Premedication with benzodiazepines for upper gastrointestinal endoscopy: Comparison between oral midazolam and sublingual alprazolam

Vahid Sebghatollahi, Elham Tabesh, Ali Gholamrezaei¹, Amir Reza Zandi², Mohammad Minakari, Ahmad Shavakhi
Department of Internal Medicine, Division of Gastroenterology, Isfahan University of Medical Sciences, ¹Medical Student’s Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, ²Department of Chronic Diseases, Metabolism and Ageing, Translational Research Center for Gastrointestinal Disorders, University of Leuven, Leuven, Belgium

INTRODUCTION

Esophagogastroduodenoscopy (EGD) is a common procedure for investigating various medical conditions. Besides procedural anxiety, EGD can cause pain or discomfort for many patients.¹⁻² Anxiety can increase pain/discomfort during the procedure which, in turn, decreases patient’s tolerance.³⁻⁴ Appropriate sedation can decrease procedural anxiety and discomfort and increase patient’s tolerance and satisfaction.⁵⁻⁶

Intravenous administration of benzodiazepines (e.g., midazolam) is a popular sedation method in endoscopic procedures.⁷⁻⁸ However, intravenous sedation requires close patient monitoring, full equipment, and trained personnel for managing possible serious hemodynamic events.⁷⁻⁸ Non-intravenous (oral, sublingual, intranasal) administration of benzodiazepines may be a cost-effective alternative sedation method for EGD. Evidence has shown that such methods can reduce procedural anxiety and discomfort and increase patient’s tolerance and satisfaction.⁹⁻¹³

Although it is shown that oral midazolam is an effective premedication for endoscopic procedures,⁹⁻¹⁰ it is not widely available and yet has a higher cost comparing to other benzodiazepines. Moreover, there is a concern regarding hemodynamic side effects with its use.⁹⁻¹⁴⁻¹⁵

Key words: Anxiety, benzodiazepines, endoscopy, esophagogastroduodenoscopy, premedication, sedation
Among other benzodiazepines, alprazolam has a relatively rapid onset and short duration of action and has been applied effectively for sedation before surgery,[16,17] and also for diagnostic EGD.[18] However, only a few head-to-head comparisons between benzodiazepines are conducted so far, most of them in children.[19] Accordingly, we compared the efficacy and safety of oral midazolam and alprazolam in reducing anxiety and pain/discomfort associated with EGD in adult patients.

MATERIALS AND METHODS

Participants and study settings
This study was conducted at the endoscopy unit of Alzahra University Hospital (Isfahan, Iran) from September 2016 to February 2017. Elective diagnostic EGD candidates were evaluated according to the following inclusion criteria: age between 18 and 65 years, the first experience of EGD, American Society of Anesthesiology physical status class of I or II, and willingness to participate in the study. Patients with the following characteristics were not included into the study: severe psychiatric, neurologic, cardiac, pulmonary, or other serious diseases interfering with conducting the study or outcome assessment; concomitant treatment with benzodiazepines; current opium use or alcohol consumption; history of allergy to lidocaine or benzodiazepines; history of surgery on upper gastrointestinal tract; and current pregnancy or lactation. Patients who needed therapeutic endoscopic intervention or additional intravenous sedatives during EGD were excluded from the study. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (protocol ID 395569) and was registered in the clinicaltrials.gov (NCT03130842). Informed consent was obtained from all patients.

Study design
The study was designed as a comparative clinical trial with two parallel arms. Eligible patients were consecutively entered into the study and were alternately allocated into two groups of oral midazolam or sublingual alprazolam. Allocation was performed based on the day of the procedure; all patients in the same day received the same medication. The nursing team was responsible for providing the medications to the patients. The nursing team and the gastroenterologist who performed the procedure were aware of the study arms and the premedication that patients received. Patients were informed (with the consent form or verbally for illiterates) about receiving an active medication that could reduce their anxiety (if any) and increase their tolerance during the endoscopy. They were aware that two non-intravenous medications are going to be compared in this study but were blinded to the name of the medications.

Intervention
Patients in the oral midazolam group received midazolam hydrochloride (7.5 mg, Tehran Chemie Pharmaceutical Co., Tehran, Iran) mixed with 15 cc apple juice to be taken orally at 30 min before the procedure.[19] Patients in the sublingual alprazolam group received one tablet of the standard oral formulation of alprazolam 0.5 mg (Sobhan Co., Tehran, Iran) to use sublingually at 30 min before the procedure.[19] Lidocaine spray 10% (Sina Darou Co., Tehran, Iran) was applied for local pharyngeal anesthesia before the procedure. Endoscopy was performed for all patients by an experienced gastroenterologist (VS) using the same devices (PENTAX Medical, NJ, USA). For patients with extreme discomfort and lack of tolerance during the procedure, 2 mg midazolam was slowly injected intravenously at the discretion of the endoscopist.

Assessments
The study primary outcomes included (1) EGD-related anxiety and (2) pain/discomfort. Anxiety was assessed before the drug administration (baseline) and then just before EGD (30 min after medication) using a numerical rating scale, scored from 0 (no anxiety) to 10 (the most anxiety).[18] Pain/discomfort related to EGD was evaluated when patients were fully alert (at the discretion of the nursing team) using a numerical rating scale scored from 0 (no pain/discomfort) to 10 (the most pain/discomfort).[18]

Patient’s overall tolerance and satisfaction, willingness to repeat the procedure in future (if necessary), duration of the procedure, and hemodynamic events were considered as the secondary outcomes. Patient’s tolerance was evaluated using a four-point Likert scale (poor to excellent tolerance).[10] Satisfaction was assessed using a numerical rating scale scored from 0 (the least satisfaction) to 10 (completely satisfied).[18] Blood pressure, heart rate, and arterial oxygen saturation were recorded at baseline, at the beginning of the EGD, and then at 5 min intervals up to 30 min after starting the procedure (Cardioset LX110, Isfahan Optics Industries Co., Isfahan, Iran). Hypotension episode was defined as systolic blood pressure of <90 mmHg, bradycardia as heart rate of <60 bpm, and desaturation as arterial oxygen saturation of <90%.[19] The nursing team who administered the medication to patients also was responsible to assess the study outcomes.

Statistical analyses
Sample size was calculated based on the equivalency of the two drugs in reducing EGD-related anxiety with equivalence limit considered as 20%.[10] Sample size was calculated as 72 participants for each of the study groups considering a study power of 80% and type I error of 2.5% (Bonferroni-type adjustment for the two primary outcomes) and a dropout rate of about 10%.
Data were analyzed using IBM® SPSS® Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were checked for normal distribution using one-sample Kolmogorov–Smirnov Test. Data are presented as means ± standard deviation (SD) for continuous variables. Categorical data are presented as number and percentage (%). Independent Samples t-test (for normally distributed data), Mann–Whitney U-test (for non-normally distributed data), and Chi-square or Fisher’s exact tests (for categorical data) were applied for comparisons between the two groups. The Wilcoxon test was used to test change in anxiety score before and after medication (since data were not normally distributed). More detailed analyses of the hemodynamic variables are explained in supplementary data [Appendix 1]. \( P < 0.025 \) was considered significant for analysis of the two primary outcomes (Bonferroni-type adjustment). No correction was applied for the secondary outcomes (\( P < 0.05 \) was considered statistically significant).

RESULTS

A total of 136 patients were included in the study and were allocated to the study groups [Figure 1]. Two patients in the alprazolam group required intravenous sedation during EGD (between-group comparison, \( P = 0.241 \)). The study groups were similar regarding demographic data and baseline characteristics [Table 1].

Primary and secondary outcomes

According to the Wilcoxon test, anxiety was significantly reduced with midazolam (mean ± SD of reduction = 1.86 ± 1.63, \( P < 0.001 \)) as well as with alprazolam (mean ± SD of reduction = 2.02 ± 1.99, \( P < 0.001 \)). Patients in both groups experienced equal reduction in anxiety after using the medication (34.7% vs. 42.2%, \( P = 0.44 \)) [Table 2]. Pain/discomfort scores were significantly lower with alprazolam compared to the midazolam (4.80 ± 3.01 vs. 3.68 ± 3.28, \( P = 0.024 \)). There was no significant difference between the two groups in tolerance, satisfaction, willingness to repeat the procedure, and duration of the procedure [Table 2].

Hypotension and bradycardia episodes were rare, transient, and with no significant difference between the two groups [Table 2]. Desaturation was relatively more common compared to other events (11.9%, 16 out of 134). There was no significant difference between the study groups in cumulative hemodynamic events [Table 2]. Hemodynamic changes are presented in [Figure 2 to 4]. More details are provided in supplementary data [Appendix 1].

DISCUSSION

This study is the first head-to-head comparison between two benzodiazepines in adults undergoing EGD and showed that sublingual alprazolam is as efficient as oral midazolam for reducing procedural anxiety as well as increasing patient’s tolerance and satisfaction with the procedure. Pain/discomfort was lower with alprazolam compared to midazolam. The two drugs were similar regarding hemodynamic events. Frequency of desaturation episodes with oral midazolam in our study (8.8%) was higher compared to a previous study (4.5%),\(^ {10} \) and patients had relatively more common desaturation episodes with sublingual alprazolam (15.2%). Accordingly, patients must be monitored more closely for possible excessive sedation that can cause respiratory depression.\(^ {20} \)
Midazolam can be administered intranasally which has a faster onset of action and higher bioavailability compared to its oral administration. Studies have shown that patients undergoing endoscopy have similar tolerance and satisfaction with both treatments; however, sublingual alprazolam was accompanied with less sedation than intranasal midazolam.[22] However, another study could not find a benefit for intranasal midazolam over placebo for patients undergoing EGD.[23] Therefore, further studies are needed to investigate the optimal route of administration, dosage, and time interval between drug administration and EGD for premedication with non-intravenous benzodiazepines. Combination with non-pharmacological treatments (e.g., providing patient information materials[21,23]) may increase the efficacy of premedication while has no additional risk and therefore warrants further investigation.

There are some limitations to this study worth mentioning: (1) we could not use a third group with placebo as the control because of ethical concern. Hence, the study design was comparative trial. (2) We applied alternative allocation for assigning patients to the study groups which is not a standard randomization method though the two groups were similar in baseline characteristics. (3) Preparation and administration of the study drugs in the same format (sublingual midazolam tablet) was not possible for us, and therefore, patients and investigators were not blinded to the study arms which might have affected our findings. (4) Although our study sample size was appropriate for the primary study outcomes, since hemodynamic side effects were not common, investigation and comparison of the safety of oral benzodiazepines required larger sample size.

**CONCLUSION**

We found that sublingual alprazolam is as effective and safe as oral midazolam for sedation during EGD. They were similar in reducing procedural anxiety, and patients had similar tolerance and satisfaction with both treatments; however, sublingual alprazolam was accompanied with less pain/discomfort during EGD. Hemodynamic side effects

---

**Table 1: Comparison of demographic data and baseline hemodynamic variables and anxiety score between the two study groups**

|                              | Midazolam (n=68) | Alprazolam (n=66) | P   |
|------------------------------|------------------|-------------------|-----|
| Age (years), mean±SD         | 40.91±12.70      | 39.09±13.80       | 0.42*|
| Female: male, n (%)          | 40 (58.8):28     | 35 (53.8):30      | 0.68*|
| Baseline anxiety score in NRS, mean±SD | 4.52±3.44        | 3.95±3.27         | 0.28*|
| Baseline SBP (mmHg), mean±SD | 126.95±17.75     | 126.22±18.16      | 0.81*|
| Baseline HR (bpm), mean±SD   | 90.58±14.30      | 88.40±13.43       | 0.34*|
| Baseline oxygen saturation (%), mean±SD | 95.01±2.35       | 95.07±2.72        | 0.52*|

*Independent samples t-test; †Chi-square test; *Mann–Whitney U-test. NRS = Numerical rating scale from 0 to 10; SD = Standard deviation; HR = Heart rate; SBP = Systolic blood pressure.

**Table 2: Comparison of the primary and secondary outcomes between the two study groups**

|                              | Midazolam (n=68) | Alprazolam (n=66) | P   |
|------------------------------|------------------|-------------------|-----|
| Pre-EGD anxiety score in NRS, mean±SD | 2.94±2.62        | 2.5±3.00          | 0.13*|
| Change in anxiety score after medication, mean±SD | 1.86±1.63        | 2.02±1.99         | 0.91*|
| Percent of change in anxiety score after medication, mean±SD | 34.74±30.35      | 42.26±39.26       | 0.44*|
| Pain/discomfort score in NRS, mean±SD | 4.80±3.01        | 3.68±3.28         | 0.02*|
| Overall tolerance on four-point Likert scale, n (%) | Excellent or good | 40 (58.8)          | 63 (45.2) | 0.56*|
| Satisfaction score in NRS, mean±SD | 7.79±2.35        | 8.13±2.52         | 0.15*|
| Willing to repeat procedure, n (%) | 57 (83.8)        | 50 (75.8)         | 0.34*|
| Procedure duration (min), mean±SD | 6.95±3.47        | 6.19±2.82         | 0.14*|
| Hypotension (SBP <90 mmHg), n (%) | 1 (1.5)           | 2 (3)              | 0.61*|
| Bradycardia (HR <60 bpm), n (%) | 1 (1.5)           | 0                  | >0.99*|
| Desaturation (SaO₂ <90%), n (%) | 6 (8.8)           | 10 (15.2)         | 0.38*|
| Cumulative hemodynamic events, n (%) | 7 (10.3)          | 11 (16.7)         | 0.40*|

*Mann–Whitney U-test; †Chi-square test; *Significant between-group difference using Mann–Whitney U-test (P < 0.05)

---

**Figure 3:** Heart rate (±1 standard error of the mean) at baseline and during and after endoscopy. *Significant between-group difference using Mann–Whitney U-test (P < 0.05)
Premedication with orally administered midazolam in using intranasal midazolam spray to prevent identification of factors that influence tolerance of upper gastrointestinal endoscopy. A comparison of oral diazepam versus alprazolam or oral midazolam, depending on availability and costs, for patients undergoing diagnostic EGD. Further studies on optimizing the efficacy of premedication by combination with non-pharmacological interventions and also investigating the optimal route of administration, dosage, and time of administration are suggested.

Acknowledgments
This study was supported by the Isfahan University of Medical Sciences (Grant No. 395569). Authors are thankful to Dr. Samaneh Khanpour Ardestani (University of Alberta, Canada) for editing this report.

Financial support and editing
This study was financially supported by the Isfahan University of Medical Sciences (Grant No. 395569).

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Brandt LJ. Patients' attitudes and apprehensions about endoscopy: How to calm troubled waters. Am J Gastroenterol 2001;96:280-4.
2. Campo R, Brullet E, Montserrat A, Calvet X, Moix J, Reu M, et al. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. Eur J Gastroenterol Hepatol 1999;11:201-4.
3. Lee SY, Son HJ, Lee JM, Bae MH, Kim JJ, Paik SW, et al. Identification of factors that influence conscious sedation in gastrointestinal endoscopy. J Korean Med Sci 2004;19:536-40.
4. Abraham NS, Fallone CA, Mayrand S, Huang J, Wieczorek P, Barkun AN. Sedation versus no sedation in the performance of diagnostic upper gastrointestinal endoscopy: A Canadian randomized controlled cost-outcome study. Am J Gastroenterol 2004;99:1692-9.
5. Cohen LB, Delegee MH, Aisenberg J, Brill JV, Inadomi JM, Kochman ML, et al. AGA Institute review of endoscopic sedation. Gastroenterology 2007;133:675-701.
6. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc 2008;67:910-23.
7. Arrowsmith JB, Gerstman BB, Fleischer DE, Benjamin SB. Results from the American Society for Gastrointestinal Endoscopy/U.S. Food and Drug Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. Gastrointest Endosc 1991;37:421-7.
8. Daneshmend TK, Bell GD, Logan RF. Sedation for upper gastrointestinal endoscopy: Results of a nationwide survey. Gut 1991;32:12-5.
9. Kugasenwaran E1, Clarkston WK, Cuddy PG, Quaison SG, Pandya PK, Dierenfeldt WT, et al. A double-blind placebo controlled trial of oral midazolam as premedication before flexible sigmoidoscopy. Am J Gastroenterol 1999;94:3215-9.
10. Mui LM, Teoh AY, Ng EK, Lee YT, Au Yeung AC, Chan YL, et al. Premedication with orally administered midazolam in adults undergoing diagnostic upper endoscopy: A double-blind placebo-controlled randomized trial. Gastrointest Endosc 2005;61:195-200.
11. Rafeey M, Chojazadeh M, Feizo Allah Zadeh H, Majidi H. Use of oral midazolam in pediatric upper gastrointestinal endoscopy. Pediatr Int 2010;52:191-5.
12. Hedenbro JL, Ekelund M, Abegb T, Lindblom A. Oral sedation for diagnostic upper endoscopy. Endoscopy 1991;23:8-10.
13. Liacouras CA, Mascarenhas M, Poon C, Wenner WJ. Placebo-controlled trial assessing the use of oral midazolam as a premedication to conscious sedation for pediatric endoscopy. Gastrointest Endosc 1998;47:455-60.
14. Martinez JL, Sutters KA, Waite S, Davis J, Medina E, Montano N, et al. A comparison of oral diazepam versus midazolam, administered with intravenous meperidine, as premedication to sedation for pediatric endoscopy. J Pediatr Gastroenterol Nutr 2002;35:51-8.
15. de Alencar VM, Goncalves RD, Cruz AA. Oral medication with diazepam or midazolam associated or not with clonidine for oculoplastic office surgery under local anesthesia. Ophthal Plast Reconstr Surg 2010;26:269-72.
16. De Witte JL, Alegret C, Sessler DI, Cammu G. Preoperative alprazolam reduces anxiety in ambulatory surgery patients: A comparison with oral midazolam. Anesth Analg 2002;95:1601-6.
17. Jonas JM, Cohen MS. A comparison of the safety and efficacy of alprazolam versus other agents in the treatment of anxiety, panic, and depression: A review of the literature. J Clin Psychiatry 1993;54:25-45.
18. Shavakhi A, Soleiman S, Gholamrezaei A, Khodadoostan M, Shavakhi S, Tahery A, et al. Premedication with sublingual or oral alprazolam in adults undergoing diagnostic upper gastrointestinal endoscopy. Endoscopy 2014;46:633-9.
19. Choy Y. Treatment of acute procedural anxiety in adults. Stein MB, Hermann R, editors. UpToDate. Waltham, MA: UpToDate Inc. Available form: http://www.uptodate.com [Last accessed on 2017 Oct 01].
20. Igea F, Casellas JA, Gonzalez-Huix F, Gomez-Oliva C, Baudet JS, Cacho G, et al. Sedation for gastrointestinal endoscopy. Endoscopy 2014;46:720-31.
21. Hollenhorst J, Münte S, Friedrich L, Heine J, Leuwer M, Becker H, et al. Using intranasal midazolam spray to prevent claustrophobia induced by MR imaging. AJR Am J Roentgenol 2001;176:865-8.
APPENDIX

Appendix 1: Hemodynamic effects
Desaturation was happened during and after endoscopy in 43.7% (7 out of 16) and 50% (8 out of 16) of the cases, respectively. Only in one case (in the midazolam group) desaturation happened before the EGD. Desaturation episodes were recurrent (presented at two or more measurement intervals) in 4 (6.0%) cases of the alprazolam and 2 (2.9%) cases of the midazolam group. Compared to those who did not have desaturation, patients with desaturation episodes were marginally older (mean standard deviation [SD] of 45.9 [12.0] vs. 39.2 [13.2] years, \( P = 0.05 \)) and had lower arterial oxygen saturation at baseline (mean [SD] of 93.7 [2.3] vs. 95.0 [2.5], \( P = 0.01 \)).

Repeated measure analysis was applied for comparison of changes in hemodynamic variables within and between the two groups. Compared to baseline, systolic blood pressure was lower at 5 min after starting the procedure (\( P = 0.01 \)) and thereafter (\( P < 0.001 \)), with significant Group X time interaction at 25 min (\( P = 0.04 \)) and 30 min (\( P = 0.02 \)) after EGD. Compared to baseline, heart rate was higher at 5 min after starting the procedure (\( P < 0.001 \)) but lower at 25 min and 30 min after EGD (\( P < 0.001 \)). There was no significant between-group difference but there was a nonsignificant interaction between group and time for heart rate at 5 min after starting the procedure (\( P = 0.06 \)). Between-group comparison using the Mann–Whitney U-test was significant at this time (\( P = 0.04 \)) which might be due to more reduction in blood pressure and/or because of higher pain/discomfort in the midazolam group. Compared to baseline, arterial oxygen saturation was lower at 5 min after starting the procedure and thereafter (\( P < 0.001 \)), with no significant Group X time interaction in this case.