Clinical impact of gastroenterologist-administered propofol during esophagogastroduodenoscopy: a randomized comparison at a single medical clinic

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Abstract

Background Although midazolam is widely used during endoscopic procedures by endoscopists, propofol has been recently favored for its rapid action and metabolism. The aim of this study is to compare the clinical advantages between propofol and midazolam use during screening esophagogastroduodenoscopy (EGD) for gastric cancer and post-procedure management at a medical clinic.

Methods One hundred six healthy patients aged 20–69 years requesting sedation for screening EGD from October 2012 to May 2013 at a single clinic in Japan were randomly assigned to propofol ($n = 54$) or midazolam ($n = 52$). Medications were given by bolus injection, and the dose was adjusted by body weight. Sedation level and tolerability during EGD and recovery time were assessed. Sedation level and tolerability were evaluated by American Society of Anesthesiologists responsiveness levels and four levels of the gag reflex, respectively. For safety purposes,

endoscopists and nurses were trained in administering propofol and an anesthesiologist was on call at all times.

Results No statistically significant differences were found between the two groups in sedation level and patient tolerability. Full recovery time in the propofol group (4.7 min) was significantly shorter than that in the midazolam group (24 min, $P < 0.01$).

Conclusions Regarding post-procedure management of patients in a medical clinic, propofol use might not necessitate a recovery room and excessive assessment tasks because of rapid recovery time without any prolonged reaction, which causes patient compliance. (Clinical trial registration number: UMIN000009142.)

Keywords Esophagogastroduodenoscopy · Propofol · Recovery time · Private clinic

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Introduction

Esophagogastroduodenoscopy (EGD) is an essential diagnostic and therapeutic tool that is increasing in demand. Adequate patient tolerance during the procedure is essential for the successful completion of a safe examination and compliance with subsequent follow-up. Currently, a significant subset of patients undergo routine endoscopies with sedation [1–3].

During the last few years, demand for sedative agents for EGD has gradually shifted from benzodiazepines to propofol because of the latter's short-acting pharmacokinetic character [3, 4]. In some centers, propofol is used even for routine endoscopy to improve patient tolerance and to decrease recovery times. Furthermore, there are many reports documenting the safety and efficacy of nurse-administered propofol sedation [5–15]. Although the

administration of propofol is not restricted to anesthesiologists, in many hospitals midazolam is still commonly used for routine endoscopic procedures. The short action and narrower therapeutic range make propofol management difficult, and its use is restricted to well-resourced endoscopy suites [16].

Although most previous studies that demonstrated effectiveness and safety of propofol sedation were conducted in specially equipped hospitals, apparently no study has reported the comparison of propofol and midazolam directly at smaller private clinic recovery room settings. This may be the first randomized study to compare the clinical advantages between propofol and midazolam use during screening EGD and post-procedure management at a private medical clinic.

Materials and methods

Study design

The study was conducted at Tokyo East Hospital in Japan, using a single-blinded design with prospective randomization. The study protocol was approved by the ethics review board of the hospital, and written informed consent was obtained from each patient. Consecutive patients who planned to undergo outpatient EGD from October 2012 to May 2013 were enrolled.

Inclusion criteria were age between 20 and 69 years and the provision of written informed consent. Emergency procedures were excluded. Patients were also excluded if they were pregnant, assigned to American Society of Anesthesiologists (ASA) class III and IV, overweight (>100 kg), had severe liver dysfunction, a severe psychiatric disorder, paresis after cerebral infarction, or were allergic to the drugs used or their components (soybeans or eggs).

Eligible patients were randomly allocated in an equal ratio to either the propofol or midazolam group by assignment using opaque sealed envelopes that contained cards labeled either “propofol” or “midazolam.” These cards were prepared by an investigator with no clinical involvement in the trial. The randomization measure was performed by opening the sealed envelopes consecutively. (Clinical trial registration number: UMIN000009142.)

Procedure

EGD was performed in the lateral decubitus position while monitoring. Patients received topical pharyngeal anesthesia with lidocaine. An intravenous cannula for the bolus injection of sedative medicine was placed in the subject's forearm shortly before the start of EGD and removed when

they were discharged. Propofol (1 % propofol; Maruishi, Osaka, Japan) was administered by bolus injection, with a standard protocol of 0.6–1.0 mg/kg and midazolam (Dormicum; Astellas, Tokyo, Japan) at 0.03–0.05 mg/kg.

Adequate sedation was considered to have been achieved when the subject passed through the following sequence: eyes closing, cessation of body movements, and loss of the eyelash reflex. The target level of sedation was moderate to deep responsiveness level of the American Society of Anesthesiology (ASA) criteria [17] with the patients being able to respond purposefully to the stimulation given without respiratory depression. During the procedure, if the target level was not obtained or the subject moved significantly, additional injections of sedative medicine were administered as follows: 1/3–1/2 of the initial dosage of propofol or 1/2 of initial midazolam. The propofol and midazolam were administered by endoscopists. Endoscopists must experience anesthesiology training, and an anesthesiologist from the same hospital was on call at all times for any possible complication. Before the start of the study, endoscopists and nurses were trained in administering propofol sedation under the supervision of an anesthesiologist.

Routine standard monitoring at the endoscopic unit included continuous assessment of peripheral oxygen saturation (SpO₂) and heart rate. Clinical assessment of the patients included measurement of respiratory effort by visual assessment and by palpation of the chest wall, abdominal excursion, or exhaled breath. When oxygen desaturation (SpO₂ <90 %) continued for >20 s, which was considered as respiratory depression, supplemental oxygen was given. The endoscopic team consisted of the nurse who was responsible for monitoring the patient, the endoscopist, and the endoscopic technician or second nurse to assist the endoscopist.

Vital signs were assessed frequently, but not on a regular periodic basis. In addition to monitoring vital signs, the patient's condition was assessed more globally by visual inspection. Monitoring and complications were recorded by the nurse. SpO₂ was routinely captured by visual inspection of the monitor, and the value was recorded.

Two experienced endoscopists (H. Yamamoto, T. Gotoda) with certification from the Japanese Society of Gastrointestinal Endoscopy evaluated sedation depth according to responsiveness levels of the American Society of Anesthesiology practice guidelines, as follows: minimal sedation, normal response to verbal stimulation; moderate sedation, purposeful response to verbal or tactile stimulation; deep sedation, purposeful response after repeated or painful stimulation [17]. Patient tolerability was also assessed according to the following four levels of the gag reflex: excellent, without gag reflex; acceptable, with weak

reflex; poor, with strong reflex but eventually able to undergo the procedure; not acceptable, intubation impossible.

After the procedure, the patients' conditions were assessed as to be steady on their feet or to be transferred by wheelchair to the recovery room. Consciousness and psychomotor function were also assessed using the following three criteria [18]: (1) level of consciousness (fully awake and responding to questions from the recovery room nurse), (2) ability to stand on one foot, and (3) ability to walk in a straight line for 5 m without instability. These three criteria were assessed every 15 min starting just after the procedure; full recovery was defined as meeting all three criteria. The patients were permitted to leave the endoscopic unit if they met the full recovery criteria. They ultimately left the hospital 1 h after the procedure was completed.

Instruments

The high-resolution videoscopes (GIF-H260, GIF-Q260, GIF-XQ260, or GIF-H260Z; Olympus, Tokyo, Japan) that were used have insertion diameters of 9.8, 9.2, 9.0, and 10.8 mm, respectively. They all have an accessory channel diameter of 2.8 mm, a total length of 1,350 mm, and a working length of 1,030 mm.

Sample size and statistical analysis

Sample size was calculated in consideration of the frequency of recovery within 30 min. We assumed 50 % of the midazolam group would be fully awake at 30 min from a previous report [16]. We calculated the sample size needed to detect a 30 % difference in 30 min using the uncorrected chi-square test, with a statistical power of 0.90 using a significance cutoff of 0.05, and we determined that the number of cases required for two-sided tests was 51 patients in each group, which we then increased to 113 cases in total, in expectation of a 10 % dropout rate.

The chi-square test, with Yates' correction for continuity where appropriate, was used for the comparison of categorical data. Fisher's exact test was used when the numbers were small. The Wilcoxon signed-rank test and Student's *t* test were used when two means were compared.

A *P* value of <0.05 was considered to indicate a statistically significant difference. All *P* values are two tailed. Statistical analyses were performed with SPSS statistics, version 20 (SPSS, Chicago, IL, USA).

All authors accessed the study data and reviewed and approved the final manuscript.

Results

In total, 117 patients were invited to participate; 9 refused, 2 canceled, and 106 were enrolled. A total of 54 and 52 patients were randomly assigned to propofol and midazolam, respectively. The baseline characteristics of the two groups are shown in Table 1. Patients' characteristics, including gender, age, body weight, the amount of alcohol intake, renal and liver functioning tests by blood examination, and indications for EGD, were similar between the two groups without stratification. The majority of indications for diagnostic EGD were gastric cancer screening (31 % in both groups) or gastrointestinal symptoms (57 % of propofol and 56 % of midazolam patients).

The vital signs for the two groups were not significantly different before sedation. Blood pressure and heart rate had significantly declined in both groups from baseline after EGD and at the time of full recovery. The values of mean oxygen saturation were 97–98 % during endoscopy and recovery in both groups. The values of mean heart rate fell significantly at the time of full recovery compared with baseline or after the procedure in both groups. The medication, heart rate at baseline, heart rate after the procedure, and that at the time of full recovery, respectively, were as follows: for propofol, 73, 72, and 64; and for midazolam, 73, 77, and 66. The mean systolic and diastolic blood pressure levels fell after the procedure and at the time of full recovery compared with baseline, as follows: propofol, 129/79, 118/73, and 116/74; and for midazolam, 129/81, 119/77, and 111/73. The patients did not need infusion and were fully awake at discharge without incident.

Table 2 shows details of the procedures and sedative drugs. There was no difference in the videoscopes used in both groups. The mean total dose of propofol used was 0.93 mg/kg (56 mg/patient; range, 0.61–2.03 mg/kg) and the mean midazolam dose was 0.05 mg/kg (3.0 mg/patient; range, 0.03–0.07 mg/kg). There was no difference in the mean duration of the procedures. A total of 43 patients (80 %) receiving propofol and 48 (92 %) receiving midazolam completed diagnostic EGD after a single bolus injection.

Table 1 Patient characteristics

	Propofol	(<i>n</i> = 54)	Midazolam	(<i>n</i> = 52)	<i>P</i> value
Gender, M/F	22/32		23/29		n.s.
Mean age (range) (year)	45	(22–68)	44	(20–68)	n.s.
Mean body weight (range) (kg)	60	(40–95)	62	(42–98)	n.s.

Table 2 Details of endoscopic procedures

	Propofol	(n = 54)	Midazolam	(n = 52)	P value
Mean initial dose (range) (mg/kg)	0.84	(0.61–1.07)	0.05	(0.03–0.06)	
Mean total dose (range) (mg/kg)	0.93	(0.61–2.03)	0.05	(0.03–0.07)	
Number of additional injections (n, %)	11	(20)	4	(8)	n.s.
Successful procedure (n, %)	54	(100)	52	(100)	n.s.
Mean procedure time (range) (s)	311	(111–769)	339	(182–780)	n.s.

Table 3 Sedation level and gag reflex

	Propofol	(n = 54)	Midazolam	(n = 52)	P value
Sedation level (ASA responsiveness scale) (n, %)					
Deep	30	(56)	12	(23)	$P < 0.01$
Moderate	24	(44)	32	(62)	$P < 0.01$
Anxiolysis	0	(0)	8	(15)	$P < 0.01$
Gag reflex (n, %)					
Excellent	34	(63)	25	(48)	n.s.
Acceptable	17	(31)	26	(50)	n.s.
Poor	3	(6)	1	(2)	n.s.
Not acceptable	0	(0)	0	(0)	n.s.

Sedation depth and tolerability were similar in both groups. Almost all the patients were sedated more deeply than the moderate level with unremarkable gag reflex (Table 3).

In the propofol group, 40 (74 %) patients completed recovery criteria on arrival at the recovery room (Fig. 1), and the mean full recovery time was 4.7 min with propofol sedation, which was significantly shorter than with midazolam sedation (24 min, $P < 0.01$). In addition, 49 (91 %) of propofol-sedated patients could walk to the recovery room just after the procedures were completed whereas 44 (85 %) of the midazolam group required a wheelchair to leave.

Oxygen desaturation requiring supplemental oxygen (2 l/min) occurred in one patient (2 %); mask ventilation or endotracheal intubation was not required in any case. In no case did a respiratory event or laryngospasm occur. One patient in the propofol group fell from the examination table at the start of EGD.

Discussion

This randomized controlled clinical trial was conducted to compare propofol with midazolam, focusing on patient management after screening EGD procedures in relatively healthy Japanese individuals without functional impairment. Most of the propofol patients' sedation levels of responsiveness were moderate or deep without respiratory depression, and tolerability was similar to that of the

Fig. 1 Recovery time from propofol and midazolam sedation at recovery room. Propofol, $n = 54$; midazolam, $n = 52$. Chi-square test, * $P < 0.001$, † $P < 0.05$ between groups

midazolam patients. Furthermore, propofol patients could walk to the recovery room just after the procedures were completed. Although safety profiles were similar to those undergoing midazolam sedation, propofol use resulted in shorter times to discharge with less management after completion of EGD procedures.

A number of issues surround the use of propofol for endoscopic procedures without an anesthesiologist or nurse anesthetist in attendance. Based on many reports from

tertiary hospitals that ensured the safety of propofol administration by an endoscopist and only one nurse, Kulling et al. [7] showed that the safety was the same as that in a private practice setting. They reported that propofol sedation reduces the need for post-procedure monitoring and that it was as safe as traditional sedative agents such as benzodiazepines when administered by a gastroenterologist and a nurse. In the current survey, we focused on comparing the clinical advantages regarding post-procedure management as well as depth of sedation, tolerability, and satisfaction between propofol and midazolam used for screening EGD procedures at a private clinic.

Medication used for endoscopic sedation should be determined effectively by the type of procedure and length of time. The mean procedure time for diagnostic EGD in this study was 5–6 min, and additional injections of propofol were not required in 80 % of the patients. Many patients in the propofol group were awake at the end of the procedure but did not feel uncomfortable. Single-dose propofol appears to be suitable for the duration of screening EGD procedures. When endoscopic procedures are predicted to last longer or the patient is very anxious, the use of benzodiazepine alone or combined with a narcotic might be a better choice for achieving adequate sedation.

For most patients in this study, appropriate levels of sedation and good tolerability were achieved in both groups. Although more than half the propofol group patients were sedated to a deep sedation level in the ASA level of responsiveness, respiratory depression requiring intensive management did not occur. Together with minimal gag reflex, this should result in patient satisfaction. Almost 90 % of patients in both groups rated their overall satisfaction for this procedure as excellent or good (data not shown). This result is compatible with previous reports investigating patient satisfaction with propofol sedation [14, 16, 19, 20]. As reported previously, propofol increases acceptability, improves the diagnostic accuracy, and increases the quality of EGD [21].

The mean full recovery time was 4.7 min in the propofol group, which was significantly shorter than 24 min in the midazolam sedation group. Recovery time after propofol sedation as quantified by detailed tests in other studies [8, 9, 19, 22] ranged from 14 to 19 min. These times are compatible with our results. Patients could walk to the recovery room without support just after the procedure was completed. Propofol sedation may result in saving recovery room space, reduce the number of staff required to monitor patients, and increase the number of endoscopy examinations. After recovery from propofol sedation, patients are completely awake and alert. The stability of awareness was shown in a previous study by evaluating psychomotor and driving skills [23].

To ensure patient safety, propofol was administered in this study according to a rigid protocol that required anesthesiology training of endoscopists and nurses in the administration of the drug. Furthermore, both the sedative medications in this study were administered by weight-adjusted means. The amount of propofol used in this study was relatively low as “low-dose propofol sedation” [18–20, 24]. It was safe, and clinical recovery was rapid.

The major drawback of propofol is its respiratory depressant effect [25]. This effect can prolong an endoscopic procedure or recovery and can require medication or other intervention [26]. In this study, the safety was almost equal to that noted in previous reports. The use of propofol without an anesthesiologist or nurse anesthetist in attendance has been reported by other investigators with no episodes of oxygen desaturation that required mask ventilation [18–20, 24]. One patient in the propofol group fell down from the examination table at the start of EGD in our study. Thus, propofol can cause deep sedation rapidly and must be given by slow injection with careful attention to dosing and monitoring. Whether an anesthesiologist is in attendance or not, investigators must exercise appropriate caution when using this fast-induction drug.

In conclusion, propofol administration was associated with less management for monitoring and recovery. Our data suggest that the short recovery time of propofol may save recovery room space, reduce the number of reclining seats, the number of nurses, and staff effort and improve patient compliance even in smaller private clinics.

Limitations

This study was performed at a single institution in Japan. Elderly people were excluded.

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Conflict of interest The authors declare that they have no conflicts of interest associated with this study.

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