Original Article

Application of Midazolam and Propofol in Esophagogastroduodenoscopy: A Triple-Blind, Randomized Controlled Trial

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ABSTRACT

Background: The use of intravenous sedatives is common in gastrointestinal endoscopy. This study is to evaluate the safety and efficacy of propofol and/or midazolam in induction of proper sedation in esophagogastroduodenoscopy (EGD) compared with a control group, which does not receive sedation for EGD.

Methods: Four groups (A, B, C and D) of 30 patients each for whom EGD had been indicated were defined. Group A received no sedative, whereas groups B, C and D received midazolam, propofol and midazolam plus propofol intravenously, respectively. The four groups were compared with each other regarding heart rate (HR), oxygen saturation (O_2S), systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of endoscopy (DE), patient compliance (CM), retrograde amnesia (RA), antegrade amnesia (AA), patient activity (PA), skin color (SC), patient consciousness (CS), blood flow (BF), respiration state (RS) and pain.

Results: Patient compliance, retrograde amnesia, antegrade amnesia, patient activity, patient consciousness and pain were significantly different in our patient groups. On the contrary, no significant difference was found among the four groups regarding heart rate, oxygen saturation, systolic and diastolic blood pressures, duration of endoscopy, skin color, blood flow and respiratory state.

Conclusion: Based on our findings, no sedation is necessary for EGD unless the patient feels anxious and therefore can not cooperate appropriately. For this case, the administration of propofol alone is a priority over midazolam alone and propofol plus midazolam.

Keywords: Midazolam, Propofol, Esophagogastroduodenoscopy

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INTRODUCTION

Worldwide, various medications are available for induction of sedation in esophagogastroduodenoscopy (EGD) to decrease discomfort, anxiety and ensure better patient procedural compliance. Moreover, the endoscopist will be more satisfied with the process (1-3) On the other hand, systemic anesthetic agents can cause life-threatening adverse effects such as respiratory depression, dysrhythmia and cardiac arrest(3,4).

Propofol is a safe and effective drug with enhanced sedation for patients. Despite its limited use by non-anesthesiologists, patients benefit from faster recovery and lower rate of respiratory depression than benzodiazepines and opiates(5,6). In 2007, Meining et al. having compared propofol with midazolam in upper gastrointestinal endoscopy, postulated that propofol can have more impact on the quality of the procedure over midazolam(7). Before, Koshy and colleagues had also

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Table 1: Summary of parameters assessed in the study.

Parameter	Recording method
Heart rate (HR)	Before, during and after the procedure via three leads of the electrocardiogram.
Oxygen saturation (O_2S)	Before, during and after the procedure through pulsoximetry.
Blood pressure (BP)	Systolic and diastolic blood pressure (SBP and DBP) recorded before and after the procedure by regular recording at 5 min intervals.
Duration of endoscopy (DE)	Time period between first administration of sedative(s) and when the endoscope is brought out.
Patient compliance (CM)	From 0 to 10 according to visual analogue scale and four hours after the procedure ends.
Retrograde amnesia (RA)	Four hours after the procedure ends, whether the patient is able to remember the phrase told to him/her before the process started.
Antegrade amnesia (AA)	Whether the patient is able to recall anything from the procedure.
Patient activity (PA)	0: ability of moving the extremities, 1: ability of moving the extremities on command, 2: ability of moving the extremities without command.
Skin color (SC)	0: cyanotic, 1: pink (between cyanotic and normal), 2: normal.
Patient consciousness (CS)	1: irritable, 2: conscious.
Blood flow (BF)	BP after administration of sedative multiplied by BP before administration of sedative (%): 0: >50%, 1: 20-50%, 2: < 20%
Respiration state (RS)	0: apnea is observed, 1: respiration with distress, 2: normal respiration pattern.
Pain	No pain, moderate pain, severe pain.

demonstrated the significant efficacy of propofol over the conventional regimen of midazolam-meperidine in providing proper sedation(8).

Noticeably, the literature lack any controlled trial in which the impact of propofol and/or midazolam has been compared with a control group whose participants received no sedation. We aimed, therefore, to assess the safety and efficacy of propofol and/or midazolam application in a triple-blind randomized controlled setting.

MATERIALS AND METHODS

This study was approved by the Institutional Committee of Ethics and all participants signed the consent of enrollment.

Patient selection

Exclusion criteria consisted of patients younger than 18 years, pregnant women, extremely ill patients and class V patients, in accordance with the American Society of Anesthesiology(9).

From September 2009 to March 2010, all patients (18-75 years) with indications for EGD in the Department at Ali-ibn-Abi Taleb Hospital affiliated with Rafsanjan University of Medical Sciences (Rafsanjan, Iran) were considered for this study.

Patients were allocated into four defined groups according to the GraphPad QuickCalcs program:

Group A: No sedation

Group B: Midazolam

Group C: Propofol

Group D: Midazolam and propofol.

According to similar studies(10-12), 30 patients were categorized in each group. A total of 120 patients were selected from the mentioned time period with consideration of the inclusion and exclusion criteria. This population was allocated to the four groups based on a computer-generated randomized list.

Induction of sedation

Propofol was administered intravenously (20 mg) after the initial dose (40 mg for patients < 70 kg body weight; 60 mg for patients > 70 kg) was loaded. Further administration of this drug was performed if indicated by titration. In case of decline in oxygen saturation, nasal oxygen therapy was increased from 2 L/m (baseline) to 4-6 L/m.

Patients received intravenous midazolam at doses of 2.5 mg (< 70 kg body weight) and 3.5 mg (> 70 kg body

Table 2: Result of data achieved from assessment of each parameter within the four groups.

	HR (beats permin) [mean±SD]	O_2S (%) [mean±SD]	SBP (cmHg) [mean±SD] / DB (cmHg) [mean±SD]	DE (min) [mean±SD]	CM*	RA*	AA*	PA*	SC	CS*	pain*
A	b: 93.1 ± 9.9 d: 96.4 ± 9.1 a: 94.8 ± 18.5	b: 96.4± 0/7 d: 96.1 ±2.6 a: 96.6 ±1.5	b: 11.5 ± 1.5 a: 11.6 ± 1.7 b: 7.4 ± 1 a: 7.6 ± 1.2	5.7 ± 4.1	p: - f: 36.7% g: 63.3%	-	-	0§: - 1§: - 2§: 100%	0: - 1: - 2: 100%	1: - 2: 100%	n: 30% m: 60% s: 10%
B	b: 89.9 ± 0.2 d: 95.9 ± 1.1 a: 93.6 ± 17.7	b: 95.6 ±2.2 d: 95 ± 2.9 a: 93.6 ±3.2	b: 11.7 ± 1.4 a: 11 ± 1.3 b: 7.6 ± 0.8 a: 7 ± 0.5	6 ± 3.3	p: 13.3% f: 60% g: 26.7%	16.7%	53.3%	0: - 1: 6.7% 2: 93.3%	0: - 1: 3.3% 2: 96.7%	1: 53.3% 2: 46.7%	n: 43.3% m: 53.4% s: 3.3%
C	b: 92.6 ± 13.8 d: 100 ± 13.6 a: 97.6 ± 16	b: 95.9 ±1.4 d: 95.2 ±2.2 a: 94 ±1.4	b: 11.7 ± 1 a: 11.3 ± 1 b: 7.4 ± 0.9 a: 6.9 ± 0.9	5.8 ± 2.5	p: - f: 10% g: 90%	3.3%	20.3%	0: - 1: 3.3% 2: 96.7%	0: - 1: - 2: 100%	1: 20% 2: 80%	n: 76.7% m: 23.3% s: -
D	b: 94.8 ± 5.4 d: 96 ± 12.2 a: 94.9 ± 11.5	b: 96.4 ±1.4 d: 95.5 ±1.2 a: 94.5 ±1	b: 11.5 ± 1.5 a: 11.6 ± 1.3 b: 7.4 ± 1.2 a: 7.4 ± 1.3	4.4±2.1	p: - f: - g: 100%	13%	23.3%	0: - 1: 53.3% 2: 46.7%	0: - 1: - 2: 100%	1: 56.7% 2: 43.3%	n: 96.7% m: 3.3% s: -
p-value	b: 0.7 d: 0.6 a: 0.8	b: 0.1 d: 0.1 a: 0.1	b: 0.8 a: 0.7 b: 0.7 a: 0. 2	0. 4	<0.001	0.02	0.02	0.001	0.3	<0.001	<0.001

b: before procedure, d: during procedure, a: after procedure, n: no pain, m: moderate pain, s: severe pain, p: poor compliance, f: fair compliance, g: good compliance.

*$p < 0.05$

§ 0, 1 and 2 represent qualitative scores for each corresponding value.

weight), respectively. In case oxygen saturation of 85% or less was noted, intravenous flumazenil was given..

The induction of sedation was performed by an anesthesiologist blinded to the medications; during the procedure, patients' vital signs were examined regularly.

Data collection

All patients underwent EGD by two gastroenterologists using an Olympus GIF-E Gastrointestinal Fiberscope with the same standard endoscopy protocol as previously proposed(9).

The parameters recorded for each patient are summarized in Table 1. Neither investigators nor patients were aware of the administering sedative medications. Moreover, the statistical specialist of the project was also blinded.

Statistical analysis

Data from the EGDs were entered in SPSS 15® software (SPSS Inc., Chicago, Illinois, USA) of which chi-square and ANOVA tests were used for analysis of quantitative and qualitative data, respectively. The level of statistical significance was set to $p \leq 0.05$.

RESULTS

All 120 patients finished the procedure successfully without any remarkable event. Group A consisted of 13 men and 17 women (age range: 38.9 ± 15 years); group

B, 17 men and 13 women (age range: 38.6 ± 15 years); group C, 15 men and 15 women (age range: 34.8 ± 10 years); and group D consisted of 15 men and 15 women (age range: 36.3 ± 13 years). No significant difference was detected among the four groups regarding age and sex ($p = 0.6$ and 0.3, respectively).

Based on collected data, the patients in this study came to our institution with complaints of abdominal pain, heartburn, epigastric discomfort/pain, nausea and/or vomiting, past history of gastric/duodenal ulcer, anemia, esophagitis, gastroesophageal reflux and melena. Of these, heartburn and epigastric discomfort were the most frequent (33.3%). No significant difference was noted between the four groups ($p = 0.2$) regarding the reason for hospital attendance. Furthermore, no significant difference was found considering present comorbidities of hypertension, coronary artery disease, rheumatologic disorders, asthma, diabetes, hyperlipidemia and renal failure ($p = 0.5$). The groups of patients did not significantly differ in terms of a past history of endoscopy ($p = 0.4$).

The achieved amounts of each parameter for all groups in addition to the results of statistical analysis are summarized in Table 2. There was a significant difference in patient compliance (CM), retrograde amnesia (RA), antegrade amnesia (AA), patient activity (PA), patient consciousness (CS) and pain among the four groups.

Moreover, EGD-induced complications of retching, nausea, waterbrash and frequent vomiting were observed in 2.5%, 2.5%, 1.7% and 0.8% of patients, respectively. These were not significantly different in the four groups ($p = 0.1$). There were no complications noted in 92.5% of patients.

In addition, all 92.5% of patients with no complications were compliant ($p = 0.05$). Interestingly, of these, 72.6% had no pain, 26.2% had moderate pain and 1.2% had severe pain. Within patients with fair compliance, 40.6%, 50.1% and 9.3% had no pain, moderate pain and severe pain, respectively. All patients in the poor compliance category had moderate pain ($p < 0.001$).

No significant relation was found between patient compliance and patient activity, respiration state, blood flow, skin color and patient consciousness, respectively ($p = 0.06$ for all).

HR: heart rate, O_2S: oxygen saturation, BP: blood pressure, DE: duration of endoscopy, CM: patient compliance, RA: retrograde amnesia, AA: antegrade amnesia, PA: patient activity, SC: skin color, CS: patient consciousness.

DISCUSSION

Investigators have been using midazolam as well as propofol for patient cooperation with the aim of more desirable endoscopic results(13,14). The impact of sedatives on more efficient progression of gastrointestinal endoscopy has been demonstrated. Besides, life-threatening adverse events of these medications cannot be neglected. This conflict encourages gastroenterologists and anesthesiologists worldwide to launch more investigations to establish the facts regarding application of sedatives in gastrointestinal endoscopy through stronger evidence. We realized that CM, RA, AA, PA, CS and pain were significantly different in our patient groups.

Patient compliance was the best in group D followed by group C. respectively. In these two groups, 100% and 90% of the patients had good compliance ($p < 0.001$). However, RA and AA had the best status in group A, with no occurrence of either within patients of this group ($p < 0.02$, for both). Similarly, the best activity and consciousness in patients four hours after endoscopy were achieved in group A, of which all patients were able to move their extremities at will and with full consciousness. It is notable that 96.7% and 80% of patients in group C had the same proper activity status and consciousness, respectively, and the difference between the four groups regarding PA was significant ($p = 0.001$). The distribution of pain, however, was different in our study population. Patients who experienced no pain were mostly in group D, followed by group C whereas only 30% of patients who received no sedative did not suffer from pain ($p < 0.001$).

Seifert et al. have reported that application of propofol and midazolam result in prolonged recovery time whereas patients who received propofol alone had shorter recovery periods in a study of 239 patients who equally underwent EGD and endoscopic retrograde cholangiopancreatography (ERCP)(15). Our study reconfirmed their results through a triple-blind trial.

Chin and colleagues have proposed the idea that patients in the propofol group had significantly less AA than those in the midazolam group(6). This is similar to our study in which AA was seen less in the propofol group

Our study revealed no significant difference between the four groups regarding heart rate (HR), oxygen saturation (O_2S), systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of endoscopy (DE), skin color (SC), blood flow (BF) and respiratory state (RS). This denotes that use of midazolam and/or propofol yields no decreases in HR, O_2S, SBP and DBP. Moreover, RS did

not significantly change when midazolam and/or propofol were used in comparison to EGD without sedation.
Furthermore, Seifert et al. have found a significant decrease in the blood pressure of patients who received midazolam plus propofol when compared to propofol alone(15).
Apart from the above mentioned results satisfaction of the endoscopist from the procedure, which causes more accuracy in practice, has been evaluated by some investigators. Meining et al. having assessed the quality of EGD on two groups of patients who had received either midazolam or propofol elucidated that use of propofol can improve the process of EGD more efficiently that midazolam in 15 out of 18 defined parameters(7).
To the best of our knowledge this is the first study in which the impact of two well known sedative drugs, both mixed and separately, were assessed along with a group with no sedation. Moreover, all patients only underwent EGD, thus our study population did not belong to groups of ERCP, endoscopic ultrasonography or colonoscopy. However, separate studies are needed to investigate the impact of propofol and/or midazolam on the quality of ERCP, endoscopic ultrasonography or colonoscopy, individually, from both the investigator and patient stand point, so that more reliable conclusions can be reached.

CONCLUSION

According to the achieved results of our study, even though it seems that EGD can be performed best without any sedative in cases when the patient has no anxiety or does not intend to work immediately after the procedure; therefore when necessary, propofol alone is the drug of choice in comparison to propofol plus midazolam or midazolam alone.

REFERENCES

1. Ristikankare M, Hartikainen J, Heikkinen M, Julkunen R. Is routine sedation or topical pharyngeal anesthesia beneficial during upper endoscopy? *Gastrointest Endosc* 2004;60:686-94.
2. Jamieson J. Anesthesia and sedation in the endoscopy suite? (influences and options). *Curr Opin Anaesthesiol* 1999;12:417-23.
3. 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.
4. Fakheri HT, Kiasari AZ, Taghvaii T, Hosseini V, Mohammadpour RA, Nasrollah A, et al. Assessment the effect of midazolam sedation on hypoxia during upper gastrointestinal endoscopy. *Pak J Biol Sci* 2010;13:152-7.
5. Patterson KW, Casey PB, Murray JP, O'Boyle CA, Cunningham AJ. Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam. *Br J Anaesth* 1991;67:108-11.
6. Chin NM, Tai HY, Chin MK. Intravenous sedation for upper gastrointestinal endoscopy: Midazolam versus propofol. *Singapore Med J* 1992;33:478-80.
7. Meining A, Semmler V, Kassem AM, Sander R, Frankenberger U, Burzin M, et al. The effect of sedation on the quality of upper gastrointestinal endoscopy: an investigator-blinded, randomized study comparing propofol with midazolam. *Endoscopy* 2007;39:345-9.
8. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 2000;95:1476-9.
9. Rex DK, Imperiale TF, Portish V. Patients willing to try colonoscopy without sedation: associated clinical factors and results of a randomized controlled trial. *Gastrointest Endosc* 1999;49:554-9.
10. al-Atrakchi HA. Upper gastrointestinal endoscopy without sedation: a prospective study of 2000 examinations. *Gastrointest Endosc* 1989;35:79-81.
11. De Gregorio BT, Poorman JC, Katon RM. Peroral ultrathin endoscopy in adult patients. *Gastrointest Endosc* 1997;45:303-6.
12. Tan CC, Freeman JG. Throat spray for upper gastrointestinal endoscopy is quite acceptable to patients. *Endoscopy* 1996;28:277-82.
13. Bardhan KD, Morris P, Taylor PC, Hinchliffe RF, Harris PA. Intravenous sedation for upper gastrointestinal endoscopy: diazepam versus midazolam. *Br Med J (Clin Res Ed)* 1984 ;288:1046.
14. Church JA, Stanton PD, Kenny GN, Anderson JR. Propofol for sedation during endoscopy: assessment of a computer-controlled infusion system. *Gastrointest Endosc*1991;37:175-9.
15. Seifert H, Schmitt TH, Gultekin T, Caspary WF, Wehrmann T. Sedation with propofol plus midazolam versus propofol alone for interventional endoscopic procedures: a prospective, randomized study. *Aliment Pharmacol Ther* 2000;14:1207-14.