Comparison between dexmedetomidine and midazolam as intranasal premedications forchildren admitted for elective surgery

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ABSTRACT

Background; The intranasal route is a reliable way to administer preanaesthetics and sedatives to children. Midazolam has been accepted as a safe and effective intranasal premedication. Intranasal dexmedetomidine, a well-tolerated and convenient treatment option, has been shown to induce a favorable anxiolysis in children.

Aim of the study: To investigate the difference between the effect of midazolam and dexmedetomidine premedication on hemodynamic status, parent separation, mask acceptance, and sedation

Patients and methods: A two arms blinded randomise clinical trial study, 40 children, 3 - 10 years of age, with (ASA) class1, scheduled for elective ENT surgery, were randomly divided into two equal groups, midazolam group (M) and dexmedetomidine group (D), group (M) patients received intranasal midazolam 0.2 mg/kg and group (D) patients intranasal dexmedetomidine 1µg/kg, approximately 30 minute before induction of anesthesia, in the form of a spray. vital signs (heart rate, blood pressure, oxygen saturation) were recorded before administering the intranasal drug and again at 20 minutes.

Results: intranasal dexmedetimidine (1µg/kg) resulted in statistically significant but clinically unimportant lower heart rate and blood pressure at 20-minute following administration compared with intranasal midazolam (0.2mg/kg). There were no episodes of hypotension or bradycardia. Children in group (D) achieved better parental separation and mask acceptance scores compared with group (M).

conclusions

Dexmedetomidine resulted in better parental separation and mask acceptance scores than intranasal midazolam.

Keywords: Midazolam,dexmedetomidine,intranasal, Premedications

1. Introduction

1.1 Anesthesia in children :

Anesthesia induction is a stressful part of surgery for pediatric patients and their parents(1). Children may undergo physical, mental, and physiological distress due to anxiety at the time of induction. Stressful anesthesia induction has consequent adverse psychological impacts, can cause discomfort during recovery, and may lead to regressive behavioral disorders. Nightmares, separation anxiety , eating disorders , and bedwetting have been reported as confirmed outcomes of anxiety

among children . Children with high anxiety levels have a higher risk of expressing negative behaviors after surgery , and higher parental anxiety levels are directly associated with children's preoperative anxiety levels(2) .

Parental absence , anxiety or reduced control over the situation further demoralize the child and fear and anxiety overshadows the soothing effort of the healthcare providers . Researchers have found several factors , which contribute to the preoperative anxiety in children , which includes(3) :

1. Fear of physical harm or bodily injury in the form of pain , mutilation , or even death .
2. Separation from parents and absence of trusted adults , especially for preschool children1 ; witnessing of parental anxiety .
3. Unknown and unfamiliar place , persons and routines hospital food , clothing , and play.
4. Uncertainty about " acceptable " and normative behavior in a hospital setting.
5. Loss of control, autonomy , and competence.
6. Exposure and touching of " private parts " by strangers ; Shame .

1.2 Stress points

In the preoperative period , there are also certain time points when the anxiety reaches the maximum . These periods or the ' stress points ' , if not appropriately taken care of , the children try to put maximum resistance to the caregivers . The stress points includes(3) :

- Separation from the parents and / or trusted adults .
- Entry to operating room .
- Placement of the child on O.T. table .
- Visualization of syringes .
- Attachment of monitors .
- Placement of intravenous cannula .
- Placement of mask .

Many strategies have been used to alley anxiety , including sedation for children , education for parents/children , and developing strong interpersonal relationships between hospital staff and parents/children with a focus on rapport , communication , and honesty . Distruction techniques (i.e , audio/video devices , toys , and book) , fun transportation systems (i,e. , wagons) , favored anesthesia masks , minimal downtime/waiting before induction have also been used to alleviate anxiety.

1.3 Pediatric vital signs in normal range

The accurate assessment and recording of the vital signs are essential in pediatric age . Practitioners are aware of normal physiological parameters for blood pressure , respiratory rate and heart rate for the different ages ranges(4) .

Table 1.

Age group	Respiratory rate	Heart rate	Systolic blood pressure	Weight in kilos
newborn	30-50	120-160	50-70	2-3
1-12months	20-30	80-140	70-100	4-10
1-3 yrs	20-30	80-130	80-110	10-14
3-5 yrs	20-30	80-120	80-110	14-18
6-12 yrs	20-30	70-110	80-120	20-42
adolescent	12-20	55-105	110-120	>50

1.4 Premedication :

The major objectives of pre - anesthetic medication are to decrease the stress response with preservation of hemodynamic parameters , facilitate anesthesia induction and produce amnesia. The child's age , body weight , drug history , allergic status and underlying medical or surgical conditions are factors to be

taken into consideration prior to administration of premedication(5) .

In most cases , medications administered without a needle are more pleasant for children , the family and the care team . Oral premedication does not increase the risk of aspiration pneumonia(6) .

1.4.1 Midazolam : The role of sedative premedication is well . Midazolam has been the most widely used established as a pre - induction technique in pediatric anesthesia agent , with a long history of safety and efficacy . As a premedication, it offers several benefits , including a rapid and reliable onset , minimal respiratory depression , antegrade amnesia , and reduced emergence delirium . It is typically administered orally at a dose of 0.5 – 0.75 mg kg –1 (to a maximum of 20 mg) after which sedation and anxiolysis are reliably achieved within 20 min . In addition to the oral route , it can alternatively be administered by the i.v . (0.1 mg kg–1) , intranasal (0.3 mg kg–1) , rectal (0.5 mg kg–1) , or sublingual (0.3 mg kg–1) routes . Studies demonstrate reduced anxiety , increased cooperation , and decreased negative behavioral changes in children who receive midazolam preoperatively . Arguably , midazolam is established as the ' gold standard ' method of preoperative anxiolysis against which other pre - induction strategies are compared. Nonetheless , midazolam is not universally accepted as the optimal premedication available , and some experts have highlighted significant limitations including the potential for prolonged effect and for paradoxical reactions . Paradoxical reactions , although uncommon (<1% patients) , can result in a restless and agitated child , and are most common after IV administration . The exact mechanism of these reactions is unclear — most are idiosyncratic , although a genetic link is postulated . If a child has a history of such a reaction , then midazolam should be avoided(7, 8) .

1.4.2 Dexmedetomidine : it is a highly selective α2 adrenergic agonist demonstrating an α2: α1 selectivity ratio of 1620:1(9) . This makes it eight times more selective for α2-adrenocepter than clonidine . A defining feature of the sedative action of dexmedetomidine is its minimal effect on ventilation , even when given in doses 10 times the maximum recommended(10) .in addition , MRI studies have shown that the airway remains patent during dexmedetomidine sedation , has been shown to reduce emergent delirium when given intravenously during the intraoperative period . Dexdor , the formulation of dexmedetomidine marketed in the μk , is presented as a clear , colourless solution containing 100μg/ml concentrate . It is diluted before administration to a concentration of 4 μg/ml . In the ICU used as a bridge to extubation , does not cause respiratory depression or airway compromise . Patients sedated with it are more cooperative , communicative , and better able to follow command than other agents It has been administered preoperatively to reduce anxiety(11) . It has been demonstrated in controlled trials that preoperational administration of dexmedetomidine favors midazolam premedication in terms of effective sedation induction upon parent separation and mask acceptance(11) .

1.5 Study Parameter assessment : Three scoring , systems were used , including :

1.5.1 The modified observers assessment of alertness/sedation scale (MOAA/S) .(12)

i. Zero: Did not respond to deep stimulus .

ii. One: Did not respond to mild prodding or shaking.

iii. Two: Responded only after mild prodding or shaking .

iv. Three: Responded only after child name was called loudly and/or repeatedly.

v. Four: Lethargic but responded to name spoken in normal tone .

vi. Five: Responded readily to child name spoken in normal tone (alert)

vii. Six : The child was agitated.

1.5.2 The parent separation anxiety scale (PSAS) .(12-15)

i) Excellent : The child was unafraid , cooperative , or asleep .

ii) Good : The child was slightly afraid / crying , quiet with reassurance .

iii) Fair : The child was moderately afraid and crying , not quiet with reassurance .

iv) Poor :The child was crying , need for restraint .

1.5.3 Mask acceptance scale (MAS) .(13-15)

i. One : Combative , crying .

ii. Two : Moderate fear of mask , not easily calmed .

iii. Three : Cooperative with reassurance .

iv. Four : Calm , cooperative .

1.6 Aim of the study :

To investigate the difference between the effect **of** midazolam and dexmedetomidine premedication on hemodynamic status , parent separation anxiety , mask acceptance and sedation .

2. Patients and methods

2.1 Approval Documents : Approval permission was taken from superviser , scientific council of anaesthesia and intensive care and informed consent obtained from parents of patients to participate in clinical trial .

2.2 Study designs: Two arms blinded randomize clinical trial

2.3 Duration of data collection : The data was collected in the period from 1/10/2018 until 30/1/2019 .

2.4 Sampling technique : The study includes 40 children were randomly divided into two equal groups , group (M) midazolam , group (D) dexmedetomidine . Group (M) patients received intranasal midazolam 0.2 mglkg and group (D) patients intranasal dexmedetomidine 1µglkg , approximately 30 minutes before induction of anaesthesia , in the form of a spray . Vital signs (heart rate , blood pressure , oxygen saturation) were recorded before administering the intranasal drug and again at an 20 minute .

2.5 dosage calculator : Nasal spray connected to syringe filled with normal saline to adjustment the number of puff in 1 ml . Each 1 ml =7 puffs , for example , 1ml of midazol am contain 5mg divided by 7, each puff contain 0.7 mg , so dosage (kg) X0.2mg÷0.7mg=number of puffs .also for dexmedetomidine after dilution each ml contain 20µg divided by 7 ,so each puff contain 3µg

2.6 Study setting : The data was collected from children undergoing elective surgery in Al Yarmouk teaching hospital at the ENT operating room .

2.7 Inclusion criteria :

- elective ENT surgery .

- ASA physical status class 1 .

- age 3 to 10 years .

- weight of 14 to 20 kg .

- premedication 30 minute before surgery .

2.8 Exclusion criteria :

- parental refusal .

- patients with history of allergy to drugs used in the study .

- patients with psychological illness .

- patients on antihistamine or sedative drugs .

- patients with upper respiratory tract infection .

- patients with hearing problems.

2.9 Study parameters : In the current study , three scoring systems were used , that was adopted from previous related studies (13-15) , these parameter was taken a 20 minute after premedication ,

included :

2.9.1 Parent separation anxiety score : A four grades scoring system that ranged from Excellent to poor .

i.Excellent : The child was unafraid , cooperative , or asleep .

ii. Good : The child was slightly afraid / crying , quiet with reassurance .

iii. Fair : The child was moderately afraid and crying , not quiet with reassurance .

iv. Poor : The child was crying , need for restraint .

2.9.2 Mask acceptance scale : A four grades scoring system that ranged from 1 to 4 :

i. One : Combative , crying .

ii. Two : Moderate fear of mask , not easily

calmed .

iii. Three : Cooperative with reassurance .

iv. Four : Calm , cooperative .

2.9.3 Sedation scale (MOAA/S) : A seven grades scoring system that ranged from (0 to 6) :

i. Zero : Did not respond to deep stimulus .

ii. One : Did not respond to mild prodding or shaking .

iii. Two : Responded only after mild prodding or shaking .

iv. Three : Responded only after child name was called loudly and/or repeatedly .

v. Four : Lethargic but responded to name spoken in normal tone

vi. Five : Responded readily to child name spoken in normal tone (alert) .

vii. Six : the child was agitated .

2.10 Dropped cases ; Any signs of significant side effects will manage accordingly and the cases dropped out of the study .

Statistical analysis

The collected data was handled and analyzed by IBM© SPSS© (Statistical Package for the Social Sciences) Statistics Version 23 . Chi -square was the test used for analyzing categorical data , while independent samples T - test and Paired samples T - test were used for numerical and normally distributed data . All analyses were done with 95% confidence intervals (CI) and P-values less than 0.05 were considered statistically significant throughout this study .

3.Results

There was no any dropped cases in the study .

This study included 40 children , divided into two equal groups , who received the premedication ; midazolam and dexmedetomidine . There was insignificant statistical difference regarding demographics and baseline reading .

2.11

Table 2 : Basic characteristics of patients distributed according to group ;

Variables		Midazolam	Dexmedetomidine	P-value
		Number (%)	Number (%)	
Gender	Male	11(55.0)	13(65.0)	0.519**
	Female	9(45.0)	7(35.0)	
Variables		Mean±SD	Mean±SD	-
Age		5.53±1.42	6.13±1.55	0.210*
Pre-operative	SPO2	98.45±0.76	98.55±0.60	0.648*
	HR	107.90±4.96	111.90±9.16	0.001*
	RR	17.20±1.44	17.00±1.41	0.660*
	Systolic BP	108.65±5.67	111.25±3.60	0.91*

SPO2:peripheral capillary oxygen saturation, HR: heart rate, RR: respiratory rate, BP: blood pressure

****: Chi square test, *: independent samples t-test**

SPO2:peripheral capillary oxygen saturation,

HR: heart rate, RR: respiratory rate, BP: blood pressure

**: Chi square test, *: independent samples t-test

There was significant statistical decrease of heart rate in both groups after the premedication , the systolic blood pressure decreased statistically in dexmedetomidine group , but within normal value . There was insignificant changes in SPO2 or respiratory rate .

Group		Before	After	Difference	P-value
SPO2	Midazolam	98.45±0.76	98.65±0.59	0.20	0.104
	Dexmedetomidine	98.55±0.60	98.80±0.41	0.25	0.135
HR	Midazolam	107.90±4.96	101.75±4.24	2.150	**0.001**
	Dexmedetomidine	111.90±9.16	104.40±5.71	8.50	**0.003**
RR	Midazolam	17.20±1.44	17.40±1.32	0.20	0.163
	Dexmedetomidine	17.00±1.41	16.95±1.50	0.05	0.330
Systolic BP	Midazolam	108.65±5.67	109.35±4.98	0.70	0.474
	Dexmedetomidine	111.25±3.60	106.45±3.19	4.80	**0.002**
Paired samples T-test					

Table 3: Changes in SPO2 , HR , RR , and systolic BP before and after the operation , according to premedication type.

There was significant statistical difference of parent - separation anxiety score between study groups , there was a higher number of good and excellent scores in dexmedetomidine group (15) compared to midazolam group (11) .

Table 4: Association between premedication type and parent-separation anxiety score

Mask acceptance score	Midazolam	Dexmedetomidine	Total	P-value
	Number (%)	Number (%)	Number (%)	
1	3(15.0%)	1(5.0%)	4(10.0%)	0.0472
2	6(30.0%)	6(30.0%)	12(30.0%)	
3	8(40.0%)	9(45.0%)	17(42.5%)	
4	3(15.0%)	4(20.0%)	7(17.5%)	
Total	20(100.0%)	20(100.0%)	40(100.0%)	-
Chi-square test				

There was significant statistical difference between both study groups concerning mask acceptance score .

Table 5: Association between premedication type and mask acceptance score .

Parent separation anxiety score	Midazolam	Dexmedetomidine	Total	P-value
	Number (%)	Number (%)	Number (%)	
Poor	3(15.0%)	2(10.0%)	5(12.5%)	0.0234
Fair	6(30.0%)	3(15.0%)	9(22.5%)	
Good	7(35.0%)	11(55.0%)	18(45.0%)	
Excellent	4(20.0%)	4(20.0%)	8(20.0%)	
Total	20(100.0%)	20(100.0%)	40(100.0%)	-
Chi-square test				

There was statistically significant difference between study groups regarding sedation score , and dexmedetomidine showed better satisfactory sedation compared to midazolam .

Table 6: Association between premedication type and sedation score.

Sedation scale	Midazolam	Dexmedetomidine	Total	P-value
	Number (%)	Number (%)	Number (%)	
3	0(0.0%)	11(55.0%)	11(27.5%)	0.002
4	9(45.0%)	8(40.0%)	17(42.5%)	
5	11(55.0%)	1(5.0%)	12(30.0%)	
Total	20(100.0%)	20(100.0%)	40(100.0%)	-
Chi-square test				

4.Discussion

Preoperative anxiety is a common condition , and there are millions of children who undergo different surgical operations throughout the world , with growing interest and diverse approaches to control it (16) .

In the current study , there was a statistically significant difference in preoperative heart rate between the study groups , which was associated with significant statistical decrease in systolic blood pressure in dexmedetomidine group . This was in agreement with Chaudhary et al . (2015) (13) who studied the differences between midazolam and dexmedetomidne in 60 childrens , and reported that dexmedetomidine group had lower postoperative heart rate and blood pressure post operatively . While Mostafa and Morsy (2013) in Egypt (17) in these study that compared the effects of intranasal dexmedetomidine , midazolam and ketamine as pre-medications in 96 children , and reported that there was a statistically insignificant difference in - between these items regarding heart rate and systolic blood pressure. This could be explained by the biphasic action of dexmedetomidine , which starts as vasoconstriction due to activation of α2B receptors (located in peripheral vascular smooth muscles) , but this is surpassed by the central effect of this medication on inhibition of sympathetic outflow(18) .

In the current study , there was an significant statistical association between parent - separation anxiety score and study groups , but children with good and excellent scores were 55% among midazolam group , compared to 75% among dexmedetomidine . This was comparable to the results of Gupta et al. (2017) (19) who compared the effects of midazolam and dexmedetomidine (both had been given intranasally) in 60 children , and reported that successful parental separation was observed in 73.3 % in dexmedetomidine group compared to 46.7 % in midazolam group . Also Sudhu et al (2016) (20) who studied the difference between intranasal dexmedetomidine , clonidine and saline , they reported a successful anxiolysis in 88.5 % in dexmedetomidine group . These were encouraging findings , and dexmedetomidine was better , or at least not inferior to midazolam in reducing anxiety with lower possible side effects as compared to the former (21) .

In this study , there was a significant statistical association between mask acceptances between the two study groups . This was in comparison to the results of Keles and Kocaturk (2018)(22) who studied the differences between midazolam and dexmedetomidine in 52 children , and reported there was difference in mask acceptance between the two groups, also Feng et al (2017) (21) , in their meta-analysis of 12 randomised controlled trials that used dexmedetomidine and midazolam especially in children , they reported that there was difference between these two premedication regarding mask acceptance . Several methods were used to identify mask acceptance problems in children , and premedications is only one of them , even the timing of introducing the mask play a role in controlling the anxiety of children (23).

In this study , dexmedetomidine showed better sedation scales compared to midazolam. This was in comparison to the results of Tong et al (2014) (24) , who studied 72 children , and divided them into two equal dexmedetomidine and midazolam groups , and reported that satisfactory sedation was obtained in 38.9% of midazolam group compared to 66.7 % in dexmedetomidine group . Also Gupta et al (19) , had reported that 80% of children who received intranasal .

dexmedetomidine had satisfactory sedation, compared to 53.3% of midazolam group . The peculiar action of dexmedetomidine on locus ceruleus is reflected by the natural sleep like sedative effect, so it can be used even outside the operating rooms with acceptable safety profiles (25).

5.Conclusions

1. Dexmedetomidine showed better results than midazolam regarding parent - separation anxiety score and mask acceptance .

2. Dexmedetomidine showed statistically significant satisfactory sedation compared to midazolam .

3. statistically decrease in heart rate in both

groups , decrease systolic blood pressure in dexmedetomidine group compared with intranasal midazolam . There were no episodes of hypotension or bradycardia .

6.Recommendations

1. We recommend to use anxiolytic drugs dexmedetomidine and midazolam which have good sedative effect without side effect during intranasal route .

2. A routine preoperative assessment and direct communication with the patients help in reduce stress before enter the patient to operating room .

3. Other studies should be done comparing different methods to decrease anxiety like premedication and parent presence during induction .

4. Different routes of administration should be compared to determine the optimum one .

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