A comparative evaluation of newer sedatives in conscious sedation

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This double blind study was undertaken to determine the safety and efficacy of orally administered newer sedatives and analgesics for conscious sedation in 120 child patients. Patients were randomly assigned into: Midazolam (I), Ketamine (II), Zolpidem (III), Midazolam plus Ketamine (IV), Midazolam plus Tramadol (V) and Zolpidem plus Tramadol (VI) groups of 20 each. Onset of action, level of sedation, ease of treatment completion, recovery time, and post-operative amnesia were assessed for all and compared. Midazolam plus ketamine was found the most effective combination providing a fast and adequate analgo-sedation in anxious and uncooperative child patients.

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INTRODUCTION

The field of pediatric dentistry beholds the greatest challenge among the various other branches of dentistry in providing dental care without inflicting any adverse psychological impact upon the child. Since the child is at the most impressionable age, ideal therapy behooves the conscientious practitioner to help the child cope with the stress of the dental treatment and the environment. Most of the studies have shown negative dental experience as the root cause of dental fear[1, 2] which precipitates adult dentophobe for future dental treatment.[3, 4] The historical dogma was that children did not perceive or remember painful circumstances as did adults. However, such assumptions have been proved to be false and in the long run, painful treatment on a child leads to negative results.[5] Thus, every pediatric practitioner's ultimate aim should be to strive not to let the child carry a tale outside the dental clinic which speaks of fear and painful experience, as fear and anxiety lower pain threshold, and subconsciously lead to misinterpretation of non-noxious stimulus making it a painful one.[6]

At most of the times, conventional behavior management technique is successful in helping the child to accept dental treatment, however, there are few children who do not respond to this approach.[7] Therefore, conscious sedation has stepped in as a boon for such pediatric population. A number of pharmacological agents have been tried by many workers in the past to achieve this desirable state but none has been proved to be an ideal one. Combined drug therapy if monitored properly can potentiate the drugs effect while reducing the individual drug dose, thus decreasing some of their side effects.

Literature is full of promising results with midazolam for conscious sedation in children.[8, 9, 10] It is suitable in anxious and fearful children due mainly to its wider margin of safety, rapid action, fast excretion, excellent sedative, anxiolytic, and amnesiac properties.[11]

Zolpidem, a non-benzodiazepine drug is a relatively new addition to the class of sedative-hypnotic agents. Till date, there are no published randomized clinical trials describing use of zolpidem as a conscious sedative agent in children. In the present study, zolpidem has been used singly and with tramadol in producing conscious sedation due to its rapid absorption on oral administration, strong sedative-hypnotic action, anxiolytic/ amnesiac properties, and short elimination half life.[12] Further, clearance of zolpidem in children is 3 times higher than in young adults.[13]

Ketamine, a dissociative anesthetic is very well accepted in pediatric age group[14, 15] and has been used alone and in combination with midazolam in the present study. The favorable properties of ketamine include: rapid induction, analgesia, amnesia, a wide margin of safety, maintenance of cardiovascular and respiratory function and intact laryngeal reflexes.[15, 16]

Tramadol is an effective opioid analgesic with a very low drug interaction potential[17] which has been used in combination with midazolam and zolpidem separately in this study. Besides its proven clinical efficacy tramadol is a safe drug as respiratory depression and

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cardiovascular side effects are of minor clinical relevance, unlike other opioids.[18]

Thus the present study was carried out to evaluate the safety and efficacy of newer newer hypno-sedatives (zolpidem and midazolam) and analgesics (tramadol and ketamine) used as sole agents and in various combinations for conscious sedation in anxious and uncooperative child patients.

MATERIALS AND METHODS

This study was carried out on 120 anxious and fearful child patients (ASA Physical Status 1) aged between 2 to 9 years after obtaining informed consent from their parents. Preoperative recording of vitals (blood pressure, heart rate, respiratory rate) of the patients were done. For calculation of dose of drugs, weight of the patient was taken as 1 kg less than the actual weight when fully clothed. Patients were instructed to remain empty stomach for 4 hours in case of solid and for 2 hours in case of liquid foods prior to reporting time on the prescheduled appointment day. All procedures were preferably scheduled for early morning appointments.

Patients were assigned to one of the 6 groups of 20 each using a randomized double blind method:

Group I: Midazolam: 0.5mg/kg orally.

Group II: Ketamine: 5mg/kg orally.

Group III: Zolpidem: 0.4mg/kg orally.

Group IV: Combination of Midazolam 0.4mg/kg and Ketamine 3mg/kg orally.

Group V: Combination of Midazolam 0.5mg/kg and Tramadol 2mg/kg orally.

Group VI: Combination of Zolpidem 0.4mg/kg and Tramadol 2mg/kg orally.

On the day of dental treatment patients were again evaluated for fever, cold or any other systemic illness and the vitals were re-examined. Three readings were recorded altogether and their means were calculated to obtain pre-operative vitals. Midazolam, ketamine, and tramadol were withdrawn from a multidose vial; zolpidem was powdered and measured on an electronic balance, and their dosages were calculated. All the drugs were mixed in chilled fruit juice to mask their bitter taste and maintain uniformity, thus eliminating any possibility of error due to distinction. The vehicle and the quantity were also kept same for each group in order to avoid any fallacy in observation.

The time of drug administration was noted. After the administration of the drug the child patient was shifted to a calm room where he/she was kept under continuous observation. When the sedative effect started to appear the time of onset was recorded and the treatment was started with the administration of local anesthesia (if required). Two more readings of the vitals were taken at the interval of 10 minutes intra-operatively. Means of these readings, and any changes in them were also noted.

The level of sedation[10] was obtained by a rating scale consisting of scores ranging from 1 to 8 (Table-1). The ease of treatment completion[19] was rated as 0 (excellent), 1 (satisfactory), 2 (unsatisfactory), 3 (aborted). Once the treatment was completed, patient was kept in a quiet room free from disturbances for recovery. The time of recovery was noted when the patient was well oriented to the surroundings, sit and stand unaided or with minimal assistance.[20] Vital signs were again recorded and once closely paralleled the baseline the patient was called back again on the next day for the assessment of amnesiac effect. Recording was done using questionnaire about events after the administration of sedative and was graded as good, fair and poor.

Statistical analysis was done using paired and unpaired t-test for comparison and values presented in mean ± S.E. $p<0.05$ was taken to be significant.

RESULTS

The effects of the drugs and their combinations were assessed and compared with each other. The average age and weight of all the 6 groups were comparable. The observations of the various parameters taken were recorded and the results obtained are as follows:

Onset of Sedation

The time taken for onset of sedation was shortest in group IV, closely followed by other midazolam receiving groups, and it was longest for group III (Fig. 1). There was no significant statistical difference among the 3 midazolam receiving groups. However, these readings were highly significant in comparison to zolpidem (non-midazolam) receiving groups ($p<0.001$).

Sedative Score

The sedative score was found to be best for group IV followed by group V (Fig. 2). Patients of group III and VI showed poor sedation; highly significant results were found when these scores were compared with scores of all the other groups ($p<0.001$). Also, statistically significant results were seen between all the combinations versus sole drug groups.

Ease of Treatment Completion

The treatment was most conveniently done in group IV followed by group V. On the other hand, it was most difficult for group III and VI patients (Fig. 2). The inter-group comparisons were highly significant between group IV and VI, and group V and VI ($p<0.001$). Other significant results were seen between single and combination groups of zolpidem with other groups.

Recovery Time

The recovery time was shortest for group I and longest for group VI (Fig.1), and groups II, V, IV, and III exhibited the recovery time in an ascending order.

The inter-group comparisons between group VI with other groups, and group III with other groups were highly significant ($p<0.001$) showing longer recovery period in zolpidem treated groups. Also, comparisons between group I and IV, group II and IV, and group III and VI were statistically significant ($p<0.01$), whereas comparisons between other remaining groups were found to be insignificant.

Anterograde Amnesia

In the groups receiving drugs other than zolpidem the anterograde amnesia was found to be good in more than 50% of patients and fair in more than 25% of patients. However, maximum number of patients receiving zolpidem either alone or in combination showed a poor amnesiac effect.

Change in Vitals

There was no significant change in any of the vitals except in patients who received zolpidem either alone or in combination. In these two groups, mild increase in heart rate and blood pressure were observed during the early period of treatment. However, a close observation on all the patients had been kept throughout the post-drug administration period until complete recovery was attained. No complications arose in any patient due to these changes,

nor did we encounter any other problems.

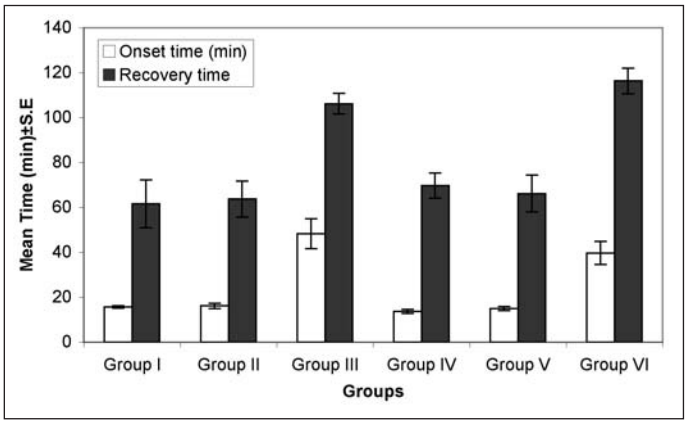

Fig. 1: Onset of Sedation and Recovery Time.

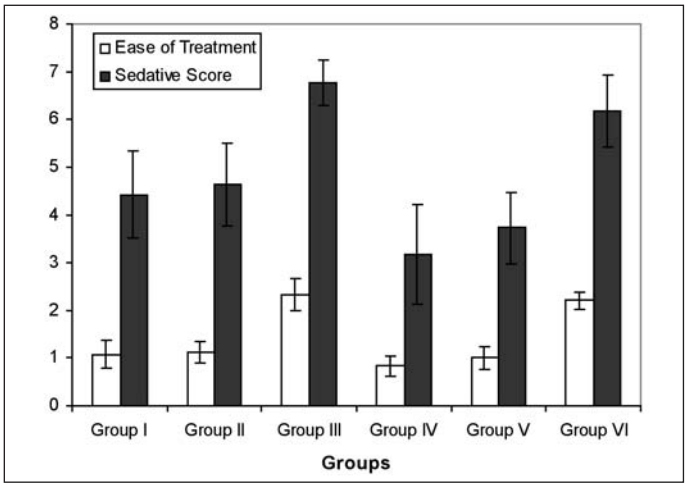

Fig. 2: Sedative Score and Ease of Treatment Completion.

Table 1: Level of Sedation

Sedative Score	Behavioral Signs	Classification
1	Sleeping, no response to patting the shoulder	Asleep
2	Sleeping, no response to calling by name 2 or 3 times. Responds to patting on the shoulder.	Asleep
3	Eyes closed, dull reaction. Responds to verbal stimulus as above.	Drowsy
4	Eyes open and closed by turns, dull reaction. Responds to verbal stimulus.	Sedated
5	Eyes open, dull reaction. Responds to verbal stimulus.	Sedated
6	Normal reaction.	Normal
7	Irritable with body movement.	Excited
8	Highly irritable with considerable body movement.	Excited

DISCUSSION

In the past pain has been so closely associated with dentistry that the words pain and dentistry have become synonymous. A 2 or 3 years old does not consider acquiring good dental health a significant motivator to tolerate painful treatment, and infact sees no obvious benefits in cooperating with the therapy. Additionally, children lack experience with uncomfortable situations and have inadequate coping skills with which to tolerate treatment, making non-pharmacological approach of behavior management technique unsuccessful for this age group.[21] Therefore, pharmacological approach is a mixed blessing for these patients and the dentist as well. With this in mind the lower limit of age group was kept as 2 years. Oral route was chosen as needle evoked anxiety/ apprehension in majority of child patients.

Pharmacological management using sedative-hypnotic drugs alone or with analgesic combinations have recently maintained a degree of popularity among pediatric dentists practitioners.[22] Among the various pharmacological agents to treat anxiety and fear, benzodiazepines are the most popular. In a previous study conducted in our department in which two of the co-workers had participated, midazolam was found to rapidly provide the state of conscious sedation with good post-operative amnesia.[10] The present study was an attempt to evaluate the best effective drug/combination in producing conscious sedation in anxious and uncooperative child patients.

Oral midazolam has been tried in various doses.[23] Among these the dose of 0.5 mg/kg has been found to be safe and effective by many workers.[24, 25] In accordance with these findings, even in this study midazolam was found to be quite an effective conscious sedative agent.

Alderson & Lerman[26] have found 5mg/kg of ketamine to produce effective sedation within 20 minutes but the effect was inferior to 0.5mg/kg of midazolam. Few patients of ketamine group in the present study showed mild disorientation and/or behavioral changes which were of short duration and minor significance. Ketamine, though not found as good as midazolam, can be preferred over the latter in cases where pain control is also required to some extent along with sedation. However, ketamine does not eliminate the need for local anesthesia whenever any invasive procedure is undertaken.

Though midazolam is a potent sedative and anxiolytic agent, use of a sedative without adequate pain control may cause the patient to become highly agitated and confused.[7] To achieve the state of analgo-sedation, workers have employed analgesics in combination with sedative/hypnotic drugs; midazolam plus ketamine is the commonest with safe and effective results.[27, 28] However, all of these studies have been conducted on American/European children and no comprehensive trial has been conducted in India so far, thus this study was carried out. This combination has also been proved beneficial in terms of reduction in dose and adverse effects of each drug[16] providing high patient acceptance. Also stated, administration of benzodiazepines especially midazolam greatly reduces emergence phenomenon.[29] In the present study also patients of this group responded excellently in terms of better sedative effect and ease during treatment. Since it also provided ample treatment time this combination can be utilized for lengthy procedures.

In another group midazolam was combined with tramadol. Tramadol was chosen due to its minimal respiratory depression in therapeutic doses and low drug interaction.[30, 31] It was found that the combination of midazolam and tramadol can be a good alternative

to midazolam plus ketamine wherein ketamine is contraindicated. However, this combination was inferior to midazolam plus ketamine in respect of ease of treatment completion.

Zolpidem 10 or 20 mg when used as an oral premedicant was found to be superior to placebo in causing sedation and reducing the anesthetic dose. However, recipients of zolpidem 20 mg tended to fall asleep again after recovery.[32] This kind of behavior was observed in the present study also and is undesirable for the purpose of conscious sedation.

Zolpidem is reported to produce sedative effect rapidly within 15-20 minutes.[12] Contrary to this report, the onset and duration of action for zolpidem either singly or in combination with tramadol was controversial in the present study. Few children receiving zolpidem and its combination showed sedative effect in about an hour, whereas others remained active throughout their stay in the clinic. Though drowsiness was observed in these patients, they were not sedated up to the sedative threshold to allow for any treatment to be instilled. Interestingly, few children of zolpidem groups were found to be uninhibited and in a very jolly mood (singing and dancing) after the administration of the drug. The dose chosen in the present study (0.4mg/kg) closely paralleled the range which has been used by other workers- 5 mg in elderly and 10-20mg in young adults.[12]

CONCLUSIONS

The newer drug zolpidem, though a powerful sedative-hypnotic did not prove to be a satisfactory conscious sedative agent. Midazolam (0.4mg/kg) plus ketamine (3mg/kg) was found to be the best combination among all the other groups for conscious sedation in pediatric patients with minimal systemic adverse effects. If ketamine cannot be used, midazolam plus tramadol can be used, and if only a single agent is permissible then midazolam is the best choice. However, zolpidem being a relatively new drug, further studies are required to confirm its effect as a conscious sedative agent.

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