premedication with midazolam [14] regarding the incidence of postoperative ED. Other studies again have proven the superiority of  $\alpha_2$  agonists over midazolam [15, 16]. We therefore aimed to investigate current premedication routine in the context of pediatric ED.

To the best of our knowledge, only one randomized controlled trial has been published exploring the therapeutic effect of, in this case, physostigmin versus placebo for treatment of emergence delirium [17]. Pharmacological prevention of ED (e.g. with opioids and  $\alpha_2$ -agonists), on the other hand, has been investigated more extensively [18, 19]. Our goal was therefore to question German anesthesiologists on how ED is pharmacologically prevented and treated from premedication to the end of post-anesthesia care.

Furthermore, little is known about the impact of clinical experience in pediatric anesthesia on clinical routine handling of ED. We therefore related ED management strategies to our participants' clinical experience in pediatric anesthesia.

With the various above-mentioned risk factors, the high discrepancy in published incidences, missing national or international guidelines, as well as existing international differences regarding ED management [20, 21], we saw the need for a survey investigating clinical routine in the perioperative management of pediatric emergence delirium as a beneficial foundation for further randomized controlled trials and to possibly indicate key aspects for the formation of common guidelines for prevention and treatment of ED. Nonetheless, it remains clear that a survey is only a snapshot of professional experience and does not necessarily reflect best practice.

## 2 Materials and Methods

A 33-item questionnaire was developed with the assistance of members from the German Scientific Working Group for Pediatric Anesthesia (WAKKA) of the German Society of

Anesthesiology (DGAI). A pre-test among ten specialists of the WAKKA was carried out in order to assess clarity, feasibility, validity, and redundancy of content. Our specialists' suggestions influenced the final version and the questionnaire was refined. The questionnaire consists of different answer types (Appendix 1, see electronic supplementary material) and respondents were allowed to skip answers. Ethical approval was not required since participation in the survey was voluntary. No financial compensations were granted and SSL (secure sockets layer) secured data transmission was ensured. Data from a preliminary questionnaire of 143 members of the WAKKA was previously published [22].

The questionnaire had three main parts. The first part surveyed the respondent's institutional characteristics, their level of experience in pediatric anesthesia, as well as their regular pediatric caseload and their patients' predominant age. The second part addressed the incidence and duration of ED and routines of premedication, induction, maintenance of anesthesia, and postoperative care. Particular attention was paid to pre-emptive strategies and therapeutic agents. In the third part we surveyed potential risk factors for ED.

After uploading the questionnaire on 'soscisurvey.de', a link was emailed on June 18, 2014 to all enlisted members of the DGAI via a directory of 11,006 email accounts. Four weeks before the ending of the survey period (August 31, 2014) one reminder was sent out.

The raw data set was downloaded as a csv (comma-separated values) file and data was inserted in Microsoft Excel 2011 software (14.6.3). Using data quality indicators of 'completion time' ( $\geq 3$  times faster than median time) and 'missing relevant answers' (cut-off  $>15\%$ ) [23], we aimed to exclude incomplete and irrelevant records. Information on statistics of our interview completion was also provided by soscisurvey<sup>®</sup>. Statistical analysis was performed using Excel and Graph Pad Prism (6.0f).

## 3 Results

The link was opened 2160 times (defined as 100% in the following) and 1683 (78%) anesthesiologists started to answer the questionnaire. We finally recorded 1330 (62% completion rate) completed questionnaires, of which 1229 (57%) were considered as meaningful after applying above-mentioned data quality indicators [23].

### 3.1 Participants and Facilities

First of all, the data shows that ED was clinically relevant for 1080 out of 1222 (88%) participating caregivers. Interviewee and institutional characteristics displayed in

**Table 1** Characteristics of participants and facility structures

Characteristic	<i>n</i> (%)
<b>Type of medical facility</b>	
Academic hospital	236 (19)
Maximum care hospital	262 (21)
Secondary care hospital	382 (31)
Primary care hospital	101 (8)
Pediatric hospital	46 (4)
Outpatient surgical facility (2–4 OTs)	82 (7)
Medical practice (1 procedure room)	58 (5)
Total	1229
<b>Individual pediatric caseload/week</b>	
<5	676 (56)
5–10	305 (25)
11–15	102 (8)
16–20	49 (4)
>20	82 (7)
Total	1214
<b>Years of professional experience in pediatric anesthesia</b>	
<1	90 (7)
1–2	182 (15)
4–6	144 (12)
>6	811 (66)
Total	1227
<b>Surgical department where anesthesia is mostly administered</b>	
ENT	607 (49)
Pediatric surgery	280 (23)
General surgery	37 (3)
Trauma surgery	71 (6)
Urology	71 (6)
Odontology	79 (6)
Ophthalmology	23 (2)
Other	60 (5)
Total	1228
<b>Predominant age group of patients (y)</b>	
<1	58 (4)
1–2	280 (20)
3–6	996 (69)
>6	102 (7)
Total	1436

OT operating theatre

Table 1 depict that 66% of all respondents worked as specialists in anesthesiology with more than 6 years of experience in pediatric anesthesia. We differentially investigated answers from anesthesiologists with a lower pediatric caseload (<5 per week,  $n = 676$ ) versus a higher pediatric caseload (5 to >20 per week,  $n = 538$ ) for relevant differences in therapy concepts. Postoperative recovery was reported to be ensured in post-anesthesia care units

(PACUs) or recovery rooms equipped with four to eight beds (42%), more than eight beds (26%) or one to four beds (21%). Parental presence was ensured in the PACU before (65%) or after awakening (23%). In every fifth PACU (19%), an anesthesiologist was stated to be directly present whereas the majority worked with nursing staff (79%).

### 3.2 Incidence and Duration of Emergence Delirium (ED)

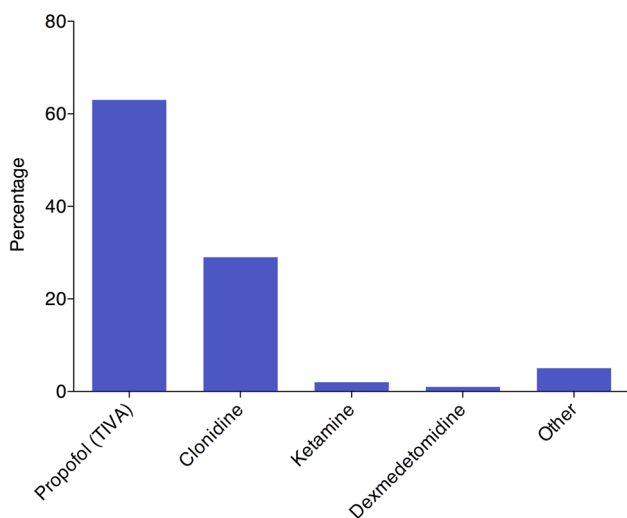
The overall incidence of ED was estimated to range between 1 and 10% by 45% of respondents; 30% stated an incidence between 11 and 20%. An incidence of >20 or <1% was less frequently chosen (18 and 7%, respectively). Every second participant (50%) indicated ED duration between 31 and 60 min and 35% stated the duration of ED as <30 min. A minority of 15% of all caregivers noted postoperative delirium to last for >1 h.

### 3.3 Premedication, Induction and Maintenance of General Anesthesia

The majority of German anesthesiologists (84%) reported the use of midazolam as a premedication drug (87% of the colleagues with less than five pediatric cases per week and 80% with a caseload of more than five children per week), while the second largest group (5%) indicated 'no premedication'. Other drugs such as ketamine or  $\alpha$ -2 agonists played a minor role in the premedication routine (3 and 1%, respectively). In a few cases (4%), combinations of drugs, mostly midazolam with ketamine or midazolam with ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), were given as premedication. The most common induction agent in pediatric anesthesia was stated to be propofol (74%) followed by mask induction with sevoflurane (24%). Forty percent of our participants assumed an association between sevoflurane induction and ED. At the same time, a majority (51%) of our participants answered that they use sevoflurane for general anesthesia maintenance whereas 38% stated that they provide propofol for general anesthesia maintenance.

### 3.4 Preventive Strategies

The first choice preventive strategy to avoid ED was stated to be total intravenous anesthesia (TIVA) by 63% of participants, and intraoperative administration of clonidine was reported by 29% as their first choice. Figure 1 shows that other pre-emptive pharmacological options during general anesthesia such as ketamine (2%) or dexmedetomidine (1%) were rarely chosen.



**Fig. 1** Percentage of choices for intraoperative pre-emptive strategies to avoid postoperative emergence delirium. Among the choice ‘Other’ were midazolam, piritramide, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and loco-regional anesthesia. TIVA total intravenous anesthesia

**3.5 Postoperative Care**

A score to assess ED postoperatively was applied by only 5% of our interviewees (mostly the Pediatric Anesthesia Emergence Delirium score [PAED]) [24]. If ED was encountered, three first-choice substances were reported as being applied in virtually equal measure: opioids, propofol, and clonidine (32, 31, and 29%, respectively). However, pharmacological treatment of ED depended on pediatric caseload. Anesthesiologists with an individual caseload of 5 to >20 per week ( $n = 538$ ) preferentially applied propofol (37%) as first choice compared with opioids (25%). In contrast, anesthesiologists with an individual caseload of less than five per week ( $n = 676$ ) preferentially applied opioids (37%) compared with propofol (26%).

Clonidine as first choice in the postoperative period was equally reported by the two groups (30% for lower caseload, 28% for higher caseload). Less popular in both groups was the application of ketamine or dexmedetomidine (3 and 1%, respectively). Free-text answers with the options ‘waiting to cease spontaneously’ and/or ‘parental presence’ as first choice therapy for ED added up to 2%. Satisfactory levels for ED treatment numerically expressed in grades are displayed in Fig. 2, revealing higher user satisfaction grades for propofol and clonidine compared with opioids.

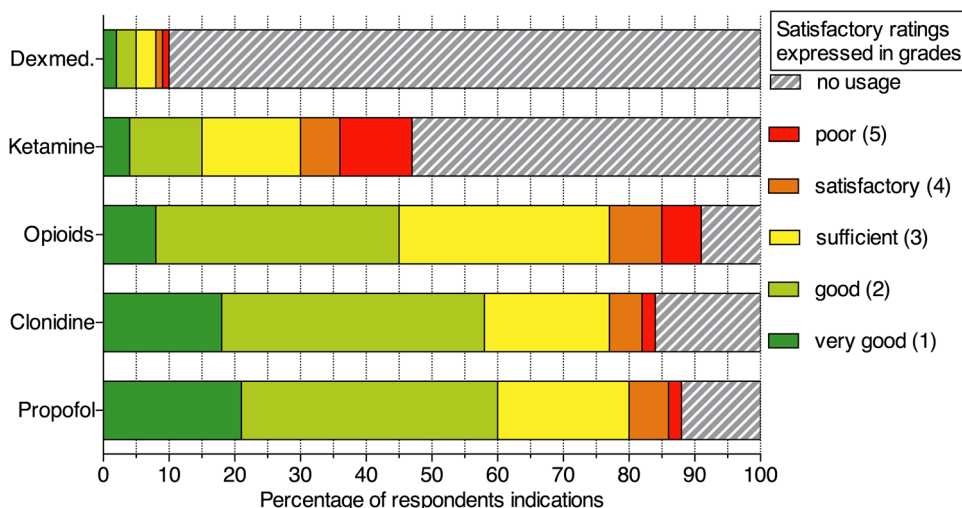
**3.6 Perceived Causes of Emergence Delirium**

Postoperative parental presence was rated very important and important by 91% of all surveyed anesthesiologists. Seventy percent connected the child’s pre-induction state (agitated versus calm) to the way they emerge from general anesthesia. Every second participant stated that loudness in the PACU highly affected ED occurrence. In Table 2 we summed up the ratings of other potential ED evocative factors.

**4 Discussion**

This large-scaled survey reveals current routines in pre-, intra- and post-operative management of pediatric ED in Germany. Our survey highlights the significance of propofol for pre-emptive and therapeutic usage with regard to ED, especially for more experienced anesthesiologists. Propofol was the drug of choice among available drugs for ED therapy in Germany. Midazolam was the most common premedication drug in German practice and the optional usage of  $\alpha$ -2 agonists or distraction strategies was low.

**Fig. 2** Displayed are satisfaction ratings (grades 1–5, 1 being very good, 5 being poor) of different agents used for pharmacological treatment of pediatric emergence delirium. Dexmed. dexmedetomidine



**Table 2** Rating of potential risk factors for ED: ‘Does one or more of the following factors more likely lead to ED?’

Factors	Yes (%)
ED stated in child’s medical history	79
Preoperative anxiety	75
Paradoxical reaction to midazolam stated in child’s medical history	42
Hospitalization or high number of previous interventions	38
ADHD	36
Impulsivity	25
Low educational background of parents	18
High educational background of parents	10
Total ( <i>n</i> )	1229

ADHD attention-deficit hyperactivity disorder, ED emergence delirium

Propofol as part of TIVA was reported by nearly two thirds of our respondents as first-line prevention strategy, if the aim was to proactively avoid ED. In contrast, the majority of respondents (61% in total) used sevoflurane and other volatile anesthetics in a routine setting as the standard general anesthesia maintenance agent. This contrast suggests that clinicians do not always focus on preventing ED. Several meta-analyses have shown that modern volatile anesthetics favor the occurrence of ED [8, 9] and 40% of respondents even quoted a link between sevoflurane induction and a higher incidence of ED. It can be stated that the use of propofol for prevention of ED (as indicated by German anesthetists) is in line with recent trials [25–27]. Moreover, as we could detect a correlation between higher pediatric anesthesia experience and therapeutic propofol usage for ED in the PACU, as well as the highest satisfactory rating for propofol, our data support the drug’s significance as a therapeutic option for ED. This is also consistent with studies leading to a reduction in ED occurrence where propofol was given as continuous infusion, a 3-min transition with 3 mg/kg, or a single 1-mg/kg bolus application at the end of anesthesia [25–27]. However, it is important to note that these studies investigated pre-emptive procedures. We cannot conclude that propofol is really the best option for postoperative ED therapy. Furthermore, it has to be stated that the option ‘wait until spontaneous cessation’ in the absence of a self-injury hazard should always be taken into consideration. Dexmedetomidine may also prove an alternative to propofol as it also reveals promising evidence for ED prevention [28, 29]. However, in German clinical practice, dexmedetomidine is not licensed for use in pediatric anesthesia. The main field of application according to the official summary of product characteristics by the only supplier is sedation of adult intensive care patients. This, and high costs, may reflect the main reasons for rare usage of dexmedetomidine in Germany.

Interestingly, midazolam is still by far (84%) the most frequently used premedication drug in German practice and

only 5% refrained from any pharmacological premedication. In a recent study, Cho et al. stated that duration of ED was prolonged after 0.5 mg/kg compared with 0.3 mg/kg midazolam preoperatively [12]. Midazolam in pediatric anesthesia has been the subject of debate for many years [30] and its effectiveness in preventing ED when used as a premedication drug has not been proven [9, 31]. Midazolam’s inferiority compared with  $\alpha_2$ -agonists such as clonidine and dexmedetomidine in decreasing postoperative delirium (as only one mentioned feature) is described in several recent meta-analyses [16, 32, 33]. Despite these facts, only a small minority of our respondents (1%) preferred clonidine for premedication purposes. This is probably owing to the fact that  $\alpha_2$ -agonists feature a longer onset time when given orally whereas dexmedetomidine is not available for oral application in Germany.

When analyzing perceptions towards ED (Table 2), one item can be mentioned as central to our surveyed anesthesiologists: preoperative anxiety. The ADVANCE program, developed and investigated by Kain et al. in 2007, focused on family-centered cognitive behavioral preparation and was proven superior to parental presence alone and midazolam premedication in anxiety reduction and postoperative behavioral outcome [14]. With only 5% of German anesthesiologists omitting pharmacological premedication, we see large potential in Germany to enhance the inclusion of parental presence during induction combined with child distraction and preoperative preparation programs prior to anesthesia.

In a recent survey on ED management between Italian and British/Irish anesthesiologists, midazolam was clearly favored for prevention and therapy of ED by Italian clinicians [21]. At the same time, British and Irish colleagues preferred propofol and opioids for prevention and waited for ED to cease without drugs [21]. The latter choice was reported to be wholly underrepresented in our study. Even though we did not clearly list the option ‘wait for spontaneous resolution’ in question number 21, the total percentage of participants checking ‘other’ and adding

‘waiting to cease spontaneously’ and/or ‘parental presence’ in the provided free-text field was 2%. According to these results, premedication and therapeutic postoperative routines in German practice are focused on pharmacological aspects rather than child distraction. These facts show obvious international differences in the practice of ED management. However, results from national surveys may not answer the question of which strategy is most effective, but may serve to reveal questions that are to be answered in future randomized controlled trials.

Although 88% of our survey respondents declared ED as clinically relevant, only a small minority (5%) used a score to clearly assess and document this phenomenon. This may be explained by the plurality of ED scales being described in the literature [34] and the absence of a clear recommendation for one of them. Respondents from our study alone who indicated usage of an assessment score at their institution refer to eight different tools. Furthermore, existing clinical scales have difficulties in discriminating between ED and pain. In a retrospective analysis by Somaini et al. [35], four different scales were investigated to identify specific variables of ED versus postoperative pain on the basis of data from three prospective observational studies. The authors described a correlation of ‘no eye contact’ and ‘no awareness of surroundings’ with ED whereas ‘abnormal facial expression’, ‘crying’, and ‘inconsolability’ were described as indicators for acute postoperative pain. Future studies and surveys have to examine if Somaini’s approach on discriminating ED and pain is reliable and if the algorithm will find better user acceptance than previous ED scales.

#### 4.1 Limitations

Inherent to the nature of surveys are several limitations we attribute to our work. We cannot provide a definite response rate, since email accounts might have been abandoned without being deleted in the directory. Assuming that no more than 30% of German anesthesiologists perform pediatric anesthesia, the authors believe that 1330 questionnaires reflect a meaningful responding collective of approximately 3000 anesthesiologists performing pediatric anesthesia in Germany. The detected completion rate of 62% was also satisfactory taking into account the elaborate questionnaire covering 33 items.

A further limitation of our survey may be seen in the fact that only 5% of respondents apply a scale to identify and document postoperative ED. The low appliance has to be taken into account when discussing incidence of ED, length of ED, and therapy of ED in Germany since we cannot rule out that a clear discrimination between pain and ED has been warranted. However, even sophisticated

scales such as the PAED scale have difficulties in discriminating between pain and true ED.

## 5 Conclusion

Propofol is the most important pharmacological option for intraoperative prevention and postoperative treatment of ED among German anesthesiologists. Other internationally accepted therapy options (e.g. dexmedetomidine, attendance, and waiting) are scarcely used. We see a need for further randomized controlled trials investigating treatment of ED in the PACU comparing the quality of propofol, dexmedetomidine, and ‘watchful waiting’ in reducing ED severity and duration in case of a clearly diagnosed ED (pain excluded) in children who are not at higher risk of self-injury.

**Acknowledgements** We thank all members of the DGAI and BDA who participated in this survey, Victoria Lehmann for establishing the survey within ‘soscisurvey.de’, and Mr Sorgatz for forwarding the emails in the name of the DGAI.

#### Compliance with Ethical Standards

**Conflict of interest** Authors CH, TB, FE, CHo, CB, AH, RKE declare that they have no conflict of interest.

**Funding** No funding was received for the survey or the manuscript.

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