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# Emergence delirium and intranasal dexmedetomidine premedication in pediatric anesthesia: a retrospective study in plastic surgery

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# Abstract

Background Dexmedetomidine is widely used in the treatment of emergency delirium (ED) in pediatric patients. However, further evidence on its use in pediatric anesthesia on potential differences in the reduction of ED according to patient's age and type of anesthesia is required. Moreover, whether dexmedetomidine influences time of discharge from the surgical area remains unclear. We evaluated whether intranasal dexmedetomidine is effective in decreasing the incidence of ED in 106 children who had anesthesia for plastic surgery undergoing general or combined anesthesia at different ages. We also assessed if this drug has an impact on time to discharge from the surgical area.

Methods In total, 106 children, aged 2–10 years, were enrolled in this retrospective study. Among them, 50 have been premedicated with dexmedetomidine (dexmedetomidine group); the remaining 56 patients served as controls (control group). The incidence of ED was evaluated according to the use of dexmedetomidine premedication, age and type of anesthesia (general vs combined). The length of anesthesia and duration of staying in the surgical area were also analyzed.

Results Three patients who received dexmedetomidine premedication showed ED (6%), compared with 43 patients in the control group (77%; $p<0.05$). This lower incidence of ED was also present when stratifying patients according to the type of anesthesia or age. No difference between the dexmedetomidine group and control group were reported in timing of discharge from surgical area.

Conclusions Premedication with dexmedetomidine is associated with decreased incidence of ED without increasing timing of discharge after surgery, regardless of patients' age or type of anesthesia. In particular, patients subjected to combined anesthesia report benefit from the use of this molecule.


# Background

Recovery from anesthesia is a very delicate moment, especially in children [1]. Indeed, children are particularly prone to the development of a delirium at the time of awakening, defined as "emergency delirium" (ED), with an estimated incidence that can be as high as 80%, although reported incidence largely varies [2,3]. ED is a dissociated state of consciousness in which the child may not be able to recognize family members or common objects. The child with ED appears inconsolable, irritable, non-cooperating, with psychomotor agitation, crying or persistent complaining and incoherent or incomprehensible language skills. Although ED episodes usually last from 5 to 15 minutes and resolve spontaneously, they can show great intensity, placing the child at risk of auto-injury. Several studies have shown that ED in children may be associated with postoperative behavioral problems that were not present before, including eating disturbances, sleep disorders, aggression, apathy, and anxiety of separating from parents [4–6].

ED seems to be associated with several risk factors, such as age (highest frequency between 2 and 6 years) [7], patient's attitude (children who are more emotional, impulsive and have difficulty in socializing,

are more prone to experience ED) [8], type of surgery (major surgery with intraoperative complications and surgery affecting the head and the neck) [9], uncontrolled pain and inhalational anesthesia [1].

Nowadays, the best approach to reduce the risk of postoperative ED is its prevention [10,11]. Dexmedetomidine is a high-affinity 2-mimetic drug. In particular, this molecule acts in the locus coeruleus determining a sedation pattern similar to natural sleep, without determining respiratory depression [12–14]. Recent studies suggest, among the remedies against ED, the use of dexmedetomidine intranasally as a premedication [10,11,15,16]. In particular, a recent meta-analysis showed that intranasal dexmedetomidine provides more satisfactory sedation and reduces the need for rescue analgesics and the incidence of nasal irritation and postoperative nausea and vomiting compared with other premedication treatments [10]. This molecule now has a well-established role in clinical practice; however, further evidence on its use in pediatric anesthesia, in particular, on potential differences in its efficacy according to the patient's age and type of anesthesia, is required [11]. Moreover, whether dexmedetomidine actually influences time of discharge from the surgical area remains unclear [17].

Therefore, we conducted a study to evaluate whether dexmedetomidine administered intranasally is effective in decreasing the incidence of ED in children who had anesthesia for plastic surgery, undergoing general or combined anesthesia at different ages, between 2 and 3 years, between 3 years and 6 years and between 6 and 10 years. We also assessed if this drug has an impact on time to discharge from the surgical area.

## Methods

# Setting and design

This retrospective study was conducted at the IRCCS Ospedale Pediatrico Bambino Gesù, a referral center for the treatment of pediatric patients in Italy, from January 2018 to January 2019. The local Ethical Committee has approved the study design (protocol number 1587_OPBG_2018), and the legal guardians of all patients signed an informed consent for the use of the patient's data for research purposes.

# Patients

In total, 106 children of any gender, aged 2–10 years who underwent plastic and reconstructive surgery (first and elective) lasting 60–90 minutes were considered. All patients had to be classified as American Society of Anesthesiologists (ASA) grade I and II; patients were not considered if they presented psychiatric disorders or mental retardation, alterations of metabolism or neurological deficit, or could not receive dexmedetomidine (e.g. due to known intolerance, history of cardiac disease, stroke, heart block, intracranial bleeding, -blocker or digital therapy).

# Procedures

All patients received anesthesia induction via facemask with increasing concentrations of sevoflurane (max: 8%) in 40% oxygen and 60% nitrous oxide. When bispectral index values were between 50 and 40, a venous access was acquired, through which 2 μg/kg of fentanyl and 0.6 mg/kg of rocuronium were administered before intubation. Anesthesia was then maintained with 2.5% sevoflurane end tidal (40% oxygen and 60% air).

All patients received a fluid therapy with physiological saline solution 5–10 ml/kg/h and ranitidine 2 mg/kg to ensure gastric protection. At awakening, intravenous paracetamol was administered at a dose of 15 mg/kg and ketorolac 0.5 mg/kg if required by internal protocols.

Clinical monitoring throughout the course of anesthesia for all patients comprised continuous ECG, $SpO_2$, temperature, bispectral index, mean arterial pressure every 3 minutes.

All patients were extubated and transferred to the recovery room where they were monitored for vital signs ($SpO_2$, continuous ECG, mean arterial pressure every five minutes and temperature).

The onset of ED was evaluated during this period using the Postanesthetic Emergence Delirium Scale [18]. Furthermore, this scale assigns scores from 0 to 20 based on the ability of the child to maintain a visual contact with those around him, if his/her movements are finalized, patient restlessness and inconsolability. Postanesthetic Emergence Delirium Scale scores >12 indicate the onset of ED [19,20].

The Aldrete scale was used to determine whether the child could be discharged [21], with scores >9 indicative of possible discharge.

# Use of dexmedetomidine

Among the 106 evaluated patients, 50 have been premedicated with dexmedetomidine (dexmedetomidine group), at the dose of 2.5 μg/kg administered intranasally 30 minutes before anesthesia induction [22]. The decision to administer dexmedetomidine was taken by the anesthesiologist, according to the consideration of the grade of anxiousness of that patient at the moment of the preoperatory visit and according to internal protocols. A nasal mucosal atomization device was used for premedication [23].

Patients who did not receive dexmedetomidine premedication represented the control group (n = 56; control group).

# Evaluations

We evaluated the incidence of ED according to the use of dexmedetomidine premedication. A subgroup analysis was also performed with respect to the use of general anesthesia or combined anesthesia

(general anesthesia and locoregional block that could be brachial plexus block, tap block, sciatic and femoral nerve block or penile nerve block). Patients were also stratified within each group according to age (2–3 years, 3–6 years, 6–10 years) to investigate the potential effects of age on the onset of ED.

The length of anesthesia and duration of staying in the surgical area were also evaluated to analyze whether the premedication with dexmedetomidine could affect these parameters. Hemodynamic parameters (heart rate, mean arterial pressure) were also monitored, and safety considerations were performed by the CTCAE, version 4.0; the potential association of adverse events with dexmedetomidine was judged by the treating physicians.

# Statistical analysis

Our sample size estimation was based on the incidence of ED in children who received preoperative intranasal dexmedetomidine and in children who received only saline solution.[16] In total, 27 patients were required in each group to detect a 45% difference in the incidence of ED between the groups with a statistical power of 90% and a type I error α equal to 1%. Considering a dropout rate of 20%, the minimum number of patients to include was increased to 34 per group.

Data were analyzed by descriptive statistics. For the incidence of ED and the hemodynamic parameters, statistical comparisons among groups were performed by the Chi square test or Fisher's exact test, the Student t-test or the Mann-Whitney test as appropriate.

Results were considered statistically significant for p-values <0.05. Stata software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) was used for statistical analysis.

## Results

# Study groups

The study groups were similar in terms of demographic characteristics, duration of operation and duration of anesthesia (Table 1). In the dexmedetomidine group, 24 patients received general anesthesia (dexmedetomidine group, general anesthesia) and 26 received a combined anesthesia (dexmedetomidine group, combined anesthesia). In the control group, 30 patients received general anesthesia (control group, general anesthesia) and 26 patients combined anesthesia (control group, combined anesthesia).

# Incidence of emergency delirium

Figure 1 summarizes the incidence of ED in the different groups. Three patients who received dexmedetomidine premedication showed ED (6%), compared with 43 patients in the control group (77%;

p<0.05). This lower incidence of ED was also present when stratifying patients according to the type of anesthesia or age (Figure 1). In particular, no patient on dexmedetomidine receiving combined anesthesia or in the age groups 2–3 years and 6–10 years presented ED.

# Time of anesthesia and time to hospital discharge

No difference between the dexmedetomidine group and the control group were reported in terms of timing of discharge from surgical area, regardless of the specific indication to plastic surgery (Table 2).

# Safety

No relevant hemodynamic effects were observed in patients in the dexmedetomidine group compared with the control group. In fact, we did not observe any significant difference in the mean heart rate and mean arterial pressure at baseline, 15 and 30 minutes after dexmedetomidine intranasal administration (Table 3). No adverse events directly associated with dexmedetomidine administration were reported.

## Discussion

The awareness of a state of agitation linked in some way to the postoperative phase and closely related to anesthesia has been described in literature as far back as the 1960s [24]. The etiology of postoperative ED remains unclear [25,26], but the introduction of modern short-acting volatile anesthetics has been associated with the increased incidence of ED, because of their interference with the balance between neuronal synaptic inhibition and excitation in the central nervous system [27].

Over the last few years, in attempt to reduce the risk of ED, prophylactic measures such as co-administration of propofol, midazolam or fentanyl were used but the risks associated with their use was greater than the benefit [27]. Therefore, strategies such as premedication with ketamine, fentanyl and α2-adrenoreceptor agonists has been demonstrated to prevent ED [3]. In a meta-analysis, Zhu et al. have showed that the intravenous intraoperative administration of dexmedetomidine can be effective in decreasing ED [17]. These authors analyzed recent literature and in their conclusion, they considered the opportunity to find out new strategies to avoid dexmedetomidine side-effects, such as the hemodynamic impact or the delay in recovery from anesthesia or in the time of staying in the surgical area [17].

In the present study, we have chosen to administer dexmedetomidine premedication intranasally, at the dose and waiting times supported by wider consensus [28], because this premedication is safe and well tolerated by patients [29]. In fact, usually most drug delivery in premedication requires an intravenous access. Although effective and associated with a fast onset of action, intravenous access is associated with pain and anxiety in children and may be difficult for inexperienced providers. Intranasal drug administration is an alternative method of medication delivery, it is painless, not associated with unpleasant sensation [30] and has a slower and more gradual onset than intravenous administration [31].

Moreover, this last characteristic is important in order to avoid 2-agonist side effects seen with intravenous administration, such as bradycardia and hypotension.

Remarkably, in our study, only a minority (6%) of patients on dexmedetomidine experienced ED, compared with more than 75% of patients showing this event without dexmedetomidine administration. Moreover, we evaluated the incidence of ED according to type of anesthesia (general or combined) or different ages: the advantage for dexmedetomidine was consistent across all these subgroups, and in those with an expected low rate of ED. In our data, in combined anesthesia and in ages over 6 years and under 3 years old, ED drops to 0% if premedication was performed, compared to, and, already low incidence of ED in these situations in controls (31% over 6 years and 33% under 3 years). This finding is of major relevance, since the use of dexmedetomidine has been poorly explored to date in pediatric patients subjected to combined anesthesia. Our data supports the reduced incidence of delirium with dexmedetomidine in these patients.

With respect to safety, our results are in line with previous reports [12,29,32], since no patients who received dexmedetomidine intranasally in premedication had significant hemodynamic effects. Moreover, at the same time, the administration given in advance compared with the intravenous one can avoid the delay in recovery from anesthesia and in length of staying in surgical area [17]. In our study, no patients in the dexmedetomidine group had longer time of recovery from anesthesia or longer time of staying in recovery room compared with the control group.

This study presents several limitations, including all those inherent to any retrospective study (e.g., poor reporting and selection of treatment according to the clinical status of the patient). Moreover, in order to enhance homogeneity, we considered only patients undergoing interventions with a relatively short surgical time (60–90 minutes), within the range of dexmedetomidine half-life.

# Conclusion

Intranasal dexmedetomidine as a premedication is a safe procedure that can be associated with decreased incidence of ED without increasing the timing of anesthesia or timing of staying in the recovery room after surgery, regardless of patients' age or type of anesthesia. In particular, patients subjected to combined anesthesia report benefit from the use of this molecule.

# Declarations

## *ABBREVIATIONS*

ASA: American Society of Anesthesiologists

ED: emergency delirium

# Ethics approval and consent to participate

The Ethical Committee of the Bambin Gesù Hospital has approved the study design (protocol number 1587_OPBG_2018). The legal guardians of all patients signed an informed consent for the use of the patient's data for research purposes.

# Consent for publication

## Not applicable

# Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

# Competing interests

The authors declare that they have no competing interests.

# Funding

The study was funded by departmental resources.

# Authors' contributions

Study conception and design: ADP, SGP

Data collection: All

Data analysis and interpretation: All

Manuscript drafting: ADP, FM,

Manuscript editing: All

Approval to submit: All

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# Tables

**Table 1. Patients' characteristics.**

| Characteristics | Dexmedetomidine group (n=50) | Control group (n=56) |
|---|---|---|
| Age (years), mean±SD | 5.32±4.68 | 5.74±4.26 |
| Age distribution, n (%): | | |
| · <3 years | 7 | 11 |
| · 3–6 years | 15 | 11 |
| · >6 years | 28 | 34 |
| Males, n (%) | 33 (66) | 38 (76) |
| Indication for surgery: | | |
| · Burns/skin lesions | 5 | 3 |
| · Vascular malformation | 7 | 8 |
| · Hypospadias | 5 | 9 |
| · Syndactyly/polydactyly | 7 | 5 |
| · Giant nevus | 26 | 31 |

**Table 2. Comparison of timing of anesthesia of the dexmedetomidine group and the control group.**

| | Duration of anesthesia (minutes) | | | Discharge time from operating area (minutes) | | |
|---|---|---|---|---|---|---|
| | *Dexmedetomidine group, mean±SD (95% CI)* | *Control group, mean±SD (95% CI)* | *p-value* | *Dexmedetomidine group, mean±SD (95% CI)* | *Control group, mean±SD (95% CI)* | *p-value* |
| Giant nevus | 78±34 (64.26–91.73) | 68±23 (59.56–76.53) | 0.20 | 96±14 (90.34–101.65) | 101±28 (90.72–111.27) | 0.40 |
| Vascular malformation | 66±15 (52.12–79.87) | 71±15 (57.12–84.87) | 0.53 | 104±25 (80.87–127.12) | 111±21 (93.44–128.55) | 0.57 |
| Hypospadia | 56±13 (39.85–74.14) | 50±17 (36.93–63.06) | 0.51 | 98±21 (71.92–124.07) | 105±18 (91.16–118.83) | 0.52 |
| Burns and other lesions | 69±30 (31.75–106.24) | 73±27 (5.92–140.07) | 0.85 | 119±38 (71.81–166.18) | 124±19 (76.80–171.19) | 0.81 |
| Syndactilia/polydactilia | 71±26 (46.95–95.04) | 76±16 (56.13–95.86) | 0.70 | 101±26 (76.95–125.04) | 106±15 (87.37–124.07) | 0.69 |

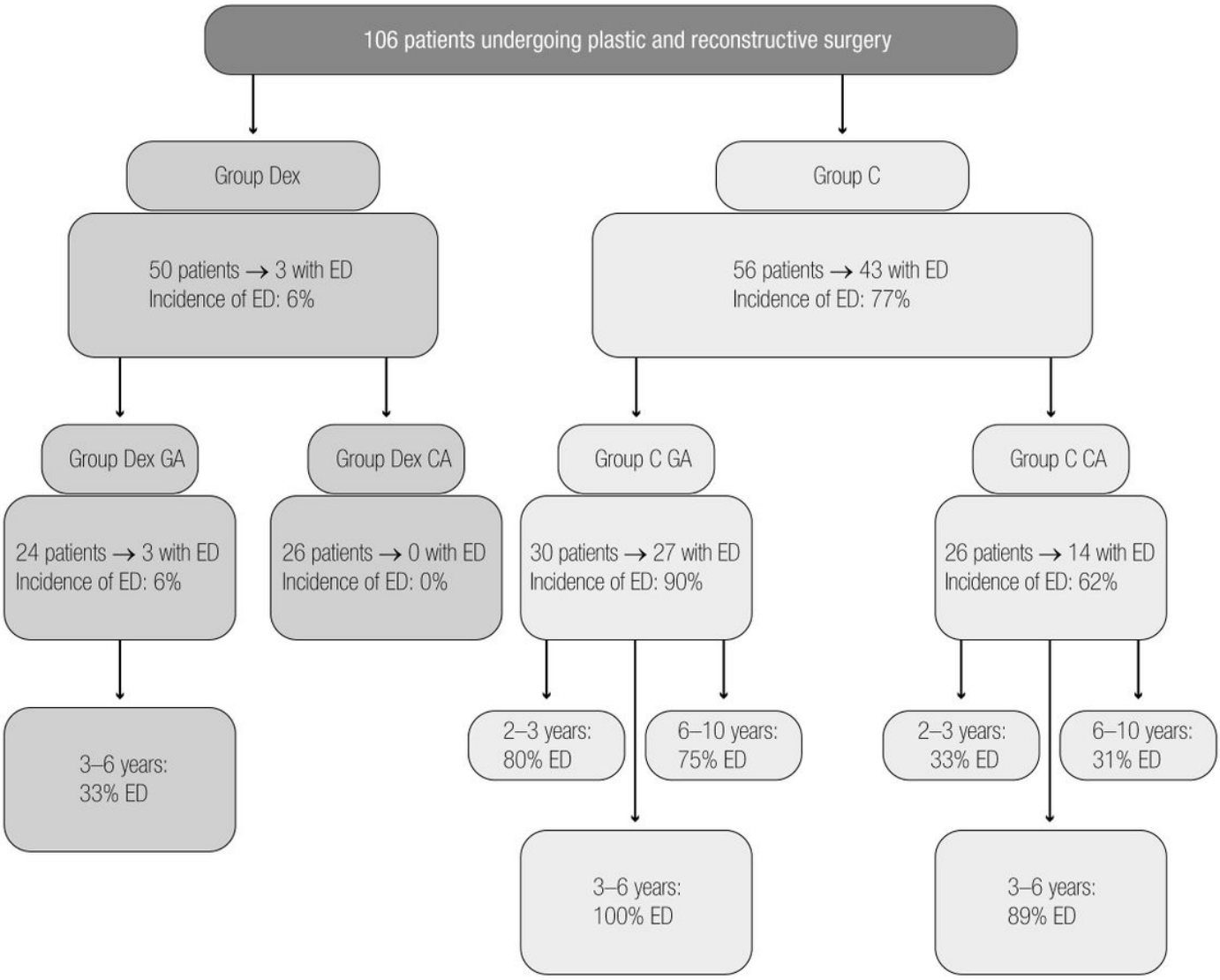
p-values are calculated using Student's t-test.

**Table 3.** Heart rate and mean arterial pressure before premedication with intranasal dexmedetomidine, 15 minutes and 30 minutes after premedication of the three groups divided by age.

| Age (years) | Heart rate (beat/min) | | | | Mean arterial pressure (mmHg) | | | |
|---|---|---|---|---|---|---|---|---|
| | *Before premedication, mean±SD (95% CI)* | *15 min after premedication, mean±SD (95% CI)* | *30 min after premedication, mean±SD (95% CI)* | *p-value* | *Before premedication, mean±SD (95% CI)* | *15 min after premedication, mean±SD (95% CI)* | *30 min after premedication, mean±SD (95% CI)* | *p-value* |
| <3 | 100±8 (92.60–107.39) | 97±7 (90.52–103.47) | 96±6 (90.45–101.54) | 0.25 | 73±2 (71.15–74.84) | 72±1 (71.07–72.92) | 71±1 (70.07–71.92) | 0.34 |
| 3–6 | 95±6 (91.67–98.32) | 93±7 (89.12–96.87) | 92±7 (88.12–95.87) | 0.67 | 75±3 (73.33–76.66) | 74±2 (72.89–75.10) | 73±2 (71.89–74.10) | 0.56 |
| >6 | 88±8 (84.89–91.10) | 86±8 (82.89–89.10) | 85±9 (81.51–88.48) | 0.56 | 81±3 (79.83–82.16) | 80±3 (78.83–81.16) | 79±1 (78.61–79.38) | 0.41 |

p-values are calculated using Student's t-test.

# Figures




## Figure 1

Distribution of emergency delirium in the study groups. CA: combined anesthesia; ED: emergency delirium; GA: general anesthesia.