

Sedative Effect of Midazolam Elixir Compare to Vial Through Oral Route in Uncooperative Pediatric Dental Patients

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Abstract

Background and Aim: Midazolam is among routine agents used for inducing safe sedation. This study was designed to compare the sedative effect of oral administration of midazolam (Elixir vs Vial) in fearful children during dental treatment.

Materials and Methods: A randomized double blind clinical trial was conducted in a cross over style on 20 young fearful aged 3-6 years with Frankl behavioral scale of 1. Children were randomly divided into two groups. Group I received 0.5 mg/kg Midazolam Vial and 1 mg/kg Hydroxyzine oral at their first visit and 0.5 mg/kg Midazolam Elixir and 1 mg/kg Hydroxyzine oral in their second visit. In group II, the medication order was reversed. Houpt scale was used to measure the sedation level in both groups. Vital signs of heart rate and SpO2 were recorded during the procedure. Paired t-test, Wilcoxon and McNamara were employed to statistically analyze and compare the collected data between two groups.

Results: Based on the collected data, Houpt scale was seemingly improved more after taking elixir compare to the vial, however the difference was not statistically significant ($P=0.393$). There was no significant difference between the success rate of the two methods ($P=0.625$). All physiologic parameters were within the normal range with no significant difference between two groups and sessions.

Conclusion: The level of success between the two groups for sedation was not statistically different and were almost the same. This may indicate a successful use of the vial for oral application in certain cases of compromised cooperation.

Key Words: Administration, Oral, Conscious Sedation, Pediatric Dentistry, Midazolam, Hydroxyzine

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Introduction

A wide range of clinicians believes on practitioner's skill as a key tool to overcome patient's lack of cooperation. Despite that, a large number of children remain untreated due to their high anxiety and lack of cooperation which eliminates the possibility of treatment [1]. A considerably high number of Iranian children under six years old (22.2%) are reported to have

some degrees of interfering anxiety towards dental treatment [2]. Those individuals who cannot be seen in regular set up or with the help of conventional behavior techniques may benefit from pharmacologic techniques including various conscious sedation methods [1].

Conscious sedation is achieved with minimal doses of medications in order to maintain patient's consciousness. Protective reflexes of Throat and

Larynx are not eliminated in this type of sedation, and therefore patient's airway remains under control. In such condition, a marked reduction is detectable at central nervous system's functional activity while vital functions are not affected [3]. Oral sedation is known as the readily, easily available and somehow frequent route for dental sedation. This route is considered as the first choice in many instances because of their ease of application, lower risks, and low costs involved [4]. Midazolam is widely seen as the most popular, fast, effective benzodiazepine used in pediatric medicine and dentistry. Its starting point of effect is very quickly reached while the chances to induce deep sedation or unconsciousness are very slim. Flumazenil is the antagonist of choice for Benzodiazepines [5]. When compared to Diazepam it appears that Midazolam can induce amnesia while acts as an anxiolytic [6]. The recommended dose for Midazolam in children is 0.25-0.5 mg/kg with the maximum dose of 20 mg oral at any attempt [7]. Hydroxyzine is an antihistaminic agent which has some degrees of sedative effect. It is widely used for its anti-vomiting effect. It has no potential to cause respiratory depression when used in recommended doses. It has a slow effect agent, but its effect remains long. Combination of the two agents may offer a more prolonged effect with minimum risk potentials in pediatric dental sedation [8]. Since the Midazolam in the form of elixir is not efficiently available and more expensive than vial form in Iran, this investigation was designed to compare their effectiveness on sedating a group of uncooperative children aged 3-6 years in need of dental treatment.

Materials and Methods

This randomized, double-blind clinical trial was registered with IRCT under the following: IRCT201406171882N5. This investigation was conducted on 20 uncooperative children aged 36-72 months with the Frankl behavior scale of I or II [9]. Patients were selected from the pool of patients referred to Pediatric Dental Clinic at the Shahid Beheshti University of Medical Sciences and required at least two equally damaged similar teeth to be repaired. A full clinical medical and dental assessment were carried out by an anesthesiologist and a pedodontist. Only cases in

ASA I physical status were eligible for this investigation, especially they were carefully screened for potential cold and flu. Excluding criteria were: Obesity, limited neck movement, Micrognathia, Macroglossia, Tonsillar hypertrophy, limited mouth opening, and history of allergy to sedative drugs. Attempts were made to keep the operator and evaluator blind to the administered medicine. Parents were instructed for pre- and post-sedation care prior to their child's first visit as well as a full description of the procedure and risks involved followed by collecting the signed consent form from child's parents. Children were randomly assigned to one of the two groups of study based on the sequence of drug administration. Group I received the combination of 5mg/ml vial Midazolam (Abureyhan Pharma co., Iran) at 0.5 mg/kg and Hydroxyzine elixir (Elixir 2.5mg/ml) at 1mg/kg (Kharazmi Pharma Co, Iran) for the first visit. In the second visit, Midazolam elixir 0.5 mg/kg (Amsed, GP Supplies, UK) along with 1mg/kg Hydroxyzine elixir was administered. Group II received similar drugs in opposite order. Patients were asked to keep 4 hours solid and 2 hours liquid preoperative fasting (NPO) times. Pineapple juice was employed to add Midazolam vial to improve the taste for oral administration. A time lapse of 20-30 minutes was observed before any attempt for initiating the dental process. Lidocaine 2% with Adrenaline (1:100000) (Darupakhsh, Iran) was used for all cases for local anesthesia (LA) during the sedated stage. Changes in physiological parameters including peripheral capillary oxygen saturation (SpO₂) and Heart Rate (HR) were recorded using a monitoring machine (Saadat Medical Supply, Iran). Vital signs (SpO₂ and HR) of each patient were documented before and after medication, and every 15-minute during the procedure [10]. Sedation level was assessed at the start and the end of the dental treatment using Houpt sedation scale by two independent trained dentists upskilled for this evaluation process [10]. Patients were carefully monitored following the treatment completion and prior to discharge. Children should be able to stand on their own, and their coordination during standing was measured before being discharged. All patients were evaluated and discharged by the anesthetist in charge. Collected data were analyzed using

Wilcoxon signed ranks test and McNamara test to assess significant differences between the two groups.

Results

From the total of 20 children, four dropped from the study because they did not attend further appointments. Of the 16 remaining, seven were female, and nine were male with the mean age of 45.3 months and the mean weight of 15.2 kg. Half of the children were selected from score 1 in Frankl system, and the other half were scored 2, both of which are categorized as having negative behavior. None of the children were asleep while premedication was administered orally. In both groups, consciousness was gradually returned at the end with little to no changes in SPO2 level during the procedure which indicates the minimal effect. The highest level of consciousness was 43.8% which reached at 15 and 30 minutes after premedication and local anesthetic injection. Details of each observation were recorded on the prepared proforma for each session and Wilcoxon Signed Ranks Test indicated no significant difference between the two groups on their sleepiness at the start, 15, and 30 minutes; $P=0.317$, $P=0.317$, $P=1.000$ respectively (Table 1). The highest number of patients with no movement in Elixir group was 81.3%, 50% and 18.8% at start, 15, and 30 minutes of LA injection, respectively. In Vial group, the maximum number of patients with no movement at the start, 15, and 30 minutes after LA injection was 56.2%, 56.2%, and 50% respectively (Table 2). Comparison of the

collected data on “sleepiness” revealed no statistically significant differences at the start ($P=0.317$), 15 minutes later ($P=0.317$), and 30 minutes of start ($P=1.000$) between two groups.

The highest level of hysteric crying was seen at 30 minutes after LA injection in both groups with 3 cases in Elixir group and 6 cases in Vial group, however, 62.5% of patients in Vial group and 87.5% in Elixir group did not cry (Table 3). The Wilcoxon signed ranks test showed no significant differences between the two groups at 15 and 30 minutes interval ($P=0.063$, $P=0.203$, $P=0.540$ respectively).

Patients with the overall Houpt scores of 5 and 6 were considered the favorable result of the premedication. Accordingly, the mean behavioral success rate was 69.2% in Elixir group while it was 62.5% in Vial group (Table 4). The differences between the two groups were not statistically significant at any of the measuring times ($P=0.098$, $P=0.398$, $P=0.903$ respectively)

The overall success rate was at its highest when procedure started, however, a gradual reduction was observed towards the ending stage in both groups. It seemed that Elixir group had a higher overall success rate compared to the Vial group, however, the differences were not significant ($P=0.250$, $P=0.625$, $P=1.000$ respectively). Changes in the HR and SPO2 was negligible during the procedure with the mean heart rate of 123 at baseline turning to 144 after 30 minutes of work and SPO2 of 96 at baseline turned to 94 at 30 minutes time.

Table 1. Distribution of sleepiness at start, 15, and 30 minutes of local anesthetic injection using Houpt scale

Sleep index	Midazolam Elixir			Midazolam Vial		
	No(%)			No(%)		
	Start	15 Min	30 Min	Start	15 Min	30 Min
Awake & Conscious	4(25)	5(31.2)	7(43.8)	6(37.5)	7(43.8)	7(43.8)
Dizzy & Sleepy	12(75)	11(68.8)	9(56.2)	10(62.5)	9(56.2)	9(56.2)
Sleepy	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Total	16(100)	16(100)	16(100)	16(100)	16(100)	16(100)

Table 2. The severity (extent) of child's movements at each time interval in both groups using Houpt scale

Movement index	Midazolam Elixir			Midazolam Vial		
	No(%)			No(%)		
	Start	15 Min	30 Min	Start	15 Min	30 Min
Severe & interruptive	1(6.2)	3(18.8)	4(25)	4(25)	4(25)	5(31.2)
Continuous	0(0)	1(6.2)	2(12.5)	3(18.8)	0(0)	1(6.3)
Controllable	2(12.5)	4(25)	7(43.7)	0(0)	3(18.8)	2(12.5)
No movement	13(81.3)	8(50)	3(18.8)	9(56.2)	9(56.2)	8(50)
Total	16(100)	16(100)	16(100)	16(100)	16(100)	16(100)

Table 3. Frequency and severity of crying at each measuring time based on Houpt Scale

Group/Crying index	Midazolam Elixir			Midazolam Vial		
	No(%)			No(%)		
	Start	15 Min	30 Min	Start	15 Min	30 Min
Hysteric	1(6.2)	2(12.5)	3(18.8)	4(25)	4(25)	6(37.5)
Continuous & severe	0(0)	2(12.5)	2(12.5)	0(0)	0(0)	1(6.2)
Slightly and short	1(6.3)	6(37.5)	10(62.5)	2(12.5)	2(12.5)	3(18.8)
No Crying	14(87.5)	6(37.5)	1(6.2)	10(62.5)	10(62.5)	6(37.5)
Total	16(100)	16(100)	16(100)	16(100)	16(100)	16(100)

Table 4: Overall behavior score at each measuring interval of the study using Houpt Scale

Group/Overall score	Midazolam Elixir			Midazolam Vial		
	No(%)			No(%)		
	Start	15 Min	30 Min	Start	15 Min	30 Min
No treatment	1(6.3)	2(12.5)	2(12.5)	4(25)	4(25)	4(25)
interfered and incomplete	0(0)	0(0)	1(6.2)	0(0)	0(0)	1(6.3)
Interfered but completed	0(0)	1(6.2)	2(12.5)	0(0)	2(12.5)	1(6.3)
Interrupted but completed	0(0)	2(12.5)	2(12.5)	0(0)	1(6.2)	1(6.3)
Little Cry and move	2(12.5)	6(37.5)	8(50)	2(12.5)	3(18.8)	6(37.5)
No interruption and completed	13(81.3)	5(31.3)	1(6.3)	10(62.5)	6(37.5)	3(18.8)
Total	16(100)	16(100)	16(100)	16(100)	16(100)	16(100)

Discussion

The effectiveness of various sedative medications has been investigated based on their dose, type of

medication, and the route of administration. Among all, oral Midazolam and Hydroxyzine have been introduced as a relatively safe, simple, yet

effective medicine in sedating children. Since Midazolam elixir is not readily available in the country of Iran and has a relatively high price, oral administration of Midazolam vial in sweetened syrup would be considered as a potential replacement for many indications including preoperative, general anesthesia (GA), and medical diagnostic procedures. The hypothesis of the current investigation was that the Midazolam vial could be beneficial as a sedative in specific dental procedures. The results indicated that two forms of Midazolam had a similar sedative outcome when used as an oral premedication. The success rate in the group that received the vial form was 62.53% while this rate was 69.03% for the group which received elixir. It seemed that the first 15 minutes of dental treatment was performed in a more relaxed mood when elixir was given; however, the difference between the two groups was not significant in all three measuring intervals ($P=0.250$, $P=0.625$, $P=1.000$ respectively). The success rate was the same after the first 15 minutes up to the end in both groups. This was an indication of the limited effect of the medications in both groups. Patient's perception was almost equal for both groups. One child initially resisted taking the elixir, and two kids did not like the vial syrup, nevertheless, this distaste was not statistically significant. Based on the results obtained, it appears that the Elixir form of the medication has some degree of advantages over the Vial but the differences in various aspects were not significantly different; therefore, oral administration of the vial form might be beneficial where the Midazolam elixir is not available. Because Midazolam Elixir was not markedly available in Iran and since the sedative effect of oral vials on uncooperative children was still unclear, case recruitment proved to be difficult.

Somri et al [11]. believed that 1mg/kg oral Midazolam is a safe dose in children and showed that even a dose of 0.75 mg/kg could be efficient in many children with no harm. Jing et al [12]. have also indicated that the range of 0.5-0.75 mg/kg of oral Midazolam is a safe dose for sedating and premedication in children of 3 years and over. Results of current investigation have indicated that relative degrees of sedation could be achieved through oral administration of the combination of

two medications. Hydroxyzine helps to obtain efficient and safe sedation while reducing the side effects. Earlier studies have shown that Midazolam can be considered as the drug of choice for dental sedation [11,13-15]. Also, it has been indicated that Hydroxyzine along with N₂O–O₂ could produce almost similar sedative effects to Midazolam [16, 17]. Ghajari et al [18]. have reported a relatively similar outcome; children exhibited improved behavior during dental works after 15 and 30 minutes of premedication (18 or 4). A dose of 0.5 mg/kg of Midazolam Elixir has produced a similar level of cooperation at the start and 15 minutes similar to the current study's outcome but lower success at 30 minutes. This could be explained by the potential long-term effect of Hydroxyzine. Lourenço-Matharu and Roberts [15] had obtained similar results to Hass et al. [19] when 0.5 mg/kg Hydroxyzine was administered orally [15,19]. Sheron et al. [20] have reported similar success rate when administered combination of Midazolam or Meperidin with Hydroxyzine. Based on the findings of the present study, there was no evidence of reduced or noticeable changes in the SPO₂ rate in the arterial blood which was similar to earlier reports [11,15,16,18,20]. However, Johnson et al. [21] have reported 4 cases with reduced levels of SPO₂. An overall consensus is suggesting that Midazolam could be considered as a safe medication for use in pediatric dental sedation with minimal to no changes in SPO₂. This would enable pediatric dentists to selectively sedate mildly uncooperative children for short dental procedures using oral Midazolam in one of the two forms tested in this investigation.

Conclusion

The sedative effects of Midazolam vial in children, when used orally, were comparable to Midazolam elixir and the difference between two groups was not significant even after 15 and 30 minutes of premedication. No significant changes in vital signs were recorded in both groups.

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