Original Article

Conscious Sedation Efficacy of 0.3 and 0.5 mg/kg Oral Midazolam for Three to Six Year-Old Uncooperative Children Undergoing Dental Treatment: A Clinical Trial

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Abstract

Objectives: Midazolam with variable dosages has been used to induce sedation in pediatric dentistry. The aim of this study was to compare the efficacy of two dosages of oral midazolam for conscious sedation of children undergoing dental treatment.

Materials and Methods: In this randomized crossover double blind clinical trial, 20 healthy children (ASA I) aged three to six years with definitely negative Frankl behavioral rating scale were evaluated. Half of the children received 0.5mg/kg oral midazolam plus 1mg/kg hydroxyzine (A) orally in the first session and 0.3mg/kg oral midazolam plus 1mg/kg hydroxyzine (B) in the next session. The other half received the drugs on a reverse order. Sedation degree by Houpt sedation rating scale, heart rate and level of SpO2 were assessed at the beginning and after 15 and 30 minutes. The data were analyzed using SPSS 19 and Wilcoxon Signed Rank and McNemar's tests.

Results: The results showed that although administration of 0.5mg/kg oral midazolam was slightly superior to 0.3mg/kg oral midazolam in terms of sedation efficacy, the differences were not significant (P>0.05). The difference in treatment success was not significant either (P>0.05). Heart rate, oxygen saturation (SpO2) and respiratory rate were within the normal range and did not show a significant change (P>0.05).

Conclusions: The overall success rate of the two drug combinations namely 0.5mg/kg oral midazolam plus hydroxyzine and 0.3mg/kg oral midazolam plus hydroxyzine was not significantly different for management of pediatric patients.

Keywords: Conscious Sedation; Pediatric Dentistry; Midazolam; Hydroxyzine

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INTRODUCTION

Dental treatment of an anxious child is a major challenge for many clinicians. In many cases, children may avoid necessary dental treatments due to fear or tolerate it with fear and stress [1]. Behavior of children in the age range of one to six years is hard to manage in the dental office. Fear and anxiety mainly originate from the lack of experience and poor coping mechanisms with the new environment [2]. In such cases, a combination of behavioral therapy and pharmaceutical methods is recommended to avoid a substandard and unsafe dental treatment [3]. As sedation leaves a little or no memory of a dental visit, it enables high quality treatment and is an acceptable alternative to general anesthesia [4]. Protective airway reflexes remain active when a child is sedated and this is why many patients and dentists prefer this technique to general anesthesia [5]. In the recent years, the term conscious sedation was modified to mild and moderate sedation to better express the context of the procedure [6]. Among various routes of drug administration, oral sedation is considered as the oldest, easiest and a cost effective way of administration of sedative drug to pediatric patients [7]. Oral sedation has a delayed onset, and the absorption level of the drug is somehow unreliable. Lack of titration capacity and the resultant delay in patient's

discharge are other issues related to oral sedation [8]. Midazolam is among the most commonly used benzodiazepines in children. The oral form of this drug is the best accepted route of administration in children [9]. Midazolam is a well-known sedative capable of inducing sleep while acting as an effective anxiolytic, muscle relaxant, and amnesic agent [10]. Its effect initiates within 20-30 minutes of oral administration and has a half-life of one to four hours. The highest plasma level of this agent is reached after 30 minutes [11]. Flumazenil is a known antagonist of benzodiazepines capable of reversing the sedative effects and reducing amnesia [12]. A single oral dose of 1mg/kg is suggested as an effective dose of midazolam in children with a maximum of 20mg in total [13]. Hydroxyzine also has antiemetic properties while it is effective for sedation in some patients with no reported complication. Its sedative effects appear late but last long enough for conduction of dental procedures. When administered along with midazolam, it serves as a supplement and enhances the sedative effect of midazolam. It is recommended that administration of combinations of sedatives must be limited to certain hospital centers with on-call attending anesthetists [14]. It is believed that combination of the two drugs will enable the clinician to reduce the individual required doses while increasing their combined effect [15]. Various studies have looked at the effects of oral midazolam alone and in association with several other agents with a wide range of results in children [16]. Since the oral form of midazolam is not commercially available in many countries, the injectable midazolam in combination with a flavoring agent (to modify the undesirable taste and adjust the pH) known as extemporaneous form has been used as an alternative [17,18]. Therefore, the aim of this study was to evaluate and compare the safety and efficacy of two oral preparations of midazolam and find the most effective dose (comparing 0.3 and 0.5mg/kg) for use in uncooperative children requiring dental treatment by assessing physiological parameters and Houpt behavioral scale.

MATERIALS AND METHODS

This randomized controlled double blind clinical trial was conducted on 20 young fearful children aged three to six years ranked as Frankl scale 1 [19] (definitely negative) by two pediatric dentists. All patients were in ASA I category. Patients were referred to the Sedation Unit of Pediatric Dentistry Department at SBMU where they received a thorough intraoral examination in order to ensure their two-session dental treatment needs. This was done to ensure the need for the two drug doses to be tested for their sedative efficacy on the same patients. Sample size was calculated based on similar earlier studies [10,20-22] to be 16 with four extra samples to compensate for those lost between sessions. Level of significance was set at $\alpha=0.05$ and $\beta=0.2$. The inclusion criteria comprised of fearful children aged three to six years ranked as Frankl scale 1 and ASA I category (which means a normal healthy subject). Patients were excluded from the study if they had physical or mental disabilities, history of respiratory diseases in the past two weeks, and tonsil/adenoid hypertrophy that occupied more than 50% of the pharyngeal space. Other exclusion criteria were anatomical deformities in the face and neck such as micrognathia and macroglossia and any known allergy to midazolam. Ethical approval from the Ethics Committee of Shahid Beheshti Medical University Tehran, Iran and written informed consent signed by parents were obtained. This clinical trial was registered at www.irct.ir (IRCT201406171882N6). All necessary instructions were given to the parents prior to sedation induction. Children were randomly assigned to two groups in the first session. Half of the patients (group A) received 0.3mg/kg midazolam syrup (Amsed, Oxford, UK) plus 1mg/kg hydroxyzine (Kharazmi Pharma Co.,

Tehran, Iran) in their first visit and 0.5mg/kg midazolam plus 1mg/kg hydroxyzine (Kharazmi Pharma Co, Tehran, Iran) in their second visit. Group B received the same regimen on a reverse order. A six-hour NPO period was instructed to be observed for solid food and four hours for liquids for each sedation session, preoperatively. Dental treatment was started 20-30 minutes after drug administration while local anesthesia was administered by injection of 2% lidocaine with 1:80,000 epinephrine (Daroupakhsh, Tehran, Iran). Both the operator and patients were blinded to the administered doses. Physiological parameters including SpO2, heart rate and respiratory rate were recorded at baseline, at the time of drug administration, at the time of local anesthetic administration, at 15-minute intervals, after completion of treatment and at the time of discharge using a monitoring device (Alborz B9, Saadat Medical Co., Tehran, Iran). The level of sedation was assessed and judged by two independent pediatric dentists using the Houpt scale [23].

Table 1: The Houpt sedation rating scale

Rating scale	Definition	Score
Rating scale for sleep	Fully awake, alert	1
	Drowsy, disoriented	2
	Asleep	3
Rating scale for movement	Violent movement that interrupts treatment	1
	Continuous movement that makes treatment difficult	2
	Controllable movement that does not interfere with treatment	3
	No movement	4
Rating scale for crying	Hysterical crying that interrupts treatment	1
	Continuous, persistent crying that makes treatment difficult	2
	Intermittent, mild crying that does not interfere with treatment	3
	No crying	4
Rating scale for overall behavior	Aborted: No treatment	1
	Poor: Treatment interrupted, only partial treatment completed	2
	Fair: Treatment interrupted but eventually all completed	3
	Good: Difficult, but all treatment performed	4
	Very good: Some limited crying or movement, e.g. during anesthesia or mouth prop	5
	Excellent: No crying or movement	6

The Houpt scale of sedation is presented in Table 1. The pediatric dentist was blinded to the dose of administered midazolam and only judged the behavior of patients. Those who were not efficiently sedated were excluded from the study and their treatment was completed under more efficient intravenous sedation. Parents were asked to watchfully stay next to the child in the recovery room when treatment ended until full recovery. Crying, movements and overall behavior scores were compared using Wilcoxon Signed Rank test, and the treatment success rates in the two intervention groups were evaluated by McNemar's test. P-values less than 0.05 were considered significant. The data were analyzed using SPSS version 19 (SPSS Inc., IL, USA).

RESULTS

From a total of 20 children, four patients did not show up for their second visit and were excluded from the study. The remaining population consisted of six boys and 10 girls with a mean age of 48 months and mean body weight of 16.2kg. Based on the Frankl behavioral rating scale, six individuals were ranked definitely negative (37.5%) while 10 individuals were ranked negative (62.55%). Looking at the condition of patients following sedative drug administration, no deep sleep condition was observed in any of the two groups with a decline in sleepiness towards the end of each session.

In group A, patients were dizzy and sleepy but awake while they were sleepier after 15 minutes and again returned to normal state after 30 minutes.

Group B patients were sleepy at first and returned to normal state after 15 minutes and stayed alert until 30 minutes later. Wilcoxon Signed Rank test showed no significant difference in the level of sleepiness between the two groups at 15 and 30 minutes. Status of each group of patients was recorded during the treatment under oral sedation. The Houpt scales of sedation are presented in Table 2.

Table 2: Distribution of patients in terms of their sleepiness in the two groups based on the Houpt scale

Groups	Group B			Group A		
Sleep Score	**Onset N (%)**	**15 minutes N (%)**	**30 minutes N (%)**	**Onset N (%)**	**15 minutes N (%)**	**30 minutes N (%)**
1	6 (37.5%)	7 (43.8%)	7 (43.8%)	8 (50%)	6 (37.5%)	9 (56.3%)
2	10 (62.5%)	9 (56.2%)	9 (56.2%)	8 (50%)	10 (62.5%)	7 (43.8%)
3	0	0	0	0	0	0
Total	16 (100%)	16(100%)	16 (100%)	16(100%)	16 (100%)	16 (100%)

Scores: 1=Fully awake and alert, 2=Dizzy and sleepy, 3=Sleepy

The sleep index was not found to be significantly different between the two tested groups at the onset and at 15 and 30 minutes (P=0.056, P=0.157 and P=1.00, respectively). Group A represented the highest score in movements at the onset, lowest at 15 minutes and moderate controllable moves at 30 minutes. Group B showed the highest movement score at the onset and at 15 minutes. No significant differences were found between the two groups when Wilcoxon Signed Rank test was used (Table 3). The movement index was not significantly different when the two groups were compared at the three time points (P=0.102, P=0.336 and P=0.516, respectively). The highest score of crying was at the onset, score 4 (no crying) was recorded at 15 minutes and score 3 (little crying) at 30 minutes in group A while group B had score 4 (no crying) at the onset and score 1 (hysteric crying) at 15 and 30 minutes.

These results were not statistically significant when Wilcoxon Signed Rank test was used (Table 4). The crying score was not significantly different between the two groups of "A" and "B" at the three time points (P=0.194, P=0.285, P= 0.557, respectively).

Assessing the overall behavior changes with scores of 5 and 6 being considered as success showed that group A had a success rate of 68.8% at the onset with 62.5% and 68.8% at 15 and 30 minutes, respectively (Table 5). These values were 56.3%, 56.3% and 56.3% at the three time points, respectively in group B.

The Wilcoxon Signed Rank and McNemar's tests showed no significant difference between the groups at the three time points (P=0.194, P= 0.726 and P=0.417, respectively).

The heart rate and blood oxygen saturation were within the normal range in both groups at all-time points.

Table 3: Distribution of children in terms of their movements in the two groups based on the Houpt scale

Groups	Group B			Group A		
Movement Score	**Onset N (%)**	**15 minutes N (%)**	**30 minutes N (%)**	**Onset N (%)**	**15 minutes N (%)**	**30 minutes N (%)**
1	7 (43.8%)	7 (43.8%)	7 (43.8%)	5 (31.3%)	5 (31.3%)	5 (31.3%)
2	0	0	0	0	0	0
3	1 (6.3%)	1 (6.3%)	2 (2.5%)	0	3 (18.8%)	6 (37.5%)
4	8 (50%)	8 (50%)	7 (43.8%)	11 (68.8%)	8 (50%)	5 (31.3%)
Total	16 (100%)	16 (100%)	16 (100%)	16 (100%)	16 (100%)	16 (100%)

Movement scores: 1=Severe and disruptive to treatment, 2=Continuous disruption of treatment, 3=Controllable, no interruption, 4=No movement.

Table 4: Distribution of children with various crying levels by Houpt scale

Groups	Group B			Group A		
Crying Score	**Onset N (%)**	**15 minutes N (%)**	**30 minutes N (%)**	**Onset N (%)**	**15 minutes N (%)**	**30 minutes N (%)**
1	7 (43.8%)	7 (43.8%)	7 (43.8%)	5 (31.3%)	5 (31.3%)	5 (31.3%)
2	0	0	0	0	0	0
3	1 (6.3%)	2 (12.5%)	3 (18.8%)	1 (6.3%)	4 (25%)	3 (18.8%)
4	8 (50%)	7 (43.8%)	6 (37.5%)	10 (62.5%)	7 (43.8%)	6 (37.5%)
Total	16 (100%)	16 (100%)	16 (100%)	16 (100%)	16 (100%)	16 (100%)

Crying Scores: 1=Hysteric, 2=Continuous and severe, 3=Controllable and little, 4=No crying.

Table 5: Distribution of overall behavior scores in the two groups

Groups	Group B			Group A		
Overall behavior score	Onset N (%)	15 minutes N (%)	30 minutes N (%)	Onset N (%)	15 minutes N (%)	30 minutes N (%)
1	7 (43.8%)	7 (43.8%)	7 (43.8%)	5 (31.3%)	5 (31.3%)	5 (31.3%)
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	1 (6.3%)	1 (6.3%)	0
5	1 (6.3%)	2 (12.5%)	4 (25%)	0	4 (25%)	7 (43.8%)
6	8 (50%)	7 (43.8%)	5 (31.25%)	10 (62.5)	6 (37.5%)	4 (25%)
Total	16 (100%)	16 (100%)	16 (100%)	16 (100%)	16 (100%)	16 (100%)

Overall behavior scores: 1=No treatment, 2=Treated partially (stopped), 3=Treatment completed despite interruption, 4=Difficult but done, 5=Little crying and movement, 6=No crying or movement.

DISCUSSION

Based on the results of this study, the mean success rate for the higher dose of midazolam (0.5mg/kg) at the onset and 15 and 30 minutes was 68.8%, 62.5% and 68.8%, respectively. These values were lower (56.3%) at all three time points when a lower dose (0.3mg/kg) was administered. Despite the difference between the success rates of the two groups, it did not reach statistical significance. All physiological parameters remained within the normal range. Earlier studies have suggested that the effective dose of midazolam is between 0.25-0.5mg/kg in children with a maximum threshold of 20mg [24].

Day et al, [25] indicated that an effective dose of 0.5-0.7mg/kg could increase the success rate to as high as 91% while this rate drops to 65% when the dose is lowered to 0.2-0.3mg/kg with a statistically significant difference in the results. Silver et al, [26] stated that the dose of 0.5mg/kg oral midazolam resulted in higher success rate compared to the dose of 0.3mg/kg (90% and 75%, respectively) with statistically significant differences. It is of note that all tested dose ranges have been within the safe limit of the drug. Somri et al, [3] even went further and suggested the effective and safe dose of oral midazolam to be 1mg/kg in children. Midazolam elixir (Amsed, Oxford, UK) was suggested as an effective and safe drug in children with average dose of 0.75mg/kg [24]. Jing et al, [27] stated that the dose range of 0.5-0.75mg/kg was safe and effective in children of three years and younger. Oral midazolam successfully sedated children of 11-13 months when it was administered in 0.5mg/kg dosage [28].

Ghajari et al, [21] used a combination of 0.5mg/kg midazolam and 1mg/kg hydroxyzine with a reasonably high success rate of 93.8% at the onset and a reduction to 62.5% at 15 and 30 minutes similar to the findings of the current study. Pandey et al, [22] reported a 47.83% success rate following the use of 0.5mg/kg midazolam oral suspension, which was lower than the value obtained in the current study; this can be explained by the additional use of hydroxyzine. Based on the recorded data from the patients in this study, no considerable changes occurred in vital signs of patients following sedation with the use of midazolam/hydroxyzine similar to earlier reports [23,25-27]. On the contrary, 16% of children in a study by Johnson et al, [29] experienced a fall in blood oxygen saturation. This study had a cross over design and each patient served as the control for himself. This was a major strength of this study since it eliminated the effect of many confounders. However, clinical trials often have limitations in terms of number of available participants. A larger sample size in future studies is recommended.

CONCLUSION

The overall success rate of oral sedation was not significantly different when the two combinations of 0.5mg/kg and 0.3mg/kg midazolam/hydroxyzine were compared.

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