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INTRANASAL MIDAZOLAM, FENTANYL AND DEXMEDITOMITIDINE AS A PREMEDICATION IN PEDIATRIC SURGICAL PATIENTS

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ABSTRACT

Background: For providing premedication to pediatric surgical patients, various drugs and many routes have been studied. Intranasal route is one of them. It's one of the preferred routes because of the ease of administration. **Objectives:** To evaluate the safety and efficacy of midazolam, fentanyl and dexmedetomidine as intranasal premedication in pediatric surgical patients, to study their hemodynamics and respiratory consequences in paediatric patients and their effects on post anaesthesia recovery. **Methods:** Prospective, randomized double blind study.50 children of 2-8 years were studied in each group. **Results and Conclusion:** We found that midazolam, fentanyl and dexmedetomidine produced adequate sedation with little side effects. We prefer to use midazolam due its efficacy and safety as well as availability and its low price in comparison to fentanyl and dexmedetomidine. Overall recovery profile was better in patients who received dexmedetomidine.

KEYWORDS: Midazolam, fentanyl and dexmedetomidine.

INTRODUCTION

Premedication is drug administration before general anesthesia to decrease anxiety and obtain smoother induction, maintenance and emergence. The term "premedication" was first used by McMahan in 1920. The concept was initially developed to counteract the side effects of general anesthesia when ether and chloroform were widely used as inhalational anesthetics in the 1850s.[1]

The preoperative period is a stressful event, especially in the pediatric patients.[2] Pharmacological and behavioral interventions are used to treat preoperative anxiety in children and their parents.

Besides achieving amnesia, optimization of preoperative conditions and prevention of physiological stress, the primary aim of premedication in children is anxiolysis. Almost 50% of children show signs of significant preoperative fear and anxiety.[1] It has been reported that there are correlations between heart rate, blood pressure, and behavioral ratings of anxiety.[3] In most cases, medications administered without a needle are more pleasant for children, the family and the care team.

Approaches

1. Psychological approach
2. Pharmacological approach

Drugs used for premedication

Benzodiazepines
Barbiturates
Non-Barbiturate sedatives e.g. Chloral hydrate
Phenothiazine
Alpha-2-agonists e.g. Clonidine, Dexmedetomidine
Ketamine
Opioids e.g. Morphine, Fentanyl, Sufentanyl, Meperidine etc.

The ideal agent should have rapid onset, predictable duration and rapid recovery.

In our study we use three drugs i.e. midazolam, fentanyl and dexmedetomidine via intranasal route.

- **Midazolam**

Midazolam is a water-soluble benzodiazepine and most commonly used sedative premedicant in children [4]. The advantages include rapid onset, effective sedation, anterograde amnesia, anxiolysis, and a reduction in postoperative vomiting.[5,6] Owing to high mucosal vascularity, intranasal route offers rapid and virtually complete absorption within 1-2 hours into systemic circulation. As midazolam has high hepatic clearance, avoidance of hepatic first pass metabolism offers greater systemic bioavailability. Despite having a number of beneficial effects, it is far from an ideal premedicant having untoward side effects such as restlessness, paradoxical reaction, cognitive impairment, amnesia, and respiratory depression.[7]

One relative disadvantage of the nasal administration is its dependence on the nasal mucous membrane for drug absorption, thereby permitting the common cold to be a contraindication for its use. Intranasal administration was found to have many advantages including rapid onset of sedation, ease of administration, and safety. The first study of intranasal administration of midazolam in children was conducted by Wilton in 1988[8] and other studies have been performed since. Children sedated with intranasal midazolam are passive and moderately drowsy but usually do not fall completely asleep. The average time to peak plasma concentrations and maximal effect is 10 min and recovery time is approximately 30 min, with the degree of the sedative effect similar to that obtained with IM administration.[9]

- **Fentanyl**

In paediatric patients, acute pain is one of the most common presenting complaints in the postoperative period. Fentanyl offers an advantage when a short acting agent is required. It is synthetic opioid with a shorter half life than morphine and no significant metabolites.. Intranasal fentanyl was first used to provide postoperative analgesia in adult patients by demand-adapted technique and the effect was comparable to the intra-venous route. Intranasal fentanyl does not irritate the nasal mucosa and has a very low ciliotoxic effect; hence the drug may be used for prolonged periods without any adverse effect.[10]

- **Dexmedetomidine**

New drugs such as Dexmedetomidine, the α2-agonists, have emerged as alternatives for premedication in pediatric anesthesia.It is a potent, highly specific α-2-adrenoreceptor agonist with a shorter terminal half-life (approximately 2 h in children) that has both sedative and analgesic effects.[11] The qualities of the ideal premedication agent include anxiolysis, sedation, analgesia and hemodynamic stability. Dexmedetomidine exhibits all these properties and in comparison to benzodiazepines, may offer additional benefits such as an antisialogogue effect and reduced gastric secretions. It can be given via the oral, buccal and intranasal routes.

Considering these aspects, the current study is planned to find out the effect of midazolam, dexmedetomidine & fentanyl through nasal route as a premedication in paediatric patients and also to find out the optimum dose for the desired effect without any undesirable side effect.

AIMS AND OBJECTIVES

1. To evaluate the safety and efficacy of midazolam, fentanyl and dexmedetomidine and to compare them as intranasal premedication in paediatric surgical patients.
2. To study their hemodynamics and respiratory consequences in paediatric patients.
3. To study their effects on post-anaesthesia recovery.

MATERIALS AND METHODS

This study " Intra-nasal Midazolam, Dexmedetomidine and fentanyl as a premedication in paediatric surgical patients –was a prospective, randomized double blind study", was performed in department of Anesthesiology and Critical Care at Sher-I-Kashmir Institute of Medical Sciences, Srinagar, J&K and Hamdard Institute of medical sciences, New Delhi.

A written informed consent was obtained from the parents or legal guardians of the patients. Patients of ASA physical status 1 or 2, aged 1-8 years, scheduled for elective surgery were enrolled.

Children with chronic pain, central nervous system disorders, known allergy to the study drugs were excluded.

Children were randomly allocated to one of three groups;
1. Group M: received intranasal midazolam (0.2mg/kg) (n=50), one hour prior to induction
2. Group D: received intranasal dexmedetomidine (2µg/kg) (n=50), one hour prior to induction
3. Group F: received intranasal fentanyl (1.µg/kg) (n=50), one hour prior to induction of general anesthesia.

Baseline non-invasive blood pressure, oxygen saturation and heart rate was recorded and then at 15 min interval after intranasal administration of study drugs. Henceforth, sedation scores was assessed every 15 mins for one hour (at 0, 15, 30 and 45 min) by a blinded observer using a four-point sedation scale (Table 1). Before shifting the patients to operating room, at the time of their separation from their parents, their behaviour score was also assessed (Table 2).

Sedation score

Criterion	Score
Alert, awake	1
Drowsy, sleepy, lethargic	2
Asleep but responds to mild prodding or shaking	3
Asleep and does not respond to mild prodding or shaking	4

Behaviour score

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

Anaesthetic Procedure

In operating room multi channel monitor attached and I/V line secured. The patient were induced with injection Propofol 2mg/kg, oxygen, sevoflurane and atracurium 0.5mg/kg. Either ETT or LMA was placed. General Anaesthesia was maintained with O2 in N2O 1:1 with sevoflurane.
Reversal was with injection Neostigmine 0.07mg/kg and Glycopyrolate 10 µg/kg body weight, thereafter patient

was extubated, shifted to recovery and assessed by post anaesthesia recovery score.

Post anaesthesia recovery

It was assessed at arrival and every 15 mins in recovery room using post anaesthesia recovery score as follows:

Stage 1 Awake; does not feel sleepy and initates conversation.

Stage2 Awake; but feel sleepy.

Stage3 Asleep; responds to both verbal and painful stimuli.

Stage4 Asleep; responds to painful stimuli only.

Stage5 Asleep; does not respond to painful stimuli.

Pain was assessed at arrival and every 15 min in the recovery room using the observer pain scale.

All vomiting episodes were recorded.

Physiological parameters: BP, HR, RR and SpO2 were recorded every 15 min during postoperative period.

The patients were discharged from the recovery room when all of the following criteria met: fully awake, hemodynamic stability, absence of pain, bleeding, nausea and vomiting.

Statistical Analysis

The patients were randomized into three groups using a table of random numbers which was computer generated. After completion, data was analysed statistically using the student t-test, Mann Whitney U-test, and repeated measurement analysis to detect differences between three groups. A P-value of <0.05 was considered stastically significant.

OBSERVATION AND RESULTS

Comparison of demographic profiles between three study groups

- In midazolam group mean age of patients was 3.8 ± 2.30 years, in fentanyl group 4.3±2.30 and in dexmedetomidine 4.1±2.51 which was statistically insignificant (p value of 0.563).
- Gender distribution was statistically insignificant with p-value of 0.936.
- Comparison of mean weight between the three groups was found to be statistically insignificant with p-value of 0.993.

Table. 1: preoperative heart rate (beats/min) among various groups at different intervals of time.

Heart Rate	Group M		Group F		Group D		P-value
	Mean	SD	Mean	SD	Mean	SD	
0 Min	121.80	22.70	119.74	22.29	122.88	26.45	0.801
15 Min	118.44	22.46	117.84	22.02	116.32	25.02	0.895
30 Min	112.70	21.63	112.86	21.27	110.96	23.64	0.893
45 Min	112.58	20.39	110.06	20.85	101.74	20.39	0.024*
60 Min	109.86	20.35	108.44	20.81	90.38	16.29	<0.001*

M= midazolam; F= fentanyl; D= dexmedetomidine.SD= standard deviation.
**= statistically significant.*

- Baseline **heart rate** was statistically insignificant (p value 0.801). Heart rate at 45 and 60 min was lower in dexmedetomidine group with a p value of 0.024 and < 0.001 (statistically significant).

Overall mean heart rate was lower in dexmedetomidine group with p value of < 0.001which was statistically significant.

Table. 2: preoperative MAP (mmHg) among various groups at different intervals of time.

MAP	Group M		Group F		Group D		P-value
	Mean	SD	Mean	SD	Mean	SD	
0 Min	66.03	4.93	65.75	4.84	66.22	4.90	0.324
15 Min	62.86	4.83	63.51	5.03	62.77	5.42	0.114
30 Min	61.34	5.05	62.33	4.63	60.17	5.62	0.110
45 Min	59.27	5.24	61.45	4.85	54.29	5.39	<0.001*
60 Min	57.91	4.97	59.15	4.79	50.53	5.26	<0.001*

SD = standard deviation.

- The baseline **MAP** had p value of 0.324. At 15 and 30 min MAP decreases from baseline in all three groups (statistically insignificant).

Overall MAP was lower in dexmedetomidine group with p value of < 0.001 at 45 and 60 min,which was statistically significant (p value of < 0.005).

- **Respiratory rate**- At 15 min RR decreases from baseline in all three groups but was statistically insignificant (p value 0.462). The RR at 30min, 45min and 60min was lower in midazolam and fentanyl group with no significant decrease in RR in dexmedetomidine group, (statistically significant with value of < 0.05.)

- The baseline **SPO2** was statistically insignificant with p value of 0.543. 15 mins after drug there was no significant change. SPO2 at 30min, 45min and 60 min showed significant decrease in spo2 in midazolam and fentanyl group as compared to dexmedetomidine group (statistically significant with p value of < 0.001.)
- The **sedation score** at 15min was statistically insignificant (p value < 0.096).Overall sedation score at 30min, 45min and 60min was better in dexmedetomidine group (p value < 0.001).
- **Separation score** at 60min of drug administration was better in dexmedetomidine group as compared to midazolam and fentanyl group; and this difference was statistically significant (p value < 0.05).
- **Postoperative heart rate** was lower in dexmedetomidine group at all of these time intervals and this difference was statistically significant (p value < 0.05).
- **Postoperative mean MAP** (mmHg) was lower in dexmedetomidine group at all of these time intervals and this difference was statistically significant (p value < 0.05).
- **Postoperative mean respiratory rate** at all time intervals was found to be stastically significant, with higher respiratory rate in dexmedetomidine group (p value < 0.05)
- Comparison of **postoperative SPO2** at all time intervals between three study drugs was statistically insignificant (p value < 0.05).
- Comparison of **postoperative recovery score** was better in the patients who received dexmedetomidine and difference was found to be statistically significant (p value < o.o5).
- Comparison of **postoperative PONV** - In midazolam group, 4 childrens had PONV, in dexmedetomidine only 1 child while in fentanyl group 13 children had PONV, which was statistically significant with p value 0.002 (p value < 0.05).
- Comparison of **postoperative pain score** was was better in patients who received dexmedetomidine and fentanyl, which was statistically significant with p value of < 0.001 (p value < 0.05).

DISCUSSION

Anxiety can produce aggressive reactions, increases distress, and may make the control of postoperative pain difficult. When behavioral management strategies fail, some form of pharmacological sedation become necessary. An important goal of premedication is to have child arrive in operating room calm and quiet with intact cardio-respiratory reflexes.

Our study evaluated the efficacy of intranasal midazolam, intranasal fentanyl and intranasal dexmedetomidine as premedicant in pediatric patient. Many sedative analgesic agents and routes of delivery for facilitation of painful procedures have been studied, with varying degrees of patient acceptance, efficacy and safety.[12] The intranasal route may be irritating to nasal mucosa and drugs administered through it may traverse directly into the central nervous system through the cribriform plate by traveling along the olfactory nerves.

In our study, we selected children between 2 and 8 years where this age is most susceptible to the separation anxiety and their understanding is limited. The intranasal administration of midazolam 0.2 mg/kg, fentanyl 2µg/kg and dexmedetomidine 1.5 µg/kg produced effective and significant sedation which was seen at 30 min in dexmedetomidine group and at 15 min in midazolam and fentanyl groups and this change was maintained in all groups at 45 min and at the time of induction of anesthesia and these results were comparable with the results of Naill et al.[13]

Malionovsky et al.[14] found that intranasal midazolam 0.2 mg/kg had produced more rapid sedation than when administered through other routes. Shashikiran et al[15] found that on 40 children requiring conscious sedation, intranasal and intramuscular midazolam produced effective and comparable sedation with equal efficacy and safety profiles. But Lam et al. [16]proved that intramuscular midazolam produced better sedation and less movement at venous puncture than when used intranasally.

The variation in the onset of sedation in our results may be due to the site and mechanism of action of these drugs, as the site of action of midazolam and dexmedetomidine in central nervous system in locus coeruleus where it induce electroencephalogram activity similar to natural sleep.[16]

Intranasal fentanyl has been found to be effective over a range of ages, from infants as young as 6 months to adolescents.[18,17] Cole and colleagues evaluated pain scores in 46 children between 1 and 3 years of age given intranasal fentanyl for acute pain in the ED.7 The mean FLACC score of 8 at baseline declined to a mean of 2 at 10 minutes (p < 0.0001).

Within the past year alone, four new randomized comparison studies of pediatric intranasal dexmedetomidine have been published, representing work in four different universities in three countries.

In their 2012 study in Anaesthesia, Yuen and colleagues randomized 116 children between 1 and 8 years of age to receive an intranasal dexmedetomidine dose of either 1 mcg/kg or 2 mcg/kg as a pre-induction sedative.[19]

Cimen and colleagues enrolled 62 children (2-6 years of age) scheduled to undergo minor elective surgery into a randomized, double-blind trial comparing buccal and intranasal dexmedetomidine as a pre-induction sedative.[20] Sedation scores were significantly higher in the intranasal group, beginning at the 10 minutes and continuing until the final assessment at 45 minutes.

Our study showed that there was statistically significant change in heart rate, respiratory rate and systolic blood pressure in each group after 30 min and this may be due to increased level of sedation which is in agreement with Remadevi et al.[21] Munro et al.[22] reported that the reduction of blood pressure and heart rate were <20% of baseline in children who were sedated with initial dose of 1 µg/kg IV dexmedetomidine.

In conclusion we found that midazolam, fentanyl and dexmedetomidine produced adequate sedation with little side effects. So, we prefer to use midazolam due its efficacy and safety as well as availability and its low price in comparison to fentanyl and dexmedetomidine.

CONCLUSION

Intranasal drug administration is relatively quick, simple, and may have benefits over other routes which requires more patient cooperation. We have established that this route is more feasible for dexmedetomidine administration and future studies could now be directed to further evaluate the effect of this drug in various outcome measures including preoperative anxiety levels, induction time, emergence excitation, postoperative analgesic requirements and post operative behavioral disturbances.

Our study concluded that 2µg/kg intranasal dexmedetomidine produces significant sedation in children between 2-8 years of age. Behavior of the children at parental separation and at induction of anesthesia was better than children who received intranasal fentanyl and midazolam, with no post operative respiratory depression and better post operative pain scores.

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