



## Use of Midazolam Mixture as Premedication for Children Undergoing General Anesthesia for Dental Care

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### Abstract

**Background:** Oral midazolam is one of the most frequently used agents for the preceding anesthesia induction. The injectable form of midazolam can also be given orally. However, the bad taste of it has negative effects on ingestion of the drug. In this study, it is aimed to evaluate the effect of drinks which were added to mask the bitter taste of midazolam on drug acceptance and inducing a trouble free anesthesia.

**Methods:** In the laboratory; the pH values of 2.5 ml midazolam (15 mg/3 ml) and the mixtures of fresh orange juice and grapefruit juice in equal volumes were measured. Sixty healthy patients between 5 and 8 years of age who were assessed to have anxiety with Frankl Behaviour Scale and whose dental treatment was planned under general anesthesia were randomly divided into four groups. The fresh orange juice (Group I), fresh grapefruit juice (Group II) which were added to 0.5 m/kg midazolam of equal masses, or only 0.5 mg/kg midazolam (Group III) given orally to children. The Group IV included no medication. After 15 minutes, the induction and the maintenance process of anesthesia were similar in both all groups. The manner of subjects when separated from parents, their cooperation during intravenous catheterization, and recalling the pre-anesthetic events were recorded by the Ramsay Sedation Scale (RSS). Data were analyzed by adopting chi-square and Mann-Whitney tests.

**Results:** The groups had similar demographics, drug ingestion was better in Group I and the mean RSS was observed the highest in group I ( $p < 0.05$ ).

**Conclusions:** As well as making drug ingestion much simpler, the addition of orange juice to the midazolam administered orally to the children increases the effectiveness for comfortable separation of children from parents and restful IV catheterization and also forgetting the pre-anesthetic events.

### Keywords

Midazolam, Premedication, General anesthesia, Pediatric dentistry, Frank behavior scale, Ramsay sedation score

### Introduction

Generally accepted that most children who are undergoing medical procedures and who are fearful and uncooperative can and should be managed with behavioral management techniques. Unfortunately, a small percentage of pediatric patients cannot be

successfully managed only with these techniques [1]. Occasionally, by reason of anxiety and fear in children which make dental treatment impossible, use of sedation and general anesthesia becomes a need [2,3]. Midazolam is also one of the most frequently used agents for the purpose of sedative premedication in children. In known doses, midazolam does not cause depression in cardiovascular system and respiratory function, and has amnesic, sedative and hypnotic characteristics. Because of its efficacy of oral ingestion and its wide margin of safety, midazolam is being preferred by dentistry [2-4]. Even though oral form of midazolam is commercially available in some countries, its injectable form is also being used orally when its oral form is not available and when it can't be used because of its high price [4-9]. But, because of its bad taste has negative effects on ingestion of the drug in children, various flavourings have been used in previous studies [4,10].

Oil solubility, some physical characteristics and pH values of drugs are among the factors which effect the absorption of drugs ingested orally [11]. It is informed that sodium citrate, sugared water, orange, grapefruit, berry or grape juice, added to midazolam, affects the sedation onset time [3-5].

In consequence of our literature review, we have not come across to any study that evaluates in what manner the drinks mixed with midazolam affect pH value and sedation success of the drug, and acceptance of drug by child.

Nowadays, most of the hospital pediatric dental procedures are performed under outpatient general anesthesia. One of the drawbacks of this method is the challenging separation of children from their parents which may consequently cause a psychological trauma in the children [12,13]. The anxiety with separation is experienced enormously at age one whilst the genetic, personality, the previous experiences and the anxiety of parents are the factors concerned in the severity of the children anxiety [13]. Recalling the early phases of anesthesia which begins with the placement of anesthesia mask and follows with the smelling an unpleasant anesthetic gas is an unlikable experience [14].

The inherent anxiety of pre-anesthesia and the recalling of the pre-anesthetic events could proceed to psychological trauma and affect the quality of children's life, therefore, evaluating the effect of

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**Table 1:** Midazolam and mixtures pH values.

Midazolam and mixtures	pH value
Midazolam (15 mg/3 ml)	3.22
Fresh orange juice	2.93
Fresh grapefruit juice	2.73
2 cc Fresh orange juice + 2.5 cc Midazolam (15 mg/3 ml)	2.87
2cc Fresh grapefruit juice + 2.5 cc Midazolam (15 mg/3 ml)	2.58

**Table 2:** Frankl behavioral scale.

Score	Skoring	Observed behavior
1	Definitely positive	Good rapport with the dentist, interested in the dental procedures, laughing and enjoying the situation.
2	Positive	Acceptance of treatment; at times cautious, willingness to comply with the dentist, at times with reservation but patient follows the dentist's directions cooperatively.
3	Negative	Reluctant to accept treatment; uncooperative, some evidence of negative attitude but not pronounced, i.e. /sullen, withdrawn.
4	Definitely negative	Refusal of treatment, crying forcefully, fearful or any other overt evidence of extreme negativism.

**Table 3:** Ramsay sedation scale.

Ramsay sedation scale	Score
Patient anxious and agitated	1
Patient cooperative oriented and tranquil	2
Patient responding to commands only	3
Patient responding briskly to a light glabellar tap or to verbal stimulus	4
Patient responding sluggishly to a light glabellar tap to verbal stimulus	5
No response to stimulus	6

**Table 4:** Post Anesthetic Discharge Scoring System (PADS).

<b>Vital Signs</b>	2 = within 20% of preoperative value 1 = 20%-40% of preoperative value 0 = > 40% preoperative value
<b>Activity and mental status</b>	2 = Oriented × 3 AND has a steady gait 1 = Oriented × 3 OR has a steady gait 0 = Neither
<b>Pain, nausea and/or vomiting</b>	2 = Minimal 1 = Moderate, having required treatment 0 = Severe, requiring treatment
<b>Surgical bleeding</b>	2 = Minimal 1 = Moderate 0 = Severe
<b>Intake and output</b>	2 = has had PO fluids AND voided 1 = has had PO fluids OR voided 0 = Neither

\*Total PADS score is 10; Score ≥ 9 considered fit for discharge;\*\*PO = oral administration.

pre-anesthetic oral midazolam, on controlling these problems, seems to be indispensable [15].

In this study, we aimed to assess which mixture provides a more successful premedication by comparing the effects of pH and taste differences of the mixtures of midazolam on drug acceptance and inducing a trouble free anesthesia.

## Methods

During the study, the fresh orange juice (sweet) and grapefruit juice (bitter) were chosen to differentiate the tastes of drinks added to midazolam. Two milliliter each of fresh orange juice and fresh grapefruit juice were added to midazolam in equal volumes of 15 mg/3 ml and the pH value of each is measured (LABCOR Consort C833\*) (Table 1).

60 Patients, ages between 5 and 8 year of ASA grade I, whose treatments had failed with behavior guidance techniques and whose dental treatment compliance was determined as 3-4 with Frankl Behavior Scale (FBS; Table 2), were recruited for the study. Previous history of midazolam allergy, mental or motor retardation and administration of general anesthesia and sedation before were accepted as exclusion criteria.

Sample size was predetermined using a power analysis:  $\alpha = 0.05$  and  $\beta = 0.2$  (SD: 0.84, mean difference: 1.68, normal two-sided test). Difference in Ramsay Sedation Scale (RSS) (Table 2) was used to determine sample size. The analysis showed that 15 patients per group would be sufficient. According to randomization list, 60 cases were divided into 4 groups consisted of 15 case each. Parental presence was allowed during the pre-operation, operation (general anesthesia), and post-operation process.

While the mixtures of 0.5 mg/kg midazolam in which added the fresh orange juice (Group I), the fresh grapefruit juice (Group II) of equal masses were administered to cases, only 0.5 mg/kg midazolam (Dormicum®, 15 mg/3 ml) were administered to Group III. The control group (Group IV) included no medication. The medications were prepared just before administration.

For the purpose of creating double blind conditions, neither the researcher who attends to clinical applications and observations, nor the parents were informed about which mixture is administered to which child. During the whole study period, resuscitation and post-operative reaction requirements were present in the clinic [16].

Drug acceptance of child was registered as "Cooperative" if he/she had not refused to take the total dose, and "Agitated" if drug was given with difficulty; he/she had cried or refused to take the whole dose.

Children were separated from their parents 15 minutes later. The ease of separation was recorded based on the parental separation anxiety before the general anesthesia. Fifteen minutes after being given the drug (T1), The RSS (Table 3) and sedation levels were recorded.

The children under study were then laid on the operating table. Intravenous catheterization has been performed if the child exhibited cooperation; otherwise the child was managed to inhale slowly a mixture of oxygen, N<sub>2</sub>O and Isoflurane before IV catheterization. Intravenous anesthesia induction with thiopental Na and Fentanyl followed by nasal intubation was performed. The sedation was maintained with N<sub>2</sub>O/O<sub>2</sub> and Isoflurane during anesthesia, and the children were monitored in a standard approach. RSS values were recorded after IV catheterization (T2), at the beginning of the operation (T3), at the end of the operation (T4). Dental treatments were recorded.

At the end of anesthesia, the children were transferred to the recovery room and were monitored. Subsequently, the oxygen therapy with face mask, clinical observation and pulse oximetry was performed. When they were able to earn a post-operative score of 9 or higher based on post anesthesia discharge scoring system (PADS, Table 4), the children were asked if they recall the pre-operative and operating procedures [17]. The recalled events such as hand contact during IV catheterization, hearing, seeing and the placement of mask to induce anesthesia through inhalation, were recorded on a chart which was prepared by adopting the method enrolled in other studies [18,19].

## Statistical Analysis

SPSS 15.0 version was used in statistical analysis of data which have been accessed. In the evaluation of parametric data such as age and body weight One-way ANOVA test, and in the evaluation of the gender data and in inter-groups comparison Chi-Square tests were done. Descriptive statistics was done to reach the average of RSS data. Repeated measures ANOVA was used in inter-groups comparison of repeated measures belong to these data. From among post-hoc tests, under the circumstances of significant differences, multi comparison Scheffe test was used. During the whole analysis process, first type error was accepted as 0.05 and statistical interpretations were done at 95% confidential level.

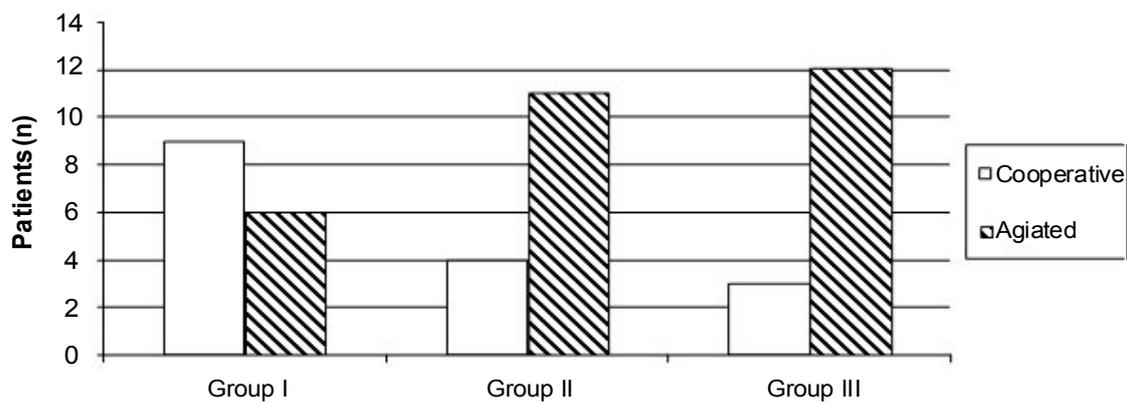


Figure 1: Drug acceptance in groups (n).

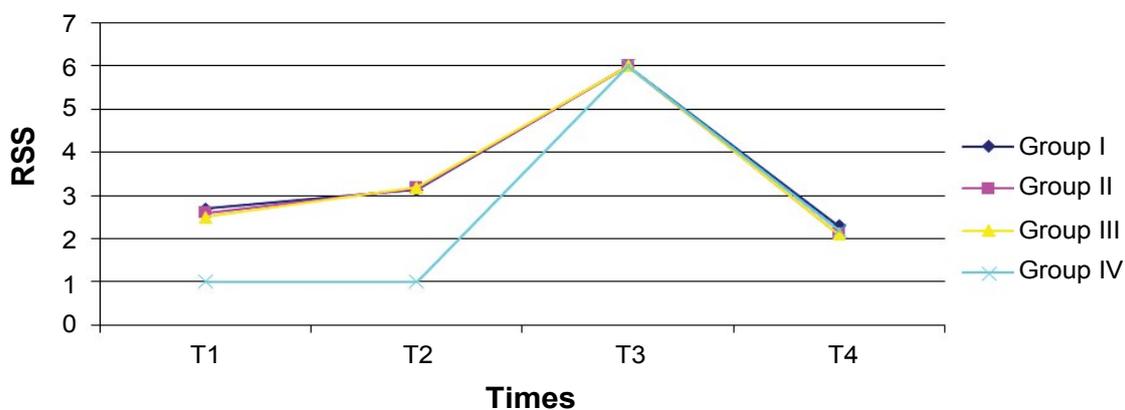


Figure 2: Ramsay sedation scores in groups (mean).

Table 5: Demographic variables (n) and scores of Frankl Behavior Scale (FBS) according to groups.

	Group I	Group II	Group III	Group IV
Gender (male/female) (%)	10 (66.7)/5 (33.3)	11 (73.3)/4 (26.7)	9 (60.0)/6 (40.0)	6 (40.0)/9 (60.0)
Age (year) (mean $\pm$ SD, min/max)	5.33 $\pm$ 0.617, 5/7	5.27 $\pm$ 0.799, 5/8	5.20 $\pm$ 0.414, 5/6	5.53 $\pm$ 0.989, 5/8
Weight (kg) (mean $\pm$ SD, min/max)	18.93 $\pm$ 2.314, 16/25	19.07 $\pm$ 3.615, 13/26	18.20 $\pm$ 2.336, 15/22	20.01 $\pm$ 3.989, 17/26
FBS (3/4)	4/11	4/11	3/12	2/13

Table 6: Treatments in groups (n).

Operation	Group I (n = 15)	Group II (n = 15)	Group III (n = 15)	Group IV (n = 15)
Resin modified glass-ionomer	3	3	5	2
Polyacid-modified composite resin	11	9	10	9
Amalgam	10	5	4	2
Formocresol amputation	1	2	1	2
Treatment of root and canal	2	2	1	2
Dental extraction	8	13	8	13

## Results

PH values of midazolam and flavored midazolam mixtures which were evaluated in the laboratory before clinical study are shown in table 1. After the comparison of values which are belong to gender, age, body weight and FDS data of 60 cases, which were assessed statistically, no difference was found between the groups ( $p < 0.05$ ) (Table 5). The distribution of dental treatments carried out for each group is presented in table 6.

When drug acceptance was evaluated, it was found out that cooperation of Group I was higher than the other groups ( $p < 0.05$ ) (Figure 1).

Mean RSS values of Group I, II and Group III were found higher than Group IV ( $p < 0.05$ ). Changes of RSS values for the groups in the

course of time (T1 and T2) are shown in figure 2. During the study, no serious side effects such as bradycardia, apnea or desaturation were observed in any of the cases.

## Discussion

In studies done before, the effect of midazolam premedication in anxious children's dental treatment was indicated [4,6,20]. The problem with injectable midazolam is that it is extremely bitter [1,15]. In addition, it is not known in detail how flavorings, added to midazolam, affect drug acceptance and sedation level. In this study we found that, during the dental treatment of children with high anxiety level, when compared with no medication, the addition of fresh orange juice to midazolam administered orally for the purpose of premedication improves drug compliance, and it enables deeper sedation level in comparison with the group IV.

Preoperative oral midazolam has proved effective in treating preoperative anxiety [1]. Orally administered midazolam can be given in a dose of 0.25 to 1.0 mg/kg up to a total dose of 20 mg depending on the duration of surgery and the anxiety level of the child [1,4,14]. Kaviani, et al. [15] was also informed that, for children with high anxiety level, 0.5 mg/kg midazolam is appropriate for sedative premedication. Levine, et al. [21] show the efficacy, safety and sufficiency of 0.5 mg/kg. In this study, we have chosen the dose of 0.5 mg/kg which we routinely use.

Clinical sedative effects of midazolam occur within 5 to 10 minutes of oral midazolam administration; the maximum effect is accomplished in 20 to 30 minutes. The sedative effects diminish within 45 minutes in most cases [1]. Midazolam has been administered orally in the doses of 0.2-1 mg/kg, having 15-30 minutes onset of action [4,14]. Malinovski, et al. [22] has indicated that after 0.5 mg/kg midazolam is administered orally, adequate sedation is provided in  $12.5 \pm 4.9$  minutes. Additionally, a study determine the minimum time interval between oral midazolam premedication and separation from parents to ensure a smooth separation, researchers found that children could be easily separated from their parents after only 10 minutes [21]. For this reason, in this study patients were separated from their parents and taken to dental unit 15 minutes after they received the drug.

Patients' anxiety levels affect the amount of sedative agent used for the purpose of adequate sedation and the sedation success [4,9]. It is much more difficult to achieve sedation with the premedication given to children who have high level of agitation. Because of this reason cases that have high level of agitation (FBS  $\geq 3$ ) have been included in this study.

Total dose should be administered to achieve adequate deepness of sedation. Children generally spit out or vomit the drugs which have bad taste. Because of this fact, in drug acceptance by the oral route, the taste of drug plays a part too [11]. In this study, we determined that the addition of fresh orange juice into midazolam had improved drug acceptance and convenient to use. High degree of intravenous induction of anesthesia in the study group indicates the higher cooperation in this groups (I, II and III) compared to the no medication group (IV).

Among the factors which affect the absorption of orally administered drugs through intestinal system, the factors such as form of drugs, their oil solubility, pH of digestive system and fullness of stomach are important. Furthermore, acute fear and anxiety increase absorption of drug [11]. As we have ensured that their stomach is empty for 4-6 hours by administrating midazolam in liquid form orally to all cases who have high level of agitation (FBS  $\geq 3$ ), we are in the opinion that there is no difference dependent on these factors which affect drug absorption among the groups.

Absorption of oral medications depends on the length of time the drug is in contact with the mucosa as well as on the local pH, the quantity and flow of saliva, and the physicochemical features of the drug and the site [23,24]. At a pH of 4.0-4.5, imidazole ring of midazolam closes, making it more lipophilic. The higher pH promotes lipid solubility and accelerates absorption across mucosal membranes [4,8]. Thus, mucosal absorption of midazolam is expected to be pH dependent [4,8,9,11,16,25]. In a study of 40 presurgical children, [8] midazolam was mixed with sodium citrate to raise the pH to 4.5 in one group, and the onset of sedation was significantly faster ( $p < 0.05$ ) than in a second group that received midazolam mixed with Hawaiian Punch (pH 3.5). In another study, it is indicated that thick grape syrup mixed with midazolam had reduced sedation time [5]. In this study, besides onset of sedation was not measured, we found that with other workers in I,II and III groups 15 min after drug ingestion, sedation scores measured with RSS were higher than the no medication group.

It is noted that as fresh grapefruit juice potently inhibits cytochrome P4503A4 (CYP3A4) activity, it extends the duration of the effect of midazolam and also slows the catabolism. On this grounds, as it may result in over-sedation midazolam should not be mixed with fresh grapefruit juice [10,26]. On the other hand, we found that RSS data of the group which was given fresh grapefruit juice, are not different from the groups given fresh orange juice in the study. We are of the opinion that besides the low quantity of fresh grapefruit juice, the low pH value of the mixture was also effective in this situation.

Compared to other benzodiazepine and non-benzodiazepine medications, midazolam is reported to be equally or more effective when used as premedication/preoperative sedation [27]. The premedication with midazolam does not prolong the discharge time from the hospital and its effectiveness and safety have been extensively studied [14,15,21]. In this study, in line with other studies [15,21], showed that the ease of separation from parents was better in the study who received the midazolam compared to the no medication group IV. Rarely, respiratory depression may develop in oral midazolam sedation [9]. In this study desaturation was not seen in cases which were under observation.

In conclusion; the present study showed that 0.5 mg/kg oral midazolam 15 minutes before starting the process of anesthesia makes the separation of child from parents easy. It also has positive effect on the cooperation of child with anesthesiologist, and prevents the child from recalling the pre-anesthetic events. Additionally, children accepted oral midazolam with fresh orange juice more than fresh grapefruit juice and only midazolam, and it was safe and efficacious (RSS), with physiological parameters remaining within acceptable clinical limits.

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