



Listening to recorded mother's voice versus intravenous dexmedetomidine to minimize postoperative emergence delirium in children after hypospadias repair surgeries: A prospective randomized trial

Omar Soliman , Fatma Nabil and Hany M. Osman

Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Assiut, Egypt

ABSTRACT

Background: Emergence delirium (ED) is a common problem after pediatric general anesthesia. Despite being self-limited, it may be hazardous. The aim of this study was to compare listening to recorded mother's voice versus intravenous dexmedetomidine on incidence and severity of emergence delirium after hypospadias repair surgeries.

Methods: This prospective, double-blind, randomized trial included 99 children (4–9 years), who underwent hypospadias repair surgeries. Patients were randomly distributed into three equal groups: group MV (listening to recorded mother's voice), group D (receiving dexmedetomidine), or group C (control). The primary outcomes were the incidence of ED and its severity using the pediatric anesthesia emergence delirium scale (PAED) at the post-anesthesia care unit (PACU).

Results: The incidence of ED was significantly variable among the three groups ($P = 0.003$). The percentages were 13.3% in group MV, 6.7% in group D, and 40% in group C. Upon arrival to the PACU, the PAED score was significantly lesser in group MV versus group C ($P = 0.006$), and in group D versus group C ($P < 0.001$). However, it was comparable in group MV and group D ($P = 0.478$). Similar significant results were detected 10, 20, and 30 minutes after arrival to the PACU.

Conclusion: This study showed that listening to the recorded mother's voice was comparable to intravenous dexmedetomidine in decreasing the incidence and subsiding severity of emergence delirium in children after hypospadias repair surgeries. Both modalities were also helpful in minimizing preoperative anxiety. Early postoperatively, dexmedetomidine had an extra advantage related to postoperative analgesia.

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1. Introduction

Emergence delirium (ED) or hyperexcitation in patients emerging from general anesthesia (GA) is an old phenomenon [1]. A kid suffering from ED is characterized by being in a dissociated condition of consciousness "irritable, uncompromising, uncooperative, incoherent, and inconsolably crying, moaning, kicking, or thrashing" [2]. ED is more common in pediatric population with a variable incidence (20% to 80%) [3].

Different drugs have been studied to prevent or reduce ED in children including midazolam, clonidine, propofol and fentanyl [4–8]. Dexmedetomidine is an α -2 agonist with sedative and analgesic actions and is commonly used for premedication [9]. Different studies reported the usefulness of dexmedetomidine for management of emergence delirium in children [10–12].

Surprisingly, in children undergoing surgical procedures, auditory stimuli such as perioperative music have shown positive impacts on the postoperative period in the form of minimizing postoperative pain, distress and anxiety [13].

The goal of this research was to compare the effect of listening to the recorded mother's voice versus intravenous dexmedetomidine on incidence and severity of emergence delirium in children after hypospadias repair surgeries.

The primary outcomes were the incidence of ED and its severity using the pediatric anesthesia emergence delirium (PAED) scale. The secondary outcomes were preoperative anxiety, acceptance of anesthesia mask, postoperative pain, postoperative nausea and vomiting (PONV) or any other medication side effects, and post-anesthesia care unit (PACU) stay time.

2. Patients and methods

This prospective, randomized, double-blind, clinical trial was accomplished in Assiut University Pediatric Hospital (between June and October 2021) after obtaining the required approval from the medical institutional review board of Assiut University (Egypt) (Number: 17,300,621). Written informed consents

were signed by the patients' legal guardians. As well, verbal assents were taken from children ≥ 7 years. This study is consistent with the Declaration of Helsinki (Revised DOH 2013) and is registered in clinicalTrials.gov (NCT04941508).

This study involved 99 children of ASA I or II (aged 4–9 years) who had hypospadias anomalies and scheduled for repair surgeries. Children with neurological disorders, developmental delays, hearing impairments, coagulation problems or known allergy to the tested drug were excluded. As well, absence of the mother mandated the exclusion.

Patients were distributed into three equal groups using a random sequence of numbers generated by an internet website (www.random.org) and kept in closed opaque envelopes till the morning of the surgery. Children in recorded mother's voice group (group MV) were assigned to listen to soundtracks of their mothers' recorded voices and to receive intravenous normal saline (placebo). Children in dexmedetomidine group (group D) were assigned to receive intravenous dexmedetomidine (0.2 $\mu\text{g}/\text{kg}$) and to wear headphones with empty soundtracks. Children in the control group (group C) were assigned to receive intravenous normal saline (placebo) and to wear headphones with empty soundtracks.

To keep blindness of the principal investigator towards groups of the study, trained nurses were responsible for releasing the closed envelop, recording mothers' voices, applying and removing noise-cancelling headphones to the children, playing the recorded or empty soundtracks at certain times according to the protocol of the study and preparing two sets of either dexmedetomidine 0.2 $\mu\text{g}/\text{kg}$ (0.2 ml/kg from a concentration of 1 $\mu\text{g}/\text{ml}$) in group D or normal saline (0.2 ml/kg) in group MV or group C. Furthermore, this nurse was responsible for injecting either the prepared drug or the placebo according to the preset protocol. This nurse did not participate in anesthesia, monitoring or any assessment of the patient perioperatively.

2.1. Scales used in the study

2.1.1. The modified Yale preoperative anxiety scale-short form (mYPAS-SF)

This four-category scale is a reliable tool for evaluation of preoperative anxiety in children [14]. The total score = [(activity/4)+(vocalizations/6)+(emotional expressivity/4)+(state of apparent arousal/4)]*100/4, with a range from 23 to 100 [14,15].

2.1.2. The mask acceptance scale (MAS)

It is a four-category scale that is designed to assess child's acceptance of the anesthesia face mask during inhalational induction. The categories are I = excellent (the child is unafraid and cooperative as he accepts the

mask easily), II = good (the child has slight fear of the mask but can be easily reassured), III = fair (the child has moderate fear of the mask that he cannot be calmed with reassurance), and IV = poor (the child is crying, terrified, or combative). The satisfactory scores are 1 and 2 while the unsatisfactory are 3 and 4 [16].

2.1.3. The pediatric anesthesia emergence delirium (PAED) scale

It is designed to measure ED in pediatric patients recovering from GA based on five items (eye contact, purposefulness of actions, awareness of the surroundings, restlessness, and Consolability). Each must be evaluated as not at all, just a little, quite a bit, very much, or extremely, where the first three items to be scored reversely (4 = not at all, 0 = extremely) while the last two items to be scored regularly. ED is directly proportional to the total score [17]. PAED score >12 indicates the presence of ED with high sensitivity and specificity [18].

2.1.4. The FLACC behavioral pain assessment scale

The Face, Legs, Activity, Cry, and Consolability scale is a frequently used tool for pain assessment in children, with a total score of 0 to 10 [19,20].

2.2. Protocol of the study

Few hours before the surgery, in a calm environment, mothers of the patients assigned to group MV were asked to record their voices on two tracks, each of not less than one minute, using the usual tone and sentences they used to calm their children in Arabic language. Soundtrack 1 [OO (name of the child), sleep my love, your mommy is still with you, OO, sleep my love, don't worry, take a deep breath]. Soundtrack 2 [OO (name of the child), open your eyes my love, wake up, let's go home with your mom] [21].

In the ward, an intravenous line was inserted. In the holding area, before any intervention, the mYPAS-SF was used by the principal investigator for assessment of the child's baseline level of anxiety. Three minutes before shifting to the operating theatre (OT), either dexmedetomidine in group D or placebo in group MV or group C was intravenously injected, then headphones were applied to the child followed by playing either soundtrack 1 to be repeated every 10 seconds at a volume set to a speech level of 50–60 decibels in group MV or an empty track in group D or group C. Listening to these soundtracks were continued during the journey to the OT and during induction of anesthesia.

2.3. Anesthetic technique

In OT, before induction of anesthesia, preoperative anxiety was reassessed again by the principal investigator using the mYPAS-SF. During inhalational

induction with sevoflurane, the child's acceptance of the face mask was assessed using the MAS. The intravenous medications included fentanyl (0.5 µg/kg), propofol (1 mg/kg), and cis-atracurium (0.15 mg/kg) to facilitate endotracheal intubation. The soundtracks were stopped, and the headphones were removed just prior to endotracheal intubation. GA was maintained with sevoflurane (2–3%) in 50% oxygen and 50% air. Incremental doses of cis-atracurium (0.03 mg/kg) were used if needed. Before surgical incision, dorsal penile block was done by the surgeon using the landmark method with 3–5 ml of bupivacaine 0.25%. Intraoperatively, intravenous paracetamol (15 mg/kg), ondansetron (0.1 mg/kg), and dexamethasone (0.2 mg/kg) were given.

During dressing, sevoflurane was stopped and either the second dose of dexmedetomidine 0.2 µg/kg (0.2 ml/kg from a concentration of 1 µg/ml) in group D or normal saline (0.2 ml/kg) in group MV or group C was intravenously injected followed by applying the headphones and playing either soundtrack 2 to be repeated every 10 seconds in group MV or an empty track in group D or group C. Listening to these soundtracks was continued during emergence from anesthesia and during the journey to the PACU. The neuromuscular block was antagonized with neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg). Children were encouraged for waking up only by gentle tapping on their bodies. No other stimulations were allowed. Gentle oropharyngeal suctioning was done, only after eye opening, and followed by extubation. The time from stopping sevoflurane to eye opening was recorded.

Upon arrival to the PACU, the headphones were removed then assessments of both ED using the PAED scale and postoperative pain using FLACC scale were done by a well-trained nurse who was blinded to the group of the patient. These assessments were repeated every 10 minutes after arrival to the PACU, then at discharge from the PACU.

In children with a PAED score >12 and/or FLACC score ≥4, fentanyl (0.5 µg/kg) was given. The same dose was to be repeated only one more time if these scores remained high on reassessment. Undesirable events including PONV, laryngospasm, or oxygen desaturation were reported. Patients were discharged from the PACU upon being calm with a modified Aldrete score ≥9, with recording of the PACU stay time.

2.4. Sample size calculation

Based on a previous study [21], a sample size of 90 patients were calculated using G*Power software to be distributed into three equal groups in order to spot an effect size of 0.3 in the rate of ED with α -error of 0.05 and study power of 80%. 10% were added to this sample (three children in each group) to compensate

for the cases who might be discontinued from the study or lost the follow-Up.

2.5. Statistical analysis

The software IBM-SPSS 24.0 was used for analysis of the data. Data are referred to as (mean ± SD), (median and IQR), or (number and percentage). Chi-square test was for comparison of the categorical data among the studied groups. ANOVA and Kruskal-Wallis tests were used as appropriate while post-hoc tests were used for pairwise comparisons. P value < 0.5 was considered significant.

3. Results

Initially, in the pediatric pre-anesthesia clinic, assessment for eligibility was done for 138 children. Out of them 99 candidates were randomly allocated into three equal groups. The study was discontinued in five patients (one patient in group MV, two patients in group D and two patients in group C) for whom surgeries were postponed due to acute medical problems which discovered during their reassessment on the morning of the surgeries, and in two other patients in group MV due to technical failure related to the process of recording the mother's voice. Follow-Up was lost in two patients (one in group D, and one in group C) as they developed laryngospasm after extubation. So, the final analysis included 90 patients (Figure 1).

Patient characteristics, duration of surgery and anesthesia were comparable among the three groups (Table 1).

In the holding area, before any study intervention, the mYPAS-MF was comparable among the three groups ($P = 0.146$). However, in OR, after study intervention but just before induction of anesthesia, the mYPAS-MF differed significantly among the studied groups ($P = 0.005$). The mYPAS-MF was significantly lesser in group MV versus group C ($P = 0.005$), without significant differences in group MV versus group D, or groups D versus C ($P = 0.733$ and 0.127 respectively) (Table 1).

Figure 2 shows that the MAS was significantly variable among the three groups ($P < 0.001$) as the percentages of the satisfactory scores (Excellent and good) were higher in group MV and group D (70% and 80% respectively) compared with only 13.3% in group C. Subsequently, the percentage of the unsatisfactory scores (Fair and poor) was higher in group C.

By the end of surgery, after turning sevoflurane off, the time to eye opening was variable in the three groups ($P < 0.001$). The pairwise analysis showed that it was higher in group D versus group MV and group C ($P < 0.001$, $P = 0.006$ respectively) but did not differ

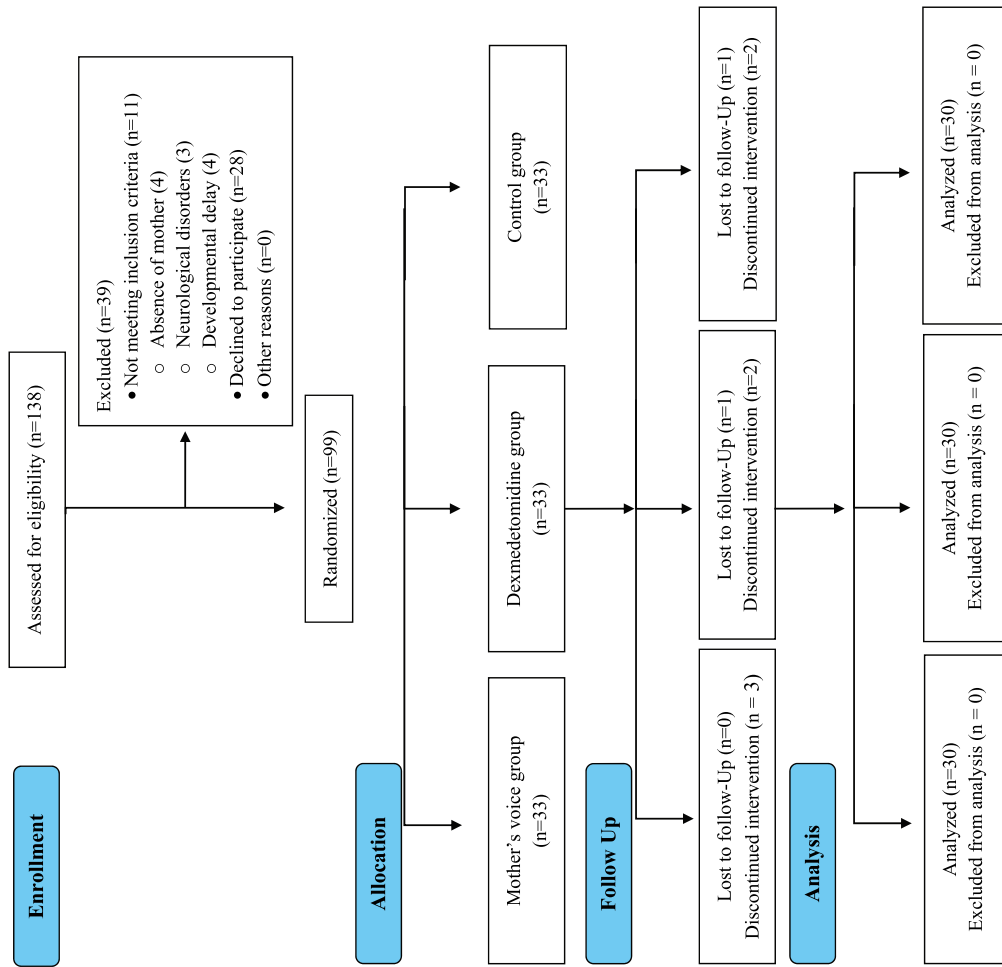


Figure 1. Flow diagram of the study.

Table 1. Patient characteristics and operative data.

Variable	Group MV (n = 30)	Group D (n = 30)	Group C (n = 30)	P value
Age (years)	6.37 ± 1.4	6.16 ± 1.3	6.20 ± 1.3	0.806
Weight (kg)	23.60 ± 4.9	22.17 ± 3.2	22.53 ± 3.4	0.341
Height (cm)	112.37 ± 10	109.57 ± 10.2	107.75 ± 11.1	0.208
Duration of anesthesia (min)	88.03 ± 6.4	91.33 ± 6.6	87.83 ± 7.3	0.089
Duration of surgery (min)	65.37 ± 6.5	68.57 ± 6.2	65.75 ± 6.7	0.117
Time to eye opening (min)	8.70 ± 1.5	10.23 ± 1.1 ^{‡*}	9.17 ± 1.2	< 0.001*
mYPAS-SF				
• Ta	37 (7)	36.5 (6)	39 (4)	0.146
• Tb	36.5 (7) [†]	37.5 (7)	40 (4)	0.005*

Data are expressed as mean ± SD or median (IQR).

MV: mother's voice; D: dexmedetomidine; C: control; mYPAS-SF: modified Yale Preoperative Anxiety Scale-Short Form.

Ta: in the holding area before study intervention.

Tb: in the operating theatre after study intervention but just before induction of anesthesia.

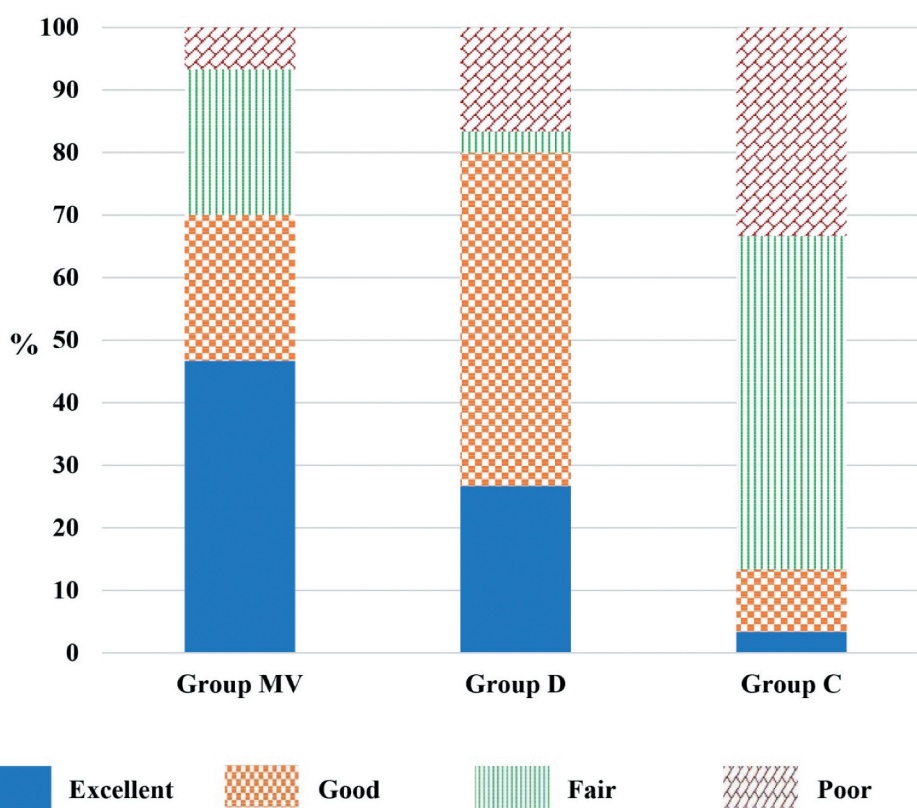
P value < 0.05 is considered statistically significant.

*: denotes significant difference among the three groups.

†: denotes significant difference between group MV and group C.

‡: denotes significant difference between group D and group C.

¥: denotes significant difference between group D and group MV.

**Figure 2.** Mask acceptance scale.

significantly between group MV and group C ($P = 0.499$) (Table 1).

Based on the cutoff value of ED as PAED score >12 [18], the incidence of ED differed significantly among the studied groups ($P = 0.003$). The percentages of cases were significantly lesser in group MV and group D (13.3% and 6.7% respectively) in comparison to group C (40%) (Table 2).

Upon arrival at the PACU, the PAED score was significantly variable among the three studied groups ($P < 0.001$). Pairwise analysis displayed that the PAED score was significantly lesser in group MV versus group C ($P = 0.006$) and in group D versus group C ($P < 0.001$)

with no significant difference with regard to group MV versus group D ($P = 0.478$). Similar significant differences among the three groups were detected 10, 20, and 30 minutes after arrival to the PACU ($P < 0.001$, 0.001, and < 0.001 respectively). At discharge from the PACU, the PAED score remained significantly different among the three groups ($P = 0.014$), however, pairwise analysis showed that the PAED score was significantly lesser in group D versus group C with no significant differences between group MV versus group D or group MV versus group C (Table 2).

Regarding the FLACC behavioral pain scale: upon arrival to the PACU, and 10 minutes later, there were

Table 2. Data at the PACU.

Variable	Group MV (n = 30)	Group D (n = 30)	Group C (n = 30)	P value
Incidence of emergence delirium	4 (13.3%)	2 (6.7%)	12 (40.0%)	0.003*
PAED scale				
at arrival to the PACU	8 (4.8–11) †	6.5 (2.8–9) ‡	12 (9–14)	< 0.001*
10 min	3 (1–7.5) †	2 (1–4.3) ‡	6.5 (3.8–10.5)	< 0.001*
20 min	1 (0–3) †	1 (0–2) ‡	2 (1.8–5.5)	0.001*
30 min	0 (0–1) †	0 (0–1) ‡	1 (1–2)	0.001*
at discharge from the PACU	0 (0–1)	0 (0–0) ‡	0.5 (0–1)	0.014*
FLACC behavioral pain assessment scale				
at arrival to the PACU	3 (2–4.3)	2 (1–3) ‡	3 (2–6)	0.002*
10 min	2 (1–3)	1 (1–2) ‡	2 (1–3)	0.048*
20 min	1 (1–2)	1 (0.8–2)	1 (1–2)	0.322
30 min	1 (0–1)	1 (0–1)	1 (0–2)	0.185
at discharge from the PACU	0 (0–1)	1 (0–1)	0 (0–1)	0.700
PONV	1 (3.3%)	0 (0%)	1 (3.3%)	1.000
PACU stay (min)	38.89 ± 7.3†	35.50 ± 6.1‡	46.17 ± 9.3	< 0.001*

Data are expressed as number (%), median (IQR), or mean ± SD.

MV: mother's voice; D: dexmedetomidine; C: control; PACU: post-anesthesia care unit; PAED: pediatric anesthesia emergence delirium; FLACC: Face, Legs, Activity, Cry, Consolability; PONV: postoperative nausea and vomiting.

P value < 0.05 is considered statistically significant.

*: denotes significant difference among the three groups.

†: denotes significant difference between group MV and group C

‡: denotes significant difference between group D and group C.

‡: denotes significant difference between group D and group MV.

significant differences among the three groups ($P = 0.002$ and 0.048 respectively). Pairwise analysis showed that FLACC score was significantly lower in group D versus group C and in group D versus group MV, but it did not differ significantly in group MV versus group C at both times. Twenty and thirty minutes later, and at discharge from the PACU, the FLACC scale became comparable among the groups of the study (Table 2).

The PACU stay time was significantly different among the three groups ($P < 0.001$). Pairwise analysis showed that the duration of PACU stay was significantly lesser in group MV versus group C and in group D versus group C. However, it was comparable in group MV and group D. The incidence of PONV was comparable among the studied groups (Table 2).

4. Discussion

Emergence delirium is a self-limiting disturbance [22]. However, it may result in harmful or unwanted incidents including self-injury, disruption of surgical repairs or accidental removal of intravenous catheters or surgical drains or dressings [2,23]. These, in addition to the possibility of self-removing the urethral catheter, may be especially hazardous after hypospadias surgeries.

Different pharmacological and non-pharmacological strategies have been tested to protect against or to manage ED [1,24]. In this research, we compared the effect of listening to the recorded mother's voice (prior to both inhalational induction with sevoflurane, and emergence from GA) versus intravenous dexmedetomidine on incidence and severity of ED.

The incidence of ED in this study using a cutoff score of >12 in PAED scale was significantly lower in both the recorded mother's voice and dexmedetomidine groups (13.3% and 6.7% respectively) in comparison to the control group (40%). Moreover, during the first thirty minutes of arrival to the PACU, the PAED scores were much lower with both interventions.

In agreement with this result, Yang YY and his colleagues reported that listening to a recorded mother's voice was linked to significant fall in the incidence of ED after ophthalmic procedures in children [25]. Similarly, a previous study reported significant reduction in the incidence and score of ED in response to listening to a recorded mother's voice compared to listening to a recorded stranger's voice in children who underwent ophthalmic or otorhinolaryngeal surgeries [21].

Among the possible etiological factors of ED in children are patient's age, surgical type, preoperative anxiety, parental anxiety, volatile anesthetics and pre-existing behavioral disorders. Preoperative anxiety is a major contributor of ED in pediatric patients. Kain and colleagues reported 10% increase in ED with every 10 points increase in the child's anxiety [26].

This study showed that, before induction of anesthesia, the anxiety score (mYPAS-MF) was significantly lower in the children who were listening to their recorded mothers' voices or who received intravenous dexmedetomidine versus those in the control group with no difference between both interventions. Similarly, in a previous study on children who were undergoing cardiac catheterization using ketamine, listening to a recorded maternal voice during the peri-anesthetic period was associated with lower anxiety scores [27].

Attendance of one of the parents during induction of GA is reported to have variable effects. Some studies

reported positive impacts in reducing anxiety [28,29], but others showed no effect or even negative impacts specially with anxious parents [24,30]. So, listening to the recorded mother's voice may be a good substitute that helps in decreasing anxiety of the child specially in case of anxious parents.

Preoperative anxiety frequently causes children to resist the application of the mask during inhalational induction of anesthesia. Hence, it extends the duration of induction and may result in postoperative psychological problems [31,32]. Different strategies have been described to help children to accept the face mask during inhalational induction of GA including premedication with sedative drugs like midazolam. Among the non-pharmacological strategies that have been attempted are mask preconditioning, behavioral and mental preparations, parental presence and distraction of attention [32]. This study showed satisfactory mask acceptance in both dexmedetomidine and mother's voice groups.

Previous studies reported pain as one of the etiological factors of pediatric ED [23,33]. However, ED may occur even after non-painful diagnostic procedures, such as MRI studies [34]. It is crucial to differentiate between both pain and ED as two early postoperative negative behaviors, since children may suffer from ED, pain, or both [22]. Misdiagnosis may lead to undertreatment of pain or the administration of unnecessary analgesics for children suffering from ED [22].

In the current study that included surgeries with anticipated high pain intensity, penile block and intravenous paracetamol were given intraoperatively in order to minimize postoperative pain and to facilitate the evaluation of ED. Upon arrival to the PACU, FLACC score was significantly lower in dexmedetomidine group. This could be explained by the effect of the second dose of dexmedetomidine. According to Mizark and his colleagues, the postoperative analgesic requirements decreased significantly if the patient was premedicated with a single dose of dexmedetomidine [35].

From our perspective, the current study had two limitations: First, no monitoring was available for the conscious level; Second, it did not include younger children as they require different scores for the evaluation of pain, anxiety, and ED.

We recommend further studies to evaluate the effect of combination of both auditory stimuli such as the recorded mother's voice, as a non-pharmacological modality, and dexmedetomidine, as a pharmacological option, to achieve the minimum levels of preoperative anxiety, postoperative ED, and postoperative pain.

5. Conclusions

This study showed that listening to the recorded mother's voice was comparable to intravenous dexmedetomidine in decreasing the incidence and subsiding

severity of emergence delirium in children after hypospadias repair surgeries. Both modalities were also helpful in minimizing preoperative anxiety. Early postoperatively, dexmedetomidine had an extra advantage related to postoperative analgesia.

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Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Omar Soliman  <http://orcid.org/0000-0002-3997-9303>

Fatma Nabil  <http://orcid.org/0000-0001-5596-4040>

Hany M. Osman  <http://orcid.org/0000-0001-7542-1481>

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