A Comparative Evaluation of Agents Producing Analgo-sedation in Pediatric Dental Patients.

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Objective: *Procedural sedation and analgesia (PSA) has reduced the need for general anesthesia (GA) for many surgical procedures in pediatric patients. The objective of this study was to evaluate the efficacy of four analgo-sedative combinations- midazolam plus ketamine (MK), midazolam plus tramadol (MT), promethazine plus tramadol (PT) and promethazine plus ketamine (PK) in facilitating dental treatment of uncooperative children.* ***Study design:*** *Thirty six uncooperative ASA type I children who required extensive dental treatment were randomly assigned to receive one of the four analgo-sedative combinations during each visit. A 4-stage cross-over design was adopted so that each child received all the four combinations. Safety was monitored through vital signs and side effects.* ***Results:*** *The overall success was 81% with MK, 69% for PK, 67% for MT and 42% for PT and the difference between the success rates of these agents was statistically significant ($p < 0.001$). The required dental treatment could be successfully completed at least during 3 sessions in 23 children (62.2%).* ***Conclusions:*** *Segmental dental treatment under analgo-sedation can be considered as a viable alternative before considering patients for dental management under GA. MK and MT were found to be safe and effective for sedating pediatric dental patients.*

Keywords: *sedation, analgesia, procedural sedation and analgesia, analgo-sedation, midazolam, ketamine, promethazine, tramadol.*

J Clin Pediatr Dent 34(2): 183–188, 2009

INTRODUCTION

Sedation and analgesia in pediatric patients for procedures outside the operating room are becoming more frequent and has substantially reduced the need for general anesthesia in medical practice.[1] Following a prospective descriptive investigation of 1244 sedation sessions in 1215 patients, Pitetti *et al* concluded that procedural sedation and analgesia (PSA) can be safely administered by non-anesthesiologists.[2] Moreover, dental offices have been identified as potential arena for outpatient PSA.[3]

Combining drugs with analgesic and sedative potential have generated greater interests in recent days as these combinations have been hypothesized to minimize pain when the child is moderately sedated, which aids in successful completion of treatment.[4]

Midazolam has given promising results since its inception in the field of pediatric moderate sedation as it is short acting, having good anxiolytic and amnesic properties and provides a greater margin of safety, which explains its wide use in pediatric age group.[5] Ketamine, a dissociative anesthetic, whose properties have been greatly questioned in the past, is now finding an important place in pediatric oral sedation. The profound analgesia offered by this drug is worth mentioning.[6, 7]

A review of the existing literature to analyze the reasons for combining benzodiazepines (especially, midazolam) along with ketamine include- (1) to minimize the effects of emergence delirium (hallucinations) in children,[8-10] (2) to reduce cardiovascular sequelae,[9,11] (3) to provide longer working time[8] and (4) greater degree of amnesia.[12]

Through a double blind, randomized, crossover study, Lokken and colleagues found MK to offer greater reduction in anxiety and pain when administered rectally, and the amnesia produced by this combination was also found to be high when compared to midazolam used alone.[13] Roelofse *et al* found MK to be a safe and effective alternative for managing children requiring minor dental procedures under local anesthesia. Moreover, the incidence of hallucinations was reported to be lower in children receiving the combination

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(14%), than patients receiving midazolam alone (42%).[8]

Promethazine is being propagated in combination with other agents for its anti-emetic and sedative action. In a study by Bui *et al*,[14] pediatric dental patients sedated with a combination of oral promethazine and ketamine (PK) were found to be devoid of intra- and post-operative vomiting, as compared to oral ketamine used alone (27%). Moreover, it has been suggested that promethazine also has a major role in reducing the emergence phenomenon associated with ketamine.[10]

Tramadol, a centrally acting opioid analgesic, has been used alone as well as in combination with other sedatives and analgesics for management of pain and anxiety in pediatric patients, with varied success. The combination of midazolam and tramadol (MT) had been administered through parenteral route by many workers to obtain analgo-sedation during many outpatient procedures.[15,16] The use of oral MT as an analgo-sedative, prior to pediatric dental treatment, has been ranked a close second to MK by Koirala *et al*.[17]

Thus, combining drugs with varying degrees of sedative (midazolam, promethazine and ketamine) and analgesic (ketamine and tramadol) properties is a viable option to facilitate outpatient procedures. However, a better understanding of their use in pediatric dental patients was felt necessary before routinely deploying these agents to facilitate dental treatment. Hence, this study was carried out to evaluate the safety and efficacy of four analgo-sedative combinations in delivering dental care to young patients.

METHODS

This study was conducted with the approval of Institutional Ethics Committee, Research Cell, CSM Medical University, Lucknow, India. A triple-blind, randomized, prospective, 4-stage crossover design was adopted in this study, to evaluate the efficacy of the following analgo-sedative combinations.

1. Midazolam (0.5mg/kg) plus Ketamine (5mg/kg) (MK)
2. Midazolam (0.5mg/kg) plus Tramadol (2mg/kg) (MT)
3. Promethazine (1mg/kg) plus Ketamine (5mg/kg) (PK)
4. Promethazine (1mg/kg) plus Tramadol (2mg/kg) (PT).

Children between 2 - 6 years of age for whom basic behavior guidance techniques were not successful in rendering dental treatment and hence, indicated for treatment under GA (response to treatment rating scale score – 1 or 2, Table 1a); were recruited for this study. It was ensured that the participants required a minimum of 4 sextants of dentistry, with at least 1 teeth in each sextant requiring endodontic treatment. The inclusion criteria also required that these children were free of any physical, mental or systemic disabilities (ASA type I) and had no known contraindications to the use of benzodiazepines, promethazine, opioids or ketamine. Airway assessment was done to ensure that these children had no abnormalities related to the size of jaws, tongue and tonsils; mouth opening, mobility of neck and had no obstructions in the airway. No child with a previous history of dental treatment under sedation or anesthesia was admitted into the study.

Table 1. Scales Used To Rate Behavior/Response To Treatment And Quality Of Sedation

SCORE	CLASSIFICATION	SIGN
Table 1a - Response to treatment (ease of treatment completion) rating scale		
5	**EXCELLENT**	Quiet and cooperative. Treatment completed without difficulty
4	**GOOD**	Mild objections or whimpering but treatment not interrupted. Treatment completed without difficulty
3	**FAIR**	Crying with minimal disruption to treatment. Treatment completed with minimal difficulty
2	**POOR**	Struggling that interfered with operative procedures. Treatment completed with difficulty
1	**PROHIBITIVE**	Active resistance and crying. Treatment could not be rendered
***'Satisfactory'* session -** response to treatment rating score of '4' or '5' through the first 50 minutes of the session		
***'Unsatisfactory'* session-** score less than '4' or '5' even in one reading during the first 50 minutes of the session.		
Table 1b - Sedation rating scale		
1	**NO SEDATION**	Typical response /cooperation for this patient
2	**MINIMAL**	Anxiolysis
3	**MODERATE**	Purposeful response to verbal commands
4	**DEEP**	Purposeful response after repeated verbal command or painful stimulation
5	**GENERAL ANESTHESIA**	Not arousable
'*Adequate*' sedation - sedation rating score of '2' or '3' through the first 50 minutes of the session		
***'Inadequate'* sedation -** score other than'2' or '3' even in one reading through the first 50 minutes of the session		

This study evaluated the extent/degree to which treatment could be completed under the influence of analgo-sedatives, in children who were initially proposed for dental management under GA. Rate of success of sedation with each analgo-sedative was the main outcome measured. The onset and depth of sedation, ease of treatment completion and period required for complete recovery were also analyzed. The changes in vital signs and oxygen saturation during treatment were also evaluated.

The sample size required to detect a 10% difference in ease of treatment completion between two drugs, with 80% power and 95% confidence limits was calculated to be around 34. Thirty six pediatric out-patients who met the selection criteria were enrolled in the study after obtaining informed consent from their parents/legal guardian.

Preparation of analgo-sedative combinations

In order to maintain uniformity in the composition of oral analgo-sedative formulations and to facilitate the triple blind nature of the study, parenteral preparations of the drugs were converted into oral formulations using the same diluent vehicle.

The order according to which these agents were administered was generated using an online randomization generator. On the day of dental treatment, the clinical status of the patient was re-evaluated by an anesthetist, who was present throughout the procedure and also knew the drug combination being administered. The vital signs and oxygen saturation levels were examined and recorded. The drug solutions were measured based on the weight of children and administered. Parents assisted those patients, who had difficulty in drinking the solution.

Dental treatment

All dental procedures were performed by the primary investigator (PI). The treatment procedures for each patient were standardized in such a manner that similar procedures were performed during all the four appointments. After the onset of sedation; pulse rate, blood pressure, oxygen saturation and respiratory rate were recorded at regular intervals of 5 minutes by a co-investigator (CI). Local anesthetic (LA) agent was administered either in the form of a nerve block or infiltrated locally (2% Lignocaine with 1:200000 adrenaline) during all the sedation sessions and the changes in pulse rate were noted every minute while LA was administered. If the child became uncooperative during treatment, physical restraints were applied by the dental assistant in the form of papoose board, mouth prop, manual hold or combination of the above and its use was documented. The treatment session was aborted when the patient became highly uncooperative, that dental care could not be performed even with the use of physical restraints.

The ease with which treatment could be completed and the level of sedation were measured using separate 5 point scales (modified from the AAPD sedation record) (Table 1). Both these ratings were done at regular intervals of 5 minutes by CI. Calibration involved rating of recorded videographic segments of sedation sessions conducted in this center, previously rated by a Professor (Pr) in the Department of Pediatric Dentistry who was involved in this study and two other studies conducted in the same center.[17, 18] Spearman rank correlation found high inter reliability between the ratings of the CI and Pr ($r = 0.828$, $p<0.001$). Around 20 sessions were randomly chosen and the level of sedation and ease of treatment completion were rated by the Pr along with the CI during these sessions, in order to assess the reliability of CI's ratings.

Once the treatment was completed, patient was transferred to a quiet room free from disturbances for recovery. Once fully recovered, the vitals were re-checked and the patient was discharged, when the AAPD sedation guidelines for discharge were met[19] and an Aldrette score[20] of 9 or greater was achieved. The time required for complete recovery was recorded. The caretaker, who was accompanying the child patient, was provided with postoperative instructions, emergency telephone number and an appointment for the next treatment. The caretakers were contacted the next day and enquired for the presence of any adverse reactions or side effects.

The treatment outcome was considered 'successful' if- (1) physiological parameters remained within 20% of baseline values, (2) oxygen saturation remained at 90% or greater, (3) response to treatment score of '4' or '5' ('satisfactory' treatment session) and sedation score of '2' or '3' ('adequate' sedation) was obtained throughout the treatment, (4) physical restraints were not used during dental treatment and (5) no major side effects were encountered during the intra- or post-operative period.

Statistical analyses

Levene's statistics revealed a lack of homogeneity ($p = 0.003$) between the variances of the four groups of values pertaining to the duration of onset of sedation and recovery. Hence, a non parametric test in the form of Friedman's test was used to detect the differences in the duration of onset of sedation and recovery between the four groups, followed by a Post Hoc Tamahane's T2 test which was used for intergroup comparisons.

The differences in the depth of sedation, response/ behavior during treatment and treatment outcome between the four groups were evaluated using Cochrans test as the response variables for all these parameters had only two possible outcomes (adequate/inadequate; satisfactory/ unsatisfactory and successful/ unsuccessful).

RESULTS

A total of 144 sedations were performed in 36 children. All 36 children had completed all the four sessions during the study. The children were between 2 – 6 years of age with a mean age of 4.76 years and a mean weight of 12.36 kg. There were 18 males and 18 females. The results obtained have been summarized in Table 2.

Friedman's test found highly significant differences ($p<0.001$) in the durations required for onset of sedation and recovery between the four groups, except for the duration of recovery between PK and MT which was non-significant ($p = 0.989$, Tamahane's T2 test). MK and MT had a faster onset with a mean duration of 20.83 and 23.03 minutes respectively. However, children recovered faster when sedated with MT (63.62 minutes) than with MK (74.63 minutes). Even though the onset of sedation was reasonable with PK (29.00 minutes), the time required for complete recovery was very high (98.16 minutes). The onset of sedation was slowest with PT.

Spearman rank correlation test found significant correlation between the response to treatment ratings ($r = 0.892$, $p < 0.001$) and sedation scores ($r = 0.912$, $p < 0.001$) of Pr and CI.

MK provided 'adequate' depth of sedation during maximum number of sessions (89%) and provided 'satisfactory'

Table 2. Characteristics Of Various Analgo-Sedative Groups Observed During The Study

	PARAMETERS	PK	PT	MK	MT	P VALUE
ONSET OF SEDATION (*in min*) n = 36*	MEAN (95% CI)	29.00 (27.85, 30.15)	42.14 (40.14, 44.14)	20.83 (20.12, 21.55)	23.03 (22.21, 23.84)	**p < 0.001 (FRIEDMAN'S TEST)**
	MEDIAN (25th ,75th PERCENTILE)	29.00 (26.00, 31.75)	40.00 (38.25, 44.50)	20.00 (19.25, 22.00)	23.00 (21.00, 25.00)	
'ADEQUATE' DEPTH OF SEDATION (PERCENTAGE) n = 36*		26 (72%)	17 (47%)	32 (89%)	26 (72%)	**p < 0.001 (COCHRAN'S TEST)**
EASE OF TREATMENT COMPLETION – 'SATISFACTORY' SESSIONS (PERCENTAGE) n = 36*		25 (69%)	15 (42%)	29 (81%)	24 (67%)	**p < 0.001 (COCHRAN'S TEST)**
RECOVERY TIME *(in min)*	MEAN (95% CI)	98.160 (94.09, 102.23)	95.65 (88.46, 102.83)	74.63 (72.63, 76.62)	63.62 (60.78, 66.45)	**p < 0.001 (FRIEDMAN'S TEST)**
	MEDIAN (25TH ,75TH PERCENTILE)	100.00 (95.00, 105.00)	95.00 (85.00, 103.00)	73.00 (71.00, 77.50)	63.50 (60.00, 68.00)	
	NUMBER OF SESSIONS$	26	17	32	26	
TREATMENT OUTCOME- 'SUCCESSFUL' SESSIONS (PERCENTAGE) n = 36*		25 (69%)	15 (42%)	29 (81%)	24 (67%)	**p < 0.001 (COCHRAN'S TEST)**
'UNSUCCESS-FUL' SESSIONS n = 36*	TREATMENT SESSIONS COMPLETED WITH PHYSICAL RESTRAINTS	5 (13.89%)	7 (19.44%)	4 (11.11%)	5 (13.89%)	
	ABORTED SESSIONS	6 (16.67%)	14 (38.89%)	3 (8.33%)	7 (19.44%)	

*n = 36, implies the number of sessions; $ recovery time calculated only from those children who were *'adequately'* sedated throughout the session

completion of treatment during 29 sessions (81%), while PT facilitated the least in completing treatment.

The differences in medians among each of the sets of vital signs recorded during each visit, was evaluated using the Friedman's test. Statistical differences were found between the medians of heart rates of different groups ($p < 0.001$). However these changes were not clinically significant as the values recorded were within 20% of baseline values. PT was found to elevate heart rate the most, while the elevation in hear rate was least with MK (Figure 1). The differences between the medians of other vital signs were not statistically significant. The oxygen saturation values never dropped below 90%.

One patient in each group experienced nausea/vomiting after they reached home. No other side effect was reported or observed.

Overall sedation success found 15 children to be sedated successfully during all the four sessions, 8 children to be sedated successfully during three out of four sessions, 2 children to be sedated successfully during two sessions, 7 children to be sedated successfully only during a single session and 4 children unsuccessful with either. When compared individually, treatment outcome was most successful with MK (81%) and least with PT (42%). The overall success of the analgo-sedatives with respect to the order in which they were administered is summarized in Table 3.

All children (4 patients) whose treatment sessions were

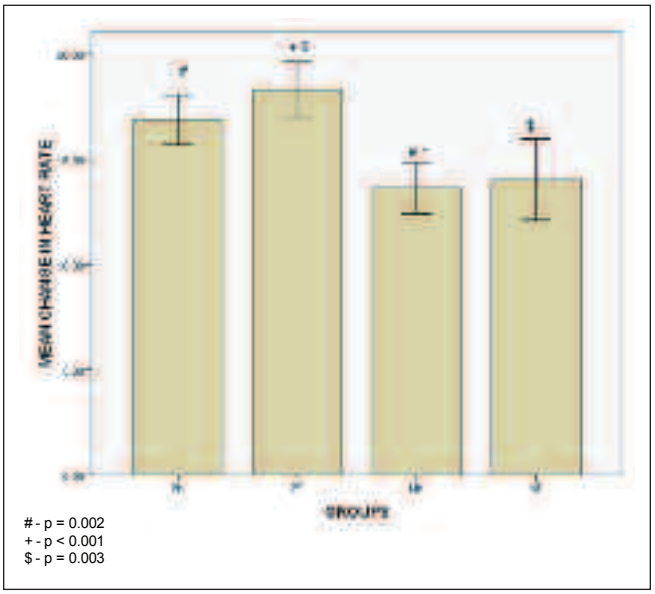

Figure 1. Changes in heart rate during dental treatment under analgo-sedation.

Table 3. Success Of Analgo-Sedatives As Related To The Randomised Order In Which They Were Administered

GROUPS	FIRST VISIT		SECOND VISIT		THIRD VISIT		FOURTH VISIT	
	NO. OF SESSIONS	SUCCESSFUL SESSIONS	NO. OF SESSIONS	SUCCESSFUL SESSIONS	NO. OF SESSIONS	SUCCESSFUL SESSIONS	NO. OF SESSIONS	**SUCCESSFUL SESSIONS**
K	6	5 (83%)	8	3 (38%)	12	9 (75%)	10	**8 (80%)**
PT	8	1 (13%)	12	7 (58%)	9	4 (44%)	7	**3 (43%)**
MK	14	13 (93%)	7	5 (71%)	7	5 (71%)	8	**6 (75%)**
MT	8	6 (75%)	9	7 (78%)	8	4 (50%)	11	**8 (73%)**
TOTAL	**36**	**25 (69%)**	**36**	**22 (61%)**	**36**	**22 (61%)**	**36**	**25 (69%)**

unsuccessful with MK had no success with other analgo-sedative combinations as well. Fifteen patients, whose treatment sessions were successful with PT, were managed successfully with other analgo-sedatives as well.

DISCUSSION

In this study, the clinical profile of all the analgo-sedative combinations used was found to be safe as determined by the stability of vital signs and adverse effect profiles. Even though statistically significant intra-operative changes were observed in vital signs, these changes were not clinically significant, as all the recorded values were within 20% of baseline values. Moreover, the oxygen saturation levels remained above 90% in all the patients. The current guidelines necessitate the presence of an anesthesiologist during procedural sedations done under the influence of multiple drug therapy. Even though no emergencies or intra-operative adverse reactions were encountered during the present study, the authors suggest that dental treatment under the influence of analgo-sedation be performed under the supervision of anesthesiologists until further studies are conducted to establish the safety of analgo-sedation in the hands of pediatric dentists alone.

The analgesic effects of tramadol and ketamine have been extensively reviewed in the literature. Apart from providing analgesia, ketamine has been reported by Lokken *et al* to minimize the respiratory depressant effects of midazolam and hence they considered this combination as an alternative to general anesthetics.[13] Tramadol was chosen as it has very less potential to depress respiration when compared to other opioids and low drug interaction.[21, 22] Moreover, it inhibits the reuptake of serotonin and nor-adrenaline which also contributes to its analgesic activity.[23] In our study too, no respiratory depression was encountered when ketamine and tramadol were combined with sedatives.

The pharmacodynamic profile of both MK and MT appeared suitable for procedural sedations with shorter waiting times following ingestion and faster recovery. The success rate of MK was about 81% and facilitated the delivery of dental treatment the most. These results were similar to those of Koirala *et al*, who also found MK to offer the greatest ease in delivering dental treatment.[20] They also considered the combination of midazolam and tramadol as an alternative to MK in those patients for whom ketamine is contraindicated. Even though the success rate of PK was comparable to that of MT, the longer recovery times associated with its use is a major limitation.

The 4 stage cross-over design adapted in this study, which is the first of its kind, ensured sample uniformity but the experience of the children at each visit could have possibly influenced their behavior/response during the subsequent visits which would have induced a potential bias during comparison of the efficacy of the individual drug combinations, which is one major limitation of the study. But, this study design allowed us to evaluate segmental treatment under analgo-sedation as a viable option for managing extensive dental problems in uncooperative pediatric patients, who were otherwise indicated for management under GA. A washout period of one week was maintained between each session and the quantity and duration of dental procedures performed for every patient during all the four sessions were standardized to ensure bias-free evaluation.

The oral route is the most preferred route of drug administration for most of the pediatric patients surveyed.[24] It is most convenient, does not require any complex instruments for administration (as in the case of nitrous oxide) and is well accepted by most patients.

Nathan and Vargas[3] had hypothesized that well-sedated subjects manifest lesser elevations in heart rate compared to subjects whose sedation proved inadequate. In this study we observed that MK and MT groups, whose sedative effectiveness was clinically appreciable, manifested lesser elevations in heart rate from baseline values.

Even under the best conditions, dentistry is not inherently pleasant for the pediatric patient. Dental treatment under the influence of GA may be the best option, but the reduced availability of operating room for elective dental procedures under GA especially in the developing countries and the economic burden associated with it may necessitate development of alternate strategies.

This study's results indicated that at least three treatment sessions could be completed satisfactorily in 23 out of 36 children (62.2%) and two treatment sessions could be satisfactorily completed in 25 out of 36 children (69.4%) and the treatment sessions of only 4 children (11.1%) were unsuccessful with all the four combinations.

Hence, it is the investigator's opinion that at the recommended doses, MK and MT can be used to routinely sedate fearful/anxious and uncooperative patients before considering them for dental treatment under GA.

CONCLUSION

Analgo-sedation is safe and cost-effective in facilitating dental care for uncooperative children, who had been indicated for treatment under GA. The combination of midazolam/ketamine and midazolam/tramadol are ideal choices for sedating pediatric dental patients.

ACKNOWLEDGEMENTS

The authors would like to thank Mr. Kamlesh Singh, Senior Research Officer, Clinical Epidemiological Unit, CSM Medical University, Lucknow for assistance related to statistical calculations.

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