Original Article

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Effectiveness of Oral Midazolam for Sedation in Patients Undergoing Upper Gastrointestinal Endoscopy: A Randomized Controlled Trial

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ABSTRACT

Background: Elective patients usually undergo upper gastrointestinal endoscopy (EGD) without any sedation. Sedation before EGD may reduce patient's anxiety and the procedure may be performed more effectively. The purpose of this study was to evaluate the effectiveness and adverse events of oral midazolam compared with placebo in patients undergoing EGD.

Methods: A double-blinded randomized controlled trial was carried out in elective EGD patients. Patients were allocated, using block-of-four randomization, to receive either 5 mg of oral midazolam or placebo 30 minutes before the procedure. Measurements were made and compared, including decreasing anxiety score (visual analog scale) between baseline and during EGD, overall tolerance, extent of amnesia, overall satisfaction, willingness to repeat the procedure, and hemodynamic changes after medication.

Results: Two-hundred-and-sixty patients were randomized to receive midazolam or placebo, 130 patients in each group. Fifty-fifth percent of study patients were male, and the mean age of all patients was 53.74 ± 11.74. The median (interquartile range) of decreasing anxiety score between baseline and during EGD was significant greater in the midazolam group than in the placebo group (-5 [-6, -4] vs -1 [-1, 0], $p<0.001$). Overall tolerance, which was classified as "Good" or "Excellent", was significantly greater in the midazolam group than in the placebo group (92.3% vs 26.9%, $p<0.001$). Patients in the midazolam group had a higher partial to complete amnesia score than in the placebo group (18.5% vs 90.8%, $p<0.001$). Overall satisfaction score for both patients and doctors were better in the group receiving midazolam (7.72 ± 1.01 vs 5.22 ± 1.59, 7.53 ± 0.99 vs 5.23 ± 1.29; $p<0.001$). Most patients in both groups were willing to repeat EGD again if necessary. No patients were observed to have aspiration, hypotension or desaturation by pulse oximetry.

Conclusion: Oral midazolam can be used effectively as a sedative drug in patients undergoing elective EGD. It reduces patient's anxiety significantly without causing any significant adverse events.

Key words : Oral midazolam, sedation, premedication, upper gastrointestinal endoscopy, EGD

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INTRODUCTION

Upper gastrointestinal (GI) endoscopy is widely used in normal daily practice. It is considered the investigation of choice in cases of dyspepsia, dysphagia, odynophagia, heartburn, protracted vomiting, GI bleeding, and even foreign material removal[1]. These cause the numbers of patients undergoing EGD have increased steadily. In western studies, over 1,400 - 1,600 upper GI endoscopy were performed per year[2]. The number of EGD at Phramongkutklao Hospital had also increased from 1,600 in 2009 to 1,800 in 2011.

EGD may be associated with patient's discomfort, anxiety and refusal to undergo a repeat procedure[3,4]. Premedication before EGD is used to reduce anxiety and obtain a good cooperation during the procedure. It also increases the endoscopist's satisfaction as well[5-7].

Midazolam is a short-acting benzodiazepine that is widely used intravenously (IV) for conscious sedation to relief anxiety for patients undergoing EGD. Anterograde amnesia for about 1 - 2 hours is often considered a beneficial effect of midazolam[8]. The drug is, therefore, commonly used in short-time procedure such as endoscopy or dentistry[5, 7, 9-11].

At Phramongkutklao Hospital, patients undergoing elective EGD are not routinely given sedative medication. IV midazolam is considered only patients for with much anxiety or poor cooperation. IV midazolam has some side effects, however, such as hypotension, bradypnea, bradycardia, and phlebitis[8,9]. In addition, IV medication increases the workload of the nursing staff and the total cost of procedure.

Oral midazolam has been used for a longtime for sedation in pediatric patients undergoing EGD, with comparable efficacy as IV midazolam but with fewer side effects[12,13].

Oral midazolam has also been reported in studies in adults such as in dental procedures[14,15]. To our knowledge, there were only two small studies using oral midazolam for premedication before GI endoscopy[16,17].

The aim of the current study was to investigate whether oral midazolam could be effectively used as premedication for adults undergoing elective upper GI endoscopy.

MATERIALS AND METHODS

This was a single-center, prospective, randomized, double-blind, placebo-controlled trial. The study was approved by the Hospital Review Board of Medical Ethics and was registered at ClinicalTrials.gov (ID: NCT01990937). Recruitment started in Oct 2013, and ended in Dec 2013. Patients aged 18 to 70 who were scheduled to undergo an elective diagnostic EGD at the GI Endoscopy Unit, Phramongkutklao Hospital, and who were class 1 to 2 by the American Society of Anesthesia (ASA) criteria, were eligible for inclusion in the study. A written informed consent was obtained from all participants. Exclusion criteria were: history of gastrectomy, esophagectomy, or pancreaticoduodenectomy; ASA class 3 to 4; history of allergy to midazolam; alcoholism; drug abuse; psychotic drug ingestion within the preceding 3 months; and pregnancy.

Demographic data including age, gender, underlying disease and anxiety score (10-cm scaled visual analog scale (VAS): 0 = absence of pain, 10 = worst possible pain) were obtained. Patients were randomized by the computer to receive either 5 mg of midazolam hydrochloride mixed with 15 cc of apple juice or placebo (15 cc. of apple juice), given 30 minutes before EGD. Midazolam hydrochloride injection was supplied as 5-mg vials (5 mg/mL) as a standby alternative by JENAHEXAL Pharma GmbH, Germany. All personnel in the study, including the, nurses and endoscopists as well as the patients, were blinded to the treatment modality.

After ingesting the medication, patients were observed along with nursing assistance. Baseline heart rates, blood pressure and oxygen saturation were recorded. Anxiety score was accessed again just before EGD, which was performed 30 minutes later by four board-certified experienced endoscopists who had each performed more than 500 procedures before. Lidocaine spray (Xylocaine Pump Spray 10%; AstraZeneca, Sweden) was applied for topical pharyngeal anesthesia. A standard upper GI endoscope (GIF Q160; Olympus Optical Co., Ltd., Japan) was used. Total procedure time and additional interventions were recorded by trained endoscopy nurses. Blood pressure, heart rates and oxygen saturation were recorded at 5-minute intervals until full recovery, defined as hemodynamic stability and full consciousness. After full recovers patients were assess for anxiety during the procedure (10-cm scaled VAS), overall tolerance, amnesia score, overall satisfaction (10-cm scaled VAS: 0 = not satisfied, 10 = very satisfied) and willingness to

undergo a future EGD if necessary (yes or no). The scale for overall tolerance was as follows: poor = very uncomfortable during the entire procedure; fair = uncomfortable during most of the procedure; good = generally comfortable but with some parts of the procedure during which sedation could have been given; excellent = comfortable over the entire procedure, no additional sedation needed. The scale for amnesia score was defined as: 1 = unable to recall any portion of procedure; 2 = able to recall and describe some parts of the procedure; 3 = able to recall and describe most parts of procedure; 4 = able to recall and describe the entire procedure. The endoscopist was also assessed for overall satisfaction (10-cm scaled VAS: 0 = not satisfied, 10 = very satisfied).

The primary endpoint was the difference between the intra-procedural anxiety score and the baseline anxiety score. The secondary outcomes were overall tolerance, amnesia score, overall satisfaction and willingness to undergo a future EGD if necessary.

Statistical analysis

Age, sex and underlying disease were shown in the descriptive analysis as frequency, percent, mean and standard deviation. Between-group differences in gender, age, and blood pressure were analyzed using a *t*-test and chi-square test for independent samples. Between-group differences in anxiety score was analyzed by Mann-Whitney U test. Between-group differences in overall tolerance, amnesia score, willingness to repeat EGD and overall satisfaction of patients and endoscopists were analyzed by chi-square test and t-test. A two-sided p-value < 0.05 was considered significant. All statistical procedures were performed using STATA version 11.

Results

A total of 260 patients were enrolled in the study and randomly assigned to midazolam or placebo group, 130 patients in each group. The mean age of all patients was 53.74 ± 11.74, and 55% were male. There were no significant differences between the two groups with respect to participant age (midazolam, 53.02 ± 11.10 years; placebo, 54.45 ± 12.35 years; p= 0.327) or gender (Table 1). There were no significant differences between the groups with respect to baseline mean arterial pressure (MAP) (midazolam, 94.4 ± 12.24 mmHg; placebo, 95.71 ± 10.82 mmHg; p = 0.363) and heart rates (midazolam, 79.83 ± 58.22 bpm; placebo, 73.5 ± 12.31 bpm; p = 0.226). Baseline oxygen saturation was slightly less in the midazolam group (midazolam, 98.67 ± 1.37 %; placebo, 99 ± 1.09 %; p = 0.032) but not clinically significant. The main indication for EGD was dyspepsia (midazolam, 36.2%; placebo, 39.2%). The success rate for EGD was 100% in both groups.

The median baseline anxiety score (interquartile range) was greater in the midazolam than in the placebo group, which was statistically significant (midazolam, 6 [5, 7]; placebo, 6 [5, 6]; p = 0.002) (Table 1). The median (interquartile range) of decreasing anxiety score between baseline and during the procedure was significantly greater in the midazolam than in the placebo group (midazolam, -5 [-6, -4]; placebo, -1 [-1, 0]; p <0.001) (Table 2). Patients reported less anxiety with oral midazolam compared with placebo during the procedure (midazolam, 1 [0, 2]; placebo, 5 [4, 6]; p <0.001) (Figure 1).

Patients who received midazolam was significantly more likely to grade overall tolerance as "good or excellent" than those who received placebo (midazolam, 92.3%; placebo, 26.9%; p <0.001). A partial to complete amnestic response, defined as amnesia score of 1 or 2, was seen in 118 (90.8%) patients in the midazolam group compared with 24 (18.5%) patients in the placebo group (p <0.001). Overall patients satisfaction score was significantly greater in the midazolam group than in the placebo group (midazolam, 7.72 ± 1.01; placebo, 5.22 ± 1.59; p <0.001). Overall endoscopist satisfaction score was also significantly greater in the midazolam group than in the placebo group (midazolam, 7.53 ± 0.99; placebo, 5.23 ± 1.29; p <0.001). Most patients in both groups were willing to repeat EGD again in the future if necessary, but the percentage was greater in the midazolam group (midazolam, 99.2%; placebo, 92.3%; p = 0.006).

There were no significant differences between the two groups with respect to total procedure time (midazolam, 9.88 ± 3.88 minutes; placebo, 10.1 ± 4.2 minutes; p = 0.668) (Table 3). The mean recovery times were 5.04 ± 0.44 minutes in both groups. The main intervention in both groups was endoscopic biopsy, which was without significant difference between the groups (midazolam, 80%; placebo, 78.5%; p = 0.676).

There were no significant differences between the groups with respect to MAP (midazolam, 98.35 ± 11.92 mmHg; placebo, 98.96 ± 11.29 mmHg; p = 0.672),

Table 1. Baseline characteristics and indications for EGD of 260 patients.

	Midazolam (n=130)	Placebo (n=130)	*p*-value
Age; mean ± SD	53.02 ± 11.10	54.45 ± 12.35	0.327
Sex; n (%)			
- Male	70 (53.8%)	71 (54.6%)	0.901
- Female	60 (46.2%)	59 (45.4%)	
Baseline anxiety score in VAS†	6 (5, 7)	6 (5, 6)	0.002‡
Indications for EGD; n (%)			0.383
- Dyspepsia	47 (36.2%)	51 (39.2%)	
- Follow up ulcer	16 (12.3%)	25 (19.2%)	
- Surveillance EV	26 (20%)	22 (16.9%)	
- GERD	11 (8.5%)	13 (10%)	
- Anemia	9 (6.9%)	3 (2.3%)	
- Eradication EV	6 (4.6%)	4 (3.1%)	
- Other	15 (11.5%)	12 (9.2%)	
Baseline MAP (mmHg)	94.4 ± 12.24	95.71 ± 10.82	0.363
Baseline HR (bpm)	79.83 ± 58.22	73.5 ± 12.31	0.226
Baseline O_2 saturation (%)	98.67 ± 1.37	99 ± 1.09	0.032

EV, esophageal varices; VAS, visual analog scale; MAP, mean arterial pressure; HR, heart rate
†Median (interquartile range), ‡Mann-Whitney U test

Table 2. Primary and secondary outcomes.

	Midazolam (n=130)	Placebo (n=130)	*p*-value
Primary outcome			
Anxiety score just before EGD in VAS†	2 (1, 4)	5 (4, 5)	<0.001‡
Anxiety score during EGD in VAS†	1 (0, 2)	5 (4, 6)	<0.001‡
Difference of during and baseline anxiety score in VAS†	-5 (-6, -4)	-1 (-1, 0)	<0.001‡
Secondary outcome			
Overall tolerance; n (%)			<0.001
- Poor	2 (1.5%)	13 (10%)	
- Fair	8 (6.2%)	82 (63.1%)	
- Good	64 (49.2%)	33 (25.4%)	
- Excellent	56 (43.1%)	2 (1.5%)	
Overall tolerance; n (%)			
- Poor or fair	10 (7.7%)	95 (73.1%)	<0.001
- Good or excellent	120 (92.3%)	35 (26.9%)	
Amnesia score; n (%)			<0.001
- 1	54 (41.5%)	3 (2.3%)	
- 2	64 (49.2%)	21 (16.2%)	
- 3	8 (6.2%)	72 (55.4%)	
- 4	4 (3.1%)	34 (26.2%)	
Amnesia score; n (%)			
- Partial to complete	118 (90.8%)	24 (18.5%)	<0.001
- No to minimal	12 (9.2%)	106 (81.5%)	
Overall satisfaction in VAS#			
- Patient	7.72 ± 1.01	5.22 ± 1.59	<0.001
- Doctor	7.53 ± 0..99	5.23 ± 1.29	<0.001
Willing to repeat EGD; n (%)			
- Yes	129 (99.2%)	120 (92.3%)	<0.001
- No	1 (0.08%)	10 (7.7%)	

VAS, visual analog scale
†Median (interquartile range), ‡Mann-Whitney U test, #Mean ± standard deviation

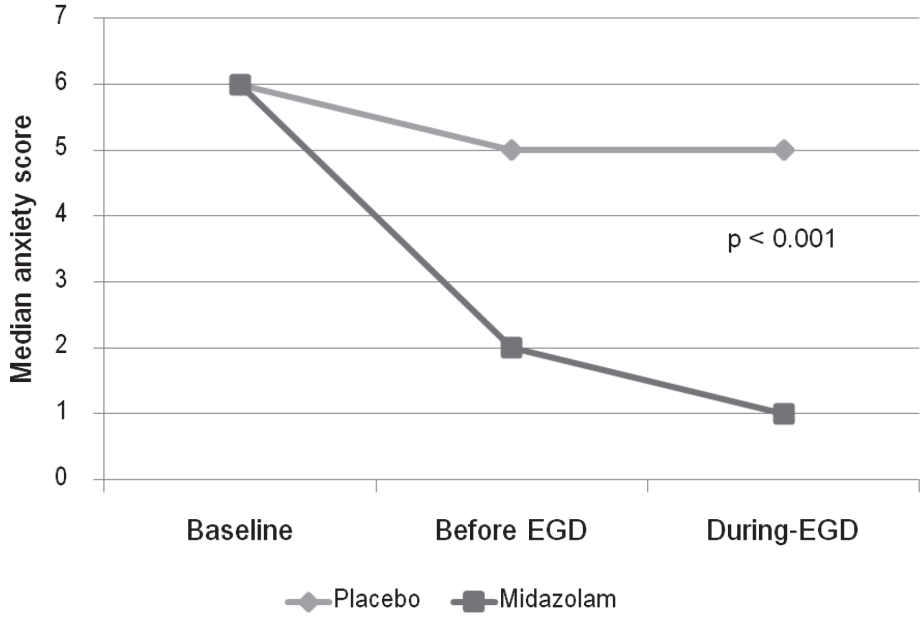

Figure 1. Anxiety score.

Table 3. Other outcomes.

	Midazolam (n=130)	Placebo (n=130)	*p*-value
Intervention; n (%)			0.676
- Biopsy	104 (80%)	102 (78.5%)	
- Rubber band ligation	6 (4.6%)	4 (3.1%)	
- None	20 (15.4%)	24 (18.5%)	
Total procedure time (minutes)†	9.88 ± 3.88	10.1 ± 4.2	0.668
Recovery time (minutes)†	5.04 ± 0.44	5.04 ± 0.44	1.000
MAP at end of EGD (mmHg)†	94.4 ± 12.24	95.71 ± 10.82	0.363
HR at end of EGD (bpm)†	79.83 ± 58.22	73.5 ± 12.31	0.226
O_2 saturation at end of EGD (%)†	98.67 ± 1.37	99 ± 1.09	0.032

MAP, mean arterial pressure; HR, heart rate
†Mean ± standard deviation

heart rates (midazolam, 79.06 ± 12.46 bpm; placebo, 78.4 ± 12.38 bpm; $p = 0.668$) and oxygen saturation (midazolam, 98.85 ± 1.2 %; placebo, 98.99 ± 1.2 %; $p = 0.329$) at the end of EGD. No patients had aspiration, hypotension (MAP < 65 mmHg) or desaturation by pulse oximetry (oxygen saturation < 90%).

Discussion

Upper GI endoscopy is a widely used investigation today. In many cases, EGD can be performed without sedation. However, patients with much anxiety may require pharmacologic premedication before EGD. Intravenous midazolam is the most commonly used benzodiazepine as a premedication for sedation. In addition to relieving anxiety, of intravenous midazolam also has an anterograde amnesia effect to null unpleasant memories.

Oral midazolam had been used for premedication before undergoing EGD in pediatric patients for a long time[12]. Rafeey M, *et al.* employed oral midazolam as premedication in children undergoing EGD and found that the anxiety score and the overall tolerance was not statically different from IV midazolam[13].

However, there have been just few studies on the use of oral midazolam in adults for premedication before EGD. Kuganeswaran E, *et al.* also used a 7.5 mg oral midazolam as premedication in adults before undergoing sigmoidoscopy and demonstrated that it reduced pain and anxiety during the procedure[16]. In a recent prospective study, Mui LM, *et al.* used a 7.5 mg oral dose of midazolam as premedication in 130 adult patients before EGD and showed that the anxiety score during the procedure in the midazolam group was significantly lower than that in the control group[17]. The present study employed only 5 mg oral midazolam and also showed that the anxiety score during the procedure in the midazolam group was significantly lower than that in the control group. The dosage of midazolam chosen in this study was lower than that in the previous study as the average body weight of our Thai subjects was lower. This reasoning is supported by Danworanan's study[18] in which only 0.2 mg/kg of oral midazolam was used as premedication in Thai patients before undergoing dental surgery and was effective in decreasing anxiety during the dental procedure[18]. Moreover, this present study showed that oral midazolam could reduce anxiety prior to EGD, as the anxiety score just before EGD in the midazolam group was significantly less than that in the control group.

Our study showed that patients in the midazolam group had anterograde amnesia and better overall tolerance compared to the placebo group. Thus, more patients in the former group were willing to repeat EGD again if necessary. None the less, in the placebo group only 7.7% refused to repeat EGD again ever if necessary.

There was no significant difference between the midazolam and the placebo group with regard to the total procedure time. But the overall satisfaction for both the patients and the endoscopists were significantly greater in the midazolam group. There was no statistical difference in the recovery time, nor the hemodynamic and oxygenation between the two groups. Furthermore, there were no episodes of hypotension, hypoxemia and aspiration in the midazolam group. These findings demonstrated that orally administered midazolam is safe and effective in patients undergoing EGD. Future study should aim at comparing the efficacy between the oral and the intravenous forms of midazolam in reducing the workload of the endoscopy personal as well as the overall cost of EGD.

There were limitations in the present study. First, a 10-cm scale visual analog scale was used in this study instead of 10-cm non-scale VAS, and this cloud have affected the validity of the result. The reason was because many Thai patients had problems understanding the non-scale pattern. Second, the dosage of midazolam in this study was less than in previous studies. This dosage may not be as effective in western populations with heavier average body weight. Future studies should help to establish the optimal dosage. Third, the anxiety score that was assessed just before EGD was difficult to interpret in some cases as the patients were still rather sleepy. However, the anxiety score during the procedure was considered reliable as it was assessed when patients were already fully conscious.

In conclusion, the results of this prospective randomized controlled trial indicated that oral midazolam can be used effectively for premedication in patients undergoing EGD. It reduces patient's anxiety significantly without causing significant adverse events. Further study is designed to should compare the efficacy between the oral and the intravenous forms.

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