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A comparative study of oral premedication in children with ketamine and fentanyl

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ABSTRACT

Aim and Objectives: To do a comparative study of oral premedication in children with Ketamine and Fentanyl. **Materials and methods:** A randomized prospective study was conducted in 50 children scheduled for various surgical procedures in hospital. **:** In this study, the children were divided into two groups. Group A: Ketamine 6 mg/kg, Group B: Fentanyl 15 µg/kg. The groups were assessed on the basis of sedation, separation from the parents (anxiolysis), response to venepuncture, acceptance of face mask. Oxygen saturation, heart rate, blood pressure and respiratory rate were continuously measured.**Results**: All children posted for elective surgeries were in the age group between 2 and 8 years. The mean age in group A was 3.84±1.46 years and in group B it was 3.6 ± 1.32 years. The difference in the mean age was not statistically significant (p>0.05). The two groups were more or less homogenous. The mean weight for group A was 14.08 ± 2.8 kg and group B was 13.96 ± 2.52 kg. The difference in the mean weight was not statistically significant. (p> 0.05). Similarly, the sex between the two groups were comparable. The mean height for group A was 155.70 ± 2.74cm and group B was 155.60 ± 2.83cm. The difference in the mean sex was not statistically significant. The sedation score has degree of freedom 3, Chi square of 2.14, for significance at 0.05 level, Chi square should be greater than or equal to 7.81. The parental separation score has degree of freedom 3, Chi square of 5.81, for significance at 0.05 level, Chi square should be greater than or equal to 7.81. The sedation score has degree of freedom 3, Chi square of 7.99, for significance at 0.05 level, chisquare should be greater than or equal to 7.81. The sedation score has degree of freedom 3, chisquare of 6.51, for significance at 0.05 level, chisquare should be greater than or equal to 7.81. **Conclusion:** In conculsion ketamine and fentanyl are equally effective premedicants. However, oral ketamine may be preferable to fentanyl because of lower cost.
Key words: Ketamine , Fentanyl, Separation score.

Introduction

Premedication may be considered as administration of drug or drugs to the patient before surgery primarily to allay anxiety, produce analgesia, sedation and amnesia. Appropriate drug is selected on the basis of child's age, weight, drug history, allergic history, emotional maturity, personality, anxiety level, physiological and psychological status. Children of 2-8 years of age are at vulnerable stage of development and always experience fear of hospitalization, pain, separation, uncomfortable with strangers and the unknown[1].They recognize strange alien environment, suffer anxiety of separation from parents, can predict and anticipate pain from past experiences. Premedication for these children allows smooth separation from parents and induction without struggle. Route of administration of pre-medicants in children play very crucial role. A drug that may be more effective by the I.V or I.M route, but often causes aggressive behavior due to fear of pain on injection and this can be their worst experience[2]. The concern of oral premedication increasing gastric residual volume is ruled out and unless large volume is ingested, oral premedication is not associated with increased risk of regurgitation and aspiration. Rectal route is undesirable and awkward, sublingual and nasal route are irritating with unpleasant sensation. Because of the above reasons we preferred oral route for premedication of children. We administered the drugs with honey for easy acceptance and also to make it viscous for increased transit time for mucosal absorption. Ketamine and Fentanyl were selected for our study

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because of their easy availability in our pharmacy and also to assess for analgesic potential. The parenteral formulations available were used for oral route by mixing with honey.

Materials and Methods

A randomized prospective study was conducted at Niloufer Hospital for Women and Children, Osmania Medical College, Hyderabad. The study population included 50 children scheduled for various surgical procedures in our hospital. **Inclusion Criteria:** ASA physical status I / II without CNS disease, 2-8 years of age, various surgical procedures ranging from duration of about 30 minutes to 2 hours.

Exclusion Criteria: Age group above 8 years & those patients with CNS disease.

50 children of ASA grade I/II aged 2-8 years undergoing surgeries of 30-120 min duration were selected for this study and they were randomly allocated into two groups of 25 each. Group A will receive ketamine 6mg/kg and Group B Fentanyl 15 µg/kg in the randomized prospective controlled study. Sedation and anxiolysis scores before induction, cooperation at separation and induction of anaesthesia and recovery times and complications were assessed others included postoperative analgesia and behavioural outcomes. Both medication were diluted in 0.2ml/kg of honey mixed thoroughly and administered to the children by their parents. If the premedication was not completely administered or retained that child was excluded for further analysis. The pre induction room where the premedication was administered the anesthesiologist has observed the child at 5 min intervals for the onset of the action of the drug. Demographic data included age, sex, and weight of the children. The extent of sedation and anxiolysis before the premedication were recorded. All the children were monitored with the use of multi channel monitor. Heart rate, Blood Pressure, Respiratory rate and Oxygen saturation were monitored every 5,10,15,20 and 30 minutes. Sedation was graded by evaluating the child's appearance with the sedation scale described in the table. An emotional scale, response to venepuncture and acceptance of face mask were recorded using Oucher's scale of facies. Sedation and separation scores were recorded at 30 minutes after premedication. Response to venepuncture was based on the scale graded by child's appearance and withdrawal, if any was recorded. A final assessment was made at the time of application of face mask. In all children anaesthesia was induced with Thiopentone 5-7mg/kg body weight, Glycopyrrolate 0.06-0.08 mg/kg body weight, intubated with Inj. Atracurium 0.5mg/kg and maintained with N2O + O2 + IPPV. Neuro muscular blockade reversed with Neostigmine 0.06mg/kg and Glycopyrrolate 0.01mg/kg. During recovery the HR, BP, SPO_2 were recorded and the children were observed for any unanticipated complications and delayed recovery. Sedation scale, emotional scale indicating separation from parents, response to venepuncture and scale for acceptance of mask are all subjective assessment scales. These scales were used for objective purposes. We have universally adopted the pain scale of Oucher's though the pain scale was for subjective assessment of pain by the child himself, we have found this as an excellent method for interpreting the response by objective assessor also and ready reckoning method without going into the extensive verbal questioning of the parents. The facies scale comprehensively expresses all the emotional and physical trauma experienced by preinduction paediatric patient. These are the criteria which have no means of quantification unlike the physiological changes. We feel that it also eliminates the minor variations that are liable to occur as these children were anaesthetized by different anesthesiologist who are familiar with the study, through all the patients were premedicated by the same anaesthesiologist.The data was analyzed statistically. Parametric data were reported as Arithmetic means $\pm$ Standard derivation and Chi-square test was used to analyze discrete variables (e.g. sedation score). A p value <0.05 (level of significance) was considered statistically insignificant.

Results

In this study, the children were divided into two groups. The groups were assessed on the basis of sedation, separation from the parents (anxiolysis), response to venepuncture and acceptance of face mask. Oxygen saturation was continuously measured and heart rate, blood pressure and respiratory rate and other side effects were measured throughout the preanaesthetic evaluation period until the children were taken to the operating room. The analgesia requirements, the incidence of vomiting and behavioral changes were assessed for 6 hours post operatively.

Demographic Features: All children posted for elective surgeries were in the age group between 2 and 8 years. The mean age in group A was 3.84$\pm$1.46 years and in group B it was 3.6 $\pm$ 1.32 years. The difference in the mean age was not statistically significant (p>0.05). The two groups were more or less homogenous. The mean weight for group A was 14.08 $\pm$ 2.8 kg and group B was 13.96 $\pm$ 2.52 kg. The difference in the mean weight was not statistically significant. (p> 0.05). Similarly, the sex between the two groups were comparable. The mean height for

group A was 155.70 ± 2.74cm and group B was 155.60 ± 2.83cm. The difference in the mean sex was not statistically significant.

Table 1: shows demographic features

	Ketamine (Group A)	Fentanyl (Group B)	Statistical Significance
Age (years)			
Mean	3.84±1.46	3.6±1.32	p>0.05 (NS)
Standard Deviation	1.46	1.32	
Weight			
Mean	14.08±2.8	13.96±2.52	p>0.05 (NS)
Standard Deviation	2.8	2.52	
Sex			
Male	22	18	p>0.05 (NS)
Female	3	7	
No. of Patients	25	25	

Table 2: Types of Surgeries in the study

Types of Surgeries	Ketamine	Fentanyl
Herniotomy	5	6
Hydrocele	4	5
Circumcision	6	6
Hypospadias correction	2	1
Cystolithotomy	2	1
Thyroglossal Cyst	2	2
Dermoid Cyst	1	0
Orchidopexy	1	0
Cystoscopy	1	2
Lymphangioma	1	1
Urethroplasty	0	1
Total	25	25

Table 3: Sedation score and Parental separation score

	Sedation Score				
	IV	III	II	I	Total
Ketamine (6mg / kg)	12	7	4	2	25
Fentanyl (15 µg /kg)	8	10	3	4	25
Total	20	17	7	6	50
Expected value	10	8.5	3.5	3	25
	Parental Separation Score				
Ketamine (6mg / kg)	15	6	3	1	25
Fentanyl (15 µg / kg)	7	9	5	4	25
Total	22	15	8	5	50

The sedation score has degree of freedom 3, Chi square of 2.14, for significance at 0.05 level, Chi square should be greater than or equal to 7.81. The parental separation score has degree of freedom 3, Chi square of 5.81, for significance at 0.05 level, Chi square should be greater than or equal to 7.81.

Table 4: Response to Venepuncture and acceptance to face mask

	Response To Venepuncture				
	IV	III	II	I	Total
Ketamine (6mg /kg)	13	8	2	2	25
Fentanyl (15 µg / kg)	6	6	9	4	25
Total	19	14	11	6	50
Expected Value	9.5	7	5.5	3	25
Acceptance To Face Mask					
Ketamine (6mg / kg)	12	8	3	2	25
Fentanyl (15 µg / kg)	5	7	8	5	25
Total	17	15	11	7	50
Expected Value	8.5	7.5	5.5	3.5	25

Response to venepuncture degree of freedom is 3, Chi square is 7.99. For significance at 0.05 level, Chi square should be greater than or equal to 7.81. Acceptance to face mask degree of freedom is 3, Chi square is 6.51, For significance at 0.05 level, Chi square should be greater than or equal to 7.81.

Discussion

Anxiety in children undergoing surgery is characterized by subjective feeling of tension, apprehension, nervousness and worry. Children of 2-8 years age group are at high risk for developing extreme anxiety and the need for pharmacological premedication is highest[11].Separation anxiety does not develop before the age of 8-12 months,and thus there is no need for intervention before that age. Preoperative anxiety in children is associated with adverse outcomes, and thus it is imperative to treat with sedative premedication. Sedative drugs in children is a noble principle that of minimizing trauma related to anaesthesia and surgery. Multiple randomized controlled trials studies have found that sedative premedication is far superior to either preoperative preparation or parental presence during induction of anaesthesia.Oral route is the one most preferred by the child. Previously Vallergan, Triclofos, and presently Midazolam, Ketamine single or in combination have become very popular for oral administration with children and the anaesthesiologists alike. Fentanyl transmucosal delivery[14] is another attractive option and oral Clonidine ,although less popular than Midazolam, its use is constantly increasing. The intravenous formulation of both Midazolam and Ketamine have a bitter and astringent taste. So to make it palatable they have been mixed with cola, honey, apple juice, etc. Ketamine in a dose range of 3-10mg/kg causes a dissociative state in which the child is distant or totally unaware, unlike with midazolam where the child is aware but calm. It also has the added advantage of providing analgesia (in the higher range) for the prick of the I.V. or regional block. Whether the children get dreams with this is not known but obvious emergence phenomena have not been reported.Ketamine can be used orally or nasally to give a reasonably rapid onset of sedation with cardiorespiratory stability without the ventilator depression assosciated with opioid analogues. The use of Ketamine remains popular for procedures carried out in emergency room that requires a certain degree of sedation and analgesia because of its relative safety[12,13].There is still no completely satisfactory way to premedicate children and ensure smooth induction of anaesthesia. As injections, pills, rectal and nasal administration of drugs can be traumatic or difficult for children, we chose oral route of administration of premedicant as safe and reliable although absorption of these drugs depend on several other factors.We compared oral Ketamine 6mg/kg body weight with oral Fentanyl 15µg/kg body weight mixed in honey to alter the taste and given by mother to the child. The groups were assessed on the basis of sedation, separation from the parents (anxiolysis), response to venepuncture and acceptance of face mask. Oxygen saturation was continuously measured and heart rate, blood pressure and respiratory rate and other side effects through out the preanaesthetic evaluation period until the children were taken to the operating room. The analgesia requirements, the incidence of vomiting and behavioral changes were assessed for 6 hours post operatively.The major disadvantage in our

study was that Fentanyl is not available as a lollipop or lozenge form (oralet). The interpatient variability associated with oral Fentanyl administration is dependent on the critical factor of duration of exposure (drug permeability) to the mucosal surfaces. liquid preparations can increase the chances of swallowing. Honey being viscous influences the dissolution process by increasing the duration of exposure in the mucosal surfaces. Saliva production is effected by the taste and pH of the dissolved sucrose base. Diffusion through biologic membranes occurs most favourably when a drug is in its non ionized most lipid soluble from. Ionization of fentanyl (a weak base, having a PKa of 8.4) depends on environmental pH. The pH in the mouth after oral fentanyl administration results from a combination of saliva (pH 6.5-6.9) and dissolved sucrose base (pH 5.5-6.0)[15]. Facial pruritus (50%) occurred in patients receiving oral Fentanyl and usually heralded the onset of sedation. Ketamine 6mg/kg dose was associated with increased salivation, nausea in some of the cases. Aspiration has never occurred in our study due to oral premedication. No obvious emergence phenomenon have been reported with Ketamine in our study. Most of the patients had calm and smooth recovery.In our study we also observed that none of the children in either of the groups required any oxygen supplementation to prevent hypoxemia. There were no episodes of respiratory depression, oxygen desaturation before during or after surgery. Neither of the groups showed any unanticipated complications nor delayed recovery. With proper monitoring Ketamine and Fentanyl can be used safely in the outpatient clinical settings. Continuous monitoring of respiratory function and other parameters is essential.Chlorpromazine has been used as a sedative in the dosage of 0.5- 1 mg /kg. Midozolam has been shown to induce satisfactory sedation and anxiolysis with in 20 min with a dose of 0.25-0.5 mg/kg. Advantages of midazolam include shorter time to effect,antegrade amnesia responsible for the decreased incidence of postoperative behavioural changes.Oral Ketamine 6mg/kg produced effective sedation in most children.the mean time spent in recovery roomwas 42 minutes and the mean time to hospital discharge was 158 minutes[13].Clonidine has significant sedative and analgesic properties because of its α2 adrenergic agonism. It has been shown that oral clonidine effectively produces preoperative sedation and anxiolysis in children, acts as an analgesic, decreases volatile anaesthetic requirements, and improves perioperative hemodynamic stability[19]. Clonidine can be administerd orally 4µg/kg and intranasally 2µg/kg about 30-60 minutes prior. Dexmedetomidine has a shorter onset time and a faster elimination half life (1-2 h) compared to clonidine and is best administered intranasally[17,18].Transmucosal Dexmedetomidine 1µg/kg 45 minutes before induction in children 7-12 years of age was as effective as oral midazolam 0.5 mg/kg or clonidine 4µg/kg administered 30 and 90 minutes before induction respectively[20]. Many studies have been reported related to oral premedication in children with ketamine and fentanyl. Alderson PJ, Lerman J et al[3] , did a comparison of midazolam and ketamine. They compared the clinical characteristics of two oral premedicants, midazolam (0.5 mg/kg) and ketamine (6 mg/kg), in 40 healthy children, one to six years of age. Sedation and anxiolysis scores before induction, cooperation at induction of anaesthesia and recovery times and complications were assessed. They found that both drugs effectively sedated the children within 20 min of administration. Gutstein HB et al [4],have done a study in which oral ketamine preanaesthetic medication was used in children. The authors sought to define a dose of oral ketamine that would facilitate induction of anaesthesia without causing significant side effects and concluded that the oral dose of 6mg/kg ketamine is easily administered and well accepted in young children and provides predictable, satisfactory premedication without significant side effects. Suranjith Debnath et al [5],compared the characteristics of ketamine 6mg/kg and midazolam 0.5mg/kg in 60 ASA grade I children aged 1-10 years and observed the both drugs are well accepted by children sedation and anxiolysis were better in ketamine group both during separation from parents and at I.V. cannulation. Turhanoglu S et al[6], studied 80 children undergoing elective surgery under general anaesthesia in a prospective, randomized, double – blind placebo controlled study and compared the reaction to separation from parents transport to the operating room response to IV cannulation and application of an anesthetic face mask and concluded that oral ketamine 8mg/kg (-1) is an effective oral premedication. Sekerci C et al[7],have done a study in which oral ketamine premedication was given to children (placebo controlled double – blind study). They found the ketamine 3-6 mg/kg-1 given by mouth to paediatric patients for anaesthetic premedication made separation from the families easier, gave an increased level of sedation, made acceptance of mask application easier and improved the emotional state in the recovery phase. Stanley TH et al[8], have done a study in which they found doses of 15-20ug/kg (fentanyl Lollipop or oral transmucosal febtanyl citrate) is an effective, non traumatic method of premedication i.e., self administered and extremely well accepted by children. Side effects include facial pruritus (90%), slow onset

time (25-45 min to peak effect). Deepa Jadhav et al[9], studied 80 patients of either sex aged 2-10 years of ASA grade 1 ,2 undergoing radiotherapy, CT scan and MRI. They were randomly allocated in two groups. 40 each to compare the efficacy, safety and tolerability of injection ketamine-midazolam combination to injection Fentanyl-midazolam combination for sedation of children during radiotherapy (RT)/ computerized Tomography Scan/Magnetic Resonance Image. Both groups were given IV injection midazolam 0.05 mg/Kg before giving IV injection Ketamine 1mg/Kg in group 1 while IV injection Fentanyl 2 µg/Kg in group 2. The results were that in both the groups, after giving sedation, there were no significant changes in heart rate. Degree of sedation was better in group 1 than in group 2.Recovery from sedation was more prolonged in group 1 than in group 2. From this study, it was concluded that injection ketamine-Midazolam combination offers good sedation without compromising respiration but more prolonged recovery and higher incidence of post procedural vomiting while injection Fentanyl-Midozolam combination has lower sedation score and higher incidence of respiratory depression. Darlong V et al[10], have done a randomized, controlled prospective study conducted in 87 children who were scheduled for ophthalmologic surgeries. Group M received oral midazolam 0.5 mg/Kg, Group MKL received oral midazolam 0.25 mg/Kg and Ketamine 3 mg/Kg and Group MKH received midazolam 0.5 mg/Kg and ketamine 6mg/Kg. Standard general anaesthesia technique was used. Sedation levels and ease of parental separation were noted. The results were that a linear increasing trend in sedation was seen in the preoperative sedation scores of all the three groups. At 30 minutes, 23 children in group MKH had good sedation scores as opposed to 20 in Group MKL and 12 in Group M. The best parental separation time was much shorter in the combination groups. From this study, it was concluded that a combination of low dose midazolam and ketamine was as effective as high dose of midazolam and ketamine for achieving optimum anxiolysis and a faster recovery, with a lower incidence of excessive salivation in children undergoing ophthalmic surgery. Ashburn MA et al[16], studied oral trans mucosal fentanyl citrate (OTFC) for premedication in pediatric outpatients. The onset and depth of sedation is dose-dependent.Time to peak sedation is30-45 min.After 10-15 µg/kg 50% of children were sedated or asleep at this time. OTFC produces preoperative anxiolysis, increased likelihood of cooperation at induction, less emergence phenomenon post operatively, and delayed post anaesthesia care unit discharge.

Conclusion

In concluosion ketamine and fentanyl are equally effective premedicants. However, oral ketamine may be preferable to fentanyl because of lower cost. The disadvantages being its bitter taste-hence we gave it in honey. An anxious, crying struggling, fearful and an uncontrollable paediatric patient can be a major disadvantage. Crying and struggling makes securing an I.V. line, holding a mask difficult. Crying also increases intra ocular tension, central venous pressure that in turn increases the blood loss at the operative site increase oral and nasal secretions. An unpremedicated child is traumatized psychologically and can lead to new onset postoperative negative psychological effects such as nightmares,eating disturbances,apathy and withdrawal,separation anxiety,and enuresis. Paediatric sedation and analgesia continues to evolve.Most of the premedicants were effective but not always, even when used by variety of routes, drug combinations and it is very difficult to compare their efficacy and side effects in light of modern anesthesia practice. Among the most interesting and exciting recent alternatives to Ketamine, Midazolam are the ∞_2 adrenoceptor agonists clonidine and dexmedetomidine. In emergency medicine field evidence is emerging that fasting status is not particularly important factor in genesis of critical elements during sedation and analgesia. All this is occurring in the face of mounting evidence that sedation and analgesia depth needs to be adequate to provide optimal operating conditions and patients satisfaction, keeping in mind balanced anaesthesia concept of Lundy. Recovery criteria needs to be carefully considered in order to optimize the child safety.

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