How to Cite:
Sheashia, H. A. E., Elnoury, A. S., & Abdelkader, S. S. (2021). Effect of premedication with intranasal dexmedetomidine or intranasal midazolam on the incidence of perioperative respiratory adverse events in children undergoing tonsillectomy and adenoidectomy: A randomized clinical trail. *International Journal of Health Sciences*, *5*(S1), 1629–1641. https://doi.org/10.53730/ijhs.v5nS1.13270

Effect of premedication with intranasal dexmedetomidine or intranasal midazolam on the incidence of perioperative respiratory adverse events in children undergoing tonsillectomy and adenoidectomy: A randomized clinical trail

Hazem Ali Essa Sheashia
Lecture (Fellow) of Anesthesia for Teaching Hospitals and Institutes, Egypt

Ahmed said Elnoury
Lecture of Anesthesia, ICU & Pain, Faculty of Medicine, Benha University, Benha, Egypt

Salsabil Sayed Abdelkader
Lecture of Anesthesia, ICU & Pain, Faculty of Medicine, Benha University, Benha, Egypt

***Abstract*---Background:** Catastrophic event in paediatric anesthesia is perioperative respiratory adverse events (PRAEs), which happen twice as often in infants younger than one year old as they do in older ones. This study set out to investigate the prevalence of respiratory complications during surgery in children having tonsillectomy or adenoidectomy done. The effectiveness of midazolam and intranasal dexmedetomidine was evaluated prior to administration. **Methods:** This prospective randomized clinical trial was carried out on 105 children who undergoing elective tonsillectomy with or without adenoidectomy. Children were randomly assigned into three groups (35 children in each): dexmedetomidine group, midazolam group, and control group (normal saline). All PRAEs were recorded during the perioperative period till the recovery period. **Results:** There was a statistically significant difference in the rates of PRAEs between the dexmedetomidine group and the midazolam group, with the midazolam group exhibiting a significantly higher incidence than the control group (P value <0.05). The control and midazolam groups had a significantly higher incidence of PRAEs than the dexmedetomidine group (P value <0.05), even though there was no statistically

Manuscript submitted: 21 Feb 2021, Manuscript revised: 27 April 2021, Accepted for publication: 25 May 2021

significant difference between the two groups during the recovery phase. **Conclusions:** Dexmedetomidine provided protective effects against the incidence of PRAEs in contrast to midazolam which showed increased PRAEs during the perioperative period, especially desaturation.

***Keywords*---**Dexmedetomidine, Midazolam, Perioperative Respiratory Adverse Events, Tonsillectomy, Adenoidectomy.

Introduction

The most prevalent critical incident in pediatric anesthesia, perioperative respiratory adverse events (PRAEs) comprise approximately one-third of cardiac emergencies related to anesthesia [(1)]. The prevalence of Potentially Preventable Adverse Events (PRAEs) within the general pediatric population is 15%; however, this rate is observed to be doubled in neonates aged one year or younger [(2)]. PRAEs remain the primary cause of significant postoperative morbidity and mortality, even though pediatric anesthesia has undergone significant improvements [(3)]. During the recovery period, adverse drug events (PRAEs) are particularly common in children who have undergone general anesthesia [(4)]. Children possess elevated oxygen requirements coupled with limited oxygen reserves, rendering them more vulnerable to Pediatric Respiratory Acute Events (PRAEs). The avoidance of PRAEs during the removal of tracheal tubes or laryngeal masks in pediatric anesthesia presents a significant challenge [(1, 5)].

Dexmedetomidine, the active form of medetomidine, is an imidazole derivative known for its sedative properties and for being an extremely selective agonist of the α2 adrenergic receptors [(6)]. Without causing any significant respiratory depression, dexmedetomidine has a number of analgesic, anti-sensory injury, and excitability-enhancing effects on the cardiac vagus nerve [(7, 8)]. During the postoperative recovery phase of anesthesia, this pharmaceutical agent has the potential to alleviate agitation and nausea, decrease intraocular pressure, attenuate hemodynamic responses associated with tracheal intubation and surgical stimulation, and significantly reduce the need for anesthetics and opioids [(9)].

Dissolving midazolam in an acidic solution (pH < 4.0) produces a stable, water-soluble salt; the chemical is lipophilic. It quickly crosses the blood-brain barrier after releasing its lipophilic bases under physiological pH conditions [(10)]. Consequently, midazolam exhibits a high degree of lipid solubility, resulting in rapid absorption following oral administration. The concentration of blood reaches its maximum level within a timeframe of 0.5 to 1 hour. Due to the significant first-pass metabolism in the liver, it has a bioavailability of about 50% [(11)].

It is not yet known, however, whether PRAE rates in minors are reduced by premedication with intranasal dexmedetomidine and midazolam. This study aimed to examine PRAEs in children who were having tonsillectomy or adenoidectomy done. Premedication with intranasal dexmedetomidine and midazolam was used to assess their impact.

Patients and Methods:

In this prospective randomized clinical trial, 124 children were assessed for eligibility, 10 children did not meet the criteria, and parents of 9 children refused to participate in the study. The remaining 105 children were randomly allocated into three groups (35 children in each): dexmedetomidine group, midazolam group, and control group (normal saline). All children were followed up and analyzed statistically **(Figure 1)**.

Inclusion criteria:

- Children aged 0 to 12 years.
- Physical status I and II as assessed by the American Society of Anesthesiologists (ASA).
- Adenoidectomy along with tonsillectomy, if desired.

Exclusion criteria:

- Conditions affecting the heart and lungs that are known to exist, such as congenital heart defects that have not been corrected, pulmonary hypertension (primary or secondary), tumors, or structural lung diseases.
- Neuromuscular diseases.
- Body mass index (BMI) greater than 30 kg/m^2.
- Severe URTI and the anesthesiologist recommended delaying surgery.
- Allergy to either dexmedetomidine or midazolam.
- Parents refusing to allow their children to participate

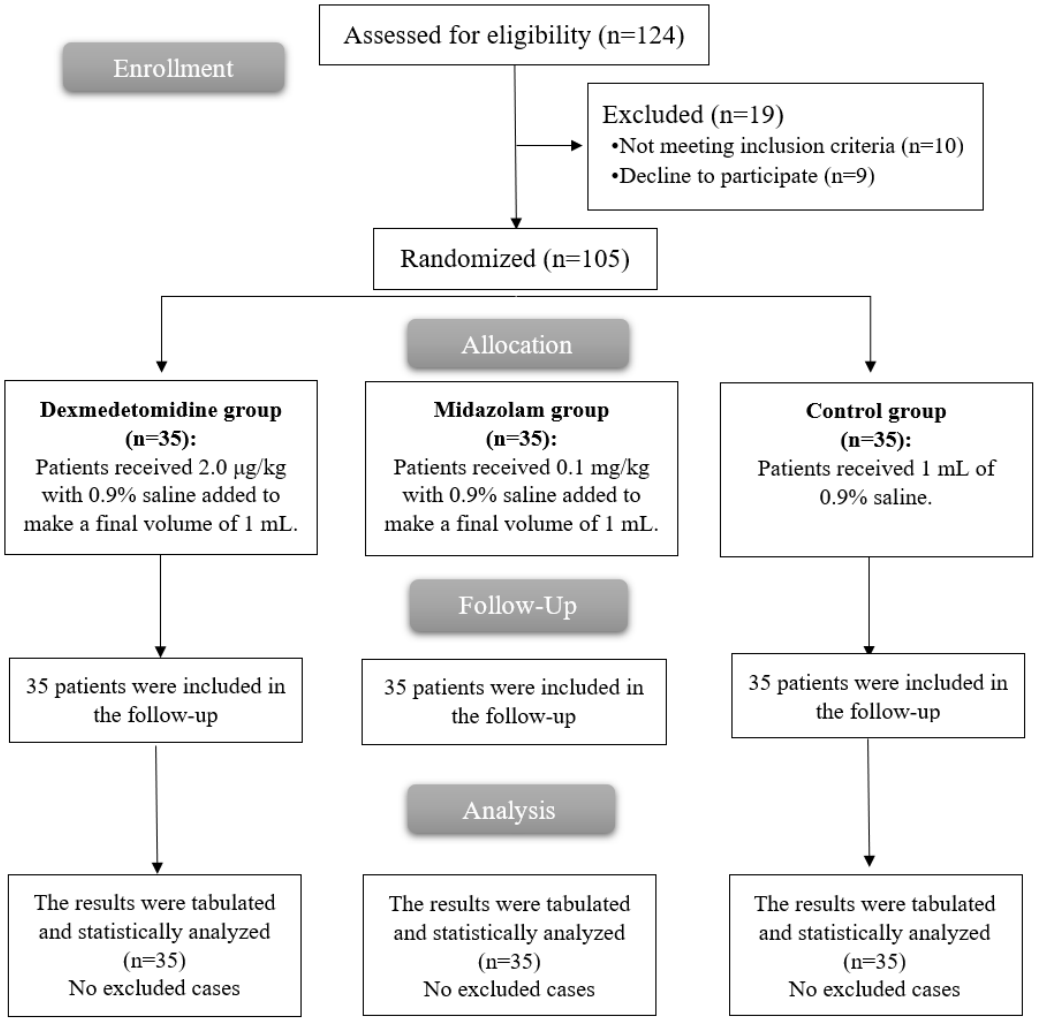

Figure 1: CONSORT flow chart

Procedures and Interventions:

After giving consent to parents or guardians of children to participate in our study, baseline characteristics and risk factors were obtained. Before surgery, all children were required to fast for at least 8 hours without solid foods and 2 hours without clear liquids. An impartial healthcare provider who was not involved in the children's clinical management or data collection opened opaque, sealed envelopes that contained their group assignments. The envelopes were numbered sequentially. Children were given intranasal premedication 30 to 60 minutes before they arrived in the anesthetic preparation room.

Carefully, using a needleless 1-mL syringe, the prepared medicinal solution was injected into both nostrils in a dropwise fashion. Kids were asked to lie down on their parents' laps while the injection was being given to them.

The attending anesthetist had complete autonomy in deciding whether inhalational or intravenous methods of anesthesia induction were to be used. The use of preoxygenation was routine and unwavering. All pediatric patients had tracheal devices used for airway management. For the purpose of managing pain, inject 15 mg/kg of paracetamol and 0.1 mg/kg of dexamethasone intravenously. To ensure that no aspiration occurred after the surgery, the oral cavity was aspirated to remove any secretions and intraoperative irrigation fluid. The child was awakened and fully recovered before tracheal extubation was done. The patient was placed in the Post Anesthesia Care Unit (PACU) after extubation. We used a visual analogue scale (VAS) to measure postoperative pain. An intravenous injection of 1 μg/kg of fentanyl was given if the score went beyond 4. For the purpose of assessing postoperative emergence delirium, the PAED scale was utilized. When patients' discharge criteria permitted it, they were readmitted to the ward.

End Points:

The incidence of PRAEs among the three groups was the main outcome. Infections, nausea, and vomiting following surgery were the secondary outcomes. Emergence delirium.

Sample Size Calculation:

Using MedCalc ® program version 18.2.1 (MedCalc Software, Ostend, Belgium), based on prior data from Zhang et al. [12] who found the PRAEs incidence was in 29.9% patients in the dexmedetomidine group versus 58.2% patients in the placebo group. So, using Chi-square test at power 90% and 0.05 alpha error, the number of patients required in each group was 34 patients. We raised the number to become 35 in each group.

Statistical Analysis:

We used SPSS 26 (IBM Inc., Armonk, NY, USA) to analyze the data. Histograms and the Shapiro-Wilk test were employed to ascertain if the data followed a normal distribution. The quantitative data was analyzed using the ANOVA (F) test and a post hoc Tukey test to determine the means and standard deviations (SD). The qualitative data was analyzed using a Chi-square test that takes percentages and numbers into account. A two-tailed p-value of 0.05 or lower was deemed statistically significant.

Results:

Demographic, clinical, and surgical elated data were presented in **(Table 1)** and all were insignificantly different between the studied groups.

Table 1: Baseline characteristics

	Dexmedetomidine (n=35)	Midazolam (n=35)	Control (n=35)	P value
Age (years)	7.17 ± 2.9	6.29 ± 3.32	6.6 ± 3.09	0.484
Sex				
Male	17 (48.57%)	20 (57.14%)	15 (42.86%)	0.485
Female	18 (51.43%)	15 (42.86%)	20 (57.14%)	
BMI (kg/m²)	19.75 ± 1.49	19.31 ± 1.6	19.25 ± 1.63	0.356
ASA physical status				
I	14 (40%)	12 (34.29%)	15 (42.86%)	0.756
II	21 (60%)	23 (65.71%)	20 (57.14%)	
URTI	13 (37.14%)	10 (28.57%)	11 (31.43%)	0.738
Asthma	2 (5.71%)	1 (2.86%)	1 (2.86%)	0.771
Allergy	3 (8.57%)	6 (17.14%)	5 (14.29%)	0.562
Eczema	7 (20%)	4 (11.43%)	4 (11.43%)	0.497
Passive smoking	16 (45.71%)	18 (51.43%)	15 (42.86%)	0.765
OSA	25 (71.43%)	27 (77.14%)	29 (82.86%)	0.523
Preterm delivery	2 (5.71%)	3 (8.57%)	3 (8.57%)	0.873
Time from premedication to induction (min)	31.69 ± 1.95	30.8 ± 1.61	31.8 ± 2.1	0.059
Induction of anesthesia				
Inhalation	3 (8.57%)	2 (5.71%)	4 (11.43%)	0.695
Intravenous	32 (91.43%)	33 (94.29%)	31 (88.57%)	
Type of surgery				
Tonsillectomy	0 (0%)	1 (2.86%)	1 (2.86%)	0.745
Adenoidectomy	6 (17.14%)	5 (14.29%)	8 (22.86%)	
Tonsillectomy and Adenoidectomy	29 (82.86%)	29 (82.86%)	26 (74.29%)	
Anesthesia duration (min)	47.03 ± 16.35	44.51 ± 14.59	46.71 ± 15.85	0.764
Surgery duration (min)	42.54 ± 9.42	42.89 ± 9.47	43.29 ± 12.15	0.957

Data are presented as mean ± SD or number (percentage %), BMI: body mass index, ASA: American Society of Anesthesiologists, URTI: upper respiratory tract infection, OSA: obstructive sleep apnea.

In relation to the perioperative period, the PRAEs was markedly elevated in both the midazolam group and the control group when compared to the dexmedetomidine group. Furthermore, the incidence of PRAEs was significantly greater in the midazolam group than in the control group, with a P value of less than 0.05 **(Table 2)**.

Table 2: PRAEs over the perioperative period (from induction of anesthesia to discharge from the PACU)

	Dexmedetomidine (n=35)	**Midazolam (n=35)**	**Control (n=35)**	**P value**
Laryngospasm	0 (0%)	4 (11.43%)	1 (2.86%)	0.065
Bronchospasm	0 (0%)	0 (0%)	0 (0%)	---
Desaturation	6 (17.14%)	17 (48.57%)	11 (31.43%)	0.019*
	P1 =0.005*, P2 =0.163, P3 =0.143			
Cough	3 (8.57%)	8 (22.86%)	6 (17.14%)	0.264
Airway obstruction	2 (5.71%)	6 (17.14%)	3 (8.57%)	0.267
Stridor	1 (2.86%)	2 (5.71%)	1 (2.86%)	0.771
PRAEs	9 (25.71%)	26 (74.29%)	18 (51.43%)	<0.001*
	P1 <0.001*, P2 =0.027*, P3 =0.048*			

Data are presented as number (percentage %), PRAEs: perioperative respiratory adverse events, PACU: post anesthesia care unit, *: significant as P value ≤0.05, P1: P value between Dexmedetomidine and Midazolam, P2: P value between Dexmedetomidine and control, P3: P value between Midazolam and control.

Regarding the recovery period, PRAEs were significantly higher in midazolam group and control group compared to dexmedetomidine group (P value <0.05) with no significant difference in the incidence between midazolam group and control group **(Table 3)**.

Table 3: PRAEs during the recovery period

	Dexmedetomidine (n=35)	**Midazolam (n=35)**	**Control (n=35)**	**P value**
Laryngospasm	0 (0%)	2 (5.71%)	0 (0%)	0.130
Bronchospasm	0 (0%)	0 (0%)	0 (0%)	---
Desaturation	4 (11.43%)	15 (42.86%)	10 (28.57%)	0.013*
	P1 =0.003*, P2 =0.073, P3 =0.212			
Cough	2 (5.71%)	7 (20%)	5 (14.29%)	0.209
Airway obstruction	1 (2.86%)	4 (11.43%)	2 (5.71%)	0.343
Stridor	1 (2.86%)	2 (5.71%)	1 (2.86%)	0.771
PRAEs	7 (20%)	23 (65.71%)	15 (42.86%)	0.001*
	P1 <0.001*, P2 =0.039*, P3 =0.055			

Data are presented as number (percentage %), PRAEs: perioperative respiratory adverse events, PACU: post anesthesia care unit, *: significant as P value ≤0.05, P1: P value between Dexmedetomidine and Midazolam, P2: P value between Dexmedetomidine and control, P3: P value between Midazolam and control. The three groups did not differ significantly in terms of time to extubation, length of hospital stay, VAS, PAED scale, vomiting, or time in the post-extubation care unit (PACU) **(Table 4)**.

However, compared to the dexmedetomidine and control groups, the midazolam group appeared to have a higher number of children who needed analgesics and experienced emergence delirium; however, the differences were not statistically significant **(Table 4)**.

Table 4: Postoperative non-respiratory adverse events

	Dexmedetomidine (n=35)	**Midazolam (n=35)**	**Control (n=35)**	**P value**
Extubation time (min)	18 ± 6.44	19.2 ± 7.24	16.86 ± 6.44	0.349
Time spent in PACU after extubation (min)	13.54 ± 3.01	14.26 ± 3.24	14.2 ± 3.21	0.576
Length of hospital stay (days)	1.69 ± 0.76	1.86 ± 0.77	1.89 ± 0.87	0.530
VAS	1.89 ± 1.35	1.91 ± 1.46	2 ± 1.31	0.937
Children requiring analgesics	4 (11.43%)	9 (25.71%)	6 (17.14%)	0.295
PAED scale	6.06 ± 3.83	6.54 ± 4.82	5.69 ± 4.54	0.719
Emergence delirium	3 (8.57%)	10 (28.57%)	6 (17.14%)	0.093
Vomiting	1 (2.86%)	2 (5.71%)	0 (0%)	0.357

Data are presented as mean ± SD or number (percentage %), PACU: post anesthesia care unit, VAS: visual analogue scale, PAED: pediatric anesthesia emergence delirium.

Discussion

Despite advancements in pediatric anesthesia, respiratory adverse events continue to cause a significant portion of perioperative morbidity and mortality. Of the critical incidents and perioperative cardiac emergencies in pediatric anesthesia, 75% involve the respiratory system, and 33% involve other systems. Preoperatively identifying infants at high risk presents a significant challenge **[13, 14].** Because of their unique anatomy and physiology, children are more likely to experience respiratory adverse events, and URTIs are a common cause of this. Less oxygen saturation, holding one's breath, laryngospasm, bronchospasm, and coughing are the most common respiratory problems that can occur during anesthesia. Death and other catastrophic consequences are possible outcomes of laryngospasm, bronchospasm, and chronic hypoxemia **[2, 15, 16].**

PRAEs and their risk factors during elective pediatric surgical procedures were previously investigated. The prevalence of PRAEs was 21% overall, with a rate of 13% in the PACU, according to the study. The results also showed that the risk of PRAEs decreased by 8% per year of age and by a significant margin when the anesthetic method used tracheal intubation in combination with muscle relaxants [17].

Adverse events following tonsillectomy or adenoidectomy in pediatric patients treated with intranasal dexmedetomidine and midazolam were the focus of this literature review.

Compared to the dexmedetomidine group, the midazolam and control groups had much higher rates of PRAEs. The incidence of PRAEs was also significantly higher in the midazolam group than in the control group. Compared to the dexmedetomidine group, neither the midazolam nor the control groups had a statistically significant lower incidence of PRAEs during the recovery period. Interestingly, we did not find a correlation between the two groups.

In line with our findings, Ghali et al. [18] In comparison to children who received oral midazolam during the transfer to the operating room, it was shown that children who received intranasal dexmedetomidine showed significantly lower levels of sedation and anxiety and had an easier time separating from their parents. Similarly, Talon et al. [19] Indicated that dexmedetomidine demonstrated greater efficacy than midazolam in facilitating sleep induction prior to surgical procedures.

In Bi et al. [20] Dexmedetomidine significantly reduced the rates of laryngospasm (15% vs. 50%), breath-holding (10% vs. 40%), and coughing (5% vs. 30%) in patients compared to saline. Postoperative agitation was also significantly reduced ($P = 0.004$) in these patients when intranasal dexmedetomidine was administered.Also, Zhang et al. [12] The administration of intranasal dexmedetomidine was found to significantly decrease the incidence of PRAEs ($P=0.001$), with a notable reduction in oxygen desaturation events ($P=0.012$) when compared to the placebo group (normal saline). Furthermore, the majority of PRAEs were observed during the emergence phase. On the contrary, Michel et al. [21] It has been established that midazolam premedication yields effective outcomes in the management of PRAEs. Furthermore, analogous results were obtained through in vitro studies [22, 23].

This disparity might be because of the paradoxical effects of midazolam; as sedation and hypnosis are supposed to bring about desirable outcomes, children often display irritability and other behaviors that run counter to these expectations. One possible explanation for the increased frequency of post-operative respiratory events (PRAEs) linked to midazolam is the increased sympathetic nerve activity and stress response seen in children [24].

It is possible that dexmedetomidine reduced airway reflexes by increasing the depth of anesthesia [25]. Furthermore, the direct impact of dexmedetomidine on airway smooth muscle may have also played a contributory role. Consequently, it has been established that dexmedetomidine mitigates contractions of isolated tracheal rings induced by both exogenous acetylcholine and C-fiber stimulation. This indicates that dexmedetomidine possesses the capacity to relax airway smooth muscle and inhibit cough reflexes [26]. The inflammatory process, linked to increased airway sensitivity, may have been influenced by dexmedetomidine. Significant reductions in interleukin-6 and tumor necrosis factor-α levels were observed following this drug's administration [27].

The three groups in our study did not differ significantly with respect to the time to extubation, length of hospital stay, time in the PACU, vomiting, visual analog scale (VAS), PAED scale, or PAED. However, compared to the dexmedetomidine and control groups, the midazolam group appeared to have a higher number of

children who needed analgesics and experienced emergence delirium; however, the differences were not statistically significant.

Supporting our results, Ghali et al. [18] In the dexmedetomidine group, there were significantly fewer children who required fentanyl as an emergency analgesic. Dexmedetomidine and clonidine were associated with reduced pain scores in comparison to midazolam [28, 29] while in contrast, Talon et al. [19] found both medications were comparable for postoperative discomfort.

It is apparent that the administration of intravenous fentanyl is correlated with the occurrence of wheezing and respiratory depression [30]. Dexmedetomidine may therefore be linked to less desaturation and wheezing because it decreases the requirement for fentanyl.

Use of midazolam as a pharmaceutical preventive for emergence delirium is controversial [31]. Midazolam may increase the likelihood of emergence delirium, according to some research [32], Additionally, others have regarded midazolam as a valuable pharmacological intervention for preventive purposes [33]. Dexmedetomidine has been established as having a prophylactic effect against emergence delirium [34], and that clarified why the dexmedetomidine group had a lower incidence compared to the midazolam and normal saline groups.
.
Limitations: The sample size was relatively small, and a single dose of dexmedetomidine and midazolam was chosen. Also, the identification of behavioral appearance of used medications was easy making the study hard to be blinded. Cardiac examination is recommended to evaluate the two drugs efficacy and further dose comparison study is needed.

Conclusions

Dexmedetomidine provided protective effects against the frequency of PRAEs in contrast to midazolam which showed increased PRAEs during the perioperative period, especially desaturation.

“Financial support and sponsorship: Nil”
“Conflict of Interest: Nil”

References

1. **Li L, Zhang Z, Yao Z, Wang H, Wang H, An H, et al.** The impact of laryngeal mask versus other airways on perioperative respiratory adverse events in children: A systematic review and meta-analysis of randomized controlled trials. Int J Surg. 2019;64:40-8.
2. **Drake-Brockman TF, Ramgolam A, Zhang G, Hall GL and von Ungern-Sternberg BS**. The effect of endotracheal tubes versus laryngeal mask airways on perioperative respiratory adverse events in infants: a randomised controlled trial. Lancet. 2017;389(10070):701-8.
3. **Gupta N, Rath GP, Prabhakar H and Dash HH**. Effect of intraoperative dexmedetomidine on postoperative recovery profile of children undergoing surgery for spinal dysraphism. J Neurosurg Anesthesiol. 2013;25(3):271-8.

4. **Bong CL, Tan J, Lim S, Low Y, Sim SW, Rajadurai VS, et al.** Randomised controlled trial of dexmedetomidine sedation vs general anaesthesia for inguinal hernia surgery on perioperative outcomes in infants. Br J Anaesth. 2019;122(5):662-70.
5. **Bhat R, Mudukanagouda M, Shetty S and Kamath S**. Study of dose related effects of dexmedetomidine on laryngeal mask airway removal in children-a double blind randomized study. Anaesthesia, Pain & Intensive Care. 2019:368-73.
6. **McCarren HS, Chalifoux MR, Han B, Moore JT, Meng QC, Baron-Hionis N, et al.** α2-Adrenergic stimulation of the ventrolateral preoptic nucleus destabilizes the anesthetic state. J Neurosci. 2014;34(49):16385-96.
7. **Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR and Colin P**. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893-913.
8. **Bao N and Tang B**. Organ-Protective Effects and the Underlying Mechanism of Dexmedetomidine. Mediators Inflamm. 2020;2020:6136105.
9. **Tang C, Hu Y, Zhang Z, Wei Z, Wang H, Geng Q, et al.** Dexmedetomidine with sufentanil in intravenous patient-controlled analgesia for relief from postoperative pain, inflammation and delirium after esophageal cancer surgery. Biosci Rep. 2020;40(5).
10. **Kanto JH**. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. Pharmacotherapy. 1985;5(3):138-55.
11. **Nordt SP and Clark RF**. Midazolam: a review of therapeutic uses and toxicity. J Emerg Med. 1997;15(3):357-65.
12. **Zhang S, Zhang R, Cai M, Zhang K, Zhang M and Zheng J**. Intranasal dexmedetomidine premedication in children with recent upper respiratory tract infection undergoing interventional cardiac catheterisation: A randomised controlled trial. Eur J Anaesthesiol. 2020;37(2):85-90.
13. **Lee S, Reddington E, Koutsogiannaki S, Hernandez MR, Odegard KC, DiNardo JA, et al.** Incidence and Risk Factors for Perioperative Cardiovascular and Respiratory Adverse Events in Pediatric Patients With Congenital Heart Disease Undergoing Noncardiac Procedures. Anesth Analg. 2018;127(3):724-9.
14. **Murat I, Constant I and Maud'huy H**. Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. Paediatr Anaesth. 2004;14(2):158-66.
15. **Hackett S, Jones R and Kapila R**. Anaesthesia for pneumonectomy. BJA Educ. 2019;19(9):297-304.
16. **Ramgolam A, Hall GL, Zhang G, Hegarty M and von Ungern-Sternberg BS**. Inhalational versus Intravenous Induction of Anesthesia in Children with a High Risk of Perioperative Respiratory Adverse Events: A Randomized Controlled Trial. Anesthesiology. 2018;128(6):1065-74.
17. **Mamie C, Habre W, Delhumeau C, Argiroffo CB and Morabia A**. Incidence and risk factors of perioperative respiratory adverse events in children undergoing elective surgery. Paediatr Anaesth. 2004;14(3):218-24.
18. **Ghali AM, Mahfouz AK and Al-Bahrani M**. Preanesthetic medication in children: A comparison of intranasal dexmedetomidine versus oral midazolam. Saudi J Anaesth. 2011;5(4):387-91.

19. **Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L and Benham T**. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. J Burn Care Res. 2009;30(4):599-605.
20. **Bi Y, Ma Y, Ni J and Wu L**. Efficacy of premedication with intranasal dexmedetomidine for removal of inhaled foreign bodies in children by flexible fiberoptic bronchoscopy: a randomized, double-blind, placebo-controlled clinical trial. BMC Anesthesiology. 2019;19(1):219.
21. **Michel F, Vacher T, Julien-Marsollier F, Dadure C, Aubineau JV, Lejus C, et al.** Peri-operative respiratory adverse events in children with upper respiratory tract infections allowed to proceed with anaesthesia: A French national cohort study. Eur J Anaesthesiol. 2018;35(12):919-28.
22. **Koga Y, Sato S, Sodeyama N, Takahashi M, Kato M, Iwatsuki N, et al.** Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle. Br J Anaesth. 1992;69(1):65-9.
23. **Yoshimura H, Kai T, Nishimura J, Kobayashi S, Takahashi S and Kanaide H**. Effects of midazolam on intracellular Ca2+ and tension in airway smooth muscles. Anesthesiology. 1995;83(5):1009-20.
24. **Ayerza Casas A, Ayerza Casas V and Crespo Escudero P**. Paradoxical reaction after intranasal midazolam administration. Med Clin (Barc). 2017;148(7):335-6.
25. **Najafi N, Veyckemans F, Van de Velde A and Poelaert J**. Usability of dexmedetomidine for deep sedation in infants and small children with respiratory morbidities. Acta Anaesthesiol Scand. 2016;60(7):865-73.
26. **Mikami M, Zhang Y, Kim B, Worgall TS, Groeben H and Emala CW**. Dexmedetomidine's inhibitory effects on acetylcholine release from cholinergic nerves in guinea pig trachea: a mechanism that accounts for its clinical benefit during airway irritation. BMC Anesthesiol. 2017;17(1):52.
27. **Tang C, Huang X, Kang F, Chai X, Wang S, Yin G, et al.** Intranasal Dexmedetomidine on Stress Hormones, Inflammatory Markers, and Postoperative Analgesia after Functional Endoscopic Sinus Surgery. Mediators Inflamm. 2015;2015:939431.
28. **Saad BB, Tharwat AI, Ghobrial HN and Elfawal SM**. Intranasal dexmedetomidine versus intranasal midazolam as pre-anesthetic medication in pediatric age group undergoing adenotonsillectomy. Ain-Shams journal of anesthesiology. 2020;12(1).
29. **Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simões CM and Auler JO, Jr.** Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Paediatr Anaesth. 2007;17(7):667-74.
30. **Han JI, Lee H, Kim CH and Lee GY**. The frequency of fentanyl-induced cough in children and its effects on tracheal intubation. J Clin Anesth. 2010;22(1):3-6.
31. **Dahmani S, Stany I, Brasher C, Lejeune C, Bruneau B, Wood C, et al.** Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth. 2010;104(2):216-23.
32. **Almenrader N, Galante D and Engelhardt T**. Emergence agitation: is there a European consensus? Br J Anaesth. 2014;113(3):515-6.

33. **Urits I, Peck J, Giacomazzi S, Patel R, Wolf J, Mathew D, et al.** Emergence Delirium in Perioperative Pediatric Care: A Review of Current Evidence and New Directions. Adv Ther. 2020;37(5):1897-909.
34. **Mason KP**. Paediatric emergence delirium: a comprehensive review and interpretation of the literature. Br J Anaesth. 2017;118(3):335-43.