Introduction

Preoperative anxiety and respiratory complications are the commonest complications in children undergoing adenotonsillectomy [1]. Perioperative respiratory complications are the most common and dangerous complication during pediatric anesthesia, manifested as minor adverse events (oxygen desaturation, airway obstruction, coughing, or wheezing) and major adverse events (laryngospasm and bronchospasm). These complications can prolong hospitalization time and costs, and bring varying degrees of physical and psychological trauma to children and parents [2].

Anxiety in children undergoing surgery is characterized by subjective feelings of tension, apprehension, nervousness, and worry that may be expressed in various forms [3].Postoperative maladaptive behaviors, such as new onset enuresis, feeding difficulties, apathy , and sleep disturbances, may also result from preoperative anxiety [4] .

In fact, studies in 60% of all children undergoing surgery may present with negative behavioral changes at 2 weeks postoperatively [5]. Variables such as age, and anxiety of the child and parent in the preoperative holding area have been identified as predictors for these behavioral changes. Extreme anxiety during induction of anesthesia is also associated with an increase of these postoperative negative behavioral change [6].

Premedication in children is helpful for both separating the child from their parent and reducing the child's stress and anxiety, thus facilitating smooth induction of anesthesia [7].

Many drugs can be taken by the intranasal route such as glucocorticoids, nasal decongestants, naloxone, midazolam, ketamine, and dexmedetomidine [8]. The administration of intranasal dexmedetomidine, ketamine or midazolam avoids the need for intravenous cannulation. Intranasal drug administration is a relatively easy noninvasive route with high bioavailability as it bypasses first-pass hepatic metabolism and also because of the high blood supply in the nasal mucosa [9].

Dexmedetomidine is a selective alpha 2 agonist like clonidine, but with higher affinity to the alpha 2 receptor. Dexmedetomidine produces dose-dependent sedation, anxiolysis, and analgesia without respiratory depression. Dexmedetomidine triggers and maintains natural sleeping status without eye movement by stimulating the locus coeruleus in the brain stem, so it increases the activity of inhibitory gamma aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus [10].

Ketamine is proved to interact with many receptors, including the N-methyl-D-aspartate receptor (NMDA-R) producing a dissociative anesthesia.

Ketamine is known to reduce central sensitization to pain, decrease overall opioid utilization, and produce effective sedation [11].

Intranasal midazolam is one of the benzodiazepines. It is characterized by rapid onset (10–12 min) and short duration, with high bioavailability (55–83%) [12]. the benzodiazepine receptors are found to be expressed in olfactory nerves. Therefore, it is likely that intranasal midazolam acts on the benzodiazepine receptors of olfactory neurons in the nasal epithelium and that this nerve impulse affects hippocampal function, leading to an increased amnesic effect. In contrast to the amnesic effect, the neuronal process of sedation may be associated with a wider network of the brain [13].

A study using intranasal dexmedetomidine at a dose of 1 μg/kg as a sedative premedication has demonstrated a favorable perioperative anxiolysis without prolongation in anesthesia recovery, and its hemodynamic effect was well tolerated by the patients [14].

A literature review by Poonai et al. (2017) identifed seven prospective studies involving 264 participants, evaluating IN ketamine for procedural sedation and anxiety in children outside the operating room . In this systematic review , IN ketamine produced adequate sedation to perform the procedures under study, resulting in adequate sedation for 85% of

participants. However, the superiority of IN ketamine over comparators was inconsistent [15].

Also regarding the literature evaluating intranasal (IN) medications for the treatment of procedural anxiety, evidence supports the use of IN midazolam for its amnestic and anti-anxiety properties. Multiple studies have shown IN midazolam to be safe and effective in the treatment of procedural anxiety during laceration repair in pediatric emergency department [16].

Because the published literatures did not reveal which of intranasal dexmedetomidine, ketamine or midazolam is more efficient in prevention or at least lowering the incidence of respiratory complications and anxiety after tonsillectomy and adenoidectomy in children , so this thesis will be carried on to reveal that.

Rationale

- Perioperative respiratory complications and anxiety are the most common complication during pediatric anesthesia, that can prolong hospitalization time and costs, and bring varying degrees of physical and psychological trauma to children and parents.

- Many drugs can be used intranasally to decrease these complications such as glucocorticoids, fentanyl, naloxone, midazolam, ketamine, and dexmedetomidine.
- In this study we will compare between Intranasal Dexmedetomidine, ketamine, or midazolam as premedication in prevention of anxiety and respiratory complication in children undergoing adenotonsillectomy.

Research question

Which of these intranasal drugs can be more efficient as premedication for prevention of preoperative anxiety and Respiratory complications in children undergoing adenotonsillectomy using intranasal dexmedetomidine, ketamine or midazolam?

Hypothesis

Null hypothesis:

- No difference between the effect of intranasal dexmedetomidine, ketamine or midazolam as a premedication for prevention of anxiety and respiratory complications in children undergoing adenotonsillectomy.

Alternatives hypothesis:

- there is a difference between the effect of intranasal dexmedetomidine, midazolam or ketamine as a premedication for prevention of anxiety and respiratory complications in children undergoing adenotonsillectomy, one of them is better than the others.

Aim of the work

Prevention or decreasing the preoperative anxiety and respiratory complications in children undergoing adenotonsillectomy using intranasal dexmedetomidine, ketamine or midazolam as a premedication.

Objectives.

To determine the incidence and severity of laryngospasm during 30 minutes after extubation in all group.

To assess and compare the level of sedation and distress in the groups.

To determine time of discharge from post anesthesia care unit.

Methods

- **Type of study:** prospective randomized controlled clinical trial.
- **Sample size calculation**

  By assuming that the mean of the heart rate intraoperative before induction of general anesthesia among groups taken intranasal dexmedetomidine and intranasal ketamine was105.29$\pm$6.02beat/minutes and among groups taken intranasal dexmedetomidine and intranasal midazolam was 108.45$\pm$5.47beat/minutes with CI 95% and power of test 80%, the sample size is calculated to be 148 patients allocated into 4 groups, each group will be 37 patients.

  Inclusion criteria

  - Parent or first-degree relative acceptance
  - Children with age ranged from 4 to8

- Body mass index is equal to or greater than 5th and not more than 85th percentiles
- ASA classifications Ⅰ and Ⅱ
- Both sex

Exclusion criteria

- History of difficult intubation or extubation, cardiac, respiratory, renal and muscle diseases beside passive smoking and allergy to the tested drugs
- History of obstructive sleep apnea (OSA).
- The presence of the upper respiratory tract infection
- The need to reoperation after tonsillectomy due to hemorrhage of more than 100ml of blood during surgery
- Surgery duration is longer than 1.5 hour.

Site of the study: The study will be carried out at zagazig University hospitals, zagazig city, sharkia, Egypt.

Duration of the study 6 month's

Ethical approval: the study will be done after obtaining approval from university institutional review board (IRB). A written informed consent will be obtained from the parents or first degree relative of all patients participating in the study. the study will be carried out in according to the

Code of Ethics of the World Medical Association (declaration of Helsinki) for studies involving humans.

All children will be visited the night before the surgery for assessment, preparation and take an informed consent on the type of anesthesia which intended to be given from their parents or first-degree guardians. Assessment of patients includes identification of patient' age/years, body, weight/kg, BMI and vital signs, taking history about medical disorders, previous surgical procedure, the current medications, examination of various body systems, and asking for routine investigation as complete blood count, sedimentation rate and bleeding time.

All children are routinely required to preoperatively fast 8 hours for solids and 2 hours for clear liquids. the study is double- blinded. The patients and anesthesia assistant (the person evaluating the effect of the tested drug) will not be informed about tested drug. Only the anesthesiologist (the person prescribing the tested drug) will be aware of the tested drug to take the necessary measures in case of occurrence of any adverse medical complications. According to a computer-generated randomization chart, patients will be allocated into 4 equal groups

Group C(Control Group) n=(37): patient will take 1 mL of 0.9% saline intranasal 30 min before induction .

Dexmedetomidine group (D group) n= (37): patient will take 2.0 µg/kg intranasal dexmedetomidine, with 0.9% saline added to make a final volume of 1 mL.

Ketamine group (K group) n=(37) : patient will take 2mg/kg intranasal ketamine with concentration 50 mg/ ml, with 0.9% saline added to make a final volume of 1 mL.

Midazolam group (M group) n= (37): patient will take 0.1 mg/kg intranasal midazolam with 0.9% saline added to make a final volume of 1 mL.

The prepared drug solution will be administered cautiously in both nostrils using a needleless 1-mL syringe, drop by drop, each nostril will have 0.5 ml and the children will be positioned on the parent's lap in a recumbent position during administration.

After 30 minutes in the operating room (OR), a peripheral iv cannula(22-24gauge) will be inserted and secured. Devices for monitoring heart rate (HR), noninvasive mean arterial pressure (MAP), respiratory rate(RR) and peripheral oxygen saturation(SpO_2) will be applied to the patients .

General anesthesia will be induced by iv injection of 1 ug/kg of fentanyl sulfate and inhalation of 8% sevoflurane in air/oxygen, atracurium 0.5mg/kg is given, then oral endotracheal intubation is done with a tube in appropriate size to child age, tube fixed to the middle of the chin.

Immediately after endotracheal intubation, all the patient will receive 10 mg/kg acetaminophen suppository to avoid or at least minimize postoperative pain. Anesthesia was maintained with 1.5-2%sevoflurane in air /oxygen (50%:50%) and mechanical ventilation will be aided by IV administration of 0.4mg/kg atracurium basilate keeping a tidal volume of at least 6ml/kg, respiratory rate/minute between 15 to 25, an $etCO_2$ below 40 mmHg together with a trigger flow of 2.0 .

Intra-operatively, all patients will receive ringer lactate solution IV. At the end of surgery, inhalational anesthesia will be discontinued and on the start attempts of spontaneous respiration, a mixture of 4ug/kg of neostigmine and 2ug/kg of atropine will be given IV for reversal of muscle relaxant effect, then pharyngeal suction. after that, the patient will be shifted from or to Post Anesthesia Care Unite(PACU) for continuous monitoring till full recovery from general anesthesia then shifting the patients to the ward.

In this study the following parameters and scales will be recorded in each group:

Measurements

1. **Assessment of the vital signs mean blood pressure, heart rate, respiratory rate, and oxygen saturation** preoperative baseline before administration of the intranasal drug (0 min)in the holding area, 10 min preoperative after giving the intranasal drug, at time of induction 30 min after giving the intranasal drug(0 min), 10 min intraoperative after induction of anesthesia, 30 min intraoperative after induction of anesthesia ,at the end of surgery and postoperative in recovery (0 min), 10 min postoperative in the recovery, 30 min postoperative in the recovery
2. **The incidence and severity of post-extubation laryngospasm:**

   Incidence of post -extubation laryngospasm during 30 minutes duration after extubation will be assessed using scale in table(1):

Table (1): The incidence and severity of post-extubation laryngospasm [17].

Lack of laryngospasm	0
Partial of cords, stridor during inspiration with decreased tidal volume and a stable pulse o oximeter oxygen saturation(SpO_2 >95%)	1
Total occlusion of cords(i.e respiratory silence which can be characterized by inspiratory efforts of accessory muscles and paradoxical thoracic movements, and SpO_2 >85%	2
Cyanosis associated with desaturation (SpO_2 <85%)	3

Treatment of post-extubation laryngospasm will be standardized as the following: at first removal of the offending stimulus, jaw thrust, and manual ventilation with 100% oxygen by bag and mask is performed [18]. When the first measure fail, application of a firm pressure at a laryngospasm point, which lies behind the ear lobe, between the mastoid process and the ramus of the mandible is preformed [19]. When the above mentioned two

measures fail, 0.5mg/kg of succinylcholine is injected iv and manual ventilation with 100% oxygen by bag and mask with manual face mask ventilation is performed till return back of spontaneous breathing. When the above mentioned three measures fail, laryngospasm is considered sustained and treated like severe laryngospasm from the start by airway ,breathing and circulation resuscitation will be started by paralyzing dose of vocal cord by iv injection of 0.5mg/kg of succinylcholine, endotracheal intubation and manual ventilation with 100%oxygen till return back of spontaneous breathing [20].

3**-Assessment of the sedation level done by Ramsay sedation score** will be recoded at different time intervals: preoperative baseline before administration of intranasal medication, then 10 min, just before induction and 10 min, 20 min postoperative. "Ramsay Sedation Score" is described in 1974 it divides the pts level of sedation into 6 Categories ranging from severe agitation to deep coma as shown in table (2)

Table(2): Ramsay sedation score [21].

Level 1	Patient awake, anxious and agitated or restless ,or both
Level 2	Patients awake, cooperative, oriented, and tranquil.
Level 3	Patients awake, responds to commands only
Level 4	Patient asleep, brisk response to light glabellar tap or loud auditory stimulus.
Level 5	Patient asleep, sluggish response to light glabellar tap or loud auditory stimulus
Level 6	Patient asleep, no response to light glabellar tap or loud auditory stimulus.

4-**Assessment of distress associated with potentially painful event using Groningen distress scale at time of canulation**. (GDS) was developed to grade distress associated with a potentially painful event. It can be used to monitor a phobic patient's experience towards a triggering stimulus. The original scale was developed at the University of Groningen in The Netherland as shown in table (3)

Table(3): Groningen distress scale ,[22] .

1	calm
2	Mild distress
3	Serious distress, in control
4	Sever distress , out of control
5	panic

5- **All children observed postoperative till discharge criteria will met and monitored for presence of sedation, nausea/vomiting, and/or any other complications.** Prior to discharge, each patient should be assessed and examined by an anesthesia provider to ensure patient safety before transfer to the intensive care unit, inpatient floor, or home with parents/guardians. With more pediatric cases being scheduled on an both an inpatient and outpatient basis, careful and efficient assessment of discharge readiness is important. The Modified Aldrete Score assesses patient activity, respiration, blood pressure, consciousness, and color. A score >9 is required for discharge from the post anesthesia care unit .

Table (3): Modified Aldrete Score [23].

Criteria	Characteristics	Points
Activity	Able to move 4 extremities	2
	Able to move 2 extremities	1
	Unable to move extremities	0
Respiration	Able to breathe deeply and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0

Circulation	BP +/- 20% of pre-anesthetic level BP +/- 20-49% of pre-anesthetic level BP +/- 50% of pre-anesthetic level	2 1 0
Consciousness	Fully awake Arousable on calling Not responding	2 1 0
Oxygen saturation	Able to maintain O2 saturation >92% on room air Needs oxygen to maintain O2 saturation >90%	

Data collection:

Patient characteristics:

From each patient the following data will be collected upon admission:

- Name
- Age
- Body mass index
- Date of operation

- Medical and past history
- Duration of operation
- incidence and severity of post extubation laryngospasm in the first 30 minutes.
- sedation level preoperative as a baseline before administration of intranasal midazolam, dexmedetomidine or ketamine then 10 min after administration of the previous intranasal medications, then just before induction of anesthesia after (30min) and after extubation and recovery 10 minutes and 30 minutes postoperative using Ramsey sedation scale.
- Assessment of distress associated with potentially painful event using Groningen distress scale at time of canulation
- Vital signs: measuring preoperative baseline of assessment of the vital signs: mean blood pressure, heart rate, respiratory rate, and oxygen saturation before administration of the intranasal drug (0 min) in the holding area, 10 min preoperative after giving the intranasal drug, at time of induction 30 min after giving the intranasal drug(0 min).
- then 10 min intraoperative after induction of anesthesia, 30 min intraoperative after induction of anesthesia ,at the end of surgery for assessment of mean blood pressure, heart rate ,respiratory rate and oxygen saturation

- postoperative in recovery (0 min), 10 min postoperative in the recovery, 30 min postoperative in the recovery for assessment of the vital signs mean blood pressure, heart rate, respiratory rate, and oxygen saturation
- the incidences of the various associated complication as bradycardia (guidelines for bradycardia based on 24-hour Holter monitoring are as follows:2-6byears:,60bpm during sleep or awake.6-11 years:,45bpm during sleep or awake.

  Low mean arterial pressure is under 60mm Hg, bradypnea from 3 to 6 years:22to34 breaths per minute and age from 6 to 12 years :18to 30 breaths per minute.

  Hypoxemia : when arterial oxygen pressure(PaO_2) below 75mmHg .

  Hypoxia: when saturation below 90%.

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Preoperative anxiety and respiratory complications are among the most frequent challenges faced by children undergoing adenotonsillectomy. Respiratory complications during the perioperative period, ranging from minor issues such as oxygen desaturation, airway obstruction,

coughing, and wheezing to severe events like laryngospasm and bronchospasm, are particularly concerning in pediatric anesthesia. These complications can extend hospitalization, increase medical expenses, and result in both physical and psychological impacts on children and their families.

Preoperative anxiety in children, marked by feelings of tension, apprehension, and worry, often manifests in various behavioral changes. It can also lead to postoperative maladaptive behaviors such as enuresis, feeding issues, apathy, and sleep disturbances. Studies indicate that up to 60% of children undergoing surgery may experience adverse behavioral changes two weeks postoperatively, with factors like age and parental anxiety in the preoperative setting acting as predictors.

To address these challenges, premedication plays a crucial role by easing the separation from parents and reducing stress, thereby enabling smoother induction of anesthesia. Intranasal administration of medications, such as dexmedetomidine, ketamine, and midazolam, has emerged as a promising approach. This method is non-invasive, offers high bioavailability due to bypassing first-pass hepatic metabolism, and is well-suited for pediatric patients.

Dexmedetomidine, a highly selective alpha-2 adrenergic agonist, is known for its sedative, anxiolytic, and analgesic effects without causing respiratory depression. It induces a natural sleep-like state by stimulating inhibitory pathways in the brainstem. Ketamine, on the other hand, produces dissociative anesthesia by interacting with N-methyl-D-aspartate (NMDA) receptors, reducing pain sensitization and minimizing opioid requirements. Midazolam, a benzodiazepine with rapid onset and short duration, acts on receptors in the olfactory nerves, producing sedation and an amnesic effect.

Despite their individual advantages, the comparative effectiveness of intranasal dexmedetomidine, ketamine, and midazolam in minimizing respiratory complications and anxiety in pediatric adenotonsillectomy remains unclear. This study aims to evaluate and determine the most efficient intranasal premedication for reducing these perioperative challenges in children.