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Delayed Flumazenil Injection after Endoscopic Sedation Increases Patient Satisfaction Compared with Immediate Flumazenil Injection

Hyun Jung Chung*, Byoung Wook Bang*, Hyung Gil Kim*, Kye Sook Kwon*, Yong Woon Shin*, Seok Jeong*, Don Haeng Lee*, and Shin Goo Park†

Division of Gastroenterology, Department of Internal Medicine, and †Department of Occupational and Environmental Medicine, Inha University School of Medicine, Incheon, Korea

Background/Aims: Flumazenil was administered after the completion of endoscopy under sedation to reduce recovery time and increase patient safety. We evaluated patient satisfaction after endoscopy under sedation according to the timing of a postprocedural flumazenil injection. **Methods:** In total, 200 subjects undergoing concurrent colonoscopy and upper endoscopy while sedated with midazolam and meperidine were enrolled in our investigation. We randomly administered 0.3 mg of flumazenil either immediately or 15 minutes after the endoscopic procedure. A postprocedural questionnaire and next day telephone interview were conducted to assess patient satisfaction. **Results:** Flumazenil injection timing did not affect the time spent in the recovery room when comparing the two groups of patients. However, the subjects in the 15 minutes injection group were more satisfied with undergoing endoscopy under sedation than the patients in the immediate injection group according to the postprocedural survey (p=0.019). However, no difference in overall satisfaction, memory, or willingness to undergo a future endoscopy was observed between the two groups when the telephone survey was conducted on the following day. **Conclusions:** This study demonstrated that a delayed flumazenil injection after endoscopic sedation increased patient satisfaction without prolonging recovery time, even though the benefit of the delayed flumazenil injection did not persist into the following day. **(Gut Liver 2014;8:7-12)**

Key Words: Colonoscopy; Flumazenil; Midazolam; Patient satisfaction

INTRODUCTION

Gastric cancer is prevalent among South Koreans and the incidence of colon cancer is rapidly increasing due to more frequent consumption of a Westernized diet.[1] Therefore, upper endoscopy and colonoscopy are often performed during health check-ups. To reduce patient anxiety and discomfort during these procedures, sedation with benzodiazepine is commonly induced. In addition, opioids such as meperidine are used to relieve pain during endoscopic procedures. These compounds synergistically induce sedation with midazolam—while increasing amnesia and patient satisfaction.[2] Therefore, combinations of benzodiazepine and opioids are widely administered for sedation.

Flumazenil is a competitive benzodiazepine antagonist that reverses the sedative and hypnotic effects of midazolam. This drug is widely given after endoscopic sedation to promote faster recovery.[3] The use of flumazenil may also prevent sedation-related accidents such as slips and falls after endoscopy. However, there are no coherent guidelines for the proper timing of flumazenil injection. If flumazenil were administered immediately after the completion of sedative endoscopy, the patients might remember the discomfort and pain suffered during the procedure more clearly. Thus, immediate arousal from sedation could reduce patient satisfaction and lead to the refusal of undergoing future endoscopic procedures. If this drug were administered too late, medical personnel would have to monitor the patients until full recovery. Prolonged observation times impose an additional burden on medical staff and decrease patient turnover in the endoscopic unit. Therefore, the identification of an optimal flumazenil injection time after sedative endoscopy would contribute to increased satisfaction for both patients and endoscopists.

Correspondence to: Byoung Wook Bang
Division of Gastroenterology, Department of Internal Medicine, Inha University School of Medicine, 27 Inhang-ro, Jung-gu, Incheon 400-103, Korea
Tel: +82-32-890-2548, Fax: +82-32-890-2549, E-mail: bangbu@inha.ac.kr
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Here, we evaluated flumazenil injection timing after endoscopic sedation to optimize patient safety and satisfaction.

MATERIALS AND METHODS

1. Patients

This prospective study was conducted in a health promotion center at Inha University Hospital (Incheon, Korea) and approved by the Institutional Review Board. Between October 2011 and February 2012, 200 subjects undergoing concurrent colonoscopy and upper endoscopy under sedation with midazolam and meperidine during health check-ups were recruited. We included healthy adults aged 19 to 65 years. All subjects were accompanied by an adult guardian to help prevent sedation-related accidents after the procedure. Written consent was obtained from all subjects or a legal guardian. All patients were able to withdraw from the study at any time without affecting their care.

Subjects were excluded from the study due to the following conditions: 1) a significant general disease more serious than the American Society of Anesthesiology preoperative patient classification III;[4] 2) a history of benzodiazepine dependence; and 3) continuing heavy use of alcohol. In addition, the following individuals were excluded from our investigation while undergoing endoscopy or immediately after the procedure: 1) subjects who showed a paradoxical reaction which was terminated by immediate flumazenil injection; 2) patients who did not complete the endoscopic procedure; 3) subjects with a procedure time that exceeded 40 minutes; and 4) individuals who left the hospital after recovering from endoscopy without undergoing the postprocedural interview.

2. Endoscopic procedure

Interviews were conducted by one research nurse prior to the procedure to collect demographic data. Patient weight, height, history of alcohol and drug use, and previous experiences with endoscopy under sedation were recorded. For bowel preparation, we had patients drink 3 L polyethylene glycol (Colyte®; Taejoon Pharm, Seoul, Korea) solution in the evening (7:00 to 9:00 PM) prior to the colonoscopy and again 1 L polyethylene glycol in the morning (6:00 to 8:00 AM) of the colonoscopy. Meperidine (25 mg, Pethidine®; Jeil Pharmaceutical, Daegu, Korea) and midazolam (3 mg, Vascam®; Hana Pharmaceutical, Seoul, Korea) were given by intravenous bolus injection at the start of the procedure. All patients were assessed according to the Observer's Assessment of Alertness/Sedation scale before undergoing endoscopy.[5] Vital signs, oxygen saturation, and electrocardiography readings were monitored throughout the procedure.

The procedures were performed by one of five first year fellow trainees. Colonoscopy was completed first followed by upper endoscopy. Additional midazolam was administered according to the patient's conscious level and physiologic parameters at the discretion of the endoscopist. The total dose of midazolam did not exceed 10 mg. The total dose of midazolam administered and the procedure time were recorded. During the procedure, the endoscopist completed a questionnaire to note the degree of subject cooperation, procedure time, and difficulty level of the procedure.

We randomly administered 0.3 mg flumazenil (Flunil®; Bukwang Pharmaceutical, Seoul, Korea) either immediately after the completion of endoscopy (immediate group) or 15 minutes later (15-minute group). When the patients had safely recovered from sedation (Aldrete scores[6] were 9 or greater) and could walk independently in the recovery room, a postprocedural questionnaire measuring patient satisfaction, memory or recollection of the procedure, and patient assessment of pain or discomfort was administered. The questionnaire we used was based on related studies with modifications according to our needs.[7-9] Patient satisfaction with sedation and the level of pain experienced were documented according to a 5-point satisfaction scale (1=very dissatisfied, 5=very satisfied). At the end of the interview, the subjects were asked to memorize two words ("puppy" and "banana"). The next day, a follow-up telephone interview surveying patient satisfaction, recollection of the procedure, and willingness to undergo future endoscopic procedures was conducted by the same research nurse who performed the preprocedural interviews. The subjects were also asked to recall the two words that they had memorized on the day of the procedure. If a subject did not answer the telephone, we made three more attempts to contact the patient.

3. Statistical analysis

Data analyses were performed using SPSS software version 18.0 (IBM Co., Armonk, NY, USA) and a p-value less than 0.05 was considered significant. Randomization of the patients was conducted using a table of random numbers produced by a random number generator included in the SPSS software. The data were analyzed using a two-sample t-test or chi-square test for categorical data. Results are presented as the mean±SD for continuous variables or percentages with a 95% confidence interval for categorical variables.

RESULTS

One hundred eighty-two subjects completed the postprocedural questionnaire (Fig. 1). Eighteen participants dropped out from the study for various reasons. Four of these patients were excluded due to prolonged total procedure times (>40 minutes) and six left the hospital without undergoing the postprocedural interview. Additionally, four subjects developed a paradoxical response during endoscopy that was reversed with immediate flumazenil injection, and four subjects did not complete the endoscopy.

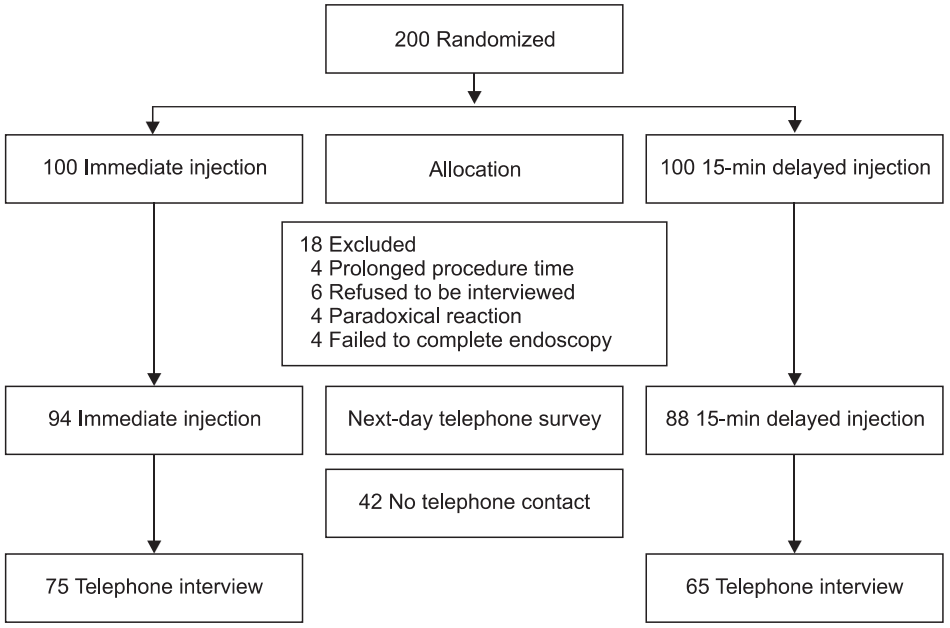

Fig. 1. Study flow diagram. Of the 200 enrolled patients, 18 were excluded from this study because they did not complete the postprocedural questionnaire. The telephone survey administered on the day after endoscopy was completed by 140 subjects.

Table 1. Baseline Patient Characteristics

Characteristic	Immediate group (n=94)	15-Minute group (n=88)	p-value
Age, yr	47.2±6.3	47.1±6.5	0.869
Sex, male/female	61/33	49/39	0.204
Body weight, kg	66.5±10.9	64.5±9.2	0.180
Height, cm	166.6±7.8	165.2±7.6	0.124
Body mass index, kg/m^2	23.8±3.0	23.6±2.6	0.652
Alcohol consumer	52 (55.3)	56 (63.6)	0.254
Amount consumed, g/day	20.3±17.2	26.8±30.6	0.183
Systemic disease	17 (18.1)	13 (14.8)	0.547
Previous experience with conscious sedation	64 (68.1)	55 (62.5)	0.429
Level of satisfaction	3.4±0.7	3.4±0.6	0.758

Data are presented as mean±SD or number (%).

Table 2. Details of the Endoscopic Procedure and Administered Sedation Medication

	Immediate group (n=94)	15-Minute group (n=88)	p-value
Preprocedural conscious level (OAA/S)			0.598
0–1	24 (25.6)	19 (21.6)	
2–3	40 (42.5)	44 (50.0)	
4–5	30 (31.9)	25 (28.4)	
Total procedure time, min	19.2±6.1	18.8±6.1	0.662
Total colonoscopy time	11.4±4.6	10.8±4.4	0.412
Intubation time	5.6±2.8	6.3±3.6	0.094
Withdrawal time	5.8±3.8	4.3±2.6	0.003
Upper endoscopy time	3.6±2.0	3.3±1.4	0.273
Scope change time	4.2±1.8	4.7±3.6	0.365
Difficulty level of colonoscopy (easy/moderate/difficult)	12/59/23	12/50/26	0.694
Upper endoscopy biopsy	22 (23.4)	21 (23.9)	0.942
Colonoscopic biopsy	15 (16.0)	10 (11.4)	0.368
Colonoscopy polypectomy	12 (12.8)	4 (4.5)	0.050
Degree of cooperation	2.7±1.4	2.5±1.3	0.204
Additional dose of midazolam, mg	5.8±1.7	6.2±1.4	0.126
Total dose of midazolam, mg	8.8±1.7	9.2±1.4	0.126

Data are presented as mean±SD or number (%).
OAA/S, modified observer's assessment/sedation scale.

No significant differences in age, gender distribution, body mass index, preprocedural sedation level, history of alcohol consumption, or previous experiences with endoscopy under sedation were found between the immediate and 15-minute groups (Table 1). There were also no significant differences in total procedure time, midazolam dose, difficulty level of the procedure, or subject cooperation between the two groups (Table 2). However, colonoscopy withdrawal time was longer and colonic polyps were more commonly observed in the immediate group than the 15-minute group. According to the postprocedural questionnaire, subjects in both groups were satisfied with their sedation (average scores were 4.24 out of 5 for the immediate group and 4.47 for the 15-minute group), However, participants in 15-minute group were more satisfied with sedation and the overall procedure than participants in the immediate group (p=0.038 and p=0.019, respectively) (Table 3). Subjects in the immediate group had better recollection of the endoscopic procedure than ones in the 15-minute group (p=0.011). Time spent in the recovery room was not significantly different between the two groups (p=0.662).

Table 3. Postprocedural Survey Results

	Immediate group (n=94)	15-Minute group (n=88)	p-value
Recovery room stay time, min	31.9±11.2	32.5±7.7	0.662
Pain	1.54±1.17	1.34±1.01	0.217
Memory of the procedure	1.22±0.61	1.05±0.21	0.011
Satisfaction with sedation	4.24±0.79	4.47±0.61	0.038
Overall satisfaction with procedure	4.24±0.81	4.49±0.55	0.019

Data are presented as mean±SD.

Table 4. Next Day Telephone Survey Results

	Immediate group (n=75)	15-Minute group (n=65)	p-value
Pain	1.39±1.24	1.23±0.65	0.333
Word recall test			0.677
None	47 (62.7)	37 (56.9)	
One word	16 (21.3)	18 (27.7)	
Two words	12 (16.0)	10 (15.4)	
Additional time spent sleeping at home, hr			0.905
None	25 (33.3)	19 (29.2)	
<2	28 (37.3)	27 (41.5)	
2–4	20 (26.7)	18 (27.7)	
>4	2 (2.6)	1 (1.5)	
Overall satisfaction with the procedure	3.79±0.72	3.92±0.69	0.258
Patients willingness to repeat the endoscopy			0.571
Yes	14 (18.7)	17 (26.2)	
Maybe	54 (72.0)	44 (67.7)	
Only if necessary	6 (8.0)	4 (6.2)	
No	1 (1.3)	0 (0.0)	

Data are presented as mean±SD or number (%).

The follow-up telephone survey conducted the day after the procedure was completed by 140 subjects of the 182 (76.9%) (Table 4). There was no significant difference in overall satisfaction, recollection of the two words the patients were asked to memorize, or willingness to undergo future endoscopy between the two groups. A majority of participants (96/140, 68.6%) required additional sleep after discharge but no significant difference in sleeping time between the two groups was noted.

DISCUSSION

Sedation with a combination of a benzodiazepine and narcotic is most commonly used for routine upper endoscopy and colonoscopy.[10,11] Among the benzodiazepines, midazolam is the most typical drug administered for endoscopic sedation because of its rapid onset, short duration of action, safety, and potent amnestic properties.[11] However, its relatively long half-life is still a concern for doctors and patients. Respiratory depression, hypotension, and other adverse effect can develop during and after endoscopy with sedation, leading to injuries from slips and falls or car accidents due to sedation-related drowsiness that may occur while on the way home after endoscopy completion.[3] To minimize these occurrences, we administered flumazenil that can immediately reverse the adverse effect of midazolam and increases safety for patients undergoing endoscopy under sedation. This compound is widely used and routine flumazenil administration after the completion of endoscopy under sedation has been proposed although the practical benefits for patients or endoscopic units have not yet been established.[12] Despite its wide usage, no study of flumazenil injection timing has been previously conducted and timing of flumazenil administration is typically determined based on the experience of the endoscopist.

In the current study, we focused on patient satisfaction according to flumazenil injection time. We have often noticed that some patients complain of pain and discomfort during endoscopy under sedation, but they tend to forget the unpleasant memories and feel better roughly 15 minutes after additional postprocedural sedation. However, no study has been performed to examine the relationship between wake-up time and patient satisfaction. Our postprocedural survey showed that subjects in the 15-minute group were more satisfied with sedation and the overall procedure than patients in the immediate group. As we expected, a 15-minute period after the procedure caused retrograde amnesia that reduced the retention of unpleasant memories. However, the level of patient satisfaction with sedation between the two groups was similar according to the next day telephone survey. This was thought to be due to an anterograde amnestic effect of midazolam because amnestic effects may persist after sedation has worn off.[13] Some subjects did not recall any details about the postprocedural questionnaire even though they appeared alert during the interview. Additionally, no differences in the word recall test results or willingness to undergo future endoscopic procedures were found between the two groups.

Flumazenil could obviate the need for long-term postsedation observation. One study showed that flumazenil reduces the mean observation time from 23.5 to 8.3 minutes compared to a placebo.[14] However, in our study flumazenil injection timing did not influence the amount of time spent in the recovery room (31.9 minutes for immediate group versus 32.5 minutes for 15-minute group; p=0.662). Although immediate injection of flumazenil led to rapid regain of alertness, it did not facilitate an earlier discharge or faster return to normal daily activities (Aldrete score was 9 or greater) than delayed flumazenil injec-

tion.

There was also no significant difference between the two groups in the number of subjects who needed more sleep after recovering from endoscopy (50/75 [66.7%] in immediate group and 46/65 [70.8%] in 15-minute group) or time spent sleeping. Hence, flumazenil injection timing did not influence the requirement for additional sleep or return to normal activities. However, there were some confounding factors to be considered. Additional time spent sleeping may be affected by insufficient rest due to the bowel cleansing preparation or having time off from work. In addition, the average duration of flumazenil action is less than 60 minutes whereas that of midazolam may persist for 80 minutes or longer. Flumazenil is structurally related to midazolam but acts as a benzodiazepine antagonist. After intravenous administration, both drugs are rapidly distributed into similar distribution volumes and undergo hepatic metabolization with a relatively high hepatic extraction ratio of around 0.3 for midazolam and 0.6 for flumazenil. However, they are cleared with different elimination half-lives of 1 (flumazenil) to 3 hours (midazolam).[15] Resedation may therefore occur.[3] On the other hand, 72% to 76% of subjects undergoing endoscopy while sedated with mainly propofol return to normal activities without spending additional time sleeping.[3,16]

A low fixed dose of flumazenil delivered in a single bolus is usually sufficient to attain and maintain the desired level of consciousness after conscious sedation for brief procedures despite the short elimination half-life of this compound.[17] In addition, it is not easy to continuously administer flumazenil in an outpatient setting. However, continuous intravenous administration of flumazenil in incremental doses may be warranted for prolonged therapeutic procedures. In our study, we excluded subjects who had prolonged procedure times (>40 minutes) and received a total midazolam dose over 10 mg because these patients needed special monitoring and repeated flumazenil injection.

Our study had some limitations. First, patient satisfaction with endoscopy under sedation is influenced by various factors such as waiting time,[18] behavior of the medical personnel, skill of the endoscopist, sedation appropriateness, and wake-up time. In the current study, some subjects complained of delayed waiting times and even refused to participate in the postprocedural survey. Second, appropriate flumazenil injection timing and dose may vary according to the dose of midazolam and procedure time. Thus, our results should be only applied to conscious sedation for short-term endoscopy. As we mentioned, patients receiving prolonged midazolam sedation required continuous or repeated flumazenil injection until they fully recovered.

In summary, our study showed that delayed flumazenil injection after endoscopy under sedation increases patient satisfaction immediately following the procedure and reduces the retention of unpleasant procedure-related memories without delaying recovery compared to immediate flumazenil injection. The timing of flumazenil injection did not appear to influence longer-term patient satisfaction or willingness to undergo future endoscopic procedures. Nevertheless, we suggest administering delayed flumazenil injection after endoscopic sedation to increase overall patient satisfaction.

CONFLICTS OF INTEREST

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

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