Sedative Effects of Oral Midazolam, Intravenous Midazolam and Oral Diazepam

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Objectives: *To evaluate and compare the behavioral changes and effect of sedative techniques in pediatric dental patients using Oral Midazolam, Intravenous Midazolam and Oral Diazepam as sedative agents.* ***Materials and Methods:*** *Triple blind randomized control trial with 40 patients aged between 2-10 years, exhibiting definitely negative behavior was considered. Patients were randomly assigned to one of the four treatment groups. Group I received midazolam 0.5mg/kg orally, Group II received 0.5mg/kg diazepam orally, Group III received 0.06mg/kg midazolam intravenously and Group IV received oral placebo. Behavioral changes (sleep, crying, movement, and overall behavior) and effect of sedative techniques on pediatric patients were assessed.* ***Results:*** *All the patients in group 3 were significantly better in post administrative behavior viz. sleep, crying and movement. Over all behavior scores for group 3 patients were significantly better than other three groups ($p<0.001$). Positive behavior of patients in group 2 and 3 did not show significant difference but positive behavior in group 3 was significantly ($p<0.05$) more than group 2. Placebo group showed the highest negative behavior.* ***Conclusion:*** *Sedative effects of oral midazolam and oral diazepam were comparable, where as intravenous midazolam produced more sedation. Anxiolysis was found to be more in both the midazolam groups than the diazepam group. Most number of positive changes were observed in midazolam groups as compared to diazepam group.*

Keywords: *Behavior, Diazepam, Midazolam, oral, Conscious sedation, Pediatric dental patients.*
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INTRODUCTION

The safe and effective treatment of uncooperative or combative children with extensive dental needs is one of pediatric dentist's ongoing challenges. The traditional methods of behavior management are no longer acceptable to parents such as intimidation, distraction, and voice control. Also, these techniques may cause traumatic memories in the child that may lead to lifelong dental phobias. A safe, fast, and non-traumatic dental treatment is needed and thus pharmacological management in the form of dental sedation comes into the picture. Earlier, parents were allowed to enter the dental operating theatre as the child was more apprehensive on separation from the parent, but entering the operatory made the parents anxious.[1,2] Anxiety in children undergoing dental treatment is characterized by subjective feelings of tension, apprehension, nervousness, and worry that may be expressed in various forms.[1] Studies have indicated that up to 60% of all children undergoing surgery/dental treatment may present with negative behavioral changes.[3, 4] Variables such as age, temperament, and anxiety of the child have been identified as predictors for these behavioral changes.[3]

In order to overcome these challenges, this study was under taken to compare the behavioral changes of the child like sleep, crying, movement and overall behavior and effect of sedative techniques on child's behavior using oral midazolam, oral diazepam and i.v. midazolam.

MATERIALS AND METHOD

A total of 40 patients aged between 2-10 years were selected for this study from the patients attending the Department of Pediatric and Preventive Dentistry.

Following criteria used for selection of patients for this study:

- Frankl rating 1 (Definitely negative) at the initial visit in spite of use of behavior modification techniques.

Patients who were mentally compromised were excluded from the study.

Thorough medical history along with physical examina-

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tion was performed prior to the selection of a patient and was noted in the form.

Vital signs including weight, heart rate, respiratory rate, and blood pressure were recorded. Parent's written informed consent was obtained after explaining the sedation procedure, its advantages, and risks involved. An appointment was scheduled for conscious sedation procedure. Parents were given oral as well as written dietary instructions to follow prior to administration of sedative agent.

Patients were randomly assigned to one of the four treatment groups according to the double blind study:

Group I:	Oral midazolam group
Group II:	Oral diazepam group
Group III:	IV. Midazolam group
Group IV:	Placebo group

All the sedation procedures were performed with the assistance of a registered anesthetist. Random assignment to different groups was done by the anesthetist so that the operator, evaluator and the patient were blinded from the type of medication used for groups I, II and IV. Since Group III was the only group involving intravenous route, blinding was not possible for this group.

Group I patients received midazolam 0.5 mg/kg orally (Fulsed, Ranbaxy) and Group II patients received 0.5 mg/kg diazepam orally (Compose; Ranbaxy). The doses for oral midazolam (Group I) and oral diazepam (Group II) group patients were calculated according to the patient's weight by the anesthetist. The sedative drug was then mixed in 15 ml of orange flavored beverage and administered to the patient in an isolated room by the anesthetist. Group IV patients (Placebo) were administered 15 ml orange beverage alone.

Group III patients received 0.06 mg/kg midazolam (Fulsed, Ranbaxy) intravenously after they were placed on the chair and all the monitoring devices were placed. Then the venipuncture procedure was undertaken by the anesthetist to administer the drug. The patient's hand was kept in a clenched fist and rubber tourniquet was applied to the arm selected for venipuncture, the most prominent superficial vein was selected and punctured with 0.23 gauge needle (scalpvan). The care was taken that site of needle entry into the skin was lateral to vein and approximately half inch below the desired point of the needle in to the vein. Calculated dose of drug was slowly administered.

Prior to the administration of the drug, baseline vital signs including heart rate, respiratory rate, blood pressure were recorded for patients in all four group. Group I, II and IV patients were allowed to rest for 30 minutes after the administration of the drug and signs of sedation like ptosis, slurred speech or drowsiness or quietness were observed. In the presence or absence of these signs, the patient was any way transferred to the dental chair after 30 minutes. Pediatric blood pressure cuff was placed on the left arm. Pulse oximeter probe was attached to the index finger of the left hand.

The dental treatment was started after monitoring devices were placed for all patients. The treatment consisted of restorations, pulp therapy and extractions with the use of local anesthesia.

Monitoring of vital signs was performed by an evaluator who was blinded for the use of oral sedative agent. AAPD guidelines for conscious sedation[5] were followed while monitoring patient's heart rate, respiratory rate, oxygen saturation and systolic and diastolic blood pressure. Respiratory rate was monitored visually. Blood pressure was recorded using a sphygmomanometer and stethoscope and heart rate and oxygen saturation were monitored by pulse oximeter.

Once the dental treatment was over, patient was made to relax in the dental chair with monitoring devices still in place. Patient was considered fit to be discharged if he/she met following criteria established by AAPD (AAPD guidelines for conscious sedation, 1999)[5]:

Written postoperative instructions were discussed with the parents before patient was discharged. Patient was called after 7 days for postoperative assessment.

Patient's behavior was assessed by the same evaluator using behavior rating scale established by Houpt *et al*.[6]

Behavior was assessed at following intervals:

1. 30 minutes post drug administration in Group I, II and IV or 5 minutes post drug administration in Group III.
2. During placement of blood pressure cuff.
3. During administration of local anesthesia whenever used or use of hand piece.
4. Every 15 minutes thereafter until the treatment was over.

A numerical score was entered at each interval for sleep, movement and crying. Overall behavior score was noted after the completion of the treatment.

To assess the behavioral changes that had taken place in the child due to the experience of dental treatment under sedative agent, a questionnaire was given to the parent to fill out at the post operative visit after 7 days. The parent recorded changes in child´s behavior at home after the dental treatment under sedation. A modification of child behavior questionnaire by Camm *et al* [7] was used for this study. Number of positive and negative were recorded for each child.

Statistical Analysis

The data was entered onto a personal computer and statistical analysis was done using SPSS version 12. The comparison of mean score between the four groups was done using one way ANOVA with Tukey's posthoc test. Test of proportion or "Z" test was conducted to find the significant differences between two sample proportions for Amnesia of the sedative procedure.

RESULTS

Demographic data of the patients in the four different groups of the present study showed no statistically significant dif-

ference between age weight and height among the four groups.

Behavioral Assessment

Patients' behavior during the dental procedure was evaluated in three categories, viz., sleep, crying, and movement post-administrative mean values for sleep, crying and movement were calculated for each group from the scores registered at different intervals after the administration of the sedative agent and were compared across the groups and data are presented in the Table 1.

Table 1. Mean values (±SD) of behavioral assessment scores measured post-administration of sedative agent

	Group I	Group II	Group III	Group IV
Sleep	1.93±0.116	1.90±0.117	2.55[a] ±0.112	1.0[b] ±0.000
Crying	3.72±0.077	3.05[c] ±0.210	3.87[d] ±0.131	2.35[e] ±0.347
Movement	3.64±0.072	3.07[f] ±0.212	3.25[g] ±0.084	1.74[h] ±0.114

a. Significantly more sleep than Groups I, II & IV (p<0.001) *b.* Significantly less than Groups I, II & III (p<0.001) *c.* Significantly less crying than Group IV (p<0.001) but more crying than Groups I & III (p<0.001) *d.* Significantly less crying than Groups II & IV (p<0.001) and Group I (p<0.01) *e.* Significantly more crying than Groups IV (p<0.001) *f.* Significantly less movement than Group IV (p<0.001) but significantly more movement than Groups I & III (p<0.001) *g.* Significantly less movement than Groups II & IV (p<0.001) but significantly more movement than Group I (p<0.001) *h.* Significantly more movement than Groups I, II & III (p<0.001).

Sleep

Sleep scores ranged from 1 (fully awake or alert) to 3 (asleep). All the patients in the Group IV (placebo group) remained alert throughout the procedure. Statistical differences (p<0.001) were noted as compared to the Groups I, II and III. All patients in the Group III (IV. midazolam) were either drowsy or asleep throughout the procedure and differences were statistically significant as compared to the Groups I, II and IV. There were no differences between Group I (oral midazolam) and Group II (Oral diazepam). All the patients in Groups I and II were drowsy or disoriented.

Crying

Crying scores ranged from 1 (hysterical crying that demands attention) to 4 (no crying). All patients in the Group IV cried continuously or intermittently throughout the procedure and the differences were highly significant (p<0.001) than the Groups I, II and III which showed less crying than the Group IV. Group III patients (IV. midazolam) were significantly better than Groups II and IV (p<0.001) Group I (p<0.01) and exhibited either no crying or intermittent mild crying that does not interfere with treatment. Group I (oral midazolam) patients were significantly better (p<0.001) than the Group II.

Movement

Movement scores ranged from 1 (violent movement interrupting the treatment) to 4 (no movement). Significant differences were found for movement between all the groups. Group IV patients showed significant movement interrupting the treatment and was found to be significantly more than the other 3 groups. Although Group II patients (oral diazepam) showed significantly less movement than Group IV (placebo) patients, it was significantly more than the group I (oral midazolam) and Group III (IV.midazolam).

Movement in the Group III patients was significantly less than the Groups II and IV. However, it was significantly more than the Group I. Patients in the Group I (oral midazolam) exhibited the least movement when compared to other groups.

Post-Administrative Behavior at the Administration of Local Anesthetic Agent or Use of Handpiece

Mean values for sleep, crying and movement at the administration of Local Anesthetic agent or use of handpiece for each group were compared to evaluate the effect of most fear producing stimulus on the behavior of the child and are presented in the Table 2.

Table 2. Mean values (±SD) of behavioral assessment scores measured post-administration at local anesthetic agent or use of handpiece.

	Group I	Group II	Group III	Group IV
Sleep	1.9±0.316	1.9±0.316	2.1±0.316	1.0[a]±0.000
Crying	3.1[b]±0.316	2.9[c]±0.316	3.6[d]±0.516	2.1[e]±0.316
Movement	2.9[f]±0.316	2.9[f]±0.316	3.59±0.527	2.0[a]±0.00

a. Significantly less sleep than Groups I, II & III (p<0.001) *b.* Significantly less crying than Groups IV (p<0.001) but significantly more crying than Group III (p<0.05) *c.* Significantly less crying than Group IV (p<0.001) but significantly more crying than Groups III (p<0.01) *d.* Significantly less crying than Groups I (p<0.001) Group II (p<0.01) and Group IV (p<0.05) *e.* Significantly more crying than Groups I, II & III (p<0.001) *f.* Significantly less movement than Group IV (p<0.001) but significantly more movement than Groups III (p<0.001) *g.* Significantly less movement than Groups IV (p<0.001) but significantly more movement than Group III (p<0.001)

Sleep

Sleep scores ranged from 1 (fully awake/alert) to 2 (disoriented/drowsy). All the patients in Group IV were alert during the administration of Local Anesthetic agent or use of handpiece and the difference between the other groups were statistically significant (p < 0.001). There was no difference between the Groups I, II and III patients. The average score for Groups I, II and III was around 2, i.e., disoriented or drowsy.

Crying

Crying scores ranged from 2 (continuous crying) to 4 (no crying). Group IV patients exhibited continuous crying making the procedure difficult during the administration of Local Anesthetic agent or use of handpiece and difference was statistically significant when compared to other groups. Most of the patients in Group III (IV. midazolam) exhibited no crying during Local Anesthetic agent administration/ handpiece use and the score was significantly different than the other groups.

No differences were found between the Groups I and II and average scores for both the Groups were 3.1 and 2.9 (intermittent or mild crying that does not interfere with treatment.

Movement

Movement scores ranged from 2 (continuous movement) to 4 (no movement). Most of the patients in the Group IV showed continuous movement during the administration of Local Anesthetic agent/use of handpiece and was significantly more than all other groups ($p<0.001$).

Most of the patients in Group III showed either controllable movement or no movement. Movement in Group III patients was significantly ($p<0.01$) less than Groups I and II.

No statistical difference was found between the Groups I and II and the average score was 2.9 (controllable movement not interfering with treatment) for both the groups.

Overall Behavior

Table 3 presents the number of patients in each group for each score of the overall behavior rating. In nine out of ten patients in Group IV, treatment was interrupted often but was completed eventually. In six patients out of ten in Group II (oral diazepam), the behavior rated was good (difficult but treatment was performed). Nine out of ten patients in Group I (oral midazolam) exhibited very good overall behavior with limited crying or movement. Eight patients out of ten in the Group III (IV. midazolam) exhibited excellent behavior (no crying or movement).

Table 4 present mean values for overall behavior scores for each group. Overall behavior for Group III patients was significantly better than the other 3 groups ($p<0.001$). Overall behavior for the Group IV was significantly worse than the other 3 groups ($p<0.001$). Overall behavior of Group I (oral midazolam) patients were significantly better than the Group II (oral diazepam) patients.

Table 3. Total number of patients in each group scored for overall behavior

Behavior Rating	Group I	Group II	Group III	Group IV
1 (Aborted)	0	0	0	0
2 (Poor)	0	0	0	0
3 (Fair)	0	0	0	9
4 (Good)	1	6	0	1
5 (Very-Good)	9	4	2	0
6 (Excellent)	0	0	8	0

Table 4. Mean values for overall behavior

	Group I	Group II	Group III	Group IV
Overall behavior rating	4.9[a]	4.4	5.8[b]	3.1[c]

a. Significantly better than Groups II &IV ($p<0.001$) *b.* Significantly better than Groups I, II & IV ($P<0.001$) *c.* Significantly worst than Groups I, II & III ($P<0.001$)

Behavioral Changes and Acceptability of the Sedative Procedure

The impact of the dental visit on the subsequent emotional behavior of the patients was of primary concern. The number of behavioral changes (positive changes, negative changes or no changes) as reported by the parents of our patients in each experimental group are presented in the Table 5.

Table 5. Behavioral changes after sedative procedure

	Group I	Group II	Group III	Group IV
Number of positive changes	31	25[a]	38	1[b]
Number of negative changes	8	5	7	27[c]

a. Significantly lower than Group III ($p<0.05$) *b.* Significantly lower than Groups I, II & III ($p<0.0027$) *c.* Significantly higher than Groups I, II & III ($p<0.0027$)

Positive Behavior

Of the children receiving oral sedation, midazolam group (Group I) and diazepam group (Group II) patients had no significant differences in positive behavior. When two midazolam groups were compared (Oral and IV midazolam) patients did not show significant difference in positive behavior. Placebo group patients had the least positive behavior, which was highly significant ($p < 0.0027$) when compared to the other three groups. Positive behavior of patients in Group III (IV midazolam) was significantly ($p < 0.05$) more than Group II (oral diazepam).

Negative Behavior

Children in both oral sedative agent groups (Oral midazolam and oral diazepam) showed no significant differences in the negative behavior; the same was true when the two midazolam (Group I and III) were compared. Placebo group patients (Group IV) showed the highest negative behavior which was highly significant (0.0027) when compared to other three groups.

DISCUSSION

Among benzodiazepines diazepam has been used for many years successfully. Midazolam has gained recent popularity as it is reported by many researchers to be better in producing anxiolysis as well as amnesia.[8,9] In our study we included both diazepam and midazolam in order to compare their ability to produce anxiolysis. There are conflicting reports investigating effects of different route of administration of midazolam on both anxiolysis and amnesia[10] and therefore the Group III (IV. midazolam) was included in the design of our study. Placebo group (Group IV) was included as a control group.

Although 0.5 mg/kg dose of oral diazepam has been

recommended by many researchers[11,12,13] and produces the same level of sedation for younger as well as older children. A dose range of 0.05 mg/kg to 0.1 mg/kg is recommended for intravenous use of midazolam and 0.06 mg/kg is reported to be safer.[14]

Behavior Assessment

Behavior rating scale developed by Houpt *et al*[6] has been used by many researchers to assess the child's behavior throughout the dental treatment. It is the most easy, practical and reliable scale used so far.

In none of our patients the treatment had to be aborted. In the placebo group overall behavior was significantly worse than the other sedation groups (Groups I, II and III) and mean score was 3.1 (treatment interrupted often but was eventually completed). In our study all the sedative groups (Group I, II and III) showed less crying, movement and more sleep and better overall behavior than the control group (Group IV), when the post-administration (average) as well as scores at administration of local anesthetic agent or use of headpiece were compared across the groups. This was an obvious finding.

In a study evaluating effectiveness of diazepam (0.5 mg/kg) and midazolam (0.5 mg/kg) as pre anesthetic agents, found that midazolam group exhibited significantly better behavior than diazepam group.[15,16]

In our study two midazolam groups (Group I and III) were significantly better than the diazepam group (Group II) in overall behavior, crying and movement.[17] There was no significant difference in sleep between the diazepam group and the two midazolam groups. The mean scores of overall behavior in diazepam group were 4.4 (difficult, but treatment completed). In this group, 6 patients out of 10 showed good behavior where as 4 patients out of 10 showed very good behavior. The percentage of patients showing very good and excellent behavior was more in the two midazolam groups than the diazepam group. Similar conclusions were drawn by Roelofse and Van der Bijl[18] and kantovitz *et al.*[19] However, our finding is contrary to the findings of Vetter[20] who observed that there was no difference between the behaviors of children in oral diazepam and oral midazolam groups, when these agents were used as pre-anesthetic medications.

When the IV. midazolam group (Group III) was compared with the oral midazolam group (Group I), overall behavior was found to be significantly better in Group III than in Group I.[21] Eight out of ten patients with IV midazolam group showed excellent behavior whereas none of the patients in Group I showed excellent behavior. Nine out of ten patients in Group I showed 'Very Good' behavior and one showed 'Good' behavior.

Group III patients exhibited significantly more sleep and less crying than group I patients. Movement scores were conflicting Intravenous midazolam group was found to show significantly more movement than Group I when post-administration averages were compared. This may be explained by slight uncomfortable feeling due to presence of scalpvan in IV. midazolam group patients. However, more movement in this group did not cause any hindrance in the dental treatment. It can be noted that Group III patients showed significantly less movement than the Group I patients at the most fear-producing stimulus that is administration of local anesthetic or use of headpiece.

Behavioral Changes and Acceptability

Better experience in the dental office with no painful memories may culminate into better behavior of children at home post-sedetively. Poor dental visit with painful memories may cause psychological trauma to the child and may affect child's behavior at home.

A questionnaire was designed carefully to evaluate child's behavior at home post sedatively. Higher number of positive changes in any group would mean that children in that group had better dental experience and the acceptability of the dental treatment was better.

Group IV (placebo) patients showed least positive changes and more negative changes. Although in these patients the treatment was completed with interruptions, children definitely did not accept the procedure.

Number of negative changes in all the sedative groups was significantly less than the control group. However, Group III (i.v. midazolam) patients showed higher percentage of positive changes in spite of use of venipuncture, which is similar to finding of Sievers *et al.*[22] Our finding is concurrent with Mc Cluskey *et al*[23] and Uldam[24] who reported better acceptability in intravenous midazolam as compared to the placebo group. We did not find any significant difference in number of positive or negative changes in both the midazolam groups.[25] Acceptability of the procedure in the Group II was found to be better than the placebo group.

CONCLUSIONS

1. Sedative effects of oral midazolam and oral diazepam were comparable. Intravenous midazolam produced more sedation.
2. Anxiolysis was found to be more in both the midazolam groups than the diazepam group when the indicator behavioral parameters viz. crying, movement and overall behavior were compared across the groups.
3. Anxiolysis in intravenous midazolam group was found to be better than the oral midazolam group in spite of the invasive route of administration.
4. Patients in all the three sedative groups exhibited least number of negative post-sedative behavioral changes, so it can be concluded that all the sedative techniques were acceptable to the patients.
5. Most number of positive changes were observed in intravenous midazolam group. We conclude that patient's acceptance was higher for intravenous midazolam group despite the invasive route of administration.

REFERENCES

1. Lawrence SM, McTigue DJ, Wilson S, Odom JG, Waggoner WF, Fields HW Jr. Parental attitudes towards behavior management techniques used in pediatric dentistry. Pediatr Dent, 13: 151–155, 1991.
2. Murphy MG, Fields HW Jr., Machen JB. Parental acceptance of pediatric dentistry behavior management techniques. Pediatr Dent, 6: 193–198, 1984.
3. Kain ZN, Mayes CC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: Predictors and outcomes. Arch Pediatr Adolesc Med, 150: 1238–1245, 1996.
4. Kotiniemi LH, Ryhanen PT, Moilanen IK. Behavioral changes in children following day-case surgery: A four week follow-up of 551 children. Anaesthesia, 52: 970–976, 1997.
5. American academy of pediatric dentistry. "Guidelines for the elective use of conscious sedation, Deep sedation, General anesthesia in pediatric patients." Pediatr Dent, 21(5): 68–73, 1999.
6. Houpt MI, Sheskin RB, Koenigsberg. "Assessing chloral hydrate dosage for young children". ASDC J Dent Child, 52(3): 364–369, 1985.
7. Camm JH *et al*. "Behavioral changes of children undergoing dental treatment using sedation verses general anesthesia". Pediatr Dent, 9(2): 111–117, 1987.
8. Barclay JK, Hunter KM, McMillan W. "Midazolam and diazepam compared as sedatives for outpatient surgery under local analgesia". Oral Surg Oral Med Oral Pathol, 59: 349–355, 1985.
9. Tolia V, Fleming SL, Kauffman RE. "Randomized, double blind trial of midazolam and diazepam for endoscopic sedation in children." Dev Pharmacol Ther, 14: 141–47, 1990.
10. Saxen MA, Wilson S, Paravecchio R. "Anesthesia for pediatric dentistry." In: Anesthesia in dentistry, Saxen MA (Ed.). Dent Clin N Am, 43(2): 231–245, 1999.
11. Fell D, Gough MB, Northan AA *et al*. "Diazepam premedication in children: plasma levels and clinical effects." Anesth, 40: 12–17, 1985.
12. Brandt SK, Bugg JL Jr. "Problems of medication with the pediatric patient". In: symposium on pharmacology and therapeutics. Dent Clin N Am, 28(3): 563–579, 1984.
13. Houpt MI, Kupietzky A, Tofsky NS. "Effects of nitrous oxide on diazepam sedation of young children." Pediatr Dent, 18(3): 236–241, 1996.
14. Kupietzky A, Houpt MI. "Midazolam; a review of its use of conscious sedation for children." Pediatr Dent 15(4): 237–241, 1993.
15. Parnis SJ, Foate JA, Vander Walt JH. "Oral midazolam is an effective premedication for children having day-stay anesthesia". Anaesth Intensive Care, 20(1): 9–14, 1992.
16. Mc Cann ME, Kain ZN. The management of preoperative anxiety in children: An Update. Anesth & Anal, 93(1): 98–105, 2001.
17. AL-Zaharine AM, Wyne AH, Sheta SA. Comparison of midazolam with a combination of oral midazolam and nitrous oxide-oxygen inhalation in the effectiveness of dental sedation for young children. J Indian Soc Pedod Prev Dent, 27(1): 9–16, 2009.
18. Roelofse JA, Biji PV. "Cardiac dysrhythmias associated with intravenous lorazepam, Diazepam, and midazolam during oral surgery." J Oral Maxillofac Surg, 52: 247–250, 1994.
19. Kantovitz KR, Puppin-Rontani RN, Dgaviao MB. Sedative effect of oral diazepam and chloral hydrate in the dental treatment of children. Indian Soc Pedod Prev Dent, 25(2): 69–75, 2007.
20. Vetter TR. "A comparison of midazolam, diazepam and placebo as oral anesthetic premedicants in younger children". J Clin Anesth, 5(1): 58–61, 1993.
21. Knott JC, Taylor D, Castle DJ. Randomized clinical trial comparing intravenous midazolam and droperidol for sedation of the acutely agitated patient in the emergency department. Annals of Emergency Medicine, 47(1): 61–67, 2006.
22. Sievers TD, Yee JD, Foley ME, Blanding PJ, Berde CB. "Midazolam for conscious sedation during pediatric oncology procedures; safety and recovery parameters". Pediatrics, 88(6): 1172–1179, 1991.
23. Mc Cluskey A, Meakin GH. Oral administration of midazolam as a premedicant for pediatric day-case anaesthesia. Anaesthesia, 49(9): 782–785, 1994.
24. Uldam B, Hottonsten A-L, Poulsen S. Midazolam conscious sedation in large Danish municipal dental service for children and adolescents. International Journal of Pediatric Dentistry, 18(4): 256–261, 2008.
25. Damle SG, Gandhi M, Laheri V. Comparison of oral ketamine and oral midazolam as sedative agents in pediatric dentistry. J Indian Soc Pedod Prev Dent, 26, 97–101, 2008.