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"Comparative Evaluation of Oral Midazolam, Oral Ketamine And Oral Midazolam-Ketamine Combination As Conscious Sedative Agents in Uncooperative Pediatric Dental Patients"

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Abstract: *Conscious Sedation is a technique in which the use of a drug produces a state of depression of central nervous system enabling treatment to be carried out, but during which verbal contact with the patients is maintained throughout the period of sedation. Various drugs have been used as sedative agents in pediatric dentistry to produce conscious sedation such a nitrous oxide, diazepam, midazolam, propofol, Ketamine, temazepam, chloral hydrate, hydroxyzine hydrochloride, promethazine.*
The aim of the research is to record the onset of action, any changes in the vital parameters, body movements, sleep and crying and compare between the following: a) Oral midazolam (M) b)Oral Ketamine (K) c)Oral midazolam-oral Ketamine combination (MK) and also to note down the behavioral outcome of uncooperative pediatric dental patients following the administration of oral midazolam, oral Ketamine and oral midazolam-Ketamine combination as conscious sedation agents as per: sleep, Bodily movement, crying. Study also observes any adverse reactions following the administration of drug during the duration of recovery.
Statistical tools are used for study. Results show that Ketamine is a better anxiolytic agent followed by midazolam then midazolam-Ketamine combination. Although midazolam-Ketamine combination was not a good agent for conscious sedation it could counteract the side effects of Ketamine .Thus, we can conclude that the combination could be used in smaller doses for conscious sedation while taking safety into consideration.
Keywords: *Conscious Sedation, midazolam, Ketamine*

I. Introduction

Pediatric dentists often encounter young, fearful and uncooperative patients. Managing anxious children in the operatory has always been a challenging task. Various aversive and non-aversive techniques have been employed to manage such patients. But these techniques cause a traumatic experience in the child's mind leading to lifelong dental phobias and thereby instilling a negative attitude towards dentistry.
Conscious Sedation is a technique in which the use of a drug produces a state of depression of central nervous system enabling treatment to be carried out, but during which verbal contact with the patients is maintained throughout the period of sedation.

Conscious sedation is different from general anesthesia, it requires less fasting time, and the patient is discharged on the same day unlike general anesthesia wherein the patient has to fast for 24 hours and has to be carefully monitored post operatively as well. Moreover, airway is maintained since the patients are conscious.
Oral sedation is the oldest known yet effective, economic and easy to use among all routes of CS. High patient acceptance is the key advantage of the oral route on top of its other advantages. However, this is not necessarily the case in very young fearful individuals. Several side effects including overdose, idiosyncrasy, and allergy could be seen with any drug administration. However, the oral route represents the least reactions amongst the different routes. Late effect is considered as one of the disadvantages of oral sedation along with unpredictable absorption rate and titration limitations.

Various drugs have been used as sedative agents in pediatric dentistry to produce conscious sedation such a nitrous oxide, diazepam, midazolam, propofol, Ketamine, temazepam, chloral hydrate, hydroxyzine hydrochloride, promethazine. James et al compared combination of oral midazolam-Ketamine and oral trimeparazine- methadone and found to be more effective than the latter. Similarly Tina et al, compared Ketamine alone with Ketamine-promethazine and found that Ketamine yielded better sedation than the

combination. Shabbier et al also conducted a study comparing oral midazolam and triclofos and found that oral midazolam was more effective in regulating patient behavior as compared to triclofos.

Ketamine, when used in lower doses, its acts as a conscious sedative agent. Ketamine, in its oral form undergoes first pass metabolism and is converted into nor Ketamine. This drug is easy to administer, has a rapid onset of action, there is a wide margin of safety and its exhibits short duration of action.

Midazolam is an imidazobenzodiazepine that can be given in the oral dose. It has a short half life of 1-2 hours; high potency and rapid onset of action. It has sedative, anxiolytic properties, provides ante grade amnesia, and also has anticonvulsant properties.

Combination of oral midazolam and oral Ketamine produces a synergetic effect. The combination is said to minimize the effects of delirium in children, reduce the cardiovascular sequel, provides longer working time and greater degree of amnesia. Thiago et al, compared the combination of midazolam and Ketamine in children as young as 36 months. They found that the combination provided more sedation as compared to midazolam alone and concluded that it was even effective in children for minor dental procedure.

The purpose of the present study was to evaluate the efficacy of oral midazolam, oral Ketamine and the combination of oral midazolam-Ketamine as conscious sedative agent in un-cooperative pediatric dental patient. Also record any variations in the vital statistics of the patient and any adverse caused due to the drugs.

II. Review of Literature

Sobczak Om (1975) conducted a study on the use of Ketamine in pediatric dentistry. Study reveals that Ketamine provided good operating conditions and free access to the patient's mouth no evidence of respiratory depression. Whereas Rosenber M (1991) used a combination of oral Ketamine and glycopyrrolate in conjunction with an oral benzodiazepine and sodium citrate to produce profound sedation for a violent, mentally handicapped patient. No abnormalities were noted on the electrocardiogram throughout the procedure. Recoverywas uneventful, with no postanesthesiaemergence delirium, nausea or vomiting. Silver T, Wilson, Webb M (1994) carried out a study to evaluate two dosage of oral midazolam as conscious sedation for physically and neurologically compromised pediatric dental patients. There was no statistical difference in the effectiveness of the two regimes when overall success rates were analyzed.

La Harpe, D., & Jacques, C. (2005) compared the safety and efficacy of two dosages of oral midazolam when used for conscious sedation of children undergoing minor procedures in the accident and emergency setting. Results showed that at higher dose oral midazolam had an onset of action of 15 minutes and was effective in 76% of children. Amnesia was reported in 66 % of children. There were no adverse side effects except paradoxical hyper agitation in three children (6%)

Rai K, Hegde AM, Goel K (2007) conducted a comparative evaluation of midazolam, propofol and Ketamine. The results revealed that the propofol was highly effective in terms of onset of sedation, although increased body movements and crying, pain on injection and intermittent cough was observed as the main side effects of the drug. Midazolam showed the longest duration of action but was not very effective in terms of treatment completion due to increased movements and crying.

Blonk M I, Koder BG, Bemt PMLA, Huygen FJPM(2009) reviewed the use of oral Ketamine in chronic pain management. Ketamine as an analgesic has proven to be effective in patients with severe pain who have failed to respond to routine pharmacotherapy. In these patients with intractable pain, the use of oral Ketamine can be beneficial.

Bahetwar S K, Pandey RK, Saksena AK, Chandra G (2011) evaluated and compared the efficacy and safety of intranasal administration of midazolam Ketamine and their combination to produce moderate sedation in young, uncooperative pediatric dental patients. Intranasal Ketamine found to have the highest overall success rate in modification of behavior of the uncooperative pediatric dental patients to accept treatment. The combination of midazolam and Ketamine provides no benefits as compared to Ketamine but it is better than midazolam alone.

Chopra R, Marwaha M (2013) conducted a study to access the acceptance and efficacy of aerosolized midazolam through buccal mucosa for conscious sedation. Study concluded that none of the patients slept during treatment but remained relaxed or drowsy, which could be clinically related to the low dose of the drug owing to gradual behavioral change and no side-effects.

Peretz B, Kharouba J, Somri M (2104) compared the two different dosage of oral midazolam along with nitrous oxide on the same patient when no cooperation could be achieved with the lower dose. Their effects on procedure completion rates and parental satisfaction as well as any untoward events were also investigated. Vitals were recorded and other adverse reactions such as nausea, vomiting, aspiration, hypotension, arrhythmias, and paradoxical reactions were also recorded. Results showed that there were no respiratory events or other adverse effects with their regimes. There were no gender differences in any parameter regarding the two doses of midazolam.

III. Research Methodology

3.1. Aims and Objectives:

- Record the onset of action, any changes in the vital parameters, body movements, sleep and crying and compare between the following:

a) Oral midazolam (M)
b) Oral Ketamine (K)
c) Oral midazolam-oral Ketamine combination (MK)

- Note down the behavioral outcome of uncooperative pediatric dental patients following the administration of oral midazolam, oral Ketamine and oral midazolam-Ketamine combination as conscious sedation agents as per:

a) Sleep
b) Bodily movement
c) crying

- Observe any adverse reactions following the administration of drug during the duration of recovery.

3.2 Materials Used:

- Intravenous vials of midazolam (Benzosed, midazolam injection IP 10mg/10ml)
- Intravenous vial of Ketamine (Ketamine 50, ketamine hydrochloride injection I.P 50 mg/10ml)
- 2% Lignocaine HCL local anesthetic agent
- Syringes
- Dispensing cup
- Flavored Drink (Frooti- Parle Agro India Pvt. Ltd.)

3.3 Sample Selection:

The study group comprising of seventy five children aged 4-8 years, who were indicated for procedures requiring administration of local anesthesia, was randomly selected from the outpatient Department of paedodontics and Preventive Dentistry, Faculty of Dental Sciences, SGT Medical College, Budhera, Gurgaon. The child should have undergone at least two appointments previously and exhibited an uncooperative behavior in both the appointments.

3.4 Study Group:

This study was double blind as neither the patient nor the operating dentist was aware of the medication that was administered. This was done to avoid bias in the study. The nurse was trained to dispense the drug as per the dosage randomly. The drug was administered by researcher itself. The child was instructed to report empty stomach or at least not to eat solid food 6 hour prior and liquid food 3 hours prior to procedure as per the AAPD Guidelines. The drug was revealed once the patient was discharged.

3.5 Study Design:

This study was carried out in SGT Medical College and written consent was taken from parents/guardian prior to the procedure. An arrival from the ethical committee of SGT University was taken to carry out this study.

Vital signs of each patient each patient were recorded 30 minutes prior to procedure using a digital pulse oximeter provided at the major OT before drug administration and at regular interval of 10 minutes after drug administration. Vital signs such as oxygen saturation levels, pulse rates and temperature were recorded. Any value below 90% ofSpO2 was regarded as respiratory distress and pulse rates below 80 and above 140 was set as safety limit. Temperature and respiratory rates were also noted.

Each child was weighed and the amount of medicine to be given was prepared according to the weight of the child. The patient was given the medication 30 minutes prior to the procedure and the time was noted. Children were administered either oral midazolam 0.5mg/kg, oral Ketamine 3mg/kg or the combination oral midazolam-Ketamine 0.3mg/kg and 3mg/kg, 30 minutes prior to the procedure. Once the drug was administered, onset of actions was noted. Once the sedative effects set in, procedure began.

During the course of procedure the behavioral response of the child in terms of degree of sedation, body movement, crying and overall behavior, throughout the procedure were recorded using the Modified Houpt et al Scale.

3.6 Statistical Tool:

All the compiled data was statistically analyzed using ANOVA and significant p value was set <0.05.

IV. Results

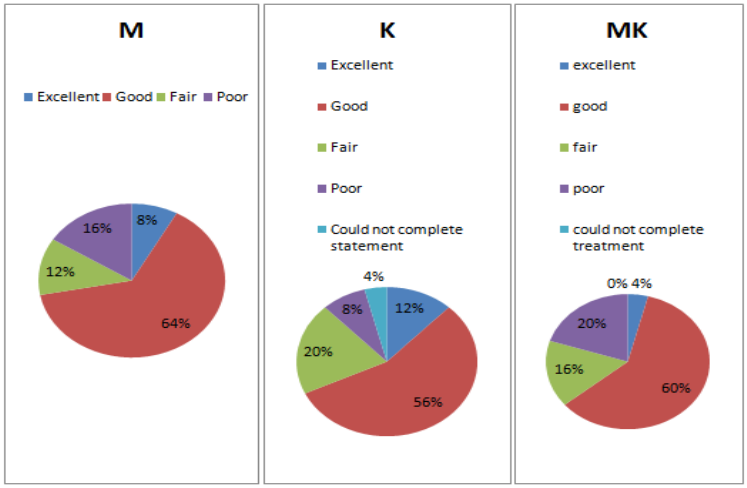
Anova was used for statistical analysis. The mean age was found to be 6.31 years with the mean weight of 16.41 kgs and onset of action of Ketamine was faster than midazolam and midazolam Ketamine combination but was statistically insignificant. The efficacy of Ketamine was found to be the best amongst the drugs used followed by midazolam and then the combination but this was also statistically insignificant. Adverse reaction were most commonly seen in Ketamine with 14/25 patients exhibiting various, reactions followed by midazolam that showed 11/25 patients with adverse reactions and only 2/25 patients showed adverse reactions in the combination group and this was statistically significant.

Table 1: Mean Age, Mean Weight and Mean Onset of Action

Conscious sedation agent	Sample Size	Mean age (yr)	Mean Weight (kg)	Mean onset of action (mins)
M	25	6.82	17.5	40.833
K	25	5.88	16.7	37
MK	25	6.24	15	40

#p value-not significant

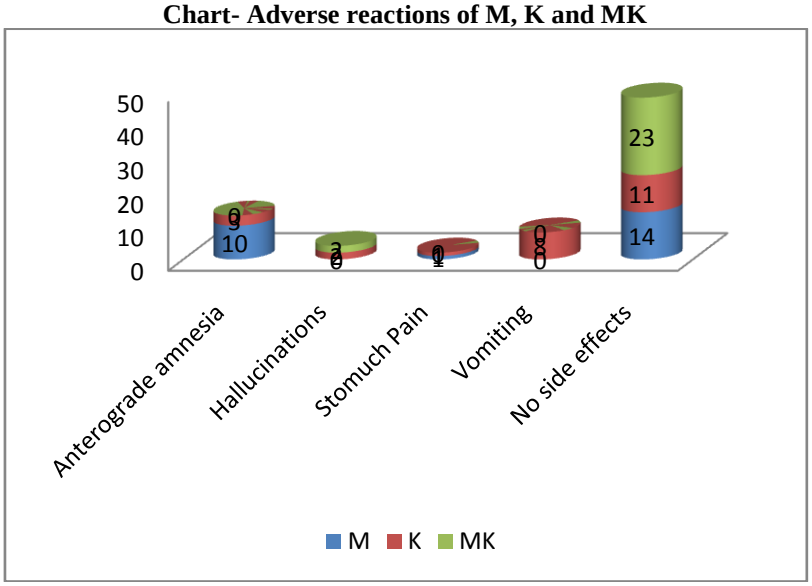
Chart: Comparing overall behavior of the child in each group



K>M>MK

P value- 0.764 statistically insignificant

Chart- Adverse reactions of M, K and MK



P value-0.000772 statistically significant

V. Discussion

A variety of methods are available for producing sedation or alteration of mood in the pediatric patient which include inhalation, oral, sub mucosal, intramuscular, intravenous and rectal. The most universally accepted and easiest method of drug administration is the oral route.

Research is based on Houpt et al scale for assessing the behavior. This scale measures the degree of sleep, movement and crying to determine the overall behavior. This scale was chosen as it was found to be most easy, practical and reliable. Also it is the most commonly used scale for assessment of behavior and has been previously used in several studies.

Study found that Ketamine was a better conscious sedative agent followed by midazolamand then the combination. Study conducted by Bahetwar et al (2011) where they compared Ketamine, midazolam and combination intransally they found that Ketamine (89%) (6mg/kg) gave better results followed by the combination (84%)(0.2mg/kg + 4mg/kg) and then midazolam (69%) (0.3mg/kg) this may be attributed to large variance in the dose of Ketamine.

When comparing among groups researcher found that Ketamine was a better conscious sedative agent than midazolam but on the contrary Damle (2010) found that midazolam (0.5mg/kg)a better conscious sedative agent that Ketamine (5mg/kg). They found that Ketamine exhibit side effects such as vomiting and behavioral changes which was also a finding in our study.

Study states that when midazolam was added to Ketamine the side-effects were greatly reduced and the result was statistically significant.

Several studies show that successful use of Ketamine alone and in combination with midazolam administered via the oral route. Ketamine also produced superior anxiolysis and analgesia than midazolam alone. However, significant respiratory depression was reported at the higher doses of Ketamine, especially when midazolam was used in combination with Ketamine but research did not show any patients with respiratory depression.

Research showed 14/25children exhibiting side effects with Ketamine such as retrograde amnesia (3/25)hallucinations (2/25), vomiting (8/25), stomach pain(1/25). The side effects caused by Ketamine which were more than the other two groups. This made us question the safety of the drug and its usage in routine practice. Even though the overall behavior was poor with the MK combination the side effects were found to be least.

Midazolam showed amnesia in 10/25 cases which can be beneficial to us as the child was unable to remember the unpleasant experience he underwent. Similar results were found in a study conducted by F C Davis (1988) who reported of 66 % partial amnesia and 44% for the whole procedure with (0.2mg/kg) and (0.5mg/kg) of oral midazolam.

VI. Conclusion

As most of the drugs for sedation are capable of inducing general anesthesia in higher doses, care should be taken while administered in chair side. In this regard, sufficient training should be obtained prior to any attempt to sedate children in dental practice. During the study, guidelines of Dental Council of India were followed properly.

Though our results did not yield a statistically significant but result found

- Ketamine was a better anxiolytic agent followed by midazolam then midazolam-Ketamine combination.
- Although midazolam-Ketamine combination was not a good agent for conscious sedation it could counteract the side effects of Ketamine.
- Thus, we concluded that the combination could be used in smaller doses for conscious sedation while taking safety into consideration.

Furthermore, research is required in this field to discover better conscious sedative agents.

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