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Original Article

Use of oral midazolam in pediatric upper gastrointestinal endoscopy

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Abstract ***Background***: The purpose of this prospective, randomized study was to compare the safety and efficacy of oral versus i.v. midazolam in providing sedation for pediatric upper gastrointestinal (GI) endoscopy.

Methods: Sixty-one children (age <16 years) scheduled for upper GI endoscopy were studied. Patients were randomly assigned to receive oral or i.v. midazolam. Measurements were made and compared for vital signs, level of sedation, pre- and post-procedure comfort, anxiety during endoscopy, ease of separation from parents, ease and duration of procedure, and recovery time.

Results: Patients were aged 1–16 years (mean 7.5 ± 3.42 years); 30 patients received oral medication, and 31 received i.v. medication. There were no statistically significant differences in age or gender between groups. There were no significant differences in level of sedation, ease of separation from parents, ease of ability to monitor the patient during the procedure, heart rate, systolic arterial pressure, or respiratory rate. Oxygen saturation was significantly lower in the i.v. group than the oral group 10 and 30 min after removal of the endoscope, and recovery time was longer in the oral than the i.v. group.

Conclusions: Oral administration of midazolam is a safe and effective method of sedation that significantly reduces anxiety and improves overall tolerance for children undergoing esophagogastroduodenoscopy.

Key words children, endoscopy, midazolam, oral, sedation.

As the frequency of pediatric gastrointestinal procedures has increased in recent years, the safety and efficacy of medications used for sedation during the procedure have received increased attention. The goals of sedation are generally threefold: cooperation, amnesia, and alleviation of anxiety.[1,2] The benefits of oral premedication for pediatric outpatient surgery and other diagnostic and therapeutic procedures include anxiolysis, reduced distress during i.v. insertion, ease of separation from parents, decreased need for i.v. medication, and shortened procedure and recovery times.[3,4] Various medications have been used, most commonly benzodiazepines such as diazepam and midazolam. Studies to date have not consistently demonstrated clinical superiority among these agents, and the optimal drug and dose to produce pre-procedural sedation in children remains unclear.[3,4] Children, however, may experience significant anxiety before undergoing esophagogastroduodenoscopy, especially during separation from parents and during vein puncture. Routes of administration that are often thought of as more appropriate for children include the oral, rectal, and intranasal routes. Rectally administered midazolam is sometimes unpleasant and poorly accepted by children and may be erratically absorbed.[4–7] I.v. conscious sedation has been shown to be both effective and safe and is now the most common form of sedation used for pediatric upper endoscopy.[8,9] This type of sedation, however, can be administered only after placement of an i.v. line and is usually given immediately before the start of the procedure. Thus, many children remain anxious up to the time of the procedure. This makes i.v. placement difficult, promotes increased doses of conscious sedation medication, makes separation from parents more difficult, and occasionally prolongs the procedure.[10] Oral premedication may alleviate these problems. Midazolam, a watersoluble benzodiazepine, is a widely used sedative-hypnotic drug that also provides anxiolysis, muscle relaxation, and anterograde amnesia.[11,12] We sought to determine whether sedation with midazolam, administered orally before separation from parents and before the endoscopy procedure, reduces the stress and anxiety caused by these events and provides adequate sedation during esophagogastroduodenoscopy. This prospective, blinded, placebo-controlled study was designed to evaluate the effect of oral midazolam when used as sedation for pediatric endoscopy.

Methods

Between 1 March 2007 and 1 March 2008, 61 consecutive children who underwent upper gastrointestinal endoscopy were prospectively included in the study. The study was conducted at Children's Hospital Tabriz Medical University, Iran. The Institutional Review Board of the university reviewed and approved the study protocol. The study has the clinicaltrial.gov identifier NCT00636428. Informed consent was obtained from each

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child's guardian (assent was obtained in children older than 7 years). All endoscopies were performed by one endoscopist. A trained anesthetist administered the sedative and carried out the anesthetic protocol. Two nurses were in attendance: one was assigned to observe the patient and secure the endoscope, and the other recorded vital signs and assisted in tissue biopsies. Patients were randomly assigned to one of the two protocols for sedation. The endoscopist was not blinded to study conditions because the sedatives were clearly visible. Exclusion criteria were as follows: age younger than 1 year; significant neurological disability; history of allergies to benzodiazepines or to their components; metabolic, cardiac, or renal disease; previous complications associated with i.v. sedation and respiratory distress.

Study medication

After arrival in the endoscopy suite, each patient was weighed and vital signs were obtained. I.v. access was established, and each patient was brought to the procedure room accompanied by parents or guardians. Each child was given a spray of lidocaine 10% to the posterior pharynx to diminish discomfort (gag reflex) during the endoscopy. The study medication, oral midazolam (0.5 mg/kg), was prepared as a solution (2.5 mg/mL) from injectable midazolam hydrochloride (Hypnoszol, Darou Pakhsh, Iran) and an orange-flavored syrup. For preparation, midazolam injection (5 mg/mL) was diluted 1:1 with the flavored syrup.[13,14] The oral midazolam solution was prepared in batches and packaged per unit of use in calibrated oral syringes approximately 30 min before beginning sedation for endoscopy. No additional doses of study medication were given. The i.v. midazolam medication was administered in slow i.v. boluses lasting as long as 1 min. The dose of midazolam administered was 0.05–0.1 mg/kg bodyweight, and the maximum individual dose was 2 mg. Each patient's vital signs, that is, heart rate (HR), respiratory rate (RR), systolic arterial pressure (SAP), and peripheral oxygen saturation (SpO_2), were measured before administration of the study drug, at the time of i.v. placement, after receiving the study medication but before the procedure, during the endoscopy, and during the recovery period every 5 min. Anxiety was subjectively measured for all patients by an independent nurse and physician by assessing each patient's apprehension during drug administration and immediately before performing the procedure, and by parental assessment of the child's ability to separate from the parent before the procedure. Pulse oximetry was continuously monitored. The level of sedation, separation from parents, patient complications, ease of performing the procedure, time of preparation, time for recovery, and patient/parent satisfaction with the procedure process were assessed by the physician and nurse involved in the procedure. The comfort scale was used: a score of 8–16 points corresponds to deep sedation, 17–26 indicates light sedation and 27–40 indicates inadequate sedation.[15,16] The level of sedation was assessed with a (University of Michigan Sedation Scale) 5 point observational scale for the depth of sedation: 0, awake and alert; 1, minimally sedated (tired/sleepy, appropriate response to verbal conversation and/or sound); 2, moderately sedated (somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command); 3, deeply sedated (deep sleep and arousable only with significant physical stimulation); 4, unarousable.[17] A score ≥3 was considered satisfactory. On completion of the procedure, each patient recovered in the day medicine unit and was discharged. Immediately after the procedure the endoscopist rated the procedure based on the ease of performance of the procedure and the need for restraining the child (1, poor; 2, fair; 3, good; 4, excellent). HR, SAP, SpO_2, RR, and the level of sedation and comfort score were recorded for all patients.

Statistical analysis

Baseline characteristics of the two groups (oral and i.v.) were compared using independent samples *t*-test or χ^2 test and Fisher exact test. Repeated measures analysis of variance was used to assess changes in variables in relation to time after medication administration and time during endoscopy. Data are expressed as mean ± SD. $P < 0.05$ was considered statistically significant. All statistical procedures were performed using SPSS version 14 (SPSS, Chicago, IL, USA).

Results

A total of 71 patients were considered as possible study participants; of these, four refused to participate and six met exclusion criteria, resulting in a study population of 61 patients. These 61 patients were enrolled in the study and randomly assigned to two groups, namely oral versus i.v. administration of midazolam. The mean age of the 61 patients was 7.5 ± 3.42 years (range, 1–16 years), and 37.7% were male. There were no significant differences between groups with regard to participant age (oral, 6.30 ± 2.91 years; i.v., 7.98 ± 3.71 years) or gender. Maximum sedation was achieved at 25–30 min after oral administration. There were no statistically significant differences between the groups with respect to duration of endoscopy. The success rate for endoscopy was 100% for both groups. There was, however, a significant difference in recovery time until discharge: oral group, 55.34 ± 10.85 min; i.v group, 42.74 ± 12.57 min ($t = 4.144$, d.f. = 58, $P = 0.0005$; Table 1). There were no significant differences in comfort scale between the oral group and the i.v. midazolam group before (17.8 ± 3.9 vs 17.2 ± 3.5, respectively; $t = 0.566$, d.f. =59, $P = 0.57$) or during endoscopy (16.16 ± 3.27 vs 16.54 ± 3.30, respectively; t = 0.453, d.f. = 59, $P = 0.62$). Comfort scale scores, however, were higher for the i.v. group after endoscopy ($P = 0.02$). Comparison of the sedation score in the oral and i.v groups showed no difference between the two groups and 97% maintained satisfactory scores ($P = 0.59$). Parental attitude did not differ between the two groups ($P = 0.84$).

SpO_2, HR, SAP, and RR were recorded just before the midazolam was introduced (T_{0m}), 10 min after midazolam (T_{10m}), during the procedure (T_{en}), and 10 min after removal of the endoscope (T_{en10}). There were no significant differences in HR, SAP, or RR between groups (Fig. 1). SpO_2, however, was significantly lower in the i.v. group than the oral group at T_{en10} and T_{en30}. (repeated measures analysis: $F_{(1,59)} = 0.057$, $P = 0.042$; Fig. 1).

During endoscopy in the oral and i.v. groups, SpO_2 declined below 95%, but not below 90%. But statistically significant differences in SpO_2 at different measurement times were seen in

Table 1 Subject data (mean ± SD)

Group	Oral mizazolam (n = 30)	i.v. midazolam (n = 31)	P
Age (years)	6.30 ± 2.91	7.98 ± 3.71	NS
Duration of procedure (min)	23.9 ± 13.1	25.5 ± 11.3	NS
Comfort scale:			
Before endoscopy	17.8 ± 3.9	17.2 ± 3.5	NS
During endoscopy	16.16 ± 3.27	16.54 ± 3.30	NS
Anxiety score, mean (range)	3.08 (2.8–3.2)	3.03 (2.9–3.3)	NS
Maximum sedation score	3	4	NS
Children with satisfactory sedation score (%)	95	98	NS
Parents with satisfactory premedication assessment (%)	88	82	NS
Recovery time (min)	55.34 ± 10.85	42.74 ± 12.57	0.0005

each group separately (i.v. group, P = 0.008; oral group, P = 0.0005). Repeated measures analysis also showed that the difference was not statistically significant with regard to HR ($F_{(1,59)}$ = 1/53; P = 0.93) or RR ($F_{(1,59)}$ = 2/52; P = 0.117) for different times in the two groups ($F_{(1,59)}$ = 2.56, P = 0.115) (Fig. 2).

Repeated measures analysis of variance showed that SAP was significantly higher during endoscopy when comparing data for T_{0m}, T_{10m}, T_{en}, and T_{en10} within groups, but there was no significant difference between groups ($F_{(1,59)}$ = 2.56, P = 0.115). Mean diastolic blood pressure over the course of the entire procedure did not differ significantly within groups, but there was a significant difference between the two groups ($F_{(1,59)}$ = 4.27, P = 0.041).

There were no significant differences in ease of monitoring or need for child restraint during the procedure (P = 0.78). Separation from parents was similar in the two groups (P = 0.911). Ninety-seven percent of families were reached by telephone following discharge from the hospital. There were no statistically significant differences between groups regarding the frequency of procedural-related symptoms experienced by the children. Symptoms reported most frequently for both groups included sleepiness upon arrival home (29%), dizziness (32%), headache (16%), nausea and emesis (3%), and dysphagia (2%). There were no differences in the endoscopist's rating of the two methods.

Discussion

Most gastrointestinal endoscopy is performed with the benefit of conscious sedation or general anesthesia. Conscious sedation refers to a controlled state of diminished consciousness wherein protective reflexes, the ability to respond to moderate physical or verbal stimuli, and ability to maintain a patent airway are retained. Pediatric sedation techniques should ideally be customized for the patient and the procedure to be performed. The present study demonstrates that oral midazolam is a safe and efficacious premedication for upper endoscopy in children. Prior studies also have demonstrated that oral midazolam, when used

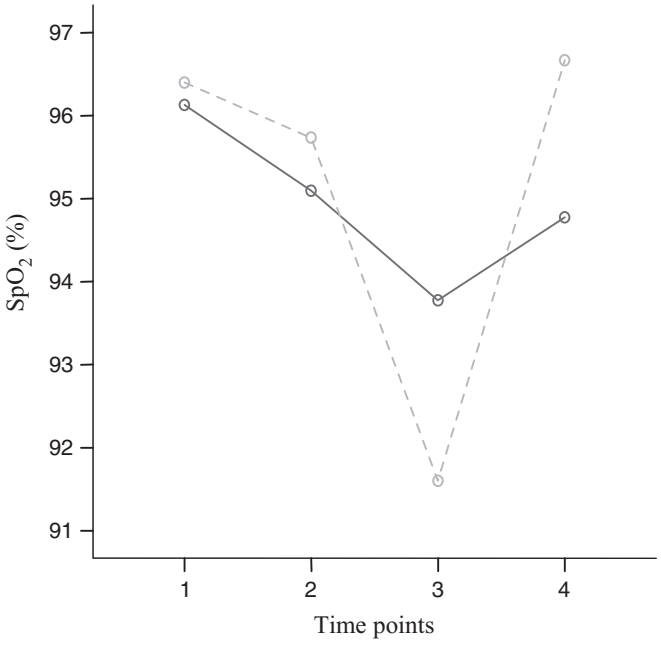

Fig. 1 Changes in mean SpO_2 in the (—) i.v. and (- - -) oral midazolam groups: 1, before induced sedation with midazolam; 2, 10 min after administration of midazolam; 3, during endoscopy; 4, after endoscopy.

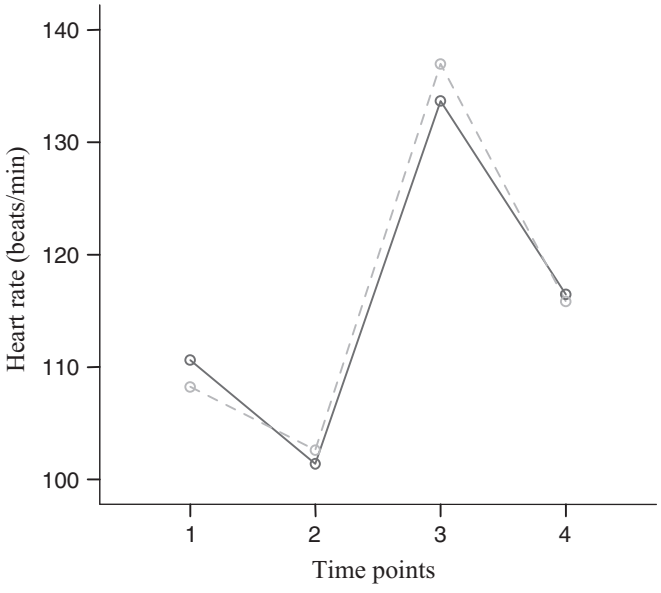

Fig. 2 Changes in mean heart rate in the (—) i.v. and (- - -) oral midazolam groups: 1, before induced sedation with midazolam; 2, 10 min after administration of midazolam; 3, during endoscopy; 4, after endoscopy.

as a premedication, not only improves the ease of separation from parents but also increases the patient's acceptance of events surrounding the procedure.[13]

The present study demonstrates significant improvements in pre-procedural sedation and separation from parents when patients received oral midazolam as compared with i.v. midazolam. Although oral midazolam decreased patient anxiety and improved both patient and parent acceptance of the procedure (on subjective assessment), it had no effect on patient vital signs and did not shorten endoscopic procedure time; it did, however, slightly increase the recovery time when compared with the i.v. group.

In the present study all episodes of hypoxemia were transient, and no patient required bag/mask ventilation. No serious complications were encountered, and discharge time from the hospital was similar in the two groups.

In almost all cases, patients given oral midazolam became somewhat drowsy and were more relaxed and cooperative than patients who received i.v. midazolam. We attempted to eliminate ascertainment bias by using subjective evaluation of patients performed by independent observers who had not previously met the patient. In the present study oral midazolam not only decreased patient anxiety but also improved both patient and parent satisfaction for the procedure, which is consistent with the results of the Liacouras *et al.* study.[14] In a multivariate logistic regression analysis of characteristics associated with cardiopulmonary complications, Thakkar *et al.* showed that, after adjusting for all other variables, i.v. sedation was independently associated with a 5.3-fold higher risk of cardiopulmonary complication (95% confidence interval: 3.7–7.7) than general anesthesia.[18] Mamula *et al.*, in a study of children sedated with i.v. fentanyl and midazolam, noted mild or moderate adverse events including oxygen desaturation ≤92% for <20 s in 100 patients (9%), vomiting in 64 (5%), agitation in 15 (1%), oxygen desaturation 92% for >20 s in 12 (0.7%), and rash in eight (0.7%).[2]

In the present study mild hypoxia occurred at only two points: 10 and 30 min after endoscopy in the i.v. group. Several factors may contribute to hypoxia in patients undergoing upper digestive tract endoscopy. Pharyngeal obstruction or tracheal compression with the endoscope may occur, causing oxygen desaturation during insertion of the endoscope. This occurs more frequently with endoscopes of large diameter and in small children.[19,20] In infants and children, gastric distension with air insufflations may also hinder the diaphragmatic course and may lead to severe hypoxia.[21]

Medications used for sedation are potent central nervous system depressants and can lead to hypoventilation, particularly when several drugs are combined.[22] Hypoventilation or aspiration may also result when local anesthetic is sprayed on the pharynx.[23]

In the present study there was no statistically significant difference between the oral and i.v. groups in homodynamic changes; no patient required resuscitation. Although recovery time was significantly longer in the oral group, all patients in both groups were fully recovered within 30 min after the procedure. These findings demonstrated that orally administered midazolam is safe and effective for pediatric patients undergoing upper endoscopy and can be offered on a routine basis, especially in situations when i.v. administration of sedative drugs is not feasible or appropriate. Intestine and hepatic metabolism, however, may be important factors in interindividual viability of oral administration of midazolam.[24] According to the study by Reed *et al.* the difference in route of administration is probably not clinically important.[25]

A recent prospective evaluation of rigorously standardized conscious sedation during pediatric endoscopy (all ages of children) noted equivalent efficacy and safety with markedly reduced costs compared with general anesthesia.[26] Considering the current status of pediatric sedation and the safety issues involved, future collaborative research and clinical program development can provide valuable information with which to evaluate pediatric sedation protocols. Large clinical trials or databases are required to assess the frequency of critical events.

Conclusion

The present study suggests that orally administered midazolam is a safe and effective means of sedation during upper endoscopy in children. Larger studies would allow analysis of data on current use and outcomes for sedatives used in a variety of pediatric specialties and settings.

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