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Intranasal Dexmedetomidine Versus Midazolam as Sedative Premedication for Children in Day Case Surgery

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ABSTRACT

Background: Anxiety in children undergoing surgery was considered challenging situation for anesthesia. The intranasal dexmedetomidine and intranasal midazolam as preoperative sedation drugs are used.

Objective: The aim of the current work was to evaluate and compare intranasal dexmedetomidine versus midazolam as premedication in pediatric anesthesia according to sedation scale, anxiety scale, child - parent separation scale, and mask accepting scale, heart rate, blood pressure, oxygen saturation and respiratory rate.

Patients and methods: The study was carried out on 90 children, 2 to 6 years old, who underwnt day surgical procedures at Zagazig Univerisity Hospital. They were randomly assigned into three equal groups, all were given the study drug intranasally diluted in 1 ml NS. C-Group given 1 ml NS, D-group given 2ug/kg dexmedetomidine, and M-group given 0.3mg/kg midazolam. The groups were compared rgarding onset and degree of sedation, child parent separation scale, mask acceptance scale, hemodynamic parameters, and postoperative analgesic requirements.

Results: The three groups were comparable with respect to basic demographic data. D - group showed higher alert sedation scale compared to M - group and C - group from 10 min intraoperative. Anxiety scale was significantly higher in C - group in comparison to other groups from 20 min intraoperative. Child parent separation scale was significantly lower in M - group in comparison to M - group and C - group. The median mask acceptance scale was significantly lower in D - group in comparison to M - group and C group.

Conclusions: Intranasal dexmedetomidine 2 μg/kg could be used effectively and safely as a pre-anesthetic medication in children undergoing day case surgery compared to Intranasal midazolam 0.3 mg/kg.

Keywords: Dexmedetomidine, Intranasal, Midazolam, Sedation.

INTRODUCTION

Pediatric premedication provides a difficult scenario. The youngsters are unable to properly comprehend the need for their procedure. Young children's minds are traumatized by their fears of the operation room, needles, and being apart from their parents before general anesthesia [(1)]. Preoperative anxiety increases postoperative pain and causes hemodynamic instability, metabolic side effects, and emerging agitation [(2)].

Alpha2-receptor agonist dexmedetomidine has no respiratory depressing side effects and instead has sedative, analgesic, and anxiolytic effects. This makes it a potentially beneficial anesthetic premedication [(3)]. The most popular sedative used for premedication in children is midazolam, a Gamma-amino-butyric acid (GA B A) receptor inhibitor [(3)].

Midazolam can be rapidly absorbed through the nasal mucosa resulting in a rapid and reliable onset of action, avoidance of painful injection and ease of administration. Also, intranasal rout of administration avoids degradation in the gastrointestinal tract and first-pass metabolism in the liver [(4)].

In this study we have evaluated and compared intranasal dexmedetomidine versus midazolam as premedication in pediatric anesthesia according to sedation scale, anxiety scale, child - parent separation scale, and mask accepting scale, heart rate, blood pressure, oxygen saturation and respiratory rate.

PATIENTS AND METHODS

This study included a total of 90 Children aged 2 to 6 years, attending at the Zagazig University Hospitals for day case surgical procedures e.g., herniotomy. tonsillectomy and hypospadias.

The included 90 subjects were divided according to a computer-generated randomization chart, into three equal groups; **C-Group** received 1 ml 0.9 % normal saline (NS), **D-group** received dexmedetomidine at a dose of 2 μg/kg diluted to 1m (NS), and **M-Group** received midazolam of 0.3 mg/kg. All study drugs were diluted to 1ml NS and administrated intranasally by nasal dropper. The groups were compared rgarding onset and degree of sedation, child parent separation scale, mask acceptance scale, hemodynamic parameters, and postoperative analgesic requirements.

Inclusion criteria: Children with ASA physical status I and II scheduled for elective day case surgery were included. Duration of surgery (60 – 90 Minute).

Exclusion criteria: Parent refusal, nasal pathology or infection, upper respiratory tract infection, neurologic disease, Patient on sedative drugs, History of allergy to the study drugs, and hyperactive syndrome.

Preoperative holding area:

Data including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR) and oxygen saturation (SpO2), were recorded before administering the intranasal drug and then every 10 min for 45 minutes after the

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intranasal administration of the study drug [5]. Moreover, sedation scale, anxiety scale, child - parent separation scale, and mask accepting scale all were assessed after drug administration.

Intraoperative:

Children were transported to the operating theatre (OT) where face mask induction was carried out using sevoflurane in oxygen, while another anesthesiologist is securing an intravenous line. Pulse oximeter, non-invasive blood pressure, and electrocardiogram were attached. One microgram per kilogram of fentanyl was injected intravenously and muscle relaxant (atracurium dose 0.5mg/kg) was given. Oral endotracheal tube was inserted. Anesthesia was maintained with tidal volume 7 ml/kg 0.8−1 MAC level of isoflurane in oxygen. Breathing was maintained and monitored using capnography. Intraoperative HR, SBP, DBP, and SpO2 was recorded every 10 min. After completion of surgery, isoflurane will be discontinued and extubation was done in the lateral decubitus position when the patient had fulfilled criteria of extubation.Then, they were brought to the Post-Anesthetic Care Unit (PACU).

Ethical Consideration:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). Repeated measures ANOVA test was used to compare more than two repeated measurements of normally distributed variables while Friedman's test was used for non- normally distributed variables; pairwaise comparison with baseline level was done by paired t-test or Wilcoxon signed ranks test according to normality. Percent of categorical variables were compared using Chi-square test. All tests were two sided. p-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered very highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

From the table the study groups well comparable regarding demographic data and BMI and duration of operation. There were no statistically significant demographic differences between both groups regarding age, sex, body mass index (BMI), and duration of surgery (table 1).

Table (1): Comparison between the 3 studied group regarding demographic data

	C-Group N=30		**D-Group N=30**		**M- Group N=30**		**F**	**P**
Age years X±SD Range	3.9 ± 1.2 2-6		4.2 ± 1.2 2-6		4 ± 1.3 2-6		0.5	0.58
Gender	**N**	**%**	**N**	**%**	**N**	**%**		
Male	18	60	17	56.1	18	60	**0.09**	**x^2 0.9**
Female	12	40	13	43.3	12	40		
BMI (Kg/m^2) X±sD Range	17.5±1.15 16 – 20		17.5±1.1 16 - 20		17.8±1.0 16.5 - 20		0.8	0.4
Duration of operation(min) X±SD Range	74.7 ± 12 60 – 90		70 ± 11 60 - 90		75.7±9 60 - 90		1.9	0.1

x2 = chi-square test p > 0.05 non significantp ≤ 0.05 significant f-test= ANOVA

Table 2 shows that there were no statistically significant differences between group as regard heart rate during preoperative. the only significant difference was at 30 min there was a decrease in heart rate in D - group (P < 0.05). P < 0.05 when compared with pre-operative value with each group

Table (2): Comparison between studied groups regarding heart rate after administration of studied drugs.

	C-Group N = 30	D-Group N = 30	M- Group N = 30	F	P
Pre op (0 Min)	110.7±7.6	107±7	108±7.3	1.9	0.4
10 Min	108.7±6.5	105.3±5.7	106±6.4	2.3	0.09
20 Min	105.6±4.8	104.1±4.2	104±4	1.1	0.3
30 Min	107±5.2	104±4.2	106±4.4	4.0	0.02*
40 Min	105.6±4.1	*103±4.4	104.3±3	2.4	0.09
Intraoperative 50 Min	*104±4.9	101.3±6.2*	*102±2	2.2	0.1
60 Min	*100±8	*101.3±7	*103±4	2.3	0.1
70 Min	*100±8	*100.3±7	*103±4	2.2	0.1
80 Min	*100±8	*100.9±7	*103±4	2.3	0.1
90 Min	*100±8	*100.9±7	*103±3	2.3	0.1
100 min	*100±8	*100.9±7	*103±3	2.3	0.1
110 Min	*100±8	*100.9±7	*103±3	2.3	0.1

f-test ANOVA (analysis of variance)

Table 3 shows that there were no statistically significant differences between study groups from pre-operative and during intra operative (P > 0.05) and there was non-significant change within each group.

Table (3): Comparison between studied groups regarding peripheral oxygen saturation (Spo2)

	C- Group N = 30	D- Group N = 30	M- Group N = 30	F	P
Pre op(0Min)	99±0.7	98.6±0.8	99±0.7	2.3	0.09
10 Min	98.8±0.7	99±0.7	99.5±0.5	2.3	0.09
20 Min	99.2±0.7	99.1±0.7	99±0.5	1.6	0.19
30 Min	98.8±0.6	98.8±0.6	99±0.5	1.9	0.2
40 Min	99±0.7	98.8±0.9	99±0.7	2.0	0.09
Intraoperative 50 Min	99±0.7	99±0.7	99.5±0.5	2.3	0.09
60 Min	99.2±0.7	99.1±0.7	99±0.5	1.6	0.19
70 Min	99.1±0.7	99.1±0.8	99±0.6	1.6	0.19
80 Min	99±0.7	99±0.7	99±0.7	0.9	0.9
90 Min	99±0.7	99±0.8	99±0.7	1.0	0.9
100 Min	99±0.7	99±0.8	99±0.7	1.0	0.9
110 Min	99±0.7	99±0.8	99±0.7	1.0	0.9

f-test ANOVA (analysis of variance)

Table 4 shows that the sedation score was significantly lower in the midazolam group at 10 and 20 min after the administration of the drug (p < 0.001). At 30 and 45 min, there was a statistically decrease in sedation score in D-group compared with M -group (p = 0.002 and < 0.001, respectively). This indicted that alert sedation scale was higher in D- group compared to other groups (P < 0.001) from 10 min preoperative.

Table (4): Comparison between studied groups regarding sedation scale

		C- Group N = 30	D- Group N = 30	M- Group N = 30	P
	0 Min	6(6-6)	6(6-6)	6(6-6)	1.0
	10 Min	5(5-6)	6(4-6)	4(4-6)	**< 0.001
	20 Min	5(4-6)	5(3-5)	4(3-5)	**< 0.001
	30 Min	3(3-4)	3(2-4)	3(2-3)	**< 0.001
	45 Min	3(3-4)	2(2-3)	3(2-3)	**< 0.001

f-test

Table 5 shows that at 10 min of drug administration, there were no statistically significant differences among groups. At 20 min, there was a significant decrease in anxiety score in M - group compared with D - group (p < 0.001). At 30 and 45 min, there was a statistically significant decrease in anxiety score in D - group compared with M - group. Was significantly higher in C - group in comparison to other groups (P < 0.001) from 20 min preoperative.

Table (5): Comparison between studied groups regarding anxiety scale

	C- Group N = 30	D- Group N = 30	M- Group N = 30	P
0 Min	4(4-4)	4(4-4)	4(4-4)	1.0
10 Min	3(3-4)	3(3-4)	3(2-4)	0.06
20 Min	2(2-3)	2(1-2)	1(1-2)	**< 0.001
30 Min	2(1-2)	1(1-1)	1(1-2)	*< 0.001
45 Min	2(1-2)	1(1-1)	2(1-2)	*< 0.001

f-test

Table 6 shows that, there was significantly excellent child parent separation scale in D- group (P <0.05). The median parent separation scale was significantly excellent in D- group compered to M or C - group. That C- Group have mask acceptance score fair than other groups (P <0.05). The median mask acceptance scale was significantly excellent in D- group compared to M or C- groups.

Table (6): Comparison between studied groups regarding child parent separation and mask acceptance scale

	C- Group N = 30	D- Group N = 30	M- Group N = 30	P
Child parent separation				
Median	2	1.5	2	0.02*
Inter qurtial range IQR	(1-2)	(1-2)	(1-2)	
Mask acceptance				
Median	3	2	2	0.02*
IQR	(2-3)	(1-3)	(2-3)	

Kruskal wallis test

Table 7 shows that, In D - group the need for analgesia was significantly lower compared to other groups (p < 0.05).

Table (7): Postoperative analgesic requirement among studied groups

	C - Group		D - Group		M - Group		X^2	P
Paracetamol	**N**	**%**	**N**	**%**	**N**	**%**	6.98	0.03*
Yes	16	53.3	7	23.3	12	40.0		
No	14	46.7	23	67.7	18	6.7		

X^2 = chi-square test

DISCUSSION

The sample of the study was homogenous regarding the pre-anesthetic characteristics (age, gender, weight) and duration of both groups. We have found in our patients that Modified Objective Pain Scale was significantly lower in the midazolam group at (10 and 20 min) than in dexmedetomidine group.

On the contrary at 30 min, it was significantly lower in the dexmedetomidine group. This indicated that intranasal midazolam has faster onset of sedation than dexmedetomidine which correlates with the slow onset of sedation in dexmedetomidine group where we found significant decrease in HR and BP at 30 min of the drug administration which was comparable with our study **Abdelmoneim *et al.*** [6] Stated that intranasal dexmedetomidine was more capable of causing more sedation than midazolam at 30 and 45 min pre-operative. Likewise, **Singla *et al.*** [7] showed that the Modified Objective Pain Scale was significantly less at 30 min after intranasal dexmedetomidine. Midazolam produces sedation by stimulating GABA receptors in the cerebral cortex that inhibits normal neuronal function [8].

On the other hand, dexmedetomidine produces sedation by stimulating alpha2-adrenergic receptors in the locus coeruleus, so reduces central sympathetic output, resulting in increased firing of inhibitory neurons [9]. Also, in this study, intranasal dexmedetomidine was superior to midazolam as anxiolytic, with lower anxiety score at 30-and 45 preoperative. **Singla *et al.*** [7] also proved that dexmedetomidine was more anxiolytic than Midazolam at 30 min. In disagreement with that **Akin *et al.*** [3] who found lower anxiety scores in the patients who received intranasal midazolam 0.2 mg/kg than in those who received dexmedetomidine 1 µg/kg in the operating theatre (OT).

Concerning the child parent separation, children in D - group were more easily separated from parents than in M - group but it was not statistically significant. Our study confirmed **Singla *et al.*** [7] study that found better parental separation with dexmedetomidine. Mostafa and his colleague also stated that the number

and percentage of children achieved-child parents separation score grade 1 was significantly higher in D - group than M group [10].

As for the mask acceptance in the present study there was better mask acceptance in D - group compared with M - group. In agreement with **Sun *et al.*** [11] study that compared midazolam and dexmedetomidine intranasally. They stated that the dexmedetomidine group was associated with more satisfactory sedation upon mask acceptance compared with the midazolam group.

But **Akin and his co-workers** [3] showed that midazolam was superior in providing satisfactory conditions during mask induction because the intranasal dexmedetomidine sedative effect did not reach its peak before mask induction.

In this study, intranasal dexmedetomidine was superior to midazolam as anxiolytic, with lower anxiety score at 30 and45 min pre-operative. **Singla and his colleagues** [7] also proved that dexmedetomidine was more anxiolytic than midazolam at 30 min.

Sedative effect dexmedetomidine reaches peak approximately at 30-45 while midazolam peak sedative effect at 10-20 min of administration.

CONCLUSIONS

It could be concluded that pre-medication with intranasal dexmedetomidine 2μg/kg is superior to intranasal midazolam 0.3mg/kg as it is associated with lower sedation score and anxiety score, easier child parent separation, and excellent mask acceptance. Also, it can be concluded that intranasal dexmedetomidine can be used effectively and safely as a pre-anesthetic medication in children undergoing any surgical procedures under general anesthesia.

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Author contribution: Authors contributed equally in the study.

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