Original Research Article

A Comparative Evaluation of Intranasal Dexmedetomidine and Intranasal Midazolam for Premedication in Pediatric Surgery

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Abstract

Background: We sought to compare the effects of intranasal Dexmedetomidine a more selective alpha 2 receptor with the effects of Midazolam administered via the same route

Materials and methods: After approval by hospital research ethics committee, informed written parental consent for anesthesia was taken. 60 patients with ASA grade I or II in age group (2-9 years) were enrolled for this. The study was carried out from February 2014 to May 2015 in a tertiary care hospital. For the study, 60 patients were divided in two groups: Group M: 0.2 mg/kg intranasal Midazolam and Group D: 1 µg/kg intranasal Dexmedetomidine. All patients in either group have received general anaesthesia using a standard balance anesthesia technique. Comparisons between the study groups were conducted using ANOVA by using multivariate ANOVA test, one-way ANOVA test, repeated measures ANOVA and Kruskal–Wallis ANOVA test as well as comparing mean and standard deviation.

Results: Our study demonstrated that intranasal Dexmedetomidine produces better sedation than intranasal Midazolam in pediatric age group. Ease of parent child separation at 30 minutes was satisfactory in group D though group M offered less satisfactory ease of parent child separation. In our study, the changes in heart rate and systolic blood pressure in group M and group D were clinically insignificant and modest. There were no episodes of significant bradycardia, hypotension, bradypnoea, apnea, airway obstruction, emesis and arterial oxygen desaturation at any time during the

study. None of the children were sedated to the extent that they failed to respond to stimulation or were unarousable. Ease of induction after 30 minutes was better in group D compared to group M.
Conclusion: Dexmedetomidine, in a dose of 1 microgram/ kg administered intranasally produces better sedation, better parental separation and mask acceptance as compared with intranasal Midazolam 0.2 mg/kg. The hemodynamic change produced with Dexmedetomidine are clinically insignificant (<20% of baseline) and modest.

Key words

Dexmedetomidine, Midazolam, Intranasal, Premedication, Pediatric, Surgery, Evaluation.

Introduction

Anesthesia and surgery cause severe anxiety and apprehension to the children which can effect smoothness of induction, emergence and psychological state of child in future like nightmare, enuresis and separation anxiety.

Premedication is often used to alleviate the stress and fear for surgery, ease parent- child separation and to facilitate a smooth induction of anaesthesia and reduced occurrence of postoperative behavioural disturbances associated with bad preoperative experience [1].

The risk factors which seem to be associated with high incidence of perioperative anxiety in children include: age 2 to 9 years, shy an inhibited nature, previous poor quality medical encounters, poor social adaptability, and increased parenteral anxiety [2].

The rising cost of hospital stay, increased work load on hospital institutions and the importance of ambulation in a fast moving world have prompted many anaesthesiologist to consider Premedication with renewed perspective.

Various pharmacological agents like Ketamine, Midazolam, Promethazine in various forms and by various routes are used for pre medication in pediatric patients.

Each drug has some advantage and disadvantage. An ideal agent should have rapid onset and offset, predictable duration, minimal side effects and rapid recovery, easy availability and ability to decrease anaesthetic drug requirement.

Midazolam is a gamma amino butryic acid (gaba) receptor, is most commonly used sedative drug for premedication in children. It provides effective sedation, anxiolysis and varying degrees of anterograde amnesia, however adverse effects such as post op behavioural changes, hiccups and paradoxical hyperactive reactions have been observed [3].

Premedication with Clonidine alpha 2 agonist applied via various routes, has exhibited superior sedative effects at induction, decreased the incidence of agitation at emergency, and achieved more effective early postoperative analgesia compared to Midazolam.

Dexmedetomidine is a newer alpha 2 agonist with more selective action on alpha -2 adreno receptor and a shorter half-life [4].

Therefore we sought to compare the effects of intranasal Dexmedetomidine a more selective alpha 2 receptor with the effects of Midazolam administered via the same route [5].

Aim of our study was to evaluate and compare safety, efficacy and feasibility of intranasal Midazolam (0.2 mg/kg) administered and intranasal Dexmedetomidine 1 microgram/ kg administered for premedication in paediatric patients of age group 2 to 9 years for short surgical procedures.

Materials and methods

After approval by hospital research ethics committee, informed written parental consent for anesthesia was taken. 60 patients with ASA

grade I or II in age group (2-9 years) were enrolled for this. The study was carried out from February 2014 to May 2015 in a tertiary care hospital. For the study, 60 patients were divided in two groups:

Group M: 0.2 mg/kg intranasal Midazolam

Group D: 1 µg/kg intranasal Dexmedetomidine

Inclusion criteria

Study of population

- Age between 2 to 9 years
- ASA physical status class I or II.
- Short duration of surgery lasting about 1hr

Exclusion criteria

- Parents refusal
- ASA physical status III and above
- Co-morbid diseases any nasal pathology (cardiac, pulmonary, neurological disease).
- Allergy to the drug to be used.
- Taking other sedative drugs
- Patient with upper respiratory tract infections any other congenital diseases.

Appropriate patients selected with ASA grade 1 for surgeries lasting about one hour duration and were divided into two groups who were matched for age, sex and risk factors.

One group was administered intranasal Midazolam in a dose of 0.2 mg/kg, 30 minutes prior to induction of anaesthesia (henceforth referred as group M) and other group was administered intranasal Dexmedetomidine 1 microgram /kg, 30 minutes prior to induction of anaesthesia (henceforth referred as group D). All patients in either group have received general anaesthesia using a standard balance anesthesia technique.

Pre-anesthetic assessment

- Appropriate patients were selected by preoperative assessment by eliciting proper history and physical examination.
- Thorough investigations include hemoglobin, complete blood count, blood sugar level, chest X-ray, renal function test, liver function tests and serum electrolytes.
- Patients with upper respiratory tract infection, nasal pathology, allergy to study drugs or taking other sedative drugs, cardiorespiratory or neurological disorders were excluded from study.

After obtaining approval by ethical committee and written informed parental consent, 30 ASA Grade I patients in each group were enrolled for the study.

The patients were randomly divided into two groups as designated above and demographic data was noted. Patients were kept starving for 6 hours. Baseline vital parameters were noted. Heart rate, spo2, BP, preoperative sedation score, behaviour score and mask acceptance score was noted.

Children were randomly divided into two groups. Group M received 0.2 mg/kg intranasal Midazolam; up to a maximum 5 mg. Group D received intranasal Dexmedetomidine 1 microgram/kg. Children had premedication in the preoperative holding area in the presence of parent. Intranasal drug was dripped into both nostrils using insulin syringe with the child in the recumbent position. Baseline heart rate (HR), oxygen saturation (SpO2), and blood pressure (BP) was measured before and every 15 min after intranasal drug administration until transfer to the operating room (OR) Sedation status was assessed every 5 min with a 6-point sedation scale. Behaviour score was evaluated every 5 min with a 4-point behaviour score and mask acceptance score was evaluated by the attending anaesthesiologist at induction using the same scale. Mode of induction (IV versus inhalation) was decided by the attending anaesthesiologist. The airway was maintained with a facemask or laryngeal mask airway throughout the operation. Anaesthesia was maintained with sevoflurane and 60% nitrous oxide in oxygen. The primary end-points were behaviour and sedation status at separation from the parent and at induction of

anaesthesia (mask acceptance). Secondary end-points included systolic BP (SBP) and HR changes. Patients were discharged from the PACU to the ward when they were awake, with reasonable control of pain and with vital signs within 20% of baseline values. Observations of sedation status and vital signs, including HR and SpO2 and systolic blood pressure were made at every 5minutes.

Evaluation scale

A. Sedation scores

1 - Does not respond to mild prodding or shaking
2 - Responds only mild prodding or shaking
3 - Responds only after name is called loudly or repeatedly
4 - Lethargic response to name spoken in normal tone
5 - Appear asleep but respond readily to name spoken in normal tone
6 - Appear alert and awake, response readily to name

B. Behaviour scores

1 - Calm and cooperative
2 - Anxious but reassurable
3 - Anxious and not reassurable
4 - Crying, or resisting

C. Response to induction (mask acceptance scale)

1. Combative, crying.
2. Moderate fear of mask, not easily calmed
3. Cooperative with reassurance.
4. Calm, cooperative.

Statistical Analysis

Comparisons between the study groups were conducted using ANOVA by using multivariate ANOVA test, one-way ANOVA test, repeated measures ANOVA and Kruskal–Wallis ANOVA test as well as comparing mean and standard deviation. The Turkey test was applied for post hoc pairwise comparisons. The changes of BP and HR from baseline among the groups were by Kruskal–Wallis t-test. P-value below 0.05 was considered significant. The statistical software used would be NCSS - PASS. For statistical analysis, sedation scores were categorized as being satisfactory when rate between 1 and 4 and unsatisfactory when rate is 5 or 6. Behaviour scores and wake-up scores were categorized as satisfactory when they are 1 or 2, and unsatisfactory when they are 3 or 4.

Results

Table - 1 shows distribution of samples according to the Age (in years). It indicates that majority of the patients were in the age group of 2 - 9 years.

Table - 2 shows descriptive statistics for Age in years. The mean age of patients in two groups was compared using independent samples t-test. The result indicates no significant difference in the mean age patients in two groups ($p > 0.05$). Both the groups showed there was no significant difference in the mean age in patients in both the groups.

Table - 3 shows descriptive statistics for weight in kg. The mean weight of patients in two groups was compared using independent samples t-test. The result indicates no significant difference in the mean weight of patients in two groups ($p > 0.05$). Both the groups showed that there was no significant difference in the mean weight of the patients in both the groups.

Table - 4 shows descriptive statistics for the preoperative sedation scores of patients in two groups. The preoperative sedation scores of patients in two groups was compared using independent samples t-test. The result indicates a statistically significant difference in the preoperative sedation scores of two groups ($p < 0.01$). At 5 and 10 minutes, sedation score in both group was similar and on application of chi – square test, the differences were statistically insignificant. At 15 minutes, in group M 30 patients had a score of 5 and in group D 12 patients had a score of 3, 17 patients had a score of 4 and 1 patient had a score of 5. On application of chi- square test, the difference was statistically significant. At 20 minutes In group M 30 patients had a score of 5 and in group D,1 patient had a score of 2 and 22 patients had a

score of 3 and 7 patients had a score of 4 .The difference was statistically significant. At 25 minutes in group M 19 patients had a score of 4 and 11 patients had a score of 5. In group D 21 patients had a score of 2 and 9 patients score of 3. The differences were statistically significant. At 30 minutes in group M all 30 patients had a score of 4 and in group D 23 patients had a score of 2 and 7 patients had a score of 3. The differences were statistically significant. The differences between both the groups were statistically significant. Sedation score was significantly higher in group D at 15, 20, 25 and 30 minutes compared to group M.

Table - 1: Age distribution.

Age (Years)	Group				Total	
	Dexmedetomidine		Midazolam			
	Frequency	%	Frequency	%	Frequency	%
3	3	10.0%	6	20.0%	9	15.0%
4	2	6.7%	3	10.0%	5	8.3%
5	3	10.0%	1	3.3%	4	6.7%
6	2	6.7%	0	0.0%	2	3.3%
7	5	16.7%	4	13.3%	9	15.0%
8	8	26.7%	9	30.0%	17	28.3%
9	7	23.3%	7	23.3%	14	23.3%
Total	30	100.0%	30	100.0%	60	100.0%

Table - 2: Mean age in years in intranasal dexmedetomidine and intranasal midazolam groups.

Group	N	Mean	SD	SEM	t-stat	df	p-value
Dexmedetomidine	30	6.867	1.995	0.364	0.475	58	0.637
Midazolam	30	6.600	2.343	0.428			

Table – 3: Mean weight in intranasal dexmedetomidine and nasal midazolam groups.

Group	N	Mean	SD	SEM	t-stat	df	p-value
Dexmedetomidine	30	15.433	7.514	1.372	0.489	58	0.626
Midazolam	30	16.333	6.707	1.225			

Table – 4: Preoperative sedative score in intranasal dexmedetomidine and intranasal midazolam groups.

Duration	Group	N	Mean	SD	SEM	t-stat	Df	p-value
at 5 min	Dexmedetomidine	30	4.233	0.430	0.079	-8.916	58	< .01**
	Midazolam	30	5.167	0.379	0.069			
at 10 min	Dexmedetomidine	30	4.167	0.379	0.069	-10.32	58	< .01**
	Midazolam	30	5.133	0.346	0.063			
at 15 min	Dexmedetomidine	30	3.633	0.556	0.102	-13.462	58	< .01**
	Midazolam	30	5.000	0.000	0.000			
at 20 min	Dexmedetomidine	30	3.200	0.484	0.088	-18.698	58	< .01**
	Midazolam	30	4.967	0.183	0.033			
at 25 min	Dexmedetomidine	30	2.367	0.490	0.089	-15.804	58	< .01**
	Midazolam	30	4.367	0.490	0.089			
at 30 min	Dexmedetomidine	30	2.233	0.430	0.079	-22.494	58	< .01**
	Midazolam	30	4.000	0.000	0.000			

****: Significant at 1% level of significance**

Table – 5: Separation score (behaviour score) at 30 minutes in intranasal midazolam and intranasal dexmedetomidine groups.

Separation Score (at 30 min)	**Group**				**Total**	
	Dexmedetomidine		**Midazolam**			
	frequency	**%**	**frequency**	**%**	**frequency**	**%**
1	14	46.7%	0	0.0%	20	33.3%
2	10	33.3%	11	36.7%	21	35.0%
3	4	13.3 %	15	50.0%	15	25.0%
4	2	6.7 %	4	13.3%	4	6.7%
Total	**30**	100.0%	**30**	100.0%	**60**	100.0%
*Chi-square = 21.083 DF = 3, p < .01***						

Table - 6: Mean heart rate in intranasal dexmedetomidine and intranasal midazolam groups.

	Group	**N**	**Mean**	**SD**	**SEM**	**t-stat**	**p-value**	**p-value**
at 0 min	Dexmedetomidine	30	118.667	3.651	0.667	-.808	58	.423
	Midazolam	30	119.500	4.313	0.787			
at 5 min	Dexmedetomidine	30	117.033	3.634	0.663	-2.477	58	.016*
	Midazolam	30	119.400	3.766	0.687			
at 10 min	Dexmedetomidine	30	114.400	5.593	1.021	-3.818	58	.000**
	Midazolam	30	119.233	4.099	0.748			
at 15 min	Dexmedetomidine	30	104.767	5.157	0.942	-13.155	58	.000**
	Midazolam	30	120.100	3.763	0.687			
at 20 min	Dexmedetomidine	30	101.633	3.358	0.613	-21.137	58	.000**
	Midazolam	30	120.133	3.421	0.625			
at 25 min	Dexmedetomidine	30	99.167	3.018	0.551	-25.188	58	.000**
	Midazolam	30	119.733	3.300	0.603			
at 30 min	Dexmedetomidine	30	98.067	2.638	0.482	-32.253	58	.000**
	Midazolam	30	121.000	2.865	0.523			
**: significant at 1% level of significance.								

Table - 5 shows association between separation score (Behaviour score) and drug used. The result of chi-square test indicates a significant association between Separation score and drug used ($p < 0.01$). In group D 46.7% patients had a separation score of 1 and 33.3% patients had a score of 2. In group M 36.7% patients had a score of 2, 50.0% patients had a score of 3 and 13.3% patients had a score of 4. On application of chi-square test ($p < 0.1$) the difference between both the group is statistically significant. Ease of parent child separation is better and significant in group D than group M.

Table - 6 shows descriptive statistics for heart rate per minute at various durations. Mean heart rate in group D was ranged between 118.667 to 98.067 beats / minute whereas in group M it was between 119.5 to 121 beats per minute. On application of independent samples 't' test for given p values, the differences between group D and group M was found to be statistically significant.

Table - 7 shows descriptive statistics for respiratory rate per minute at various durations. Mean respiratory rate in group D ranged between 20.767 to 19.067 per minute whereas in group M it was ranged between 20.900 – 22.607 per minute. On application of independent sample 't' test for given p values, the differences between group D and group M was found to be statistically insignificant.

Table - 7: Mean respiratory rate (rr) in intranasal dexmedetomidine and intranasal midazolam groups.

	Group	N	Mean	SD	SEM	t-stat	p-value	p-value
at 0 min	Dexmedetomidine	30	20.767	1.591	0.290	-.303	58	.763
	Midazolam	30	20.900	1.807	0.330			
at 5 min	Dexmedetomidine	30	20.467	1.196	0.218	-2.953	58	.005**
	Midazolam	30	21.700	1.950	0.356			
at 10 min	Dexmedetomidine	30	20.667	1.446	0.264	-3.121	58	.003**
	Midazolam	30	22.133	2.129	0.389			
at 15 min	Dexmedetomidine	30	20.133	1.756	0.321	-2.258	58	.028*
	Midazolam	30	22.100	4.436	0.810			
at 20 min	Dexmedetomidine	30	22.833	18.497	3.377	.022	57	.983
	Midazolam	29	22.759	1.976	0.367			
at 25 min	Dexmedetomidine	30	19.500	1.852	0.338	-6.603	58	.000**
	Midazolam	30	22.333	1.446	0.264			
at 30 min	Dexmedetomidine	30	19.067	1.143	0.209	-9.035	56	.000**
	Midazolam	28	22.607	1.792	0.339			
*****: Significant at 1% level of significance.***								

Table - 8: Mean systolic blood pressures (SBP) in intranasal and intranasal midazolam groups.

	Group	N	Mean	SD	SEM	t-stat	p-value	p-value
at 0 min	Dexmedetomidine	30	104.533	2.515	0.459	4.921	58	.000**
	Midazolam	30	101.400	2.415	0.441			
at 5 min	Dexmedetomidine	30	103.133	2.209	0.403	2.173	58	.034*
	Midazolam	30	101.933	2.067	0.377			
at 10 min	Dexmedetomidine	30	101.600	2.313	0.422	-1.128	58	.264
	Midazolam	30	102.200	1.769	0.323			
at 15 min	Dexmedetomidine	30	100.867	2.145	0.392	-1.801	58	.077
	Midazolam	30	101.933	2.434	0.444			
at 20 min	Dexmedetomidine	30	99.600	2.372	0.433	-3.411	58	.001**
	Midazolam	30	101.933	2.900	0.529			
at 25 min	Dexmedetomidine	30	98.467	2.209	0.403	-6.014	58	.000**
	Midazolam	30	102.267	2.664	0.486			
at 30 min	Dexmedetomidine	30	97.733	2.083	0.380	-8.554	58	.000**
	Midazolam	30	101.933	1.701	0.310			
*****: Significant at 1% level of significance.***								

Table - 8 shows descriptive statistics for Systolic blood pressure (mmHg). In group D mean systolic blood pressure dropped from 104.53 to 97.73 mm of Hg 30 minutes after administering intranasal Dexmedetomidine, whereas in group M it ranged between 101.4 – 101.733 mm of hg. On application of independent samples 't' test for given p values, the difference between group D and group M was found to be statistically significant.

Table - 9 shows descriptive statistics for SPO2%. Mean SPO2 in group D ranged between 99.833% - 99.700% whereas in group M it ranged between 99.667% – 99.833%. On application of independent samples 't' test for given p values, the difference between group D and group M was found to be statistically insignificant.

Table - 10 shows distribution of induction score at 30 min. The result of chi-square test indicates significant association between induction score and drug used ($p < 0.05$). In group D 50.0 % patients had a score of 1 and 33.3 % patients had a score of 2. In group M 36.7 % patients had a score of 2, 50.0 % patients had a score of 3, 13.3% patients had a score of 4. On application

of chi-square test ($p < 0.5$) the difference between both the groups is statistically significant. Induction score was better and significant in group D than group M.

Table - 11 shows distribution of complications according to drug used. The result of chi-square test indicates no significant association between complications and drug used. 93.3% of patients in group D and 93.3% of patients in group M did not have any complications. 2 patients (6.7%) in both the groups had vomiting. Overall complication rate was insignificant in either groups and both the drugs are safe through intranasal routes.

Table - 9: Mean SPO2 in intranasal dexmedetomidine and intranasal midazolam groups.

	Group	N	Mean	SD	SEM	t-stat	p-value	p-value
at 0 min	Dexmedetomidine	30	99.833	0.379	0.069	1.494	58	.141
	Midazolam	30	99.667	0.479	0.088			
at 5 min	Dexmedetomidine	30	99.600	0.621	0.113	-1.756	58	.084
	Midazolam	30	99.833	0.379	0.069			
at 10 min	Dexmedetomidine	30	99.767	0.430	0.079	-.637	58	.527
	Midazolam	30	99.833	0.379	0.069			
at 15 min	Dexmedetomidine	30	99.767	0.430	0.079	-1.385	58	.171
	Midazolam	30	99.900	0.305	0.056			
at 20 min	Dexmedetomidine	30	99.533	0.571	0.104	-3.505	58	.001**
	Midazolam	30	99.933	0.254	0.046			
at 25 min	Dexmedetomidine	30	99.633	0.556	0.102	-2.688	58	.009**
	Midazolam	30	99.933	0.254	0.046			
at 30 min	Dexmedetomidine	30	99.700	0.535	0.098	-1.47	58	.107
	Midazolam	30	99.833	0.379	0.069			
***: Significant at 1% level of significance.*								

Table - 10: Induction score (mask acceptance scale) at 30 minutes in intranasal dexmedetomidine and intransal midazolam groups.

Induction score at 30 min						
Induction Score at 30 min	**Group**				**Total**	
	Dexmedetomidine		**Midazolam**			
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
1.00	15	50.0 %	0	0.0%	20	33.3%
2.00	10	33.3%	11	36.7%	21	35.0%
3.00	3	10.0%	15	50.0%	15	25.0%
4.00	2	6.7 %	4	13.3%	4	6.7%
Total	30	100.0%	30	100.0%	60	100.0%
Chi-square = 3.695, df=2, p = 0.296, NS						

Table - 11: Complications in intranasal dexmedetomidine and intranasal midazolam groups.

Complications						
Complications	**Group**				**Total**	
	Dexmedetomidine		**Midazolam**			
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
None	28	93.3%	28	93.3%	56	93.3%
Vomiting	2	6.7%	2	6.7%	4	6.7%
Total	30	100.0%	30	100.0%	60	100.0%
Chi-square = 0.00, df=2, p=1.00						

Discussion

The aims of premedication in pediatric population is to alleviate the stress and fear of surgery as well as to ease parent – child separation and promote a smooth induction of anaesthesia thereby reducing the occurrence of postoperative behavioural disturbances associated with bad preoperative experience [1] . The rising cost of hospital stay, increased work load on hospital institutions and the importance of ambulation in a fast moving world have prompted many anaesthesiologists to consider premedication with renewed perspective as the premedicant of choice for short procedures.

The needs for premedication must be individualised depending on child's underlying medical conditions , length of surgery, smooth induction of anaesthesia, the psychological make-up of child and family and the effectiveness of the premedicant at the specific institution.

The risk factors which seem to be associated with high incidence of perioperative anxiety in children include: age 2 to 9 years, shy and inhabited nature, previous poor quality medical encounters, poor social adaptability, and parenteral anxiety [2-4].

To avoid emotional trauma associated with parent – child separation and facemask application during induction, it was planned to premedicate the children, appearing for elective surgery, with the most commonly utilized premedicants Midazolam and Dexmedetomidine via intranasal route.

Midazolam is the most commonly used anxiolytic premedication, has been used for the preoperative sedation by the intramuscular, rectal, and oral and intranasal routes. Disadvantages of these routes include painful injection (IM route), Slow onset and delayed recovery (oral and rectal routes).

Midazolam normally exists in equilibrium of both open and a closed ring structure, the proportion of which is PH dependent. At lower PH values, there is greater proportion of drug in the open ring configuration is lipophilic and physiologic active, bioavailability is sensitive to changes in PH [3].

The first clinical investigation of intranasal Midazolam in children was reported by Niall CT Wilton and colleagues [33]. Advantages of nasal administration of Midazolam include rapid absorption without passing through portal circulation, and high systemic availability. It provides effective premedication when given 30 minutes before separation from parents. The bioavailability of intranasal Midazolam have ranged from 50 – 83%.

In our study we selected 0.2 mg/ kg dose of intranasal Midazolam as preliminary studies conducted by Niall CT Wilton, et al. [33] using 2 doses of intranasal Midazolam , 0.2 mg/kg and 0.3 mg/ kg, found that significant changes in sedation occurred early in low dose Midazolam as compared to high dose. According to them, the higher dose necessitated a large volume resulting in more coughing and sneezing with expulsion of part of the dose which explains more rapid onset of the low dose. They recommended 0.2 mg/kg as the optimum dose intranasally.

Similar results were obtained in a study conducted by Pradipta Bhakta, et al. [34], and Davis PJ, et al. [35]. Who compared 0.2 mg/ kg versus 0.3 mg/ kg of Midazolam intranasally. They concluded that 0.2 mg/ kg was an effective dose and no added advantage was found with 0.3 mg/kg. With the above evidences we have opted for a lower dose of 0.2 mg/kg intranasally for our study.

Recently, alpha2 receptor agonists such as Dexmedetomidine have also been found to be useful for premedication in children. The site of action of Dexmedetomidine is in locus coeruleus where it causes EEG activity similar to normal

sleep. This results in anxiolytic effect, sedation and analgesia without excessive drowsiness. The intranasal route was used in our study as it is non-invasive, unlike intravenous and intramuscular routes, and Produces a more rapid onset of action than the oral route. Previous studies have found Dexmedetomidine to be highly effective compared with Midazolam. Mustafa et al. compared intranasal Dexmedetomidine with intranasal Midazolam and Ketamine and found that Dexmedetomidine achieved faster sedation and better child–parent separation scores. In a study by Prabhu Tilak, et al. [21] concluded that Dexmedetomidine in a dose of 1 microgram/kg administered intranasally, produces better sedation and comparable behaviour scores, during separation from the parents and induction of anaesthesia compared to intranasal Midazolam in a dose of (0.2 mg/kg). In our study both Midazolam and Dexmedetomidine were administered and children were observed for 30 minutes before induction.

In the present study, intranasal Midazolam (0.2 mg/kg) was compared with intranasal Dexmedetomidine 1 microgram/ kg for premedication in pediatric surgery. Children of age 2- 9 years were chosen for the study, as this is the most vulnerable group for the stress response. Sixty healthy children awaiting elective surgery who did not meet the exclusion criteria were randomly assigned into two groups of 30 each group D and group M. Group M received 0.2 mg/ kg of intranasal Midazolam and group D received 1 microgram/ kg of Dexmedetomidine in the preoperative holding area. Tuberculin syringe was used for undiluted Midazolam and Dexmedetomidine for accurate dosing.

We studied the following parametres like Demographic profile, preoperative sedation score using five point sedation score, ease of parent child separation (behaviour score) , ease of induction or mask acceptance, haemodynamic parametres before induction score and complications if any.

Age and weight

Patients in both groups were comparable in age with the range between 2 to 9 years .The mean age in group D was 6.867 and in group M was 6.600. The weight range of the patients between both the groups was between 5 – 20 kgs. The mean weight in intranasal Dexmedetomidine was 15.433 and the mean weight in intranasal Midazolam was 16.333. The differences being statistically not significant.

Preoperative sedation score using five point sedation scale

The preoperative sedation scores of patients in two groups was compared using independent samples t-test. The result indicates a statistically significant difference in the preoperative sedation scores of two groups ($p < .01$).

At 5 and 10 minutes, sedation score in both group was similar and on application of chi – square test, the differences were statistically insignificant.

At 15 minutes , in group M 30 PT'S had a score of 5 and in group D 12 patients had a score of 3, 17 patients had a score of 4 and 1 patient had a score of 5. On application of chi- square test, the difference was statistically significant.

At 20 minutes In group M 30 patients had a score of 5 and in group D, 1 patient had a score of 2 and 22 patients had a score of 3 and 7 patients had a score of 4. The difference was statistically significant. At 25 minutes in group M 19 patients had a score of 4 and 11 patients had a score of 5. In group D 21 patients had a score of 2 and 9 patients score of 3. The differences was satistically significant. At 30 minutes in group M all 30 patients had a score of 4 and in group D 23 patients had a score of 2 and 7 pt's had a score of 3 . The differences was statistically significant. Sedation score was significantly higher in group D at 15, 20, 25 and 30 minutes compared to intranasal midazolam group. In our present study, it was seen that Dexmedetomidine produces significantly better levels of sedation at 30 minutes compared to intranasal Midazolam.

In a study by Prabhu Tilak, et al. [21] concluded that Dexmedetomidine in a dose of 1 microgram/kg administered intranasally, produces better sedation score compared to intranasal Midazolam in a dose of 0.2 mg/kg.

Separation score (behaviour score)

In group D 46.7% patients had a separation score of 1 and 33.3% patients had a score of 2. In group M 36.7% patients had a score of 2 , 50.0% patients had a score of 3 and 13.3% patients had a score of 4. On application of chi- square test ($p < 0.1$) the difference between both the group is statistically significant.

Ease of parent child separation is better and significant in group D than group M. In our present study the behaviour of most of the children was satisfactory (score 1 and 2) during separation from parents in group D.

Mask acceptance

In group D 50.0 % patients had a score of 1 and 33.3 % patients had a score of 2. In group M 36.7% patients had a score of 2, 50.0% patients had a score of 3, 13.3% patients had a score of 4. On application of chi- square test ($p < 0.5$) the difference between both the groups is statistically significant. In our study induction score is better in group D than group M and the difference is statistically significant. In a study by Deepak Singla, et al. [24] they showed that children who received intranasal Dexmedetomidine had lower anxiety levels, and better mask acceptance and parenteral separation compared with intranasal Midazolam.

Vital parameters

We studied the following vital parameters before induction after premedicating the patients with intranasal Dexmedetomidine and Midazolam.

a. Heart rate
b. Respiratory rate
c. Systolic blood pressure.
d. SPO2

And compared them at 5 minutes time intervals.

Also a comparative analysis between the 2 groups i.e., group D and group M was done.

Heart rate

We compared the difference in the mean heart rate between group D And group M at 5 minutes intervals and also with their baseline values respectively. We observed that mean heart rate in group M in preoperative period was ranged between 119.5 to 121 beats per minute. Whereas in group D it ranged between 118.667 to 98.067 beats per minute. On application of independent sample 't' test for given p values, the differences between both the groups was found to be statistically significant. Alpha 2 agonists produce a modest reduction in heart rate. Our study showed that Dexmedetomidine reduces pulse rate in the preoperative period, though clinically significant bradycardia was not observed in children in group D. In a study by Deepak Singla, et al. [24] showed that Dexmedetomidine reduces pulse rate in the preoperative period compared to children who received intranasal Midazolam in the preoperative period.

Respiratory rate

We compared the difference in the mean respiratory rate between group D and group M at 5 minutes time intervals and also with their baseline values respectively. We observed that mean respiratory rate in group M in the preoperative period was ranged between 20.9 to 22.607/minute .Whereas in group D ranged between 20.767 to 19.067/minute. On application of independent samples 't' test, the difference was statistically insignificant.

Systolic blood pressure

The mean systolic blood pressure in group M was ranged between 101.4 – 101.933 mm of Hg whereas in group D ranged between 104.533 - 97.733 mm of Hg. On application of independent samples 't' test for given p values, the difference between group M and Group D was found to be statistically significant. Our study showed that Dexmedetomidine reduces systolic blood pressure in the preoperative period, though clinically significant hypotension was not observed in group D. In a study done by Prabhu Tilak, et al. [21] showed that intranasal Dexmedetomidine reduces systolic blood

pressure in the perioperative period, compared to children who received intranasal Midazolam. However the fall was less than 20 % of baseline and manageable.

Oxygen saturation

We observed that mean oxygen saturation in group M ranged between 99.667% - 99.833%. In group D ranged between 99.833% - 99.700%.

On application of independent samples 't' test, the difference was statistically insignificant. Overall, we observed that heart rate, respiratory rate, systolic blood pressure, and SPO2 were stable throughout the study period in both the groups. These findings suggest the safety of Midazolam and Dexmedetomidine given by intranasal route in the doses studied.

In a double blind randomised study conducted by Deepak Singla, et al. [24] using intranasal Dexmedetomidine (1 microgram/ kg) premedication resulted in statistically significant but clinically unimportant lower heart rate and blood pressure at 10,20 and 30 minutes following administration compared with intranasal Midazolam (0.2 mg/kg). There were no episodes of hypotension and bradycardia. Children in group D achieved better parental separation and mask acceptance scores compared with group M.

In our study, the changes in heart rate and systolic blood pressure in group M and group D were clinically insignificant and modest. There were no episodes of significant bradycardia, hypotension, bradypnoea, apnea, airway obstruction, emesis and arterial oxygen desaturation at any time during the study .None of the children were sedated to the extent that they failed to respond to stimulation or were unarousable.

Two patients (6.7 %) in either groups had 1 episode of vomiting.

On the whole frequency of complications in our study was very less. All the patient's relatives were satisfied with this type of anaesthesia.

Conclusion

We concluded that Dexmedetomidine, in a dose of 1 microgram/ kg administered intranasally produces better sedation, better parental separation and mask acceptance as compared with intranasal Midazolam 0.2 mg/kg. The hemodynamic change produced with Dexmedetomidine are clinically insignificant (<20 % of baseline) and modest.

References

1. Ellen McCann, Mary, Kain ZN. The management of preoperative anxiety in children: An update in paediatric anaesthesia. Anesth and Analg., 2001; 93: 98-105.
2. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. Arch Ped Adoles Med., 1996; 150(12): 1238-1245.
3. Malinovsky JM, Populaire C, Cozien A, et al. Premedication with midazolam in children: effect of intranasal, rectal and oral routes on plasma midazolam concentration. Anaesthesia, 1995; 50(4): 351- 354.
4. Petroz GC, Sikich N, James M, van Dyk H, Shafer SL, Schily M, Lerman J. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. Anesthesiology, 2006; 105: 1098–110.
5. Bhadla S, Prajapati D, Louis TPG, et al. Comparison between Intranasal Dexmedetomidine and Midazolam for premedication in pediatric surgery. Res., 2013; 7: 248-256.
6. Naill CT Wilton, John Leigh, David R Rosen, Uma A Pandit. Preanesthetic sedation of preschool children using intranasal Midazolam. Anesthesiology, 1998; 69: 972-975.
7. Pradipta Bhakta, Ghosh BR, Manjushree Roy, Gauri Mukherjee. Evaluation of intranasal Midazolam for preanaesthetic sedation in pediatric patients. Indian

journal of Anesthesia, 2007; 51(2): 111-116.

8. Davis Peter J, Tome Julie A, Mc Gowan Francis X Jr, Cohen Ira-Todd, Latta Karen RN, Felder Herman. Preanesthetic medication with intranasal Midazolam for brief pediatric surgical procedures: effect on recovery and hospital discharge times. Anesthesiology, 1995 Jan; 82): 2-5.
9. Prabhu Tilak, J. Ranganathan, P. Srinivasan, Sree Sabari S. A comparison of intranasal Dexmedetomidine and Midazolam for premedication in children - A Prospective randomised double blind control trial. 2014, 2278-2648, 2278-2656.
10. Deepak Singla, Gunjan chaudhary, Jagdish Dureja, Mishu Mangla. Comparison of Dexmedetomidine versus Midazolam for intranasal premedication in children posted for elective surgery: a double- blind, randomised study. 2014. ISSN: 2220-1181.