



## Adverse events of conscious sedation using midazolam for gastrointestinal endoscopy

Jeeyoung Jun<sup>1</sup>, Jong In Han<sup>1</sup>, Ae Lee Choi<sup>2</sup>, Youn Jin Kim<sup>1</sup>,  
Jong Wha Lee<sup>1</sup>, Dong Yeon Kim<sup>1</sup>, and Minjin Lee<sup>1</sup>

Department of Anesthesiology and Pain Medicine, <sup>1</sup>Ewha Womans University College of Medicine, <sup>2</sup>Ewha Womans University Mokdong Hospital, Seoul, Korea

Received April 25, 2018  
Revised 1st, August 8, 2018  
2nd, January 24, 2019  
Accepted February 14, 2019

### Corresponding author

Jong In Han, M.D., Ph.D.  
Department of Anesthesiology  
and Pain Medicine, Ewha Womans  
University College of Medicine, 1071  
Anyangcheon-ro, Yangcheon-gu,  
Seoul 07985, Korea  
Tel: 82-2-2650-5559  
Fax: 82-2-2655-2924  
E-mail: hanji@ewha.ac.kr

### ORCID

<https://orcid.org/0000-0002-8231-7161>

**Background:** This study was conducted to identify the types and incidence of adverse events associated with midazolam, which is the most widely used drug to induce conscious sedation during gastrointestinal endoscopy, and to analyze the factors associated with hypoxemia and sedation failure.

**Methods:** Of 87,740 patients who underwent gastrointestinal endoscopy between February 2015 and May 2017, the electronic medical records of 335 who reportedly developed adverse events were retrospectively reviewed, and analysis was performed to determine the risk factors for hypoxemia and sedation failure, the two most frequent adverse events among those manifested during gastrointestinal endoscopy.

**Results:** The overall adverse event rate was 0.38% (n = 335); hypoxemia was most frequent, accounting for 40.7% (n = 90), followed by sedation failure (34.8%, n = 77), delayed discharge from the recovery room (22.1%, n = 49), and hypotension (2.2%, n = 5). Compared with the control group, the hypoxemia group did not show any significant differences in sex and body weight, but mean age was significantly older (P < 0.001) and a significantly lower dose of midazolam was administered (P < 0.001). In the group with sedation failure, the mean rate was higher in men (P < 0.001) and a significantly higher dose of midazolam was administered (P < 0.001), but no age difference was found.

**Conclusions:** Midazolam-based conscious sedation during gastrointestinal endoscopy can lead to various adverse events. In particular, as elderly patients are at higher risk of developing hypoxemia, midazolam dose adjustment and careful monitoring are required in this group.

**Keywords:** Conscious sedation; Gastrointestinal endoscopy; Hypoxemia; Midazolam.

## INTRODUCTION

Conscious sedation is practiced in most hospitals, and increases patient satisfaction by alleviating discomfort, pain, and anxiety during various medical interventions, thus facilitating performance of the procedure. In particular, midazolam-based conscious sedation is relatively safe and has been widely used in various examinations and procedures in outpatients. However, given the reports of adverse events,

such as hypoxemia, sedation failure, and delayed recovery, depending on the use of midazolam, there is a need to seek safer methods of administration. Furthermore, with the recent increase in invasive endoscopic procedures, it is necessary to establish adequate techniques to provide safe and reliable conscious sedation [1,2].

In general, moderate conscious sedation levels during diagnostic or therapeutic endoscopy, such as gastroscopy, colonoscopy, and endoscopic mucosal resection, are adequate;

although appearing asleep, the patient can meaningfully respond to oral instructions or light tactile stimuli, with spontaneous ventilatory and cardiovascular functions maintained.

Whereas midazolam, propofol, dexmedetomidine, and opioids are available as sedatives for gastrointestinal endoscopy, most hospitals choose midazolam unless anesthesiologists prefer other drugs. Propofol has been increasingly used due to many advantages [3].

Sedation induced in places other than the operating room can be difficult to monitor and adverse events are less likely to be addressed promptly and properly. Typical sedation-related adverse events are hypoxemia, hypotension, inadequate sedation and subsequent interruption of procedure, arrhythmia, and anaphylaxis. Of these, hypoxemia is the most critical complication; it is caused by airway obstruction secondary to hypoventilation and apnea due to central nervous system depression. The incidence of hypoxemia among patients under sedation is reportedly 6–18% [4–6].

This retrospective study was conducted to analyze the risk factors associated with adverse events that occur under midazolam-induced conscious sedation for gastrointestinal endoscopy by identifying the frequency and types of adverse events through review of relevant medical record information, focusing on hypoxemia.

## MATERIALS AND METHODS

### Study population

Of 87,740 patients who underwent diagnostic or therapeutic endoscopy, including gastroscopy, colonoscopy, and endoscopic mucosal resection, under intravenous (IV) sedation in the endoscopy unit at Ewha Womans University Mokdong Hospital between February 2015 and May 2017 (27 months), the electronic medical records of 335 who reportedly developed adverse events were retrospectively reviewed, and analysis was performed to determine the risk factors for hypoxemia and sedation failure, the two most frequent adverse events during gastrointestinal endoscopy.

Of these 33,541 pediatric patients ( $\leq 15$  years), 42 who received concomitant pethidine or fentanyl along with midazolam, and 31 with missing records in any of the patient characteristics, such as body weight, midazolam dose, and procedure type, were included solely to calculate the overall

adverse event rate but were excluded from analysis.

All patients received midazolam IV sedation in the endoscopy unit. A loading dose of 5 mg was administered to all patients without underlying disease, irrespective of body weight, and elderly ( $\geq 70$  years) patients or those with American Society of Anesthesiology physical status classification 3 or higher received 2 mg or 3 mg. In case of delayed onset of sedation, an additional injection of 1–3 mg was used during endoscopy. Sedation was provided under the prescription and supervision of the surgeon in charge.

Oxygen saturation was measured with a pulse oximeter and continuously recorded during endoscopy under conscious sedation; any decrease in oxygen saturation below 90%, during endoscopy was classified as hypoxemia. Cases in which sedation did not set in even after additional midazolam injection or those in whom diagnostic or therapeutic endoscopy was interrupted due to discomfort were classified as sedation failure. Patients with a blood pressure decrease of more than 20% of the baseline level were assigned to the hypotension group, and those who stayed longer than one hour in the recovery room, even after 0.2 mg flumazenil IV, were assigned to the delayed recovery group.

Diagnostic endoscopy included gastroscopy and colonoscopy, and therapeutic endoscopy included endoscopic mucosal resection, endoscopic submucosal dissection, and polyp removal.

### Outcomes

Age, sex, body weight, midazolam dose, and the type of examination or procedure were recorded by patient group.

### Statistics

To compare the sociodemographic and clinical characteristics between the hypoxemic and non-hypoxemic groups, a control group was set by random 4-fold extraction of the number in the adverse event (AE) group from those in the non-AE group.

The chi-squared test was used to assess the sex-related intergroup fractional difference, and the *t*-test was used to assess differences in normally distributed age, weight, and midazolam doses.

Odds ratios and 95% confidence intervals were calculated

using logistic regression analysis to identify the differences in sociodemographic and clinical characteristics between hypoxic and control groups.

Statistical analysis was performed using IBM SPSS Statistics software version 23.0 (IBM Corp., USA).

## RESULTS

The adverse event rate for conscious sedation including hypoxemia, sedation failure, hypotension, delayed recovery among the 87,740 patients who underwent diagnostic or therapeutic endoscopy was 0.38% (n = 335). Of the 335 who developed adverse events, 41 pediatric patients ( $\leq 15$  years), 42 who received concomitant pethidine or fentanyl along with midazolam, and 31 with missing records, such as midazolam dose, age, and body weight, were excluded from analysis.

A total of 221 patients (0.25%) were included in analysis. Of these, 90 (0.10%) had hypoxemia, 77 (0.09%) had sedation failure, 49 (0.06%) had delayed discharge from the recovery room (delayed recovery), and 5 had (0.01%) hypotension.

A comparison between the hypoxemic group, which accounted for the highest proportion of adverse events, and the control group, with no adverse events, revealed the following (Table 1). (i) The mean age in the hypoxemic group was significantly higher than that in the control group ( $68.03 \pm 12.73$

vs.  $57.66 \pm 15.66$  years,  $P < 0.001$ ). (ii) The mean weight in the hypoxemic group was slightly greater than in the control group, but without statistical significance ( $58.57 \pm 12.25$  vs.  $60.81 \pm 10.76$  kg). (iii) The mean midazolam loading dose of 5 mg was administered without regard to body weight. When converted to dose per weight, the mean midazolam dose was significantly lower in the hypoxemic group ( $7.39 \pm 2.55$  vs.  $8.65 \pm 2.98$  mg,  $P < 0.001$ ).

Table 2 presents the results of analysis of the clinical parameters associated with hypoxemia. Age was verified to be a significant risk factor, with the risk of hypoxemia increasing 1.048 times with increasing age ( $P < 0.001$ ).

A comparison between the sedation failure group, which was comparable in size to the hypoxemic group, and controls revealed the following (Table 1). (i) Men outnumbered women ( $P < 0.001$ ). (ii) The midazolam dose per weight was considerably higher in the sedation failure group ( $10.55 \pm 3.53$  vs.  $8.65 \pm 2.98$  mg,  $P < 0.001$ ). No intergroup age difference was observed.

However, there was no case in which hypoxia, sedation failure was exacerbated by serious complications.

## DISCUSSION

Driven by the national cancer screening promotion pro-

**Table 1.** Patient Characteristics

Variable	Comparison between patients with and without hypoxemia			Comparison between patient with and without sedation failure		
	Hypoxemic group (n = 90)	Control group (n = 401)	P value	Sedation failure group (n = 77)	Control group (n = 401)	P value
Age	$68.03 \pm 12.75$	$57.66 \pm 15.66$	$< 0.0001$	$58.01 \pm 14.39$	$57.66 \pm 15.66$	0.853
Sex (male)	37 (41.1)	191 (47.6)	0.293	52 (67.5)	191 (47.6)	0.002
Body weight	$58.57 \pm 12.25$	$60.81 \pm 10.76$	$< 0.0001$	$59.55 \pm 12.37$	$60.81 \pm 10.76$	0.362
Dose range (mg*100/kg)	$4.31 \pm 1.70$	$5.12 \pm 1.53$	$< 0.0001$	$6.17 \pm 2.07$	$5.12 \pm 1.53$	0.000
	$7.39 \pm 2.55$	$8.65 \pm 2.98$	$< 0.0001$	$10.55 \pm 3.53$	$8.65 \pm 2.98$	0.000

Values are presented as mean  $\pm$  SD or number (%).

**Table 2.** Logistic Regression Analysis for Hypoxemia

Variable	P value	Exp (B)	Exp (B) 95% confidence interval	
			Lower boundary	Upper boundary
Sex	0.361	1.289	0.748	2.224
Age	0.000	1.042	1.021	1.063
Body weight	0.016	0.906	0.836	0.982
Dose range	0.026	3.097	1.146	8.364
(mg*100/kg)	0.010	0.469	0.263	0.836

gram, diagnostic gastroscopy and colonoscopy, as well as therapeutic endoscopy, have been steadily increasing in Korea. However, most patients undergoing endoscopic examinations feel discomfort and pain, with a gagging sensation, nausea, and shortness of breath. Moreover, if patients feel too uncomfortable and become agitated, move uncontrollably, or otherwise refuse to follow instructions, it becomes difficult to obtain accurate results. Such behavior increases the risk of injury from the instruments used and can result in prolonging the examination time. To address such problems, sedative-based conscious sedation has been increasingly used for its favorable effect on anxiety, discomfort, and pain tolerance [7-9]. Sedation is gaining a firm foothold as essential to safely performing prolonged therapeutic endoscopy because it reduces patient discomfort and pain and thus enhances compliance with follow-up examinations [1].

Whereas many drugs are available for sedation therapy, midazolam is the agent most widely used by non-anesthesiologists. Midazolam, a water-soluble benzodiazepine, has a number of advantages: short elimination half-life, rapid onset of effect, high efficiency in relieving anxiety and inducing antegrade amnesia and sedative hypnosis, solubility in solvents, and availability of antagonists such as flumazenil [9,10]. Although the adverse event rate is lower than for other sedatives, hypoxemia is the most serious complication secondary to hypoventilation and sleep apnea. Paradoxical reactions can also occur, presenting as hypotension, emotional instability, convulsion, and agitation. Particular attention should be paid to adverse events in patients with advanced age, respiratory failure, impaired hepatic function, and chronic renal insufficiency [11].

To ensure efficient and reliable sedation therapy, it is therefore of crucial importance to thoroughly understand the pharmacological properties of the drug, including dosage and usage, and to consider patient characteristics, such as underlying disease and age, in order to adjust the loading dose and consider additional drug administration during endoscopy.

Prior to diagnostic or therapeutic endoscopy, the patient should only receive slow infusion of intravenous midazolam, with the dose adjusted to the patient characteristics. In particular, the loading dose should be lowered in patients with advanced age, chronic debility, and hepatic or renal insufficiency. The recommended loading dose in adults up to

60 years of age is 1-2 mg (or 0.03 mg/kg), but some patients react to a dose as low as 1 mg. In case of long procedures or in patients with tolerance to midazolam, higher doses may become necessary, and additional doses can be administered at the rate of 1-2 mg (or 0.02-0.03 mg/kg). In general, the overall dose ranges between 2.5 mg and 5 mg, and the maximum allowable dose is 6-7.5 mg [12-14].

The patients analyzed in this study received a relatively high loading dose of 2-5 mg, followed by 1-5 mg additional doses, if necessary, up to a maximum dose of 10 mg. Despite this high dose range, the adverse event rate was as low as 0.38%. This may be ascribed to the small number of elderly patients and the low American Society of Anesthesiology physical status classification (1 or 2) in the majority of cases. Other factors contributing to this low adverse event rate were the presence of the doctor and many assistants in the endoscopy unit and continuous monitoring of oxygen saturation and blood pressure during diagnostic or therapeutic endoscopy.

Despite the low rate, adverse events could have resulted in serious complications. Therefore, the types of adverse events, their causes, and possible countermeasures required investigation and analysis was performed accordingly.

When the hypoxemic group, which accounted for the highest proportion of adverse events with risk of various complications, was compared with controls, the mean age was higher and the mean midazolam loading dose was lower, demonstrating that hypoxemia is not positively correlated with dose. The implication is that the older the patient, the higher the risk of developing hypoxemia, which highlights the need to adjust midazolam dose and the importance of post-medication monitoring.

In the case of sedation failure, an adverse event second only to hypoxemia, being male was a risk factor, rather than age or dose, as was the case with hypoxemia, and higher midazolam doses were used compared with the control group, which may be ascribed to additional administration required to induce sedation. The main problem associated with sedation failure is the interruption of the examination or procedure; in addressing this problem, it should be borne in mind that excessive increase in dose to continue endoscopy may trigger other adverse events such as hypoxemia or hypotension.

If a risk factor for hypoxemia applies, particular care will be

needed for correct dosing of midazolam and post-medication monitoring.

Midazolam is a sedative with various proven advantages; however, its use is associated with adverse events such as apnea and airway obstruction and increased tendency to show aggressive and hostile behavior. Efficient and reliable sedation therapy will have to be provided to prevent adverse events or paradoxical reactions [15,16]. Midazolam has been widely used for conscious sedation, but various sedatives and pain killers, such as propofol, fentanyl, and dexmedetomidine have been recently used as monotherapy or in combination. These drugs also have various adverse events: propofol can reduce cardiac output and blood pressure and induce respiratory depression; concomitant administration of midazolam and fentanyl is associated with lowered blood pressure and hypoxemia; dexmedetomidine can cause bradysphygmia, albeit rarely [17–19].

The Korean Society of Anesthesiologists provides sedation guidelines, informed consent forms, and recovery logs. However, there is an unmet need to train medical staff on the dosage and usage of sedatives to provide conscious sedation during diagnostic or therapeutic endoscopy in outpatient settings, post-medication patient monitoring, and rapid detection of and response to adverse events. Nor are there adequate guidelines tailored to specific situations.

There are some essential points to consider in providing safer and more efficient conscious sedation. Above all, it is important to thoroughly understand the pharmacological properties of the drug including dosage and usage. It is also important to check patient characteristics, such as underlying disease and age, in order to screen high-risk patients and assess their conditions, and to carefully take personalized measures in terms of the loading dose and additional administration. Furthermore, appropriate post-medication monitoring of blood pressure, heart rate, the electrocardiogram, and oxygen saturation should be provided along with accurate assessment of the patient's sedation status.

The 2002 American Society of Anesthesiology Guidelines recommend administration of oxygen during moderate sedation. This can be applied to conscious sedation to reduce the risk of adverse events [20]. End-tidal carbon dioxide monitoring and bispectral index monitoring for adequacy of ventilation and the degree of sedation, respectively, can also contribute to maintaining an appropriate level of conscious

sedation [21].

Furthermore, to ensure safe conscious sedation, medications and fluids including antidotes necessary for prevention of adverse events, as well as guidelines or standard protocols should be prepared, and instruments for airway management and respiratory support and drugs and defibrillators for emergencies should be available.

The following limitations should be noted.

First, being a retrospective study, data integrity was not sufficient, with missing records for body weight. Most patients had low American Society of Anesthesiology physical status classification (1 or 2), which did not allow analysis based on underlying disease. Moreover, the oxygen saturation value and cause of sedation failure were also missing in some cases. Due to inaccurate records of sedation scores, the degree of sedation could not be analyzed and only the absence or presence of adverse events was analyzed.

Second, since many different surgeons and professionals with unknown degrees of skill were involved, consistent diagnostic and therapeutic details could not be assured.

Third, methods of administration and procedure duration varied according to the surgeon in charge, making it difficult to derive a correlation between the total dose and adverse events.

To conclude, although midazolam-based conscious sedation during diagnostic or therapeutic gastrointestinal endoscopy has a low adverse event rate, it can lead to hypoxemia and sedation failure. It is therefore crucial to recognize patient characteristics and adjust the degree of sedation accordingly, as well as to prepare appropriate monitoring and countermeasures.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ORCID

Jeeyoung Jun: <https://orcid.org/0000-0001-8137-5629>

Ae Lee Choi: <https://orcid.org/0000-0001-5524-9928>

Youn Jin Kim: <https://orcid.org/0000-0001-9189-5839>

Jong Wha Lee: <https://orcid.org/0000-0003-3574-191X>

Dong Yeon Kim: <https://orcid.org/0000-0002-4414-5653>

Minjin Lee: <https://orcid.org/0000-0001-5811-7947>

## REFERENCES

1. Lee JK, Jang DK, Kim WH, Kim JW, Jang BI. Safety of non-anesthesiologist administration of propofol for gastrointestinal endoscopy. *Korean J Gastroenterol* 2017; 69: 55-58.
2. 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.
3. Yusoff IF, Raymond G, Sahai AV. Endoscopist administered propofol for upper-GI EUS is safe and effective: a prospective study in 500 patients. *Gastrointest Endosc* 2004; 60: 356-60.
4. 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.
5. Triantafyllidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol* 2013; 19: 463-81.
6. Agostoni M, Fanti L, Gemma M, Pasculli N, Beretta L, Testoni PA. Adverse events during monitored anesthesia care for GI endoscopy: an 8-year experience. *Gastrointest Endosc* 2011; 74: 266-75.
7. Campo R, Brullet E, Montserrat A, Calvet X, Moix J, Rué M, et al. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. *Eur J Gastroenterol Hepatol* 1999; 11: 201-4.
8. Trevisani L, Sartori S, Gaudenzi P, Gilli G, Matarese G, Gullini S, et al. Upper gastrointestinal endoscopy: are preparatory interventions or conscious sedation effective? A randomized trial. *World J Gastroenterol* 2004; 10: 3313-7.
9. Kim KO. Assessment of patient's status during sedation endoscopy. *Korean J Gastrointest Endosc* 2010; 40(Suppl 1): 106-10.
10. Chokhavatia S, Nguyen L, Williams R, Kao J, Heavner JE. Sedation and analgesia for gastrointestinal endoscopy. *Am J Gastroenterol* 1993; 88: 393-6.
11. Im JP. Patient-tailored sedation for colonoscopy. Paper presented at: The 48th Seminar of the Korean Society of Gastrointestinal Endoscopy; 2013 Mar 24; Goyang, Korea. 2013. p. 119-24.
12. Kim HU. Perfect sedation for endoscopy. *Korean J Gastrointest Endosc* 2010; 41(Suppl 2): 71-7.
13. Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI. Effect of age, gender, and obesity on midazolam kinetics. *Anesthesiology* 1984; 61: 27-35.
14. Moon SH. Sedation regimens for gastrointestinal endoscopy. *Clin Endosc* 2014; 47: 135-40.
15. Aun C, Flynn PJ, Richards J, Major E. A comparison of midazolam and diazepam for intravenous sedation in dentistry. *Anaesthesia* 1984; 39: 589-93.
16. Dietch JT, Jennings RK. Aggressive dyscontrol in patients treated with benzodiazepines. *J Clin Psychiatry* 1988; 49: 184-8.
17. Jones GM, Doepker BA, Erdman MJ, Kimmons LA, Eljovich L. Predictors of severe hypotension in neurocritical care patients sedated with propofol. *Neurocrit Care* 2014; 20: 270-6.
18. Ulmer BJ, Hansen JJ, Overley CA, Symms MR, Chadalawada V, Liangpunsakul S, et al. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 2003; 1: 425-32.
19. Demiraran Y, Korkut E, Tamer A, Yorulmaz I, Kocaman B, Sezen G, et al. The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: a prospective, randomized study. *Can J Gastroenterol* 2007; 21: 25-9.
20. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002; 96: 1004-17.
21. Moon SH, Kim HK, Myung DS, Yoon SM, Moon W. Patient monitoring and associated devices during endoscopic sedation. *Korean J Gastroenterol* 2017; 69: 64-7.