# Assessment Effect of Midazolam Oral Liquid on Alertness/Sedation Scale and Hemodynamic Parameters about Pediatrics Referred for Minimal Elective Ophthalmic Surgeries

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**Abstract: Background:** Midazolam is a generic prescription medication in the benzodiazepine drugclass used for sedation before medical procedures. The aim of the present study was to assess the effects of 0.5mg/kg midazolam oral liquid (2.5mg base/1ml) on alertness/sedation and also on hemodynamic parameters about pediatrics aged 6-12y/o, referred for minimal elective ophthalmic surgeries. **Methods:** This is a randomized double blind clinical trial performed about 100 patients with average age of 6-12 y/o and ASA class I-II (classification of physical status by American Society of Anesthesiologists). These patients were candidate for minimal elective ophthalmic surgeries, with general anesthesia between the years Jan. 2010 till Dec. 2010. After the hospital's Ethic Committee approval, the study was conducted in Tabriz University of Medical Sciences, Tabriz, IRAN. In this study patients, evaluated in recovery room before drug administration from the point of the level of alertness/sedation, anxiety and cooperation using appropriate scoring systems. Blood pressure, pulse, electro cardiogram oxygen saturation and end tidal $CO_2$, of the patients also monitored (baseline measurements). In the present study subjects received 0.5mg/kg of midazolam syrup half an hour before induction of anesthesia by a member of research team not aware of dose of prescribed medication. Patients postoperatively evaluated from the point of sedation, hiccoughing, hypoxemia, nausea and emesis. Data collection in the present study done using questionnaire. Descriptive statistical methods employed for statistical analysis, using SPSS software Ver. 17. **Results:** No significant adverse effects were observed and treatments were completed successfully. It is found that a dose of 0.5mg/kg of midazolam oral liquid could be effective in sedating of young pediatrics before minimal elective surgeries. **Conclusions:** It is concluded that midazolam oral liquid is a safe premedication about pediatrics before minimal elective ophthalmic surgeries.
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## 1. Introduction

Midazolam is widely used as a preanesthetic medication for children. Oral liquid of midazolam is effective for producing sedation and anxiolysis with minimal effects on respiration and oxygen saturation. Before the development of a commercially prepared oral midazolam which is used in the present study, formulations were prepared by mixing the IV midazolam product with a variety of additives to mask the bitter taste (Charles J Cote, 2002). The main aim of the present study was to blunt stress responses and improve surgery and anesthesia outcome. Another purpose was to evaluate effect of midazolam oral liquid on anxiety, cooperation, alertness/sedation scale and hemodynamic parameters of pediatrics referred for minimal elective ophthalmic surgeries.

## 2. Material and Methods

This is a randomized double blind clinical trial performed in Tabriz University of Medical Sciences, Tabriz, IRAN, after obtaining the hospital's Ethic Committee approval and informed parental consent. The study conducted from Jan. 2010 till Dec. 2010 at Nikoucari ophthalmologic hospital. Patients ASA class I-II aged 6-12 y/o, scheduled for minimal elective ophthalmic surgeries. Exclusion criteria included seizure disorders, gastrointestinal disorders that might affect absorption and any medical condition that could compromise the safety of the patient or interfere with the interpretation of the results. Because midazolam is known substrate of the cytochrome P4503A4 enzyme system, patients taking known cytochrome P450 3A4 inhibitors (e.g. grapefruit juice, midazole derivatives, erythromycin, clarithromycin, or cimetidine) or cytochromeP450 3A4 inducers (e.g. Phenobarbital, phenytoin, rifampin, or corticosteroids) were excluded. In this study clinical responses (sedation) and adverse effects (respiratory, hemodynamic and others) assessed by an observer blinded to midazolam dose. Safety was assessed by continuous oxygen saturation monitoring and observation. Vital signs were recorded before drug administration (baseline) and then every 5-min until the induction of anesthesia and again in the Post Anesthesia Care Unit (PACU) until a Steward Post Anesthesia Recovery Score of 6 was achieved. Anxiety was assessed on a four-point scale (poor=afraid, combative, crying, restrained; fair=fearful, moderate apprehension; good=slightly

fearful, easily calmed by strangers, non-combative; excellent=no fear or apprehension displayed; not applicable=patient asleep) every 10 min for up to 45 min afterwards. Cooperation also was evaluated as anxiety with a four-point scale (Poor=strongly refuses intervention; fair=considerable effort required to achieve compliance with intervention; good=accepts intervention reluctantly; excellent=accepts intervention readily; not applicable=patient asleep) at the same intervals. Sedation in this study was investigated with a five-point Observer's Assessment of Alertness/Sedation Scale (OAA/S). Responds readily to name spoken in normal tone(5), Responds lethargically to name spoken in normal tone (4), Responds only after name is called loudly and/or repeatedly (3), Responds only after mild prodding or shaking (2), Responds only after painful trapezius squeeze (1), and dose not respond to painful trapezius squeeze (0). Sedation assessments were made as baseline then at 10-min intervals for up to 45 min. Bis (Bispectral Index) could also be used in this stage which is equal to OAA/S from the point of its reliability. In this study oral liquid of midazolam administered 30-min before induction of general anesthesia. Patients evaluated at the time of separation from parents for anxiety and then they transferred to operating Room (O.R). After establishing an IV live at O.R, and monitoring the pediatrics, cooperation scores for face mask induction and sedation scores assessed. In this study route of anesthesia was similar, (general anesthesia with endotracheal intubation). Drugs which administered per kg/bwt included propofol, atracurium. Isoflourane as volatile anesthetic together with oxygen and nitrous oxide gases also delivered. In PACU patients observed by steward post anesthesia scoring system and discharged until a score of 6 achieved. Subject also assessed for the signs of Sedation/Alertness, hiccoughing, hypoxemia, nausea, and emesis. In this research data collection done using questionnaire. The collected data was analyzed by descriptive statistical methods using SPSS software Ver. 17.

**3. Results**

There were one-hundred patients (54%male, 46% female) in the final analysis. Average age and weight of the patients was 8.39 in years and 26.6 in kg respectively from the point of physical status classification 95% of the patients were in ASA class I and only 5% were in class II. In surgical procedures no significant blood loss occurred, and the amount of IV fluid monitored. Overall, 97% of the patients achieved satisfactory sedation (score≥3) after treatment. Cooperation scores for face-mask induction showed an overall satisfactory rate of 80.3%. Patient's behavior at separation from parents was acceptable in 77.9% of the cases. Changes of hemodynamic parameters including systolic blood pressure, diastolic blood pressure, pulse rate, saturation pressure of oxygen, was not significant (Figure 1).

End tidal CO2 reported to be 37±2 mmHg. Subjects achieved a steward post anesthesia recovery score of over 6 and then discharged from PACU. From the point of postoperative complication only 2.5% of subjects experienced emesis. It is concluded that 0.5mg/kg of midazolam oral liquid could be effective in sedation of young pediatrics without significant hemodynamic changes, and producing other considerable complications.

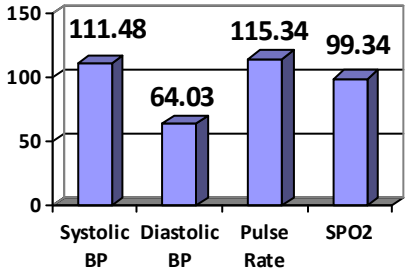


Fig1- Mean of changes in hemodynamic parameters

**4. Discussion**

Midazolam (marketed in English – Speaking Countries under brand names Dormicum, Hypnovel and Versed) is a short-acting drug in the benzodiazepine class that is used for treatment of acute seizures, moderate to severe insomnia, and for inducing sedation and amnesia before medical procedures. Midazolam has a fast recovery time and is the most commonly used benzodiazepine as a premedication. Midazolam works in the central nervous system (brain) and causes sleepiness, muscle relaxation, and reduces anxiety (Accessed, 20011). Sedating children for diagnostic and therapeutic procedures remains an area of great consideration for anesthesiologists. Reports relating to specific involvement by anesthesiologists in pediatric sedation are rare before the early 1980s. The most significant of anesthesiologist's specialty has been in the development of sedation guidelines which subsequently became international standards. The first monitoring guideline for sedation was written by Dr. Charles cote and Dr. Theodore Striker in 1983. This guideline was written in response to three deaths in a single dental office. The guideline emphasizes on need for informed consent, appropriate fasting before sedation, frequent measurement and charting of vital signs, the availability of age and size appropriate equipment, the need for basic life support skills and proper recovery and discharge procedures (Joseph,

2004). There are children who from either past experience or general lack of understanding are terrified to come to operating room, when I see a child break into tears, if the child is old enough to talk with, I stop whatever is happening at the moment, sit on the bed next to the child, and ask what exactly is concerning them, sometimes there is no response. In this situation I ask such child if they are afraid to go to sleep, afraid of feeling their operation or afraid of pain afterward. For reducing pediatrics' stress which results in hemodynamic changes and affects outcome of surgery and causes many other complications besides, of psychological support, the need for premedication which may be administered orally, intramuscularly, intravenously, rectally, sublingually, or nasally, must be individualized according to the underlying medical conditions, the need for surgery and the desired induction of anesthesia. Oral midazolam is the most commonly administered premedication in the United States. An oral dose of 0.25-0.33mg/kg (maximum, 20mg) generally results in a very compliant child who will separate from parents without crying. Midrange doses of intramuscular ketamine (2-4mg/kg) combined with atropine (0.02mg/kg) and midazolam (0.05mg/kg), or oral ketamine (4-6mg/kg) combined with atropine (0.02mg/kg) and midazolam (0.5mg/kg, maximum of 20mg) will result in a deeply sedated child. This combination is generally reserved for children who refuse oral premedication or those in whom higher premedication regimens have failed in the past. There are many researches done about oral midazolam usage and its doses for sedating pediatrics before surgery. Charles J. cote' and et al. examined the efficacy, safety and taste acceptability of three doses (0.25, 0.5 and 1.0mg/kg) of midazolam and they found than oral syrup of midazolam with a dose of 0.25mg/kg had minimal effects on respiration and oxygen saturation even when administered at doses as large as 1.0mg/kg (maximum, 20mg) as the sole sedating medication to healthy children in a supervised clinical setting (Charles J Cote, 2010). In another research done by Keith K. Brosius and Carolyn F. Bannister, two oral dosage formulations used and sedation score evaluated by the Observer's Assessment of Alertness/sedation (OAA/s) scale. It is revealed that IV midazolam mixed in syrpalta syrup yeids more reliable sedation than an equivalent dose of the commercially formulated and marketed preparation. In this regard it is suggested that IV midazolam mixed in syrpalta syrup produces greater sedative effect, as an oral anesthetic premedication in pediatric surgical patients (Charles J Cote, 2002; Chernik, 1990; Keith, 2003). Pourhashemi S.J. at 2009 assessed a low dose of oral midazolam (0.25mg/kg) of a 15mg/3ml IV midazolam mixed in black cherry syrup or the syrup alone and reported no adverse effects (Pourhashemi, 2009). In the present study which was a randomized double blind clinical trial midazolam oral liquid used with a dose of 0.5mg/kg (2.5mg base/1ml) with appropriate and continuous multiple monitoring and no significant complication observed. The researchers recommend this dose of oral liquid midazolam as a safe premedication for pediatrics aged 6-12 y/o. before minimal elective ophthalmic surgeries.

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