

Evaluation of the Efficacy and Safety of Intranasally Administered Ketamine and Midazolam for Paediatric Pre Medication

Dr. Sumeet Chugh^{1,*}, Dr. Neetu Chaudhary²

1 Specialist, Department of Anaesthesia and intensive care, Dr Baba Saheb Ambedkar Medical College and Hospital, Delhi, India

2 Specialist, Department of Anaesthesia and intensive care, Dr Baba Saheb Ambedkar Medical college and Hospital, Delhi, India

*Corresponding Author: Dr. Neetu Chaudhary

Abstract:

Objective: An evaluation of the efficacy and safety of intra nasally administered Ketamine and Midazolam for paediatric premedication.

Materials and methods: The study was a prospective randomized double blind study involving 90 ASA grade I and II paediatric patients scheduled for elective surgical procedures of less than 2 hours duration; all these patients received the drug by nasal route in a double blind manner (20 minutes prior to induction) and were divided into three groups. Group M received intranasal midazolam 0.2mg/kg; Group MK1 received intranasal midazolam 0.2mg/kg and ketamine 2mg/kg; Group Mk2 received intranasal midazolam 0.2mg/kg and ketamine 4mg/kg.

Results: The number of patients with an acceptable local effects score(3,4), sedation score(3,4) and anxiety level score(3,4) was significantly higher in Group Mk1 and Group Mk2 than in group M($p < 0.05$). The percentage of patients with an acceptable cooperation level score (3,4) was more in Group MK2 at 15 and 20 minutes as compared to Group M($p < 0.05$) where as in group MK1, it was significantly better than in Group M only at 20 minutes($p < 0.05$).

Conclusion: Intranasal Ketamine (esp. in higher dosage of 4mg/kg) and midazolam when given in combination to preschool children as a premedicant achieves better sedation, anxiolysis and cooperation without increased incidence of adverse effects as compared to midazolam alone without an increased incidence of side effects.

Keywords: Intranasal Ketamine, Midazolam, Premedication, Sedation, Cooperation.

Date of Submission: 16-04-2018

Date of acceptance: 02-05-2018

I Introduction

Anxiety in children undergoing surgery is characterized by subjective feelings of apprehension, nervousness and worry. Various drugs and techniques are employed to reduce the anxiety before surgery along with psychological methods. Drugs^{2, 3} administered through various routes have been used for preoperative premedication each with its own drawback. There is a growing interest in shorter acting compounds and alternative route of administration to ensure a smooth induction in paediatric age group. In our study we used the anxiolytic property of midazolam while adding the sedative and analgesic qualities of ketamine via nasal route ensuring a fast onset of action bypassing the portal circulation without any fear of needles. Midazolam, which is a rapidly metabolized benzodiazepine, reduces the cardiovascular stimulation and emergence phenomenon of ketamine. The combination is therefore expected to achieve a high patient acceptance^{13,18}

II Materials And Methods

The study was a prospective randomized double blind study involving 90 ASA grade I and II paediatric patients scheduled for elective surgical procedures of less than two hours duration

After approval from the Hospital ethical committee and taking informed consent, the patients were divided into three groups randomly using a computer generated assignment and each group had 30 patients. Children with history of URTI, common cold running nose, LRTI, with potential airway problems, craniofacial anomalies, developmental delay, cardiopulmonary disease, untreated gastro oesophageal reflux were excluded from the study. Adequate starvation was ensured, 4 hours for clear liquids and 8 hours for solids. Group M received intranasal midazolam 0.2mg/kg; Group MK1 received intranasal midazolam 0.2 mg/kg and ketamine 2mg/kg; GroupMK2 received intranasal midazolam 0.2mg/kg and ketamine 4mg/kg. 5ml syringes without needle

were prepared using normal saline as a diluent and the volume of administration via each syringe was 0.12cc/kg to ensure the double blind nature of study. The medication was administered by the anaesthetist not involved in observing the patient for study or actually performing the procedure; after the appropriate solution was prepared the patients name and drug dose were placed in an envelope until the code was broken and the data was analyzed at the end of the study. Post premedication, patients were observed in the preoperative holding room by a second anaesthetist who recorded the patient's vital parameters at regular interval and was unaware of the drug and the dosage used for premedication. Midazolam used in the study was preservative free Inj.Meazolam (Neon Labs 1cc=5mg); Ketamine used in the study was preservative free Inj.Aneket (Neon Labs, 1cc=50mg ketamine).The following parameters was evaluated:

Preoperative haemodynamics

Local effects (observed as per score)

- 1) Crying
- 2) Sneezing
- 3) Wincing
- 4) Smooth

Sedation Score (adapted from Wilton and colleagues)⁸

- 1) Agitated
- 2) Alert
- 3) Calm
- 4) Drowsy
- 5) Asleep

Anxiety level Score

- 1) Clinging to parent and/or Crying
- 2) Awake but not clinging to parents, may whimper but not cry loudly
- 3) Lying/sitting comfortably with eyes spontaneously open.
- 4) Lying/sitting comfortably with eyes spontaneously closing, responds to minor stimulation
- 5) Eyes closed, rousable but does not respond to minor stimulation

For statistical analysis, the sedation scale values were condensed to a variable consisting of three categories:

Unacceptable conditions (Levels 1 and 2)

Acceptable conditions (Level 3 and 4)

Unacceptable deep sedation (level 5)

Once taken inside the operation theatre, the following was analyzed

Cooperation level score (while performing manipulation/touching the child)

- 1) Previous criteria (criteria score 1) and /or vigorous refusal
2. Previous criteria (criteria score 1) and/ or initially refuses mask but accepts with persuasion.
- 3) Accepts the manipulation with difficulty
- 4) Drowsy and accepts the manipulation smoothly
- 5) Asleep and accepts the manipulation smoothly

Adverse effects

The following adverse effects were monitored:

- 1) Excessive sedation
- 2) Salivation
- 3) Involuntary movements
- 4) Muscle rigidity
- 5) Vomiting
- 6) Emergence phenomenon

22G IV cannula was secured and inj.Glycopyrollate 0.004mg/kg IV was given.Anaesthesia was induced with injection Propofol 2mg/kg IV in all the patients ;Anaesthesia was maintained on O₂,N₂O,Sevoflurane .The muscle relaxant used was Inj.Vecuronium bromide 0.1mg/kg as the loading dose. No additional IV/IM sedation /analgesia were given to these patients. The reversal agent used was Inj.Neostigmine 0.06mg/kg and Inj.Glycopyrollate 0.008mg/kg IV.Post-operative analgesia was provided by either rectal acetaminophen suppository (15mg/kg) or IV Paracetamol infusion (15mg/kg).Post surgery the anaesthetist who had monitored the patients pre operatively continued monitoring in the immediate post-operative period for heart rate, respiratory rate, oxygen saturation, activity and pain. Any complications, adverse effects were noted.

III Statistical Analysis

In this study, data was analyzed as follows

The mean and standard deviation were calculated for variables, like demographic characteristics, duration of surgery, local effect scores, sedation scores and vital parameters. They were compared using Analysis of Variance (ANOVA) and Least Significant Differential (LSD) tests. Further analysis was done using Chi Square test. A P value <0.05 was considered significant value <0.01 as highly significant P value < 0.001 as very highly significant.

IV Results

Patients in the three Groups were comparable with respect to mean age, weight and sex and underwent similar types of surgeries. Mean respiratory rate and median oxygen saturation were comparable in the three groups throughout the study period. Patients in Group MK2 had significantly lower heart rate from 20 minutes after pre-medication till induction as compared to Group M and Group MK1 ($p < 0.05$); The number of patients with an acceptable Local effects score, (3, 4), Table 1 an acceptable sedation score (3, 4) and acceptable anxiety level score (3, 4) was significantly higher in Group Mk1 and Group Mk2 than in group M ($p < 0.05$) throughout the study period. The percentage of patients with an acceptable cooperation level score (3,4) was more in Group MK2 at 15 and 20 minutes as compared to Group M ($p < 0.05$). In Group MK1, the percentage of patients with an acceptable cooperation level score was significantly better than in Group M only at 20 minutes ($p < 0.05$). The adverse effects seen in patients in the three Groups were comparable except for salivation and excessive sedation which was significantly more in Group MK2 as compared to Group M ($p = 0.010$)

V Discussion

A distressed child is at risk for potentially hazardous psychological and physiologic sequelae^{16,3}

Various pre medications and delivery systems have been developed using oral, intramuscular and rectal routes of administration with each having its disadvantages and limitations³

The rapid and reliable onset of action, avoidance of painful injections, ease of administration and predictable effects have made intranasal administration of pre induction agents popular⁴. The key features of a good premedicant are easy application, rapid onset, short duration of action and the lack of significant side effects^{5,6}. We selected the dose of Midazolam^{9,17} an imidazobenzodiazepine, intra nasally 0.2 mg/kg, as in the previous studies, the doses of less than 0.2mg/kg appeared ineffective and no additional benefit was seen from higher dosage. The dose of ketamine⁹, a cyclohexamine selected was 2mg/kg and 4mg/kg with midazolam 0.2mg/kg intra nasally. When used in combination with midazolam the dose of ketamine has to be lowered, as benzodiazepines are known to potentiate the action of ketamine¹². Combining the two, the pharmacodynamic profile can be broadened, to achieve a high patient acceptance and tolerability^{11, 18}. The effect of combination of Ketamine and Midazolam on the behavior of the patient was evaluated by sedation score adapted from Wilton and colleagues⁸.

The observations regarding separation anxiety, sedation level scores^{5,7,13,15}, anxiolysis⁵ were consistent with the ones by previous workers^{5,11,14,19}. Rescue analgesia in the immediate post-operative period was given in the form of injection tramadol 1mg/kg iv to the patients having a sedation score 1

Table 1

Groups	Local effects score (Mean +/- SD)	p value
M	2.03 +/- 1.07	M Vs. Mk1-0.00
MK1	3.33 +/- 0.71	M Vs. Mk2-0.00
Mk2	3.60 +/- 0.68	Mk1 Vs. Mk2-0.220

VI Conclusion

Intranasal Ketamine and midazolam when given in combination to preschool children as a premedicant achieves better sedation, anxiolysis and cooperation without increased incidence of adverse effects as compared to midazolam alone. A higher dosage of ketamine (4mg/kg) with midazolam results in a rapid onset, a more consistent and calm effect under different degrees of stress without any increased incidence of adverse effects. It could thus be a better alternative to any of other medications that have been used previously in children.

References

- [1]. Baker A R. Pre medication. Clinics in Anesthesiology 1986; 4:459-471.
- [2]. McCann M E, kain ZN. The management of preoperative anxiety in children. Anesthesia Analgesia 2001;93:98-105
- [3]. Steward D J. Psychological preparation and pre medication. Pediatric Anaesthesia. Edited by Gregory G A, New York. Churchill Livingstone 1989:523-538
- [4]. Helen W Karl, Anne T Kifer, James L Rosenberger, Marilyn G Larach, Joan M Ruffle. Comparison of the safety and efficacy of intranasal midazolam or sufentanil for pre induction of anesthesia in paediatric patients. Anesthesiology 1992;76:209-215

Evaluation Of The Efficacy And Safety Of Intranasally Administered Ketamine And Midazolam For

- [5]. Funk W, Jakob W, Riedl T, Taeger K. Oral pre anaesthetic medication for children: double blind randomized study of a combination of midazolam and Ketamine alone. *British Journal of Anaesthesia* 200;84(3):335-40
- [6]. Geldner G, Hubmann M, Knoll R, Jacobi K. Comparison between three trans mucosal routes of administration of midazolam in children. *Paediatric Anaesthesia* 1997;7:103-9
- [7]. Warner D L, Cabaret J, Velling D. Ketamine plus Midazolam : a most effective oral premedicant. *Paediatr Anaesth* 1995;5:293-5
- [8]. Wilton N C T , Leigh L, Rosen D R. Pre-anaesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 1988;69:972-975
- [9]. *Paediatric anaesthesia*. Third Edition. George A Gregory:33-35
- [10]. Paul F white, Walter L Way, Anthony J Trevor. Ketamine-Its Pharmacology and therapeutic uses. *Anesthesiology* 1982;56:119-136
- [11]. Frank Weber ,Hinnerk Wulf, Ghada el Saeidi. Premedication with nasal S-ketamine and midazolam provides good conditions for induction of anaesthesia in preschool children, *Canadian journal of Anaesthesia* 2003;50(5):470-475
- [12]. Non barbiturate intravenous anaesthetics .chapter 9. *Anesthesia*, fifth edition: volume 1; 228-245. edited by Ronald D Miller.
- [13]. V G Reddy. Nasal midazolam and Ketamine for paediatric sedation during computerized tomography. *Acta Anaesthesiologica Scandinavica* 1994;38:259-261
- [14]. Benedikt Trabold, Angela Rzepecki, Kay Sauer, Jonny hobbhahn. A comparison of two different oral doses of ketamine with midazolam and midazolam alone as pre medication on recovery after sevoflurane anaesthesia in children. *Paediatric Anaesthesia* 2002;12(8):690
- [15]. D P Fourie, J Diedericks, P Kruger, J Joubert, Ls Louw. Premedication in children for tonsillectomy: A comparison between intranasal ketamine and midazolam and a combination of the two drugs. Department of Anaesthesiology and Biostatistics, university of the orange Free State, Bioemfontein. PMID11310460 (Pubmed_indexed for Medline)
- [16]. Freeman A, Bachman L. *Pediatric Anesthesia: An evaluation of preoperative medication* . *Anesthesia Analgesia* 1959;38:429-437
- [17]. Reves J G, Fragen R J, Ronald H V, David J, Greenblatt D T. Midazolam: Pharmacology and uses. *Anesthesiology* 1985;62:310-324
- [18]. Reich D L, Silvay G. Ketamine: an update on the first twenty five years of clinical experience. *Can J Anesth* 1989;36(2):186-97
- [19]. Levine M F, Saphr Schopfer I A , Hartley E, Lerman J, Macpherson B. Oral Midazolam premedication in children: The minimum time interval for separation. *Can J Anesth* 1993;40(8):726-9.

Dr. Neetu Chaudhary." Evaluation of the Efficacy and Safety of Intranasally Administered Ketamine and Midazolam for Paediatric Pre Medication." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, vol. 17, no. 4, 2018, pp 48-51