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The Preoperative Administration Of Nebulized Dexmedetomidine Versus Nebulized Midazolam as a Sedative Premedication before Pediatric Surgery

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ABSTRACT

Children usually anxious and fearful at time of hospitalization and surgery making the induction period difficult   . This research   compare the premedication of nebulized dexmedetomidine and nebulized midazolam as sedative drugs used before surgery in children.

Methods: Ninety children younger than 12 years old participated in a double-blind, prospective, randomized research in which they were pre-medicated with either 2 µg/kg of nebulized dexmedetomidine (group D) or 0.2 mg/kg of nebulized midazolam (group M) . The hemodynamic parameters, the sedation scores, the parental separation anxiety scores, the mask acceptance scores, and the ease of the venipuncture for the cannulation are recorded.

Results: Although the onset of sedation was started early in   M group children , D group children were more sedated and had a higher percentage of children with a high score for parental separation and who were willing to accept an anesthetic mask. Intravenous cannulation score was comparable between both groups.

Conclusion: Nebulization with dexmedetomidine produced more satisfactory sedation , easy parental separation and face mask acceptance nebulization than those who received nebulised midazolam.

Keywords: Children, Nebulization, Dexmedetomidine , Midazolam, Pediatric surgeries.

INTRODUCTION

Sixty percent or more of children have trouble relaxing before surgery (1). Children as young as infants and as old as preschoolers might be understandably distressed when they have to be separated from their parents for medical procedures like venipuncture or mask application prior to surgery or imaging. Unmanaged anxiety can lead to difficult induction, more pain after surgery, more need for analgesia, agitation during emergence and even postoperative psychiatric and behavioral disorders are possible. Midazolam, ketamine, choral hydrate, and dexmedetomidine are some of the drugs which used as sedative premedication in children. Premedication with sedatives may alleviate these patients' fears, make induction easier and decreased the emotional truma from the procedure.(2-3).

Dexmedetomidine is a highly selective alpha-2 receptor agonist that produces moderate respiratory depression, sedation and analgesic effects via actions in the central nervous system. And also has sympatholytic effect. Despite the risks of bradycardia and hypotension associated with intravenous administration, it has lately seen widespread usage as a sedative for children. Dexmedetomidine has been shown to lower the severity of emerging agitation and the frequency of postoperative nausea and vomiting in children under general anesthesia. Premedication with an intranasal route reduces the risk of puncture pain and gastrointestinal side effects, but it may also induce discomfort (4). Recent studies have shown that nebulized dexmedetomidine (inhalation of a nasal aerosol) is an effective premedication in pediatric patients. Aerosolized drug delivery has several advantages, including reduced drug loss in the oropharynx, increased drug concentrations in CSF, increased patient acceptability and enhanced sedation. (5)

Midazolam is a one of the benzodiazepine family that is rapidly absorbed and water-soluble due to the presence of an imidazole ring; it works by inhibiting the gamma-aminobutyric acid (GABA) receptor. Midazolam is nonirritating and has anxiolytic, sedative, hypnotic, and amnesic properties. As a preoperative sedative, midazolam has been given intravenously, intramuscularly, in the nose, orally, and rectally (6). Children can more easily and smoothly administer midazolam intra-nasally and sublingually as a premedication since these routes of absorption are quick and efficient because they skip the first-pass metabolism (7). Because drug deposition after nebulization occurs throughout nasal, buccal, as well as respiratory mucosa, nebulized midazolam may present an alluring option to both intravenous and intranasal routes (8).

The primary outcome of the research is the sedation level of the child after 30 min from administration of studied drugs before general anesthesia in different surgical procedures.

The secondary outcomes are onset of sedation , parental separation score, tolerance to mask induction, response to cannulation, hemodynamic parameters, oxygen saturation and respiratory rate.

PATIENT AND METHOD

From May 2019 to December 2022, 90 pediatric cases under the age of 12 of both sex who were classified as ASA physical status I or II and were planned for elective surgery or diagnostic procedures under general anesthesia were enrolled in a prospective, randomised, double-blind, comparative study. This research was conducted in Al-Zahraa University Hospital, Al-Azhar University, Cairo . After discussing the operation with the patient's family members and gave their signed approval. **Exclusion criteria** : A family history of anaphylaxis to dexmedetomidine or midazolam, parent rejection, and emergency surgery ,a child with a suspected difficult airway or respiratory distress syndrome, congenital syndromes, mental retardation and neurobehavioral problems.

Patients fasted for 4-6 hours before surgery, according on their age, with the exception of clear drinks (2 h only). Measurements of heart rate (HR), mean blood pressure (MAP), and peripheral blood oxygen saturation (SpO2) were recorded in the preoperative room. Emergency medications and a variety of sized venous cannulas were available always on hand to facilitate rapid venous access.

Subjects were randomly divided into two groups (D and M groups; each with 45 patients) based on the sedative dosage of dexmedetomidine and midazolam:

Dexmedetomidine group(D group, n=45) : Children were given a nebulized solution of 2μg/kg of dexmedetomidine .

Midazolam group (M group, n=45): Children were given nebulized solution of 0.2 mg/kg of midazolam .

30 minutes before to the induction of general anesthesia, both drug dosages were diluted in 3 ml of 0.9% normal saline and delivered using jet nebulizers through a face mask with a continuous flow of 100% O2 at 4-6 L/min until the drugs in the nebulizer cup were gone. Based on computer-generated tables, randomization was performed. An impartial researcher who was not involved in the children's supervision or anesthetic administration prepared and administered all study medications. The study's endpoint is the induction of anesthesia.

Data collection:
All of the following information was gathered:
1- Patient characteristics: age, sex, weight.
2- Hemodynamic variables (HR, MAP, RR, and SPO$_2$) were recorded before sedation (baseline)

and at 5, 10, 15, 20, 25, and 30 minutes following the end of drug administration.

3 – The onset of sedation and evaluation of Sedation Level after the end of administration of the studied drugs using the five-point sedation scale (FPSS).

> 1= Agitated.
> 2= Alert.
> 3= Calm.
> 4= Drowsy.
> 5= Asleep.

After 30 minutes, if the child still wasn't sedated enough, they were excluded from the research.

4- A senior anesthetist was assessed the ease of venipuncture for cannulation using a 4-point scale

Grade I = crying, uncooperative , inability to begin IV line.

Grade II = withdrawal for painful stimuli but allows to crying.

Grade III = calm, no-withdrawal, for painful stimuli and IV cannulation.

Grade IV= asleep

5- Parental separation was evaluated 30 min after the end of studied drug administration using parental separation anxiety scale (PSAS).

PSAS is a 4-point scale as follows:

1 = easy separation,

2 = whimpers, but is easily reassured,

3 = cries and cannot be easily reassured, but not clinging (sticking) to parents,

4 = crying and clinging to parents.

A PSAS score of 1 or 2 was classified as an acceptable separation, whereas scores of 3 or 4 were considered difficult separations from the parents (9).

6- Pediatric acceptance of anesthesia mask was observed using 4 point mask acceptance scale **(** MAS) which is

1= Excellent , (unafraid , co-operative and mask accepted easily),

2= Good, (slight fear of mask , reassured easily)

3= Fair, (moderate fear of mask ,not calm with reassured)

4= Poor, (terrified, crying).

MAS' scores of 1 and 2 means well accepted whereas scores of 3 and 4 means not accepted.

Sample size calculation Abdel Ghaffar et al[10] found that the proportion of excellent mask acceptance scale (MAS) in dexmedetomidine group was 51% and in ketamine+ midazolam. group was 97%. The anticipated difference in the MAS for calculating sample size was 46%.

Sample size calculation done utilizing using power version 3.1 and adjusting the confidence interval to 95% ,the power of the test to 90%, As per the study we choose MAS for calculating sample size, that got to be 45 per group to compensate for any possible dropouts .

Statistical Analysis:

In order to analyses the data, the information was first gathered, reviewed, and coded before being entered into SPSS 23, a social sciences statistical programme created in 2015 by the IBM Company of Armonk, New York, United States. Several graphical representations of the data, including the mean, standard deviation, range, median, and interquartile range, were used. The independent t-test was used to compare quantitative data with a parametric distribution, while the Chi-square test was used to evaluate qualitative data. The P value was used to define the significance level at the 0.05 level since the confidence interval was set at 95%.

The p-value measures the probability statistically.

- ▪ P-value ≥ 0.05 "non-significant"
- ▪ P-value ≤ 0.05 "significant"
- ▪ P-value <0.001 "highly significant"

RESULTS

Regarding age, sex, or weight, there was no statistically significant difference between the two groups (Table 1) .

Table 1: Demographic data in both groups:

	D Group (no = 45)	M Group (no = 45)	Test value	P-value
	Mean ± SD	Mean ± SD		
Age Mean±SD Range	6.93 ± 1.95 4.3 – 9.5	6.75 ± 2.90 4 - 10	0.346•	0.731

Sex Males Females	22 (48.9%) 23 (51.1%)	25 (55.6%) 20 (44.4%)	0.401*	0.527
Weight (kg) Mean±SD Range	22.2 ± 2.11 18.1 – 25.0	21.7± 2.00 17.8 – 24.3	1.154•	0.252

•: Independent t-test; *: Chi-square test

Compared to the M group, children in group D showed significantly fall in HR values from five to thrity minutes following the end of study medication administration . **(Fig1).**
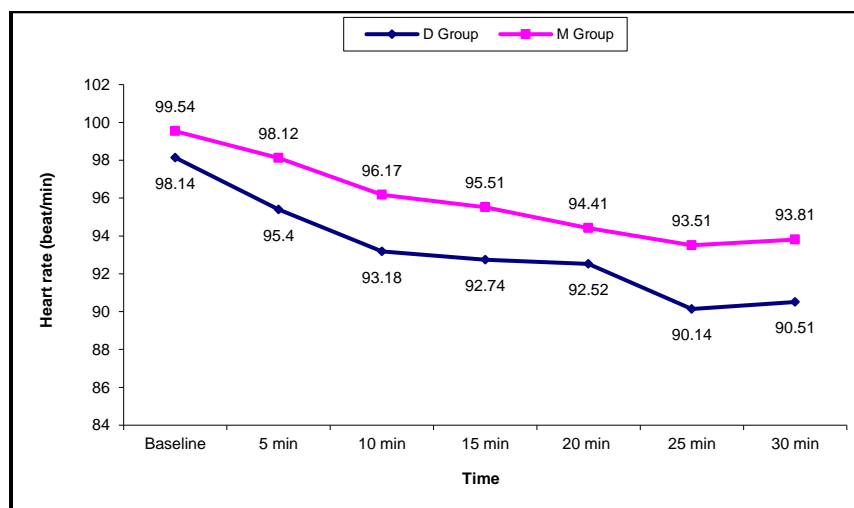

Figure 1: HR changes in two groups.

From 5 to 30 minutes following the end of study medication administration, patients in group D showed statistically fall in MAP levels when compared to those in group M. **(Fig 2).**
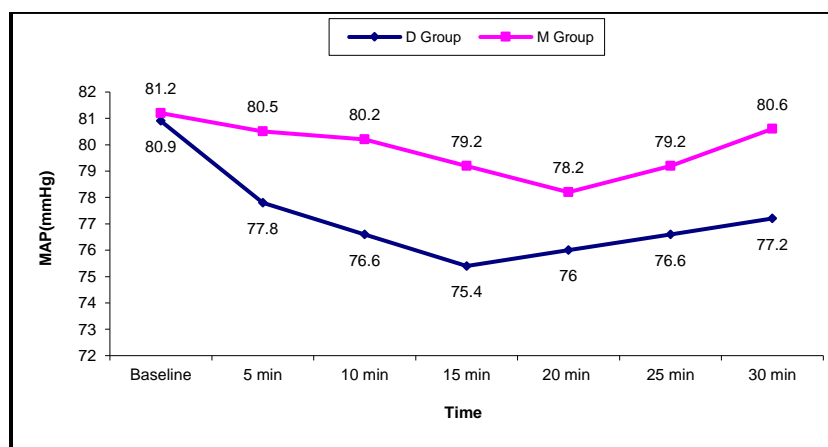

Figure 2:   MAP changes between two groups.

After the study drugs had stopped, the two groups showed statistically equivalent mean values of arterial oxygen saturation at each time period. **(Fig 3).**
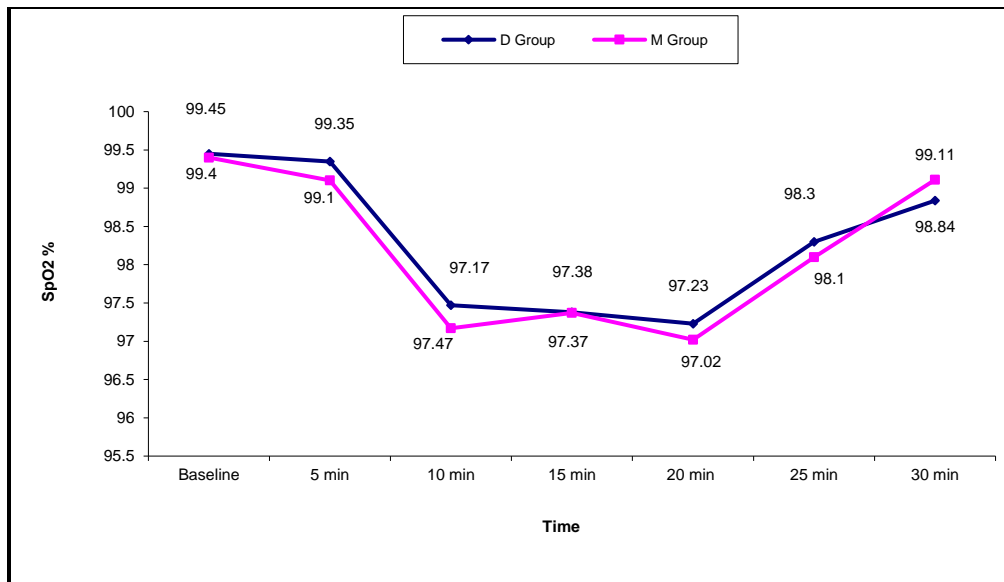
Figure 3: Arterial oxygen saturation changes between two groups.

Changes in respiratory rate were recorded at different time points, and revealed a slower rate after nebulization in both groups compared to pre-nebulization levels. Group M showed a statistically significant decreased in the rate compared to group D at 10, 15, and 20 minutes. However ,no statistically significant differences were seen among the groups at 25 and 30 minutes. **(Fig 4).**
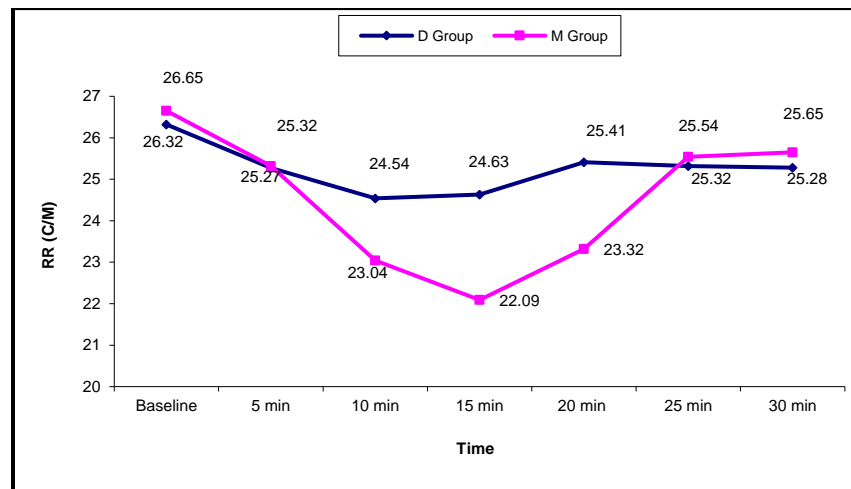

Figure 4: R.R changes between two groups.

Table 2: Onset time of sedation and level of five points sedation score.

Sedation began in children in M group significantly earlier than those in D group. However, after 30 minutes, group D had much better sedation scores than group M. **(Table 2).**

	D Group (n = 45)	M Group (n = 45)	Test value	P-value
Onset time of sedation(min) Mean ± SD	28.52 ± 4.04	20.34 ± 9.33	5.397•	<0.001
Level of five points sedation score(FPSS) Mean ± SD	3.00 ± 0.5	2.56 ± 0.9	2.932•	0.004

•: Independent t-test .

Table 3 : Reaction to venipuncture for cannulation between two groups.
The reaction to i.v. cannulation (tolerance for cannula insertion)for both groups were comparable and statistically not significant **(Table 3).**

	D Group (n= 45)	M Group (n = 45)	Test value	P-value
-Poor	1 (2.2%)	2 (4.4%)	0.550*	0.907
-Fair	4 (8.9%)	5 (11.1%)		
-Good	20 (44.4%)	20 (44.4%)		
-Excellent	20 (44.4%)	18 (40.0%)		

*: Chi-square test

Table 4 : Easy separation scale between two groups .
In group D, more than half children of this treatment group showed easy separation (51.1%) compared to M group which summarized in **(Table 4)** .

	D Group (n = 45)	M Group (n = 45)	Test value	P-value
Easy separation	23 (51.1%)	10 (22.2%)	9.306*	0.025
Whimpers	15 (33.3%)	20 (44.4%)		
Cries	5 (11.1%)	8 (17.8%)		
Crying and Clinging	2 (4.4%)	7 (15.6%)		

*: Chi-square test

Table 5 : Comparison of the mask acceptance score(MAS) between two groups.
Group D had significantly higher rate of patient acceptance of the anesthetic mask compared to group M. **(Table 5).**

	D Group (n = 45)	M Group (n = 45)	Test value	P-value
Excellent	32 (71.1%)	20 (44.4%)	8.769*	0.033
Good	10 (22.2%)	14 (31.1%)		
Fair	2 (4.4%)	10 (22.2%)		
Poor	1 (2.2%)	1 (2.2%)		

*: Chi-square test

DISCUSSION

Infants and young children at preschool who require surgery are frequently more anxious because of the withdrawal from their parents during the operation, fear of physicians, and unfamiliar surroundings so getting their cooperation is harder. It is crucial for those kids to take preoperative medicine. Inhalational sedatives were a simple, practical method of premedication that was widely accepted. (11). The current study found that aerosolized dexmedetomidine considerably reduced HR and MAP compared to the M group but the M group had slightly decreased children's respiratory rate.

The most common adverse effects of dexmedetomidine include hypotension and bradycardia., as was revealed in research by **Shereef et al.[12]** who studied the effects of pre-medicating preschoolers having general anesthesia with dexmedetomidine, midazolam, and ketamine. Also, **Abdel-Ghaffar et al**.[10] studies showed similar findings a they found midazolam produced less hemodynamic effects than dexmedetomidine when contrasted with the nebulization of ketamine, midazolam, or dexmedetomidine as premedication in young children having bone marrow biopy.

In line with our research, **Medhat and Abd Elnaby[13]** examined the effectiveness of nebulized midazolam, fentanyl, and dexmedetomidine for sedation in children who receive dental surgery and found that dexmedetomidine had a greater reduction in HR than midazolam and fentanyl.

According to the current study, **Plambech and Afshari**[14] showed that bradycardia and hypotension are the most frequent adverse effects of dexmedetomidine, with minimal impacts on respiration.

In the current study, the onset time of sedation started early in nebulized midazolam as compared to dexmedetomidine but inhaled dexmedetomidine had better sedative scores (FPSS), a scale measuring parental fear of separation and acceptance of the anesthesia face mask scales (MAS) in comparison to nebulized midazolam, on the other side the response to painful stimuli to cannulation did not show any significant variations between both groups.

Feng et al.[15], who compared the effects of midazolam and dexmedetomidine as a premedication for children and found similar outcomes came to the conclusion that the dexmedetomidine group's patients had better parental separation and more comfortable sedation than the midazolam group's patients.

According to the current study **by Abdel-Ghaffar et al**.[10]. who examined patients in groups D and M using nebulized dexmedetomidine, ketamine, and midazolam for bone marrow biopsy in preschoolers , found that group D subjects scored better on the parental separation anxiety measure and had higher mask acceptance.

Similar outcomes were seen in the research by **Shereef et al.**[12], who found that nebulized dexmedetomidine produced superior sedation score, parental separation scores and mask acceptance scale in preschoolers children undergoing general anesthesia than nebulized midazolam or ketamine.

Medhat and Abd Elnaby [13] compared midazolam nebulization premedication with nebulized dexmedetomidine and exhibited a quicker start onset, deeper degrees of sedation, ease of separating children from their parents, and a shorter duration of action in inhaled dexmedetomidine than midazolam nebulization

Research by **Akin et al.**[16]**, Sheta et al.**[17]**, and Amer.**[18] indicated that children who got intranasal dexmedetomidine as a premedication were more sedated and able to accept the face mask than those who received intranasal midazolam. Sedation also began much quicker in group M than in group D.

These findings were consistent with our findings, but they used the intranasal route instead of the nebulized route.

gainst to present research, the study of **Endigeri et al**[19]**. who** compared nebulized dexmedetomidine (group A) against using (group B) the combination of ketamine and midazolam for premedication in kids. They concluded that the sedation scores in group B and anxiety scale due to giving up parental guidance and putting on a mask were greater when compared to group A. These results were different from our research may be because they used midazolam and ketamine mixture, not midazolam only.

CONCLUSION

Nebulized of dexmedetomidine produced satisfactory sedative effects which is easier to administer, better acceptance of mask induction and provides more effective alternatives than nebulized midazolam for facilitating smooth separation from their parents before entering the operating room.

Acknowledgement:
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Conflicts of interest:
None

LIMITATIONS

1- More research is needed to determine the effectiveness of neubilized medications, and bigger sample sizes are needed for this study. Additional research into medication combinations and determining optimal dosing is necessary.

2- The efficacy of nebulized route of dexmedetomidine and midazolam for child premedication has not been compared in many recent trials. Many published studies was done on premedication by oral route, intramuscularly, intravenously or intranasal routes.

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