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Research Article

COMPARATIVE STUDY OF NASAL DEXMEDETOMIDINE VERSUS NASAL MIDAZOLAM AS PREMEDICATION IN CHILDREN UNDERGOING ELECTIVE SURGICAL PROCEDURE UNDER GENERAL ANAESTHESIA

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ABSTRACT

Dexmedetomidine is now being used in the paediatric population as a sedative and analgesic because of its central selective alpha$_2$ receptor agonistic properties with less respiratory depression. Dexmedetomidine can be administered intramuscularly and intravenously but as the children prefer noninvasive route, use of the drug by oral or nasal route may be tried. The aim of our study was to compare the efficacy and safety of intranasal dexmedetomidine with intranasal midazolam for premedication in children undergoing elective surgical procedure under general anaesthesia. A prospective randomised double blind study was undertaken on hundred (100) ASA 1&2 children undergoing elective surgical procedure. Group A (n=50) received 2 microgram/kg of dexmedetomidine and Group B (n=50) received midazolam 0.5 mg/kg intranasal one hour before induction. General anaesthesia was administered according to a standard protocol. Ramsay sedation score was noted and compared 1hour after administration and immediate postoperatively. Blood pressure and pulse were recorded continuously throughout the operation. Side effects if any, were noted. Postoperative pain was recorded by Observer Pain Scale. The results of the study showed there was no significant difference between two groups in heart rate, systolic blood pressure, SpO_2, and respiratory rate after administration of either medication. The Ramsay sedation score in group A was significantly higher compared to midazolam group after 1hour of administration of the study drug and postoperatively. Postoperative pain score was also significantly lower in group A. To conclude nasal dexmedetomidine (2mcg/kg) premedication, one hour before induction was safe and more effective compared to midazolam in children undergoing elective surgical procedure under general anaesthesia.

Key Words: *Dexmedetomidine, Midazolam, Premedication, Children and Elective Surgical Procedure*

INTRODUCTION

Dexmedetomidine, a highly selective alpha$_2$ agonist, has sedative and analgesic properties. Recently, dexmedetomidine is recommened for procedural sedation in children is stated by Koroglu, and Demirbilek *et al.*, (2005). Dexmedomidine is a newer alpha$_2$ agonist with more selective alpha$_{2:}$ alpha$_1$ (1600:1) adrenoceptor activity with a short half life. Kain *et al.*, (1997) has postulated that it is a challenge for paediatric anaesthesiologists to reduce anxiety in children for operative procedures to facilitate a smooth induction of anaesthesia. Kain Caldwell-Andrews and Krivutza (2004) documented similar findings.

Children tolerate oral and nasal route better than intravenous route for needle fear. Intranasal midazolam, fentanyl, ketamine are being practiced in children with satisfactory results as has been shown both by Weber *et al.*, (2003) and Lonnqvist *et al.*, in (2005).This study was done to find out a better alternative for pre operative anxiolysis in children for smooth induction.

MATERIALS AND METHODS

After approval from the institutional ethics committee and informed written consent from the parents, a double blind randomised prospective study was undertaken to evaluate the effects of intranasal midazolam and dexmedetomidine in children undergoing elective surgical procedures under general anaesthesia. 100 children of ASA-I and ASA-II, aged 2-8 years, body weight 12-15 kg, were randomly allocated into two equal groups. Group A (n=50) received intranasal dexmedetomidine 2 mcg/kg and Group B (n=50) received intranasal midazolam 0.5 mg/kg as premedication 1hour before induction. Each drug was taken in a 2ml syringe and normal saline was added to make the volume of 2 ml by an anaesthesiologist who was completely blind to the study and to the group allocation. Heart rate, systolic blood pressure, respiratory rate, SPO_2, was measured continuously after administration of both drugs in the pre anaesthetic room. Sedation level was evaluated by Ramsay sedation scale pre operatively and 1 hour after administration of both the study drugs before induction. General anaesthesia was administered according to a standard protocol.

Induction was done with halothane 2-3% in oxygen. Intravenous line was secured, glycopyrrolate 0.004 mg/kg and fentanyl 2 mcg/kg was administered intravenously and precordial stethoscope was fixed with tape. Suxamethonium 1.5 mg/kg intravenously was given after assessing airway under inhalational anaesthetic and trachea was intubated with proper size endotracheal tube. Anaesthesia was maintained with 0.5% halothane and 66% N_2O in 33% O_2 and controlled ventilation using atracurium 0.5 mg/kg first dose and then the dose was reduced to ½ or 1/3rd as per requirement. Jackson – Rees modification of Ayre's T piece was used for controlled ventilation. Monitors used were pulse oxymetry, NIBP, ECG, and $EtCO_2$. Intraoperatively all patients received balanced salt solution (Aerolyte P) infused at the rate of 4 ml/kg/hour for 1st 10 kg, 40 ml + 2ml/kg/hr for next 10kg + estimated fluid deficit for period of fasting (50% in 1st hour, 50% in next 2 hours, with 25% each hour) + 3rd space loss 5ml/kg/hr. Blood loss was average and replaced with 3 times the volume of crystalloid. After surgery, residual neuromuscular block was reversed with injection neostigmine and injection glycopyrrolate. Patients were extubated when they had satisfactory recovery of motor power and were fully awake. The anaesthesiologist, who was unaware of the group allocation and the drug administration, monitored all the patients in the post anaesthesia care unit. Pain sedation were assessed by Observer Pain Scale and Ramsay sedation scale respectively at 1, 3, 6 hours.

Observer Pain Scale (OPS)

Item	Score
Laughing, euphoric	1
Happy, contended	2
Calm or asleep	3
Mild to moderate pain: crying, Grimacing, restlessness; can distract with Toy, food, parental presence	4
Crying, screaming, inconsolable	5

Ramsay Sedation Scale

Patient anxious agitated and impatient
Patient cooperative oriented and calm
Patients only respond to verbal commands
Patient that demonstrates a brisk response to the glabella tap test or auditory stimulus
Patient that demonstrates a sluggish response to the glabella tap test or auditory stimulus
Patient that does not response to the glabella tap test or auditory stimulus

Statistical analysis was done using Student's t-test (unpaired t-test) & Chi-Square test, $p<.05$ was considered to be significant.

RESULTS

Table 1 showed demographic profile in between two groups. Both the groups were comparable.
Table 2 showed haemodynamic study, respiratory rate and Spo_2 in between two groups.

Table 1: Distribution of the Participants as Per Some Baseline Variables (N=50)

	Group-A (Dexmedetomidine) n=50	Group-B (Midazolam) n=50	p value
Age	4.08±1.38	4.30±1.44	p>0.05
Body weight	14.20±3.13	13.96±1.30	p>0.05
ASA I/II	12/13	13/12	p>0.05

Table 2: Comparison of Haemodynamic parameters, Respiratory rate and Spo_2 in between two Groups

	Group-A (Dexmedetomidine) n= 50	Group-B (Midazolam) n=50	p value
Heart rate (beats/minute)	75.04±2.05	77.16±2.95	0.0644
No of patient showed bradycardia	4(8%)	3(6%)	0.0655
Systolic blood pressure (mm of Hg)	103.61±2.96	104.28±2.38	0.3798
Respiratory rate (min)	15.0±2.0	16.0±3.0	0.342
SPO2	99.0±1.0	99.0±1.0	0.421

Table 3: Comparison between Ramsay Sedation Score, Successful Parental Separation and Ops Scalei in between Two Groups

	Group-A (Dexmedetomidine)n=50	Group-B (Midazolam) n=50	p value
Ramsay sedation score	2.20±0.40	1.10±0.32	0.0001*
Successful parental separation	Yes=100% No=0%	Yes=80% No=20%	0.0001*
Observer Pain Scale Score	2.5±0.5	3.5±0.5	0.001*

Both the groups were comparable. Only 8% of patient in group A showed bradycardia (pulse rate below 60/minute) whereas in group B the incidence of bradycardia was seen in 6% of patients (p >0.05).
Table 3 showed less Ramsay sedation score and lower OPS score in group A compared to group B (p<0.05).

DISCUSSION

Midazolam is most commonly used premedicant in children to minimize distress in operating room to facilitate a smooth induction of anaesthesia as was observed by Kain, Caldwell-Andrews *et al.,* (2004) as well as by Kain, Meyes & Bell (1997). They also stated that the beneficial effects of midazolam include rapid sedation, anxiolysis, and reduction of post operative nausea and vomiting. Premedication with midazolm has been proved by McGraw & Kendric (1998) to be more effective than parental presence or plecebo in reducing anxiety and improving quality of induction during anaesthesia. Cote, Cohen & Suresh in a recent evidence based clinical update has shown that nasal midazolam 0.5 mg/kg is effective in reducing both separation and induction anxiety in children with minimal effect on recovery time. Mandemma *et al.,* (1992) & Bojrkman *et al.,* (1997) have shown that intranasal route is a non-invasive route well tolerated by the paediatric patients. Drugs are rapidly absorbed by the highly vascular nasal mucosa and produce quicker action. It has a faster than oral or rectal route. Niall, Leigh, Rosen & Pandit (1988) have demonstrated that as midazolam has high hepatic clearance, avoidance of hepatic first pass metabolism offers greater systemic bioavailability. According to Davis, Tome & Gowan (1995), recovery from anaesthesia is not affected even after minor surgery. We selected children of 2-8 years age group because this age group is most susceptible to the separation anxiety. In our study 50% of children receiving 0.5 mg/kg of nasal midazolam have been shown to produce effective sedation. Davis *et al.,* (1995) demonstrated that the major drawback of intranasal midazolam was that at least 50% children cry on administration because it transiently irritates nasal passages

Virtanen, Savola, & Saano (1998) have described Dexmedetomidine as a newer alpha 2 agonist with more selective alpha2: alpha1 (1600:1) and adrenoceptor activity with a short half life.

Dexmedetomidine is effective and safe premedicant in children when administered via buccal mucosa as has been described by Tobias (2007).

Yuen *et al.,* (2008) demonstrated that intranasal 1-1.5 mcg/kg dexmedetomidine produced sedation in 45-60 minutes with peak at 90-105 minutes but it produced sedation in only >50% of children at the time of induction. So we used 2mcg/kg intranasal dexmedetomidine as premedication 1 hour before surgery. In the dexmeditomidine group, the children were less agitated and they resisted their mother slightly when halothane mask was placed on face.

Antilla *et al.,* (2003) documented the high bioavailability (73%-92%) when dexmedetomidine was given via the buccal route. Onset occurred in 10-15 minutes with a peak effect at 90 minutes. It has a pKa of 7.1. Since this drug has a neutral pH, it is virtually painless when given intranasally and it is also tasteless and odourless.

Dyck & Shafer (1993) described that dexmedetomidine, an imidazole subclass of α_2 adrenergic agonist has a high short half life (2-3 hour). Different researchers over time like Correa-Sales, Reid & Maze ,(1992), Correa-Sales, & Nacif-Coelho (1994), Sculptoreanu *et al.,* (1993) & Dose *et al.,* (1989), demonstrated that the physiological effects of dexmedetomidine are mediated via post synaptic α_2 adrenergic receptor and activation of a G protein resulting in decreased adenyl cyclase activity. A reduction of intracellular cyclic adenosine monophosphate (c AMP) and c- AMP dependant protein kinase activity results in dephosphorylation of ion channels. Alternation in ion channel function, ion translocation and membrane conductance lead to decreased neuronal activation and clinical effect of sedation and anxiolysis. Central CNS stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus cereleus in the brainstem play a prominent role in sedation and anxiolysis. Decreased nor-adrenergic output from the locus cereleus allows for increased firing of inhibitory neurone including GABA. Primary analgesic effects and potentiation of opoid induced analgesia results from activation of α_2 adrenergic receptors in the dorsal horn of spinal cord and inhibition of substance P release.

In our study, we have shown that 90% of the children attained a satisfactory level of sedation (Ramsay Sedation Scale) after 2 mcg/kg intranasal dexmedetomidine.

As with any sedative agent, the potential exists for adverse end organ effect with dexmedetomidine like hypotension, hypertension, nausea, bradycardia, atrial fibrillation, hypoxia and various atrioventricular block, but according to the current literatures, these events are relatively uncommon.

Centrally acting α_2 adrenergic agonist also activate receptors in the medullary vasomotor centre reducing nor-epinephrine with a resultant central sympatholytic effect leading to decreased heart rate and blood pressure as demonstrated by Petroz *et al.,* (2006). In a pharmacokinetic study of IV dexmedetomidine in children, it had been shown that 0.66 and 1 mcg/kg IV dexmedetomidine given over 10 min produced a significant reduction of heart rate (15% compared with baseline) and blood pressure (25% compared with baseline). Munro et al. (2007)reported that the reduction of blood pressure and heart rate were < 20% of baseline in children who were sedated with an initial dose of 1 mcg/kg IV dexmedetomidine followed by a maintenance infusion during cardiac catheterisation.

Yuen *et al.*, (2008) stated there was no significant bradycardia with nasal administration of dexmeditomidine 1mcg/kg.

In our study, 2 mcg/kg intranasal dexemedetomidine reduced heart rate and blood pressure in the 1st hour in < 10% of cases. We have used 2 mcg/kg of nasal dexmedetomidine with an idea to attain satisfactory sedation prior to anaesthetic induction in almost all children. Dexmeditomidine group also showed lower OPS score compared to midazolam group.

We accept the fact that there are some limitations in our study. First, the sample size was small. Secondly, we studied only the patients of 2-8 years of age group. Future studies might reveal the sedative effect of intranasal dexmedetomidine on children of varying age group.

Conclusion

So to conclude nasal dexmedetomidine is effective, safe and a better alternative than nasal midazolam in children undergoing elective surgical procedure under general anaesthesia.

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