Comparison of Oral Midazolam With Intravenous Midazolam for Sedation of Children During Upper Gastrointestinal Endoscopy

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Abstract- Upper endoscopy is a common procedure for the diagnosis and treatment of upper digestive tract diseases. The increasing number of pediatric gastrointestinal procedures has led to increasing attention on the safety and efficacy of medications used for sedation during the procedure. This randomized blinded interventional study was designed to compare the effect of oral midazolam with intravenous (IV) midazolam as a sedative medication in 119 children undergoing endoscopy. The mean time to sedation was 2.2±0.7 in IV midazolam group and 30.9±0 in oral midazolam group which was statistically significant difference between two groups. Separation from parents in oral midazolam group was as follow: 2 patients were high resistant (3.5%), 2 patients were resisted first and then relaxed (3.5%) and 55 patients were separated from their parents without any resistance (93%); whereas in IV midazolam group, 8 patients were high resistant (13.3%), 29 patients were relatively resistant (48.3%) and 23 patients were separated from their parents without any resistance (38.3%) that shows significant differences between the two groups. In terms of patient comfort during endoscopy, there was also a significant difference between the two groups. In oral midazolam, group parents were more consent, compared with the other group. The present study showed that oral midazolam is a safe and effective sedation during upper endoscopy in pediatrics. Oral midazolam reducing patients' anxiety during separation from parents leads the easy use of endoscopy and comfort of patients during endoscopy as compared with IV midazolam. Oral or IV midazolam were not able to put most patients in deep sedation level.

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Keywords: Gastrointestinal endoscopy; Midazolam; Sedation; Intravenous

Introduction

Upper gastrointestinal (GI) endoscopy is a fundamental procedure for evaluation and treatment of gastrointestinal disorders, which is commonly used in children for diagnostic purposes**.** Although sedation increases patient tolerance and willingness to undergo the procedure, there are potential complications, mostly associated with the administration of sedative medications (1,2).

Sedation is usually used for all children, who are undergoing endoscopy, while children may be incapable of verbalizing (3). The aims of sedation are to relieve from anxiety, ensure patient safety, bring patient analgesia and amnesia, make patient cooperate with controlling behavior during the procedure, let successful completion of the procedure, and quickly return the patient to pretreatment level of consciousness (4,5).

The best approaches for sedating children, who undergo upper GI endoscopy, has not been defined yet, while several methods and medication combinations have been used for inducing sedation in pediatrics (4).

Upper GI endoscopy can be done with no sedation, intravenous (IV) sedation, oral sedation or with general

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anesthesia (6). Currently, the most frequent form of sedation used for in pediatric endoscopy is IV sedation. Although this type of sedation is effective and safe, it makes many children anxious. Increase doses of conscious sedation medication make separation from parents more difficult and occasionally prolongs the procedure. Oral premedication may improve these problems (5,7).

Different groups of medications have been used for inducing sedation in upper endoscopy in pediatrics, including benzodiazepines (e.g., midazolam, lorazepam, diazepam), opioids (e.g., morphine, fentanyl, meperidine), sedative-hypnotics (e.g., chloral hydrate, ketamine), inhaled agents (sevoflurane and nitrous oxide), and IV propofol (6).

Midazolam is a drug that widely used for sedation, because of its excellent anxiolytic effect which also provides sedative-hypnotic, muscle relaxation, and anterograde amnesia (5,7). Midazolam is also known for rapid absorption and high excretion, which is used orally and intravenously for sedation. Oral doses between 0.25 and 0.5 mg/kg and 0.1 mg/kg to 0.3 mg/kg of IV dose and maximum dose is 10 mg (8).

Prior studies showed IV midazolam as an effective form of conscious sedation for same-day surgery and for pediatric endoscopy, while oral midazolam, as a premedication, has been shown to decrease anxiety in children undergoing laceration repair and for children undergoing general anesthesia for elective surgical procedures (7).

This randomized blinded interventional study was designed to compare the effect of oral midazolam with IV midazolam as a sedative medication in children undergoing endoscopy.

Materials and Methods

In this double-blind clinical trial, 120 patients aged from 1 to 16-year-old, who were referred to the Children's Medical Center, the Pediatrics Center of Excellence in Tehran, Iran, for diagnostic upper GI endoscopy were divided randomly into two groups. Informed consent form was filled by parents and patients older than 7-year-old after a brief description of the research purposes.

For data collection, a questionnaire was used which consisted of two parts: one part included demographic information, and other part included clinical parameters. To reduce the interventional effect of age and sex parameters, oral and IV midazolam were divided into two groups proportionally of these two criteria. Inclusion criteria included: 1 to 16-year-old patients who require diagnostic upper endoscopy and the ASA (American Society of Anesthesiologist Physical Status Classification) class I and II. Exclusion criteria included: age under one-year-old, obvious neurological disorder, Mental retardation, sensitivity to benzodiazepines, cardiovascular or renal or metabolic disease, adverse effects of sedative drugs, respiratory distress, and patients who need therapeutic intervention by endoscopy. An IV line was inserted for all patients prior to endoscopy.

The patients in the first group received 0.5 mg/kg of oral midazolam (containing 2.5 mg/ml midazolam was used, maximum dose: 10 mg), in second group 0.1 mg/kg IV midazolam was administered (maximum dose: 2.5 mg). Oral midazolam was administered 30 minutes before endoscopy and IV midazolam was injected 2 to 5 minutes before endoscopy. To avoid the confounding effect of the sweet flavor of oral midazolam, sweet orange flavored multivitamin was used in patients with IV midazolam. The patient's vital signs, including heart rate, blood pressure and blood oxygen saturation levels before and after administration of sedative medication before endoscopy were checked, heart rate and blood oxygen saturation during endoscopy were also monitored. Information recorded by doctor and nurses which included vital signs, sedation easiness, complications, separation from parents, the level of sedation, time to sedation induction, ease of endoscopy, time to return to full consciousness and consent of parents and patients older than 7 years for using this method again if needed. The doctor who was performing the endoscopy and the nurse who was recording the information were unaware of the type of sedation method. Time to reach at least Level 3 of sedation was recorded for two drugs. Drug usage and sedation induction easiness were divided into three conditions: hard (high resistance patient), relatively hard (patient is resisted first but calms down later) and easy (no resistance). If the patient separation from his parents was along with the crying, resistance and asking parents to remain, considered as hard if the patient was resisted at first but became calm after a while considered as relative resistance and if the patient had no resistance considered as easy.

The level of sedation was considered based on modified Ramsey sedation scale included: 1) The patient is anxious, agitated or restless, 2) The patient is cooperative, oriented and tranquil, 3) The patient responds to commands, 4) The patient responds to gentle shaking, 5) The patient responds to noxious stimulation, 6) Patient

has no response to firm nailed pressure or other noxious stimulation. Levels 3 and 4 were considered as the acceptable level of sedation for endoscopy (moderate sedation). Patients who failed to achieve the acceptable level of sedation excluded from our study and higher dose or other medication was used for them.

Endoscopy simplicity and patient condition were scored according to the following: 1) Patiently is sleepy during endoscopy, 2) The patient wakes up but is cooperative 3) The patient is awake, and endoscopy is performed with nurse aid, 4) The patient is awake but goes to sleep with more dose of drug, 5) The patient is awake and does not go to sleep in spite of more dose of drug use, but endoscopy is performed with nurse aid, 6. Endoscopy is not completed.

During endoscopy and after full consciousness drug side effects were evaluated including apnea, aggression, and hypotension. Time to return to full consciousness (Patients with appropriate eye contact and verbal responses and proper response to stimulation) from level 3 of sedation were recorded in the both groups.

Finally, parents and patients older than 7-year-old willingness were asked for using this sedation method again, if re-endoscopy was needed.

The collected data were entered and analyzed using SPSS software version 18. Descriptive statistics and Mann-Whitney test were used for analysis. *P*<0.05 was considered as significant.

Results

One hundred and twenty patients (1 to 16-years-old) were enrolled in this study; one patient was excluded due to incomplete data. From the remaining 119 patients (61 female and 58 male), 60 patients received IV midazolam and 59 patients received midazolam. The mean age of patients was 6.8±3.3 years old. Patients divided into three groups: 1 to 4 years, 5 to 10 years and 10 to 16 years. Most patients were in the groups of 5 to 10-year-old.

The mean heart rate with IV midazolam was 117±13.2 and oral midazolam 112.3±15.1, which was statistically significant and heart rates were lower in oral midazolam group than IV midazolam group at the time of sedation (*P*.value=0.04). O2 saturation drop and oxygen saturation were not significantly different between the two groups (*P*.value=0.1). The mean oxygen saturation was 96.8±1.8 in IV midazolam group and 98.3±7 in oral midazolam group. The mean time to sedation was 2.2±0.7 in IV midazolam group and 30.9±0 in oral midazolam group which was statistically significant difference between two groups (*P*.value<0.001) (Figure 1).

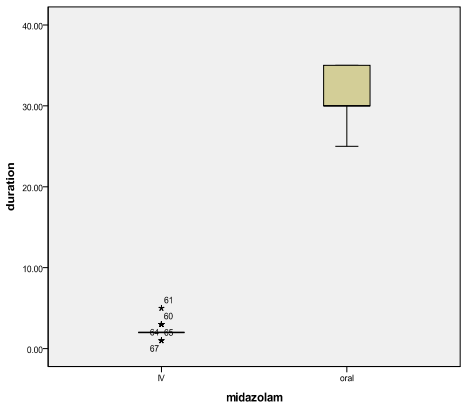

Figure 1. Comparison of the time to sedation between IV and oral midazolam groups (*P*.value<0.001)

In terms of the simplicity of sedation, resistance in patients who were received oral midazolam was low and drug administration was easy in most cases, but in another group was hard or relatively hard in most cases (*P*.value<0.001) (Figure 2).

Separation from parents in oral midazolam group was as follow: 2 patients were high resistant (3.5%), 2 patients were resisted first and then relaxed (3.5%), and 55 patients were separated from their parents without any resistance (93%) whereas in IV midazolam group 8 patients were high resistant (13.3%), 29 patients were relatively resistant (48.3%) and 23 patients were separated from their parents without any resistance (38.3%) that shows significant differences between the

two groups (*P*.value<0.001) (Figure 3).

The level of sedation was not significantly different between the two groups. In oral midazolam group 1 patient was agitated and restless (1.7%), 2 patients were alert (3.3%), 49 patients were drowsy and responsive to sound (83.3%), 6 patients were drowsy and responsive to shake (10%) and only 1 patient was deep sedated (1.7%). In IV midazolam group 3 patient was agitated and restless (5%), 2 patients were alert (3.3%), 55 patients were drowsy and responsive to sound (91.7%). In both groups 55 patients obtained moderate sedation (93.3% oral and 91.7% IV). In terms of patient comfort during endoscopy, there was a significant difference between the two groups (*P*.value=0.008). In oral midazolam group 2 patients slept during endoscopy (3.5%), 28 patients were awaked but cooperative (50%) and in 26 cases endoscopy was performed with the nurse aid (46.5%). In IV midazolam group 13 patients were awaked but cooperative (23.5%), 41 patients were awaked, and endoscopy was performed with nurse aid (74.5%) and for one patient endoscopy was performed with more dose of the drug (2%). In both groups, endoscopy was completely done in all patients.

The time of return to full consciousness was 24.4±7.3 minutes in oral midazolam and 24.4±7.9 minutes in IV midazolam, which was not a significant difference between the two groups (*P*.value=0.9).

Parents' satisfaction and willingness for using this sedation method again if they need to re-endoscopy were asked. 35 cases in oral midazolam group answered that 27 of them (77.1%) were consent, 1 case (2.9%) was dissatisfied and 7 cases (20%) were relatively consent, 32 cases in IV midazolam group also answered that 14 cases (43.7%) were consent, and 5 cases (15.6%) were dissatisfied, and 13 cases (40.6%) were relatively consent. In oral midazolam, group parents were more consent compared with the other group (*P*.value=0.01) (Figure 4).

In both groups, no major adverse effects were seen. Financially, oral midazolam was more expensive than IV midazolam during this research.

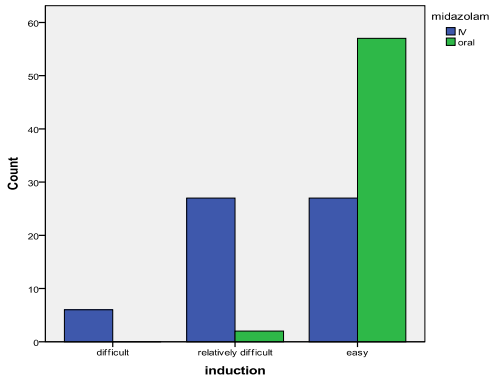

Figure 2. Comparison of simplicity of sedation between two groups of IV and oral midazolam groups (*P*.value<0.001)

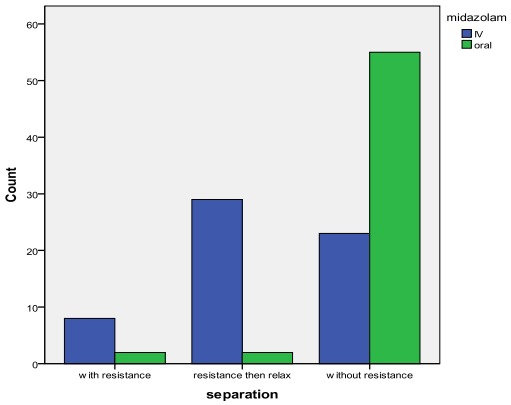

Figure 3. Comparison of separation from parents between IV and oral midazolam groups (*P*.value<0.001)

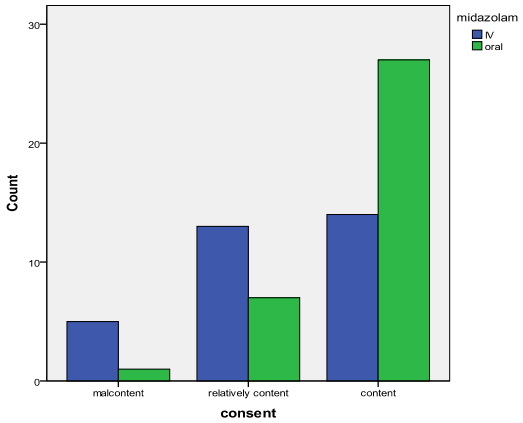

Figure 4. Comparison of consent between two groups of IV and oral midazolam groups (*P*.value=0.01)

Discussion

Upper endoscopy is a common procedure for the diagnosis and treatment of upper digestive tract diseases (4,9). The increasing number of pediatric gastrointestinal procedures in recent years has led to increasing attention on the safety and efficacy of medications used for sedation during the procedure (5).

In this study, 119 patients aged from 1 to 16-years-old were referred for sedation before upper GI endoscopy were randomly assigned to two groups with oral midazolam and IV midazolam. The aim of this study was to compare the two forms of therapy in inducing sedation, ease of applying, reducing patient's anxiety, and side effects and if these two form of drugs is appropriate for inducing sedation before diagnosis upper endoscopy.

Pain, discomfort, and anxiety during upper endoscopy are important issues for all people, even at the age of the infancy, and painful experience may reduce patient compliance for treatment. 8 Furthermore, children undergoing upper endoscopy are not able to express their pain and discomfort which make them anxious and uncooperative which may give rise to unwarranted patient and parental concerns, oxygen desaturation, poor separation from parents, difficult procedural sedation, and post-procedural behavior problems. Therefore they will need anesthesia or procedural sedation to feel comfortable and be cooperative. Therefore inducing an appropriate level of sedation seems necessary to perform invasive procedures such as diagnostic and therapeutic endoscopy (7,10).

A variety of actions and medications can be applied to relieve anxiety and discomfort. Designing a friendly and familiar environment and gentle music will reduce patient's anxiety and needed sedative drugs. Having patients' popular objects such as children's toys is also effective in this regard. Consultation before endoscopy and become familiar with the endoscopic environment is also effective (11).

Prior studies showed benefits of oral sedation for pediatric outpatient surgery and other diagnostic and therapeutic procedures include anxiolysis, reduced distress during IV insertion, improve ease of separation from parents, increases the patient's acceptance of events surrounding the procedure, decreased the need for IV medication, and shortened procedure and recovery times (5).

Midazolam has been used frequently to induce conscious sedation during upper gastrointestinal endoscopy and produces an anxiolytic, hypnotic, and amnesic effect (1).

Flumazenil also effectively and safely reverses the sedative effect of midazolam. The ability to reverse a sedative effect with a specific agent suggests a big advantage to its safety in clinical usage (1).

Patient's level of consciousness after using sedative drugs can be divided into the following levels: Minimal sedation: The patient is alert but without anxiety; Moderate sedation: The patient is asleep, but wakes up with verbal and contact stimuli; Deep sedation: The patient is asleep and wakes up with severe painful stimuli; General Anesthesia: Patient does not respond to external stimuli (20).

In the first three levels of consciousness after using sedative drugs, patients were able to maintain their airway but with the deepening of loss of consciousness the chance of apnea increases (9). Also, in general anesthesia, the patient is unable to maintain their airway (8).

As controlling the children is difficult, the level

preferred for endoscopy is deep sedation, but in some centers, moderate sedation is being considered adequate for endoscopy. Numbers of gastroenterologist prefer to create an appropriate level of sedation and general anesthesia preferably done by an anesthesiologist while others tend to perform moderate and deep sedation by themselves or by trained staffs (8). Patients and their parents have a different view about establishing sedation while general anesthesiologists and others prefer the light level of consciousness (8). IV techniques and anesthesia procedures differ in cost which must be considered.

In the study by Balsells *et al.*, in 2711 cases who were upper endoscopy during 12 years, only 96 cases (5.3%) of sedations were performed under general anesthesia and major and minor complications occurred in 3.0% of the cases (14).

The study at Hospital of Philadelphia conducted by Chuang which IV sedation was used to establish that only 1% of cases endoscopy process was not completed (15).

Among IV sedative, benzodiazepines are considered because of a sedative effect, anti-anxiety and amnesia and midazolam are considered especially for short half-life and fewer side effects. Midazolam has been used as a sedative drug by itself for endoscopy in adults but in children injectable forms and oral midazolam are used more as premedication before other sedative drugs (16).

In the study by Rafee *et al*., RCT was conducted on 61 patients divided into two groups which randomly received IV and oral midazolam for sedation. Between these two groups of patients, there was no significant difference in separation anxiety, the level of sedation and patient comfort during endoscopy but there was a greater decline in oxygen blood saturation levels in patients who received IV midazolam rather than oral midazolam (5).

In our study, like Rafee *et al*., study, no significant difference was found between the two groups regards to the level of sedation. There was lower blood oxygen saturation level in patients who received IV midazolam rather in compare to oral midazolam, but this difference was not significant in our study.

In Rafee *et al*., study, time to return to full consciousness in oral midazolam was longer than in comparison with IV midazolam (5), while our study showed no significant difference.

Rafee *et al.*, study showed the level of least deep sedation caused by IV midazolam group was 98% and in the oral midazolam group was 95%. While in our study, 7.91% of IV midazolam group had moderate sedation, and 3.93% of oral midazolam group had moderate sedation, and only 7.1% of IV midazolam group experienced deep sedation level while oral midazolam group did not enter into deep sedation level. Of course, the study conducted by Rafee *et al*., was not blind (10)

In another study by Verhage *et al.*, which was done without a control group, midazolam was used for inducing sedation, and no side effects were reported. The study was performed over 257 children aged from 2 months to 18-year-old, and only an incomplete endoscopy was reported.

In this study mean dose of IV midazolam used until the age of 6 years was 0.4 mg/kg and older than 6-year-old was 0.2 mg/kg which was higher than in our study. A measure of the level of sedation and patient comfort was not mentioned in this study. This study was also without a control group, and careful evaluation may not be achieved (17).

In another study conducted by Lamireau *et al*., 36 patients aged 3 months to 6-year-old who went under sedation with IV midazolam versus general anesthesia (halothane). The respiratory complication of IV midazolam group was 50% vs. 0% in the general anesthesia, and incomplete endoscopy occurred 50% in patients sedated with IV midazolam compared with halothane anesthesia (18).

In our study mean oxygen saturation below 90% did not occur in any of the groups, and endoscopy was completed.

In the study by Elke *et al*., about the different methods of sedation, the use of midazolam for sedation alone it is not appropriate for efficacy and patient comfort, and the information is not sufficient for its safety (19).

In another study conducted by Motamed *et al.*, 150 patients divided into three groups first group received IV midazolam and placebo, second group received oral ketamine with IV midazolam and the third group received fentanyl oral and IV midazolam in which patients in midazolam and ketamine group had less separation anxiety and more depth of sedation and patient comfort during endoscopy rather than other groups rather than other groups (6).

In our study most patients in both groups were in the moderate sedation level, 23.5% of patients with IV midazolam had good cooperation during endoscopy without resistance and 53.5% of patients with oral midazolam were perfectly fine with no need for further medication or nurse.

If the purpose of inducing sedation is a moderate level of sedation both IV, and oral midazolam is

appropriate and by the results of our study, oral midazolam patient's because of patients' comfort during endoscopy is superior to IV midazolam but if the target is a deep sedation level this drug with its doses used in our study is not appropriate; However, midazolam can be safe and low-risk in patients, although more study is needed.

In our study, despite similar levels of sedation in both IV and oral midazolam, a significant difference in patient's separation anxiety and patients comfort during endoscopy were observed between the two groups. Oral midazolam group appears to reduce patient anxiety during separation from parents and patient's comfort during the endoscopy.

Thus reducing patient anxiety before entering the room of endoscopy and also in the endoscopic room environment and parental separation anxiety patients can lead to greater patient comfort and ease of endoscopy.

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