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Research article

Preoperative intranasal dexmedetomidine versus intranasal ketamine for prevention of emergence agitation after sevoflurane in myringotomy patients: A randomized clinical trial

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1. Introduction

Emergence agitation (EA) is characterized by irritability, mental confusion, disorientation, inconsolable crying [1]. It can lead to damage to surgical dressings, possible injury, disconnected cables and monitoring instruments, lost intravenous catheters, dissatisfaction for parents, and nurses, more nursing care and supplemental sedative and/or analgesic drugs, and prolonged hospital stay [2].

A higher incidence of EA in children is observed when sevoflurane is used alone [1–3]. Propofol, ketamine, pain prevention, and alpha$_2$ adrenergic agonists seem to be effective in prevention of EA after sevoflurane anesthesia [4]. Both ketamine [5,6] and dexmedetomidine [7–9] through different routes were used to prevent EA after sevoflurane anesthesia, but to the best of our knowledge, there is no clinical trial comparing both drugs through the intranasal route before induction of anesthesia for prevention of EA. So, the aim of this study was to compare the effect of pre-operative intranasal dexmedetomidine and intranasal ketamine for prevention of EA after sevoflurane anesthesia in pediatric patients scheduled for myringotomy operations.

2. Patients and methods

This randomized double blind study was carried out in Tanta University Hospital at the Oto-Rhino-Laryngology Department on the time period from February to August 2016 on ninety pediatric patients aged from 3 to 6 years, ASA physical status I or II, of both sexes scheduled for unilateral or bilateral myringotomy. The trial is approved from the ethical committee of the Faculty of Medicine Tanta University with approval code of 30758/02/16 and registered in the Australian New Zealand Clinical Trials Registry with the number: ACTRN12616000921482.

Patients were excluded from the study in case of parent's refusal or if they presented with preoperative agitation, mental retardation, or neuromuscular disease, allergy to ketamine, and/ or dexmedetomidine, nasal deformity or nasal trauma, acute (e.g. running nose or upper respiratory tract infection) or chronic nasal problems. Patients treated with sedatives or anticonvulsants, respiratory and cardiovascular diseases were also excluded.

The primary outcome was the incidence of EA, the sample size was calculated using the incidence of EA (57%) in the study of Cravero et al. [10], and it was found that at least 42 patients were required in each group to find a significant difference of 30% in the incidence of EA between the two groups, group to group ratio 1:1 with 80% power of the study and cut off statistical significance of 0.05%. An informed written consent was taken from the parents of each child. Preoperatively, 95 patients were assessed for eligibility, 5 of them were excluded; 2 because of parents refusal and 3 were not meeting the inclusion criteria (2 had mental retardation and, 1 was suffering from nasal deformity). So, 90 patients were allocated into 2 equal groups each of 45 patients; group I (Intranasal ketamine), received ketamine intranasal in a dose 5 mg/kg using 10-mL Ketamine HCl Injection multi-dose vial, USP 500 mg/10 mL (50 mg/mL). Group II (Intranasal dexmedetomidine), received intranasal dexmedetomidine in a dose 1 μg/kg

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prepared from parenteral dexmedetomidine preparation (Precedex inj™ 200 μg/2 mL (100 μg/mL). In both groups, the study drug dose was diluted with normal saline to a total volume of 1 ml (0.5 ml for each nostril), Fig. 1.

The patients were randomized using computer generated random numbers and closed envelops. A blinded nurse read the patient's number; the parents were blind as regard the patient's group. The drugs were prepared and the data were collected, recorded and analyzed by a blinded anesthetist.

No premedication was given and anesthesia was induced 20 min after study drug administration with sevoflurane which was titrated with increments of 1% at each breath up to 8% in oxygen 100%. Once an appropriate depth of anesthesia was obtained an IV cannula and a suitable laryngeal mask were inserted and sevoflurane concentration was reduced to 3%. Spontaneous breathing was allowed provided $ETCO_2$ remained below 50 mm Hg. No muscle relaxant or narcotic was administered and the patients were monitored continuously for heart rate (HR), oxygen saturation, respiratory rate (RR), end tidal CO_2 and arterial blood pressure. Sevoflurane was discontinued immediately after T-tube insertion, and the laryngeal mask was removed 60 s later and the patient was transported to the post-anesthesia care unit in a quiet and warm environment. Parents were allowed to be at the child's bedside.

The primary outcome measures were the incidence and the severity of EA. The incidence of EA was evaluated 5 min after awakening using Aono's four point scale [11]; 1 = calm 2 = not calm but could be easily consoled; 3 = moderately agitated and not easily calmed; 4 = combative, excited, or disoriented, thrashing around. Scores of three and four were considered as presence of EA, while, one and two as absence of EA. The severity of EA was evaluated with the pediatric anesthesia emergence delirium (PAED) [12]; a five points rating scale; (eye contact, purposeful actions, awareness of surroundings, restlessness and consolability), with five grades (0–4) for each item, and a total score of 20. The severity of EA increased proportional to the total score. A score ≥10 was considered agitated, and was treated with i.v propofol (1 mg/kg) as rescue medication. A score ≥15 reflected severe agitation while, scores <10 meant no agitation. The severity of EA was evaluated at 5, 10, 15 and 30 min after awakening.

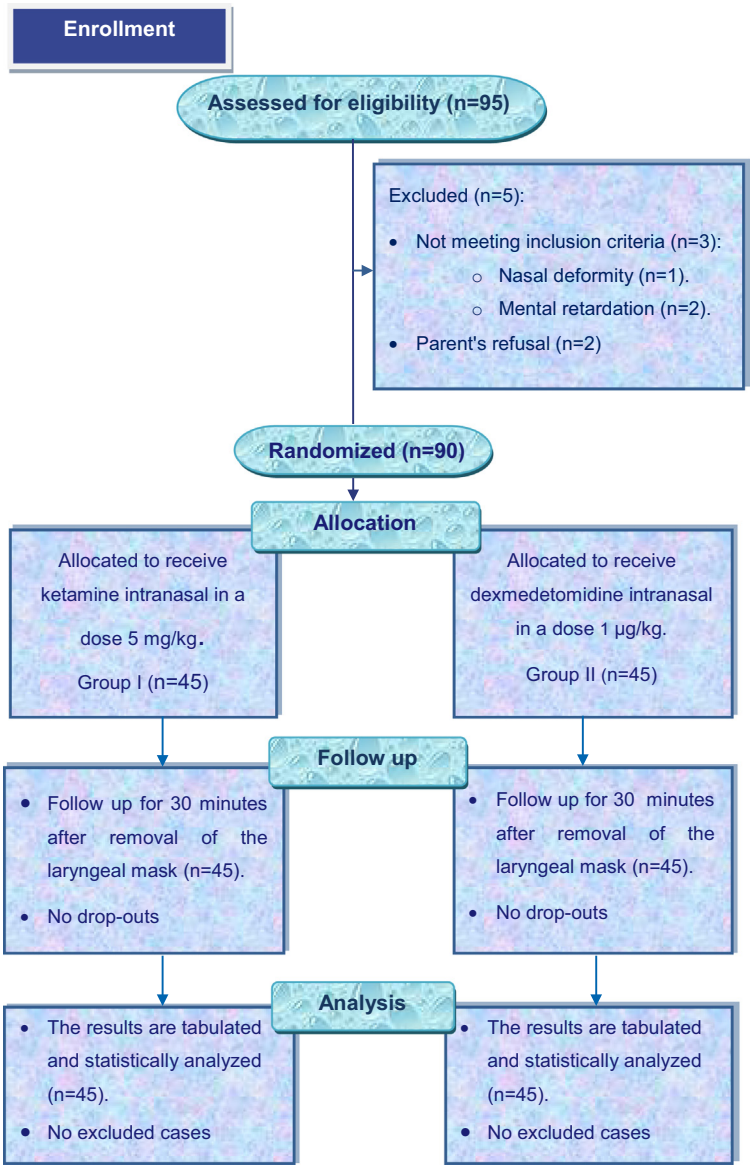

Fig. 1. Consort participant-flow diagram.

Secondary outcomes; HR, RR and degree of sedation were recorded just before and 10 min after drug administration, at induction, 5, 10, 15, and 30 min after awakening. The University of Michigan sedation scale (UMSS) [13] was used to assess the degree of sedation; 4: unarousable, 3: deeply sedated, aroused only with significant physical stimulus, 2: moderately sedated, arousable with light tactile stimulus. 1: minimally sedated, appropriate response to sound or verbal stimulus and 0: alert and awake.

The response to parental separation was assessed using parental separation anxiety scale [10]; excellent (1) the child was cooperative, unafraid or asleep. Good (2) the child was slightly afraid/crying and quiet with reassurance. Fair (3) the child was moderately afraid and no response to reassurance. Poor (4) the child was crying and needed restraint. The response to face mask induction [10] was evaluated using the mask acceptance scale; 1 = combative, crying, 2 = not easily calmed, moderate fear of mask, 3 = cooperative with reassurance, 4 = cooperative and calm. Duration of anesthesia (minutes): the time from induction till removal of the laryngeal mask. Duration of emergence (minutes): the time from switching off sevoflurane to spontaneous eye opening, and the ability to obey commands. Occurrence of complications**:** e.g. nausea, vomiting, bradycardia, Cough, laryngospasm, or desaturation (SpO_2 below 95%), or any other complication were recorded.

The data were analyzed using SPSS (version 20); quantitative data (age, weight, RR, HR, duration of surgery, anesthesia, and emergence) were expressed as mean ± SD and analyzed using independent-*t*-test for comparison between the two groups. The non-parametric data (the response to parental separation, and face mask induction, Aono's, PAED and UMSS scales) were expressed as median (Inter Quartile Range) and analyzed with Mann-Whitney test for comparison between the two groups. While, the sex, frequency of patients in Aono's, and PAED scales were expressed as number (%). $P < 0.05$ ($CI_{95\%}$) (With 95% confidence intervals of the difference) was considered statistically significant.

3. Results

There was no statistical significant difference between the two groups regarding the demographic data (age, weight), duration of surgery, anesthesia and emergence (p-values > 0.05), Table 1.

Also, there was no significant difference the incidence of EA (Aono's four point scale evaluated 5 min after awakening), Fig. 2, the severity of agitation (PAED scale at all time intervals), Table 2, and, response to parental separation or face mask induction, Table 3 between the two groups with p values > 0.05. Only 3 patients (6.6%) in each group had EA with Aono's score of 3 or 4, Fig. 2. The severity of agitation decreased gradually with time; at 5 min after awakening; only two (4.4%) patients in group I and one (2.2%) patient in group II had severe agitation (a score >15) and

Table 1
Patient characteristics, duration of anesthesia, surgery and emergence in both groups.

	Group I (ketamine) (n = 45)	Group II (dexmedetomidine) (n = 45)
Age (years)	4.3 ± 0.6	4.1 ± 0.8
Weight (Kg)	16.8 ± 1.9	16.1 ± 2.0
Sex		
Male	20 (44%)	22 (49%)
Female	25 (56%)	23 (51%)
Duration of surgery (min)	6.8 ± 2.4	6.4 ± 2.1
Duration of anesthesia (min)	12.8 ± 2.5	12.0 ± 2.2
Duration of emergence (min)	4.3 ± 0.6	4.4 ± 0.6

Data are expressed as mean ± SD except sex which is expressed as number (%).
There was no statistical difference between groups.

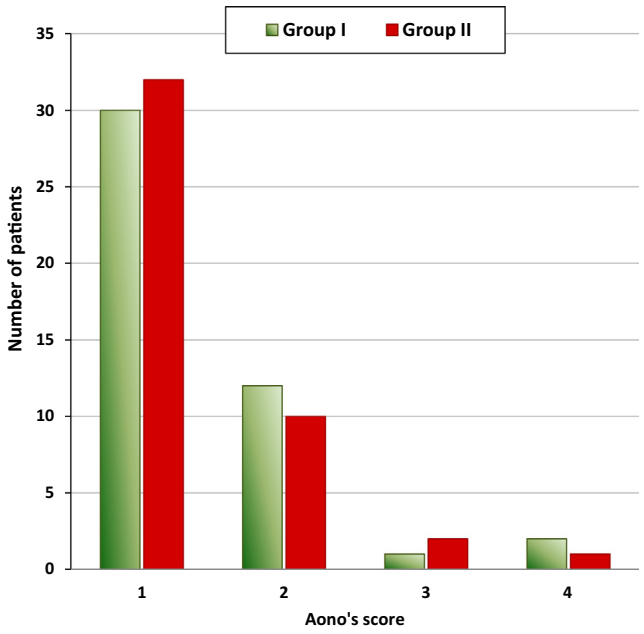

Fig. 2. Aono's score in both groups. No significant difference between the two groups. n = 45 in each group (Group I, n = 45. Group II, n = 45).

Table 2
Pediatric anesthesia emergence delirium (PAED) scale after awakening in both groups.

	Group I (ketamine) (n = 45)	Group II (dexmedetomidine) (n = 45)
AT 5 min		
Median (IQR)	2 (1–3.5)	2 (1–4)
PAED scale 10 to <15 n (%)	1 (2.2%)	2 (4.4%)
PAED scale ≥ 15 n (%)	2 (4.4%)	1 (2.2%)
At 10 min		
Median (IQR)	2 (1–2)	1 (1–2)
PAED scale 10 to <15 n (%)	3 (6.7%)	1 (2.2%)0
PAED scale ≥ 15 n (%)	0	0
At 15 min		
Median (IQR)	1 (1–2)	1 (1–1)
PAED scale 10 to <15 n (%)	1 (2.2%)	0
PAED scale ≥ 15 n (%)	0	0
At 30 min		
Median (IQR)	1 (0–1)	1 (0–1)
PAED scale 10 to <15 n (%)	0	0
PAED scale ≥ 15 n (%)	0	0

IQR; Inter Quartile Range, data expressed as median (IQR).
There was no statistical difference between groups.

Table 3
Response to parental separation and face mask induction in both groups.

	Group I (ketamine) (n = 45)	Group II (dexmedetomidine) (n = 45)
Response to parental separation		
Median (IQR)	1 (1–1.5)	1 (1–2)
(1) Excellent, n (%)	34 (75.6%)	32 (71.1%)
(2) Good, n (%)	11 (24.4%)	13 (28.9%))
Response to face mask induction		
Median (IQR)	4 (3–4)	4 (3–4)
(3) Cooperative and calm, n (%)	30 (66.7%)	26 (57.8%)
(4) Cooperative with reassurance, n (%)	11 (24.4%)	19 (42.2%)

IQR; Inter Quartile Range.
Data expressed as median (IQR) or number (%).
There was no statistical difference between groups.

one patient (2.2%) in group I and two patients in group II had a score between 10 and 15. Then at 10 min, no severe agitation was found in both groups and, 3 (6.7%) and 1 (2.2%) patients had a score ranging from 10 to <15 in groups I and II respectively then, at 15 min only one patient (2.2%) in group I had a score of 12 and no agitation was found in group II, Table 2.

The UMSS was increased significantly in group I compared to group II at 10 min after drug administration with a p-value of 0.012. Then, there was no significant difference between groups at induction, 5 and 10 min after awakening (p-values > 0.05). While, there was a significant clinical and statistical increase in UMSS in group II compared to group I at 15 and 30 min after awakening with a p-value of <0.001, Table 4.

Table 4
The University of Michigan sedation scale (UMSS) in both groups.

		Group I (n = 45) (ketamine)	Group II (n = 45) (dexmedetomidine)
At 10 min after drug	Median (IQR)	0 (IQR, 0–1)	0 (IQR, 0–0)*
	0	25 (55.6%)	37 (82.2%)
	1	20 (44.4%)	8 (17.8)
At induction	Median (IQR)	1 (IQR, 1–1)	1 (IQR, 1–1)
	0	7 (15.6%)	2 (4.4%)
	1	32 (71.1%)	35 (77.8%)
	2	6 (13.3%)	8 (17.8%)
5 min after awakening	Median (IQR)	1 (IQR, 1–2)	1 (IQR, 1–2)
	1	25 55.6%)	23 (51.1%)
	2	20 (44.4%)	22 (48.9%)
10 min after awakening	Median (IQR)	1 (IQR, 1–1)	1 (IQR, 1–2)
	1	38 (84.4%)	31 (68.9%)
	2	7 (15.6%)	14 (31.1%)
15 min after awakening	Median (IQR)	0 (IQR, 0–1)	1 (IQR, 1–1)**
	0	30 (66.7%)	0
	1	15 (33.4)	40 (88.9%)
	2	0	5 (11.1%)
30 min after awakening	Median (IQR)	0 (IQR, 0–0)	1 (IQR, 0–1)**
	0	42 (93.3%)	16 (35.6%)
	1	3 (6.7%)	29 (64.4%)

IQR; Inter Quartile Range, data expressed as Median (IQR) and number (%).
* Significant at p < 0.05 compared to the ketamine group.
** Significant at p < 0.001 compared to the ketamine group.

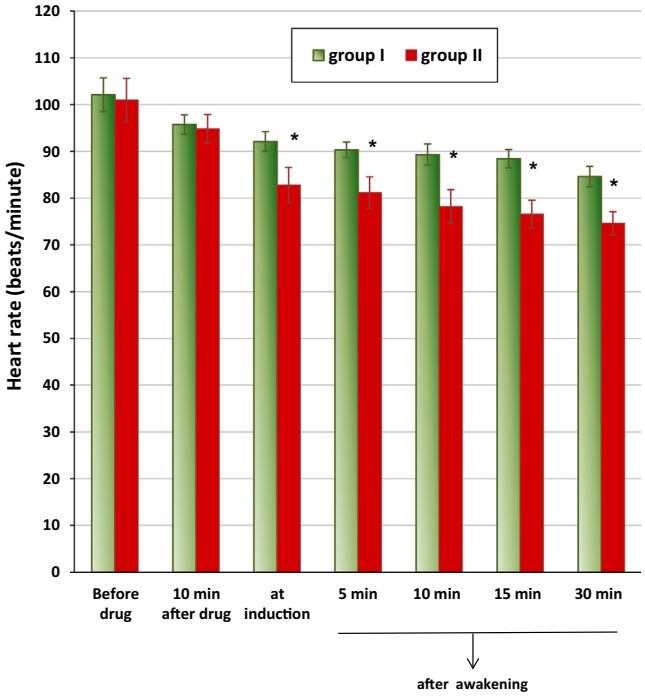

Fig. 3. Heart rate (beats/min) in both groups. *Statistically significant compared to group I (p < 0.001). n = 45 in each group (Group I, n = 45. Group II, n = 45).

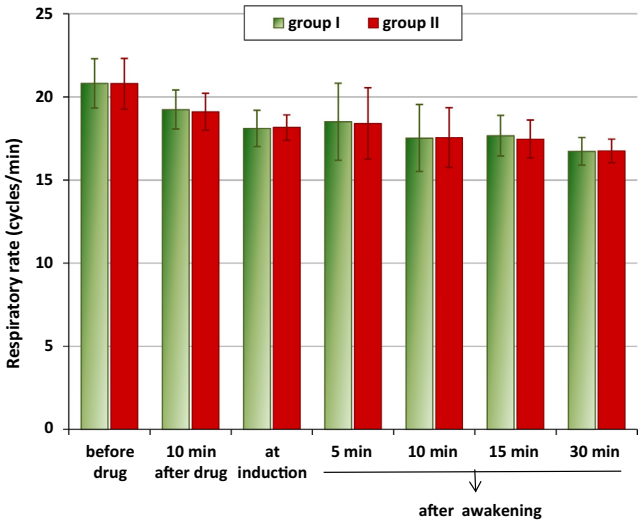

Fig. 4. Respiratory rate (breath/min) in both groups. There was no statistical difference between the two groups. n = 45 in each group (Group I, n = 45. Group II, n = 45).

Regarding the HR, There was no significant difference between the two groups before and 10 min after drug administration with p-values > 0.05, then there was a clinical and statistical significant decrease in the mean values of HR in group II compared to group I at the subsequent time intervals with p values < 0.001 and $CI_{95\%}$ of (8.02, 10.60), (8.02, 10.25), (9.82, 12.31), (10.8, 12.93) and (10.51, 12.47) at induction of general anesthesia, 5, 10, 15, and 30 min after awakening respectively, Fig. 3.

Despite the decrease in HR in group II, no patient needed treatment for bradycardia. The RR showed no significant difference between groups at all time intervals with p-values > 0.05, Fig. 4. There were three cases of increased salivary secretion in the ketamine group, (didn't need any treatment), however, there was no cough, desaturation, laryngospasm, hypotension or any other complication in both groups.

4. Discussion

In literature the reported incidence of EA has ranged from 18 to 57% [10,14] in children after sevoflurane anesthesia, while, in the present study only 3 patients (6.6%) in each group had EA. Also, the severity of agitation decreased gradually with time; no severe agitation in both groups at 10 min, then, at 15 min only one patient (2.2%) in group I had a score of 12 and no agitation was found in group II. So, both drugs were effective through the intra-nasal route to prevent EA after sevoflurane anesthesia for myringotomy operations.

The etiology of EA after sevoflurane anesthesia is not clear, it may be related to preoperative anxiety, pain, patient characteristics, type of surgery, or anesthetics and too rapid awakening [2]. Gyanesh et al. [15] compared intranasal dexmedetomidine (1 μg/kg) with ketamine (5 mg/kg) prior to IV cannulation for MRI sedation, both drugs provided adequate levels of sedation, so, in the present study, the same doses were used and both drugs were effective for preoperative sedation, as indicated by the good response to parental separation and face mask induction, however, dexmedetomidine had delayed onset and prolonged duration com-

pared to ketamine, thus, preoperative anxiety can be rolled out as a cause of EA. Many studies support the use of ketamine [15,16] and dexmedetomidine [15,17–19] for preoperative sedation. Dexmedetomidine; an alpha$_2$-agonist; has a sympatholytic effect via central and peripheral mechanisms, stimulates alpha$_2$-adrenergic receptors in the locus ceruleus producing sedation and, in the spinal cord enhancing analgesia [20]. While, Ketamine mediates its analgesic and sedative effects in the central nervous system through its non-competitive antagonism of the N-methyl-D-aspartate receptors and subsequently diminishes central sensitization, furthermore, ketamine may possess protective effects on ischemic neurons [21].

Each of ketamine [5,6,22] through intravenous route [9] and dexmedetomidine [7,8] through the intravenous route were used to prevent EA after sevoflurane anesthesia, and were found to be effective, however, in most of the studies it was given just before recovery from sevoflurane anesthesia and so, the role of preoperative anxiety cannot be rolled out. The intranasal route for anesthetic premedication has the advantages of ease of administration and avoidance of pain on injection, and first-pass metabolism [17]. In the present study each of ketamine and dexmedetomidine was given through the intranasal route 20 min before induction of anesthesia, which is the expected time of onset of sedation of dexmedetomidine based on the results of a pilot study in our institute. According to the study of Lirola and his colleagues [23] dexmedetomidine administered intranasally has good bioavailability and its effects were similar to those of intravenous route, was well tolerated, and its maximal effect was after 45–60 min [17], and Myringotomy is a minimally invasive surgery so, pain, is excluded as a causative factor for EA. The etiology of emergence agitation during sevoflurane anesthesia may be related to the cortical epileptiform EEG signs which may appear and its incidence and periodicity correlate with the increasing expired fraction of sevoflurane, usually with no clinical manifestation, lasting neurological or epileptogenic EEG sequelae. Thus, it is important to limit the anesthetic depth to a maximum of 1.5 MAC sevoflurane for maintenance of anesthesia [24]. In the present study the concentration of sevoflurane was less than 1.5 MAC for age during maintenance of anesthesia, while, it exceeded this safe limit only briefly for few breaths during induction of anesthesia.

There was a clinical and statistical significant decrease in the mean HR in group II compared to group I, however, no patient needed treatment for bradycardia, this can be explained on the basis of the increase in HR in group I and its decrease in group II. The effect ketamine is mediated through central sympathetic stimulation and increase in the concentration of nor-epinephrine due to inhibition of neuronal and extra-neuronal catecholamine uptake [21] while, dexmedetomidine causes decrease in HR through its alpha$_2$-agonist activity [20]. This is supported by the study of Yuen et al. [18] who reported insignificant clinical reduction in the HR during the first hour after administration of 0.5 and 1 μg/kg of intranasal dexmedetomidine in healthy children preoperatively. In the present study, there was increased salivary secretion in three cases in ketamine group, however, there was no cough, desaturation, laryngospasm, hypotension or any other complication in both groups, these results were in agreement with Guler et al. [7], Cimen et al. [17] and, Iirola et al. [23].

The present study has some limitations, as the results cannot be applied for surgeries of long duration, moreover, the study must be repeated on a larger sample size for more accurate results regarding the possible complications.

In conclusion, both intra-nasal dexmedetomidine (1 μg/kg) and intra-nasal ketamine (5 mg/kg) given 20 min before induction of anesthesia were effective in prevention of EA after sevoflurane anesthesia in pediatric patients undergoing elective myringotomy, and there were no significant differences between the two groups.

- The trial was performed according to *Helsinki Declaration.*
- *Financial support:* none.
- *Conflict of interest:* none.
- *Presentation:* none
- Assistance: none.

Contribution

Study design and, conduct of the study, data analysis and manuscript preparation.

What is known:

- Preoperative anxiety may be one of factors affecting EA in children.
- both I.V dexmedetomidine and ketamine before extubation were effective for preoperative sedation, and prevention of EA after sevoflurane anesthesia.

What this study adds:

- Preoperative intra-nasal dexmedetomidine and ketamine were effective to prevent EA after sevoflurane anesthesia for myringotomy operations.
- The trial is registered in *the Australian New Zealand Clinical Trials Registry* with the number: ACTRN12616000921482.
- **IRB:** The Research Ethics Committee of the Faculty of Medicine, Tanta, Egypt, approval code: 30758/02/16.
- **Publication category**: original contribution.
- **Funding source:** self funded.
- The contents **have not been published** elsewhere and the paper is not being submitted elsewhere.

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