**Original Article**

# Sedative Effect of Oral Midazolam/Hydroxyzine versus Chloral Hydrate/Hydroxyzine on 2-6 Year-Old Uncooperative Dental Patients: A Randomized Clinical Trial

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**Abstract**

**Objective:** Different drugs are used for conscious sedation in pediatric dentistry either single or in combination. This study assessed the comparative effect of midazolam/hydroxyzine and chloral hydrate/hydroxyzine on 2-6 year-old uncooperative children needing dental treatment.

**Materials and Methods:** A double blind cross-over randomized clinical trial was designed and 16 children aged 2-6 years with ASA1 status who were judged with negative to definitely negative behavior (according to Frankl) were chosen. Cases were divided randomly into two groups. The first group received midazolam/hydroxyzine (MH) at the first visit while the second group received chloral hydrate/hydroxyzine (CHH) as the first medication. Both groups received the other regimen at the second visit. Midazolam 0.5mg/kg and chloral hydrate 50mg/kg with 1mg/kg hydroxyzine were administered. Cases were subsequently assessed for sedation and then dental treatment was performed. Blood oxygen saturation (SpO2) and pulse rate (PR) were measured before and after drug administration, as well as during and after dental treatment. The Houpt scale was also used for the level of sedation before, during and after treatment. Data were analyzed using Wilcoxon signed rank test and the paired t-test.

**Results:** Sedative success rate was 64.3% in cases of MH and 33.3% in CHH. The difference between groups was significant (P=0.046). The success rate was significantly different between groups at different measurement stages as well (P<0.05). No difference was found on the child's behavior scale based on the type of drugs used first; this indicates no carry-over effect. Comparing the PR and SpO2 values at different readings showed no significant differences.

**Conclusion:** Midazolam/hydroxyzine showed a significantly higher sedative effect than chloral hydrate/hydroxyzine in this study.

**Keywords:** Conscious sedation; Uncooperative child; Dental treatment; Midazolam, Chloral Hydrate; Hydroxyzine

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## INTRODUCTION

Few medications are used to induce conscious sedation in daily dental practice. These medications are used either alone or in combination in order to boost the sedative effect in difficult cases. Varying methods are employed for se-

dation with the oral route being at the top of the list for its ease of use and high patient acceptance [1]. Nasal, rectal, IV and IM routes are also other possibilities in certain cases with their own advantages and limitations [2]. Among the common drugs used for sedation, midazolam, chloral hydrate and hydroxyzine are used more routinely in single or combined modes [3-10]. Midazolam is the most commonly used agent for IV sedation prior to dental treatment [2]. This drug is also administered through nasal, mucosal and muscular routes; however, its oral administration is yet believed as the longest acting, easiest and most cost-effective route [11]. This benzodiazepine derivate is very fast acting while no serious side effect has been reported [12]. When compared to diazepam, midazolam appears to tackle anxiety much better in such a way that the patient is relaxed during work without any memory of what has happened [13]. Midazolam is a strong benzodiazepine with high sedative and drowsiness effect for which is used routinely as a safe and effective premedication for medical and dental procedures [14-16]. Other effects of midazolam include anticonvulsant, muscle relaxant and amnesic [17]. As it is easily absorbed it reaches its plasma levels in 1.25 hours with a half- life of 2½ hours [14]. On the other hand, chloral hydrate is anxiolytic, sedative and easily absorbed [8, 10]. Its wide use as a safe and effective premedication for dental procedures has long been accepted by clinicians [18-20]. Hydroxyzine is one of the antihistaminic drugs used for its sedative effect alone prior to a dental procedure [6, 7, 21, 22]. Hydroxyzine also has antiemetic capacity while being effective for sedation in certain cases with no complication being reported over its use. Its sedative effect appears quite late but lasts long enough for lengthy dental work. When it is administered along with midazolam, it works as a supplement and a booster to enhance the sedative effect of midazolam.

It is suggested that administration of combinations of sedative drugs should be limited to certain hospital centers which are fully equipped and covered with on-call anesthetists [22]. There are different techniques for oral premedication. Previous studies have shown the efficacy of oral midazolam and chloral hydrate as anxiolytic and hypnotic drugs; which are effective on child cooperation in dental settings [14-16,18-20]. Drug combinations have been recommended by practitioners to obtain maximum sedation effects while undesirable reactions are controlled [12,13]. The aim of this investigation was to compare the sedative effect of oral combinations of chloral hydrate/ hydroxyzine (CHH) versus midazolam/hydroxyzine (MH) in 2-6 year-old uncooperative dental patients.

## MATERIALS AND METHODS

This study was a double blind cross-over randomized clinical trial(IRCT138903071882N2) with 16 children aged 2-6 yrs. being selected from healthy referral cases with dental anxiety (Frankl I and II). Each case was scheduled for two visits with similar teeth needing the same treatment. All cases were in ASA I category with no history of any systemic disease. An ethical approval from the Ethics Committee of Shahid Beheshti Medical University Tehran, Iran and written informed consent signed by parents were obtained. Patients were asked to remain NPO for 4 hours preoperatively for each session. This was one of the main criteria to allow the administration of drugs. Two groups of medications used were as follows:

Regimen MH: Patients received oral combination of 0.5mg/kg midazolam (the injectable form was used with a fruit juice) and 1mg/kg hydroxyzine. Regimen CHH: Patients received oral combination of 50mg/kg chloral hydrate with a favorite juice and 1mg/kg hydroxyzine.

Each case received both regimens in different visits with half of the cases receiving regimen

MH fist while the other half received regimen CHH first. After a time period of 20-30 minutes for regimen MH and 30-45 minutes for regimen CHH, when judged sedated, the dental procedure was started while vital signs were being monitored.

Cases were monitored every 15 minutes throughout the treatment and post treatment phases. Pulse rate (PR) and blood oxygen saturation (SpO2) were the main two parameters recorded.

Houpt behavioral and sedation scales were used to score each case at each visit. Cases were discharged following an hour of control and monitoring postoperatively in order to reassure return of all normal activity. Only 5 and 6 Houpt's scores (Box 1) of overall behavior were deemed successful. Statistical analysis was performed using Wilcoxon signed rank test for Houpt scales as well as paired t-test for PR and SpO2 at 0.05 significance level.

## RESULTS

Sixteen uncooperative children aged 2-6 years (7 boys, 9 girls) were included in this study. The mean patient's age was 2.5 years (30±6 months) and their weight ranged between 10-19 kg. Results using Wilcoxon test indicated that regimen MH was more successful (62.5%) when compared to regimen CHH (31.3%) in almost all recorded time points. The highest behavioral success rate belonged to MH and 5 and 6 indices (Table1).

Most of the failed cases were from CHH in index 3 at 15 and 30 minutes (Table 2). Wilcoxon signed rank test revealed a highly significant difference in success rate of sedative effect being seen for MH at 15 and 30 minutes evaluation times (P=0.016 and 0.013, respectively). Comparing paired groups of experiment for their SpO2 and PR values revealed no significant difference between readings (Table 3).

**Table 1.** Frequency and percentage of overall behavior using midazolam/hydroxyzine at 0, 15 and 30 minutes during treatment

| Scores of Houpt | 0 min N (%) | 15 min N(%) | 30 min N(%) |
|---|---|---|---|
| **3** | 1(6.3) | 2(12.5) | 4(25) |
| **4** | 0(00) | 4(25) | 2(12.5) |
| **5** | 6(37.5) | 5(31.3) | 4(25) |
| **6** | 9(56.3) | 5(31.3) | 6(37.5) |
| **Total** | 16(100) | 16(100) | 16(100) |

Score 1= Aborted 2=Poor 3=Fair 4=Good 5=Very Good 6=Excellent

**Table 2.** Frequency and percentage of overall behavior using chloral hydrate/ hydroxyzine at 0, 15 and 30 minutes during treatment

| Scores of Houpt | 0 min N(%) | 15 min N(%) | 30 min N(%) |
|---|---|---|---|
| **2** | 2(12.5) | 3(18.80) | 3(18.8) |
| **3** | 4(25) | 6(37.50) | 5(31.30) |
| **4** | 0(00) | 2(12.50) | 3(18.80) |
| **5** | 1(6.30) | 2(12.50) | 1(6.30) |
| **6** | 9(56.30) | 3(18.80) | 4( 25) |
| **Total** | 16(100) | 16(100) | 16(100) |

Score 1= Aborted 2=Poor 3=Fair 4=Good 5=Very Good 6=Excellent

Paired t-test showed no difference in SpO2 and PR values at baseline for the regimens. The effect of starting change on the second visit was found to be insignificant indicating no carry-over effect on the changes.

## DISCUSSION

Behavior management techniques such as voice control, intimidation or restraints have been substituted by more effective and acceptable procedures such as conscious sedation or general anesthesia for dental treatment of uncooperative children.Combination of midazolam and hydroxyzine was administered in group MH of this study to produce deep and extended sedation. Midazolam is a short-acting but fast and effective benzodiazepine and its sedative and anxiolytic effects begin 20 minutes after oral use. Hydroxyzine is a long acting, antihistaminic and anti-vomiting agent. Combination of these two drugs when administered orally, not only help to extend sedation time but also prevent nausea and vomiting during treatment [13].

Another advantage of this combination for premedication is that the operator has enough time to accomplish all the necessary procedures [12-14, 16]. Presence of nausea due to oral administration of chloral hydrate has been reported by several studies [12, 13].

The combination of chloral hydrate and hydroxyzine administered orally in group CHH takes advantage of sedative effect while nausea or vomiting has already been controlled. The result of our study indicated that both regimens were effective in controlling negative behavior of children in both groups during the course of treatment; however significantly more sedation was produced in children premedicated with MH. Flumazenil is an antidote of midazolam; which is very important and is one of the advantages of this drug over the CH for controlling the adverse reaction. Although several patients showed some drowsiness at the end of treatment but evaluation of patients' behavior and their response to the treatment was good overall for both regimens. In the present study, 56.3% and 62.5% of children in group MH showed high degree of cooperation at intervals of 15 and 30 minutes from the start of the treatment, respectively. The success rate was low compared to Lima's study (77%) but children of his study were sedated only with midazolam [24]. The advantage of hydroxyzine used in combination with midazolam or chloral hydrate in the present study was that none of the children had nausea at any time during the treatment. This indicates that the selected drug doses and their combination were well effective and tolerable by children.

**Table 3.** Comparison of Spo2 and PR between midazolam/hydroxyzine and chloral hydrate/hydroxyzine at baseline(B) and 0, 15 and 30 minutes during treatment

| Midazolam | | N | Mean | Chloral Hydrate | | N | Mean | P value |
|---|---|---|---|---|---|---|---|---|
| **SpO2** | **B** | 16 | 97.53±1.12 | **SpO2** | **B** | 16 | 98.06±1.34 | **0.155** |
| | **0** | 16 | 99.59±4.43 | | **0** | 16 | 97.12±1.31 | **0.057** |
| | **15** | 16 | 100.47±7.05 | | **15** | 15 | 97.00±1.51 | **0.094** |
| | **30** | 15 | 101.33±9.85 | | **30** | 15 | 96.47±2.72 | **0.069** |
| **Pulse** | **B** | 16 | 118.18±20.16 | **Pulse** | **B** | 16 | 112.69±21.37 | **0.052** |
| | **0** | 16 | 115.06±22.13 | | **0** | 16 | 108.06±16.63 | **0.219** |
| | **15** | 16 | 126.76±20.76 | | **15** | 15 | 124.53±22.74 | **0.584** |
| | **30** | 15 | 127.33±22.63 | | **30** | 15 | 130.87±26.40 | **0.531** |

Shapira's study [25] indicated 75% success rate when children were premedicated with midazolam in combination with 3.7 mg/kg hydroxyzine. Increase in success rate of cooperation in his study could be essentially due to not only higher dose of hydroxyzine (3.7 mg/kg) compared to our study (1mg/kg) but also using nitrous oxide oxygen simultaneously for both groups. Avalos-Arenas [26] in his study indicated that negative behavior of children premedicated with combination of chloral hydrate and hydroxyzine was better controlled compared to the children sedated by chloral hydrate alone but the difference was not significant. HR, SpO2 and two other vital signs (blood pressure and respiratory rate) were higher than normal measurements in both groups although it was not significant. He also indicated that crying and movement scores were higher in the group premedicated with drug combination than single drug group.

The result of our study was in line with Avalos–Arenas study in the group sedated with combination of chloral hydrate and hydroxyzine except for the difference in the doses of chloral hydrate and hydroxyzine. In the present study 50mg/kg chloral hydrate was combined with 1mg/kg hydroxyzine; which was less than the dose Avalos-Arenas used (70mg/kg and 2mg/kg, respectively). Drug selection, dose and combination are three important factors to be considered for favorable results when conscious sedation is underway in order to control anxiety and negative behavior during dental procedures.

Sedative effects of chloral hydrate 40mg/kg and diazepam 5mg/kg for controlling negative behavior of children during dental treatment were studied by Kantovits [27]. He indicated that both drug doses and their combination were not sufficient to control children's negative behavior [13].

**Box 1. Houpt's Scores**

| Behavior | Score |
|---|---|
| **Rating for sleep** | |
| Fully awake, alert | 1 |
| Drowsy, disorientated | 2 |
| Asleep | 3 |
| **Rating for movement** | |
| Violent movement interrupting treatment | 1 |
| Continuous movement making treatment difficult | 2 |
| Controllable movement that does not interfere with treatment | 3 |
| No movement | 4 |
| **Rating for crying** | |
| Hysterical crying that demands attention | 1 |
| Continuous, persistent crying that makes treatment difficult | 2 |
| Intermittent, mild crying that does not interfere with treatment | 3 |
| No crying | 4 |
| **Rating for overall behavior** | |
| Aborted—no treatment rendered | 1 |
| Poor—treatment interrupted, only partial treatment completed | 2 |
| Fair—treatment interrupted, but eventually all completed | 3 |
| Good—difficult, but all treatments performed | 4 |
| Very good—some limited crying or anesthesia or mouth prop insertion | 5 |
| Excellent—no crying or movement | 6 |

Although general condition of both groups in the present study was good, children of group MH had better behavior during treatment and faster recovery. This result is relatively different compared to Sheron et al, [28] study which indicated that children premedicated with oral combination of chloral hydrate with meperidine and hydroxyzine did not show different effects on behavior compared to those sedated with midazolam, meperidine and hydroxyzine. This difference could be due to differences in type of behavior classification Sheron used in his study (North Carolina Behavior Rating Scale) and the Houpt Scale used in our study. Sleepiness and drowsiness were present at the beginning and during the treatment in both groups; whereas, crying and body movement were less at the beginning of treatment and increased to some degree toward the end of the treatment in the midazolam group. This indicates that midazolam which is a short acting benzodiazepine is a good choice for shorter dental procedures when it is combined with hydroxyzine; while, for longer dental procedures chloral hydrate and hydroxyzine combination will be more effective.

## CONCLUSION

Midazolam/hydroxyzine showed a significantly higher sedative effect than chloral hydrate/hydroxyzine in children of this study

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## REFERENCES

1- Motharu LM, Ashley PF. Sedation of anxious children undergoing dental treatment (Review). Cochrane Library 2008,Issue 4:42-43.

2- Girdler NM, Hill CM, Wilson KE. Clinical Sedation in Dentistry.1st ed. Singapore, Wiley-Blackwell.2009:71-72.

3- Mosby's Drug Consult. Midazolam Hydrochloride.11th ed. St. Louis. Mosby; 2001.

4- Collins VJ. Benzodiazepines. In: Collins VJ. Physiologic and pharmacologic bases of anesthesia .1st ed. Philadelphia, Sunders, 1999:531-5.

5-Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 1990 Nov;73(5):831-4.

6- Gladney M, Stanley RT, Hendricks SE. Anxiolytic activity of chloral hydrate and hydroxyzine.. Pediatr Dent. 1994 May-Jun;16(3):183-9.

7- Ram D, Mamber E, Chosack A, Fuks AB. The effect of Metoclopramide and hydroxyzine in sedation undergoing dental treatment. ASDC J Dent Child 1999 Jan-Feb;66(1):49-52, 13.

8- Moore PA.. Pain control in dentistry: pediatric pharmacosedation. Compendium. 1987 Jan;8(1):28, 30-6, 38-9.

9- Hobbs WR, Rall TW, Verdoom TA. Hypnotics and Sedatives: ethmol. In: Hardman JG, Limbird LE. Molinoff PB, Ruddon RW, eds. Goodman and Gilmman's the pharmacological basis of therapeutics, 9th ed. New York. McGrow-Hill. Health professions Division;1996:381-2.

10- Guidelines for the elective use of pharmacologic conscious sedation and deep sedation in pediatric dental patients. Pediatr Dent 1996;18(special issue):30-4

11-Malamed SF. Sedation: A guide to patient management.5th ed. St. Louis. C.V. Mosby 2010;ch7:95-118.

12- Pinkham JR, Casamassimo PS, McTigue DJ, Fields HW, Nowak AJ. Pediatric Dentistry, Infancy through Adolescence.4th ed.China.Elsevier.2005:94.

13- McDonald RE, Avery DR, Dean JA. Dentistry for the Child and Adolescent. 4th ed.USA.Mosby.2004:303-4.
14- Kupietzky A, Houpt MI. Midazolam: a review of its use for conscious sedation of children. Pediatr Dent.1993 Jul-Agu;15(4):237-241.
15- Hartgraves PM, Primosch RE. An evaluation of oral and nasal midazolam for pediatric dental sedation. J Dent Child.1994 May-Jun;61(3):175-181.
16- Primosch RE, Bender F. Factors associated with administration route when using midazolam for pediatric conscious sedation. J Dent Child.2001 Jul-Aug;68(4):233-8.
17- Kupietzky A, Holan G, Shapiro J. Intranasal midazolam better at effecting amnesia after sedation than oral hydroxyzine: A pilot study. Pediatr Dent.1996 Jan-Feb;18(1):32-4.
18- Moore PA. Therapeutic assessment of chloral hydrate premedication for pediatric dentistry. Anesth Prog.1984 Sep-Oct;31(5):191-6.
19- Nathan JE. Management of the refractory young child with chloral hydrate: dosage selection. ASDC J Dent Child. 1987 Jan-Feb;54(1):22-9.
20- Hasty MF, Vann WF, Dilly DC, Anderson JA. Conscious sedation of pediatric dental patients: An investigation of Chloral Hydrate, hydroxyzine pamoate and Meperidine vs. chloral hydrate and hydroxyzine Pamoate. Pediatr Dent.1991;13:10-19.
21- Shapira J, Holan G, Botzer A, Kupietzky A, Tal E, Fuks AB. The effectiveness of midazolam and hydroxyzine as sedative agents for young pediatric dental patients. J Dent.1996;13:421-5.
22- American Academy of Pediatrics; American Academy on Pediatric Dentistry. Guideline for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatr Dent 2008-2009;30(7suppl):143-59.
23- Houpt MI, Wiess NJ, Koenigsberg SR, Desjardins PJ. Comparison of chloral hydrate with and without promethazine in sedation of young children. Pediatr Dent 1985;7:41-6.
24- Lima AR, da Costa LR, da Costa PS. A randomized, controlled, crossover trial of oral midazolam and hydroxyzine for pediatric dental sedation. Pesquissa Odontologica Brasileira 2003 Jul-Sept;17(3):206-11.
25- Shapira J, Kupietzky A, Kadari A. Fuks A B, Holan G. Comparison of oral midazolam with and without hydroxyzine in the sedation of pediatric dental patients. Pediatr Dent 2004;26(6):492-6.
26- Avalos-Arenas V, Moyao-Garcia D, Nava-Ocampo AA, Zayas-Carranza RE, Fragoso-Rios R. Is chloral hydrate/hydroxyzine a good option for pediatric dental outpatient sedation? Curr Med Res Opin.1998;14(4):219-26.
27- Kantovits KR, Puppin-Rontani RM, Gaviao MBD. Sedative effect of oral diazepam and chloral hydrate in the dental treatment of children. J Indian Soc Pedod Prev Dent. 2007 Apr-Jun;25(2):69-75.
28- Sheroan MM, Dilley DC, Lucas WJ, Vann WF. A prospective study of 2 sedation regimens in children: chloral hydrate, meperidine and hydroxyzine versus midazolam, meperidine and hydroxyzine. Anesth Prog 2006 Fall,53(3):83-90.