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ORIGINAL ARTICLE

Non-anesthesiologist administrated propofol (NAAP) during endoscopic submucosal dissection for elderly patients with early gastric cancer

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Abstract
Background Propofol is rapidly increasing in use in many countries because endoscopists and patients report greater satisfaction with propofol than with conventional sedatives. However, propofol infusion during lengthy endoscopic procedures in elderly patients is still controversial. We investigated the safety of gastroenterologist-guided propofol sedation in elderly patients who underwent gastric endoscopic submucosal dissection (ESD) at a single center.
Methods We reviewed 121 medical records of patients who underwent gastric ESD. We compared retrospectively the details of propofol usage, hemodynamics, and re-sedation in the elderly group to those in a younger group.
Results No significant differences in patients' baseline characteristic including ASA classification between elderly and younger groups were shown. The average maintenance dose and total dose of propofol infusion could be similarly administrated in both groups. Seven adverse events (5.8 %) occurred at the time of propofol bolus injection. Although 3 cases (2.5 %) of hypotension (systolic blood pressure <80 mmHg), 8 cases (6.6 %) of desaturation (blood oxygen saturation <90 %) and 1 case (0.8 %) of bradycardia (pulse rate <40) were found during the maintenance of propofol infusion, there were no statistically significant differences in the elderly and younger groups. All events were immediately resolved without any intervention. No patients developed a re-sedated condition.
Conclusion Gastroenterologist-guided propofol sedation during gastric ESD may be acceptable even in the elderly with ASA classification I/II under careful monitoring of vital signs and oxygen saturation.

Keywords Elderly patients · Non-anesthesiologist administrated propofol (NAAP) · Endoscopic submucosal dissection · Monitoring · ASA classification

Introduction

Endoscopic submucosal dissection (ESD) reduces the risk of local recurrence following treatment for early gastric cancer (EGC) even when large or ulcerated lesions are involved because ESD has a higher en bloc resection rate with a more accurate histological assessment [1, 2]. Since ESD is more time-consuming than conventional endoscopic mucosal resection (EMR), multiple doses of medication are usually required to provide an adequate level of sedation [3]. However, the most effective and safest sedative for ESD and the method by which to deliver this to the patient have not yet been clearly established.

Elderly patients are generally defined as individuals who are 75 years or older. They are usually treated the same as middle-aged patients in daily clinical practice. The majority of them have multiple diseases and functional disorders [4]. Life expectancy in elderly patients has increased dramatically worldwide [5].

Accordingly, we are increasingly being faced with the challenge of treating elderly patients with gastric neoplasms. Studies of aged patients with gastric cancer who either did or did not receive treatment revealed longer

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survival times for patients with cancer treatment [6, 7]. Recently, minimally invasive curative treatment has been applied for gastric cancer in elderly patients if co-morbidities are controllable [8, 9].

The use of sedation has increased in gastrointestinal endoscopy over the last decade [10]. Recently, propofol has gradually taken the demand from benzodiazepines as a sedative because of its short-acting pharmacokinetic character [11, 12]. Although most of the previous studies that demonstrated the effectiveness and safety of propofol sedation were conducted in non-elderly patients, a few studies reported the clinical usage of propofol in elderly individuals [13]. Unfortunately, those reports did not focus on the safety of propofol as applied to aged patients who underwent therapeutic endoscopy requiring lengthy sedation.

The aim of this case series study is to assess the safety of gastroenterologist-guided sedation with propofol in elderly patients who underwent ESD for EGC at a single center, because there is apparently no clinical data about propofol application in elderly Japanese.

Methods

Patients

The medical records of 85 patients who underwent ESD under propofol (1 % Diprivan Injection-kit; AstraZeneca) sedation for early gastric cancer between February 2011 and November 2012 at Yuri Kumiai General Hospital were included in this study. The patients were divided into 3 groups: patients <65 years old; patients ≥65 and <75 years old; and patients ≥75 years old. The procedure time, details of propofol administration, and the patient's re-sedated condition when returning to the ward, blood pressure, oxygen saturation, and heart rate during ESD was reviewed, and then compared among the 3 groups retrospectively. Patients with an American Society of Anesthesiologists (ASA) [14] physical status class were also assessed. Patients were excluded if they had a history of sulfite, egg, soybean, or propofol allergies, or did not provide informed consent.

Medication

Local pharyngeal anesthesia was performed using an 8 % topical lidocaine spray prior to intravenous administration of the sedative. Patients received a slow initial intravenous bolus of 0.5 mg/kg/10 s of propofol. Additional intravenous boluses of 0.5 mg/kg of propofol were slowly administered until the patient was sedated, as determined by a Ramsay sedation score of 5–6. After each bolus infusion, a waiting period of typically 30–60 s was observed to assess that the drug had completely taken effect before a decision was made to administer the next bolus. An automatic infusion pump was used to maintain a continuous infusion of 2–5 mg/kg/h to maintain the same level of sedation. The objective was to maintain a patient sedation level between moderate (the patient responds properly to verbal commands either given alone or accompanied by light tactile stimulation) and deep (the patient cannot be easily aroused, but may respond properly to repeated or painful stimulation) [15]. All patients received 15 mg of pentazocine as an analgesic agent at the start of the ESD and at 60-min intervals thereafter during the procedure.

When a patient seemed to be in discomfort or exhibited restlessness following verbal stimulation, an additional 10 mg of propofol was given as a bolus injection and the maintenance infusion rate was increased by 1 mg/kg/h. Conversely, if an adverse event occurred, such as hypotension with an SBP of <80 mmHg or oxygen desaturation <90 %, the maintenance dose was reduced by 1 mg/kg/h. Propofol infusion was continued until removal of the endoscope.

All medications were given by a gastroenterologist who did not participate directly in gastric ESD procedures. At least one physician with advanced training in basic and cardiac life support was present during every ESD. An anesthesiologist was also on standby in case of an emergency, and resuscitation equipment was always present in the endoscopic room.

Monitoring

Patients received supplemental oxygen (2 L/min) by nasal cannula in the endoscopy room as their vital signs and oxygen saturation were continuously monitored and recorded every 5 min using a standard three-lead electrocardiogram, pulse oximetry, and automatic blood pressure equipment. Chest excursion and respiratory rates were monitored visually, and consciousness levels were assessed initially after the induction of sedation using the Ramsay sedation score. Patients were discharged from the endoscopy room after the ESD, when it was confirmed that they were fully awake and responding to questions, and that their vital signs were also stable.

Management of adverse events

Adverse events were considered to be a decline in oxygen saturation to <90 % or an SBP of <80 mmHg. If a patient developed oxygen desaturation <90 % for longer than 10 s, supplemental oxygen was used to immediately increase the oxygen flow until the saturation level was

>95 %. If supplemental oxygen did not improve the patient's oxygenation condition within 3 min, the ESD procedure and sedation were interrupted to secure the airway and administer a reversal agent as necessary. In cases of hypotension, we immediately increased the rate of the intravenous drip (for example, from 100 to 150 mL/h), decreased the propofol infusion rate by 1 mg/kg/h, or administered 8 mg of ephedrine by bolus intravenous injection.

Statistical analyses

Each outcome was analyzed using the one-way ANOVA test for normal describes data and the Kruskal–Wallis test for nonparametric data. A value of $P < 0.05$ was regarded as statistically significant. All statistical evaluations were performed using SPSS version 15.0 J software (SPSS Japan Inc., Tokyo, Japan).

Results

Baseline characteristics

One hundred twenty-one patients (M/F, 88/33) receiving gastric ESD were classified into 3 groups: patients <65 years old ($N = 32$), patients ≥65 and <75 years old ($N = 41$), and patients ≥75 years old ($N = 48$). There were no statistically significant differences in the male to female ratio, BMI, frequency of co-morbidity among groups. ASA classification II was the most common class in patients ≥75 years old ($N = 45$, 93.8 %) compared to 23 patients (71.9 %) with ASA classification I in patients <65 years old. However, the frequency of ASA classification I/II was similarly found in all 3 groups ($P = 0.378$). The baseline characteristics of the patients are summarized in Table 1.

Details of propofol administration

The procedure times of gastric ESD were 97.22 ± 52.0, 94.31 ± 45.95, and 97.77 ± 47.68 min respectively, and there were no statistically significant differences in each group.

The induction dose of the bolus injection, times of additional bolus injections, times of opportunities to change the maintenance dose, average maintenance dose (mg/kg/h), and total infusion dose during the entire gastric ESD procedure for each group are shown without any statistically significant difference in Table 2.

Table 1 Baseline characteristics

	Patients <65 years old	Patients ≥65 and <75 years old	Patients ≥75 years old	*P*-value
N	32	41	48	
Gender M/F	24/8	29/12	35/13	0.922
BMI	23.7 ± 2.82	22.9 ± 3.31	23.2 ± 3.14	0.570
Co-morbidity				
Hypertension	3	7	9	0.513
Diabetes mellitus	2	1	6	0.191
Liver dysfunction	0	1	0	0.377
Chronic renal disease	0	1	0	0.380
ASA classification				
I/II	32	39	47	0.378
III	0	2	1	

N number of patients, *M* male, *F* female, *BMI* body mass index, *ASA* American Society of Anesthesiologists

Table 2 Details of propofol administration

	Patients <65 years old	Patients ≥65 and <75 years old	Patients ≥75 years old	*P*-value
Procedure time (min)	97.22 ± 52.0	94.31 ± 45.95	97.77 ± 47.68	0.938
Induction dose of bolus injection (mg/10 s)	30.3 ± 17.4	29.8 ± 16.1	27.5 ± 12.6	0.615
Times of additional bolus injection	2.35 ± 2.18	2.21 ± 2.10	2.10 ± 1.66	0.919
Times of opportunity to change maintenance dose	1.35 ± 1.53	1.36 ± 1.35	1.08 ± 1.10	0.563
Average maintenance dose (mg/kg/h)	4.09 ± 1.53	4.16 ± 1.50	3.78 ± 1.43	0.359
Total infusion dose (mg)	391.5 ± 255.13	352.1 ± 166.69	327.9 ± 177.68	0.373

Table 3 Hemodynamic during ESD and re-sedation

	Patients <65 years old	Patients ≥65 and <75 years old	Patients ≥75 years old	*P*-value
At induction of bolus injection				
Hypotension (systolic blood pressure <80 mg)	0	1	2	0.509
De-saturation (blood oxygen saturation <90 %)	1	1	2	0.902
Bradycardia (pulse rate <40)	0	0	0	–
During maintenance infusion				
Hypotension (systolic blood pressure <80 mg)	0	2	1	0.405
De-saturation (blood oxygen saturation <90 %)	2	3	3	0.976
Bradycardia (pulse rate <40)	0	0	1	0.467
Re-sedated condition				

ESD endoscopic submucosal dissection

Hemodynamics during ESD and re-sedation

In total, 7 adverse events (5.8 %) occurred at the time of propofol bolus injection. All events were immediately recovered without any intervention. Three cases (2.5 %) of hypotension (systolic blood pressure <80 mmHg), 8 cases (6.6 %) of desaturation (blood oxygen saturation <90 %) and 1 case (0.8 %) of bradycardia (pulse rate <40) were found during the maintenance of propofol infusion. There were no statistically significant differences in the elderly and younger groups. These events were also resolved by reducing the continuous infusion dose. No patients developed a re-sedated condition. Table 3 shows the hemodynamics and re-sedation in detail.

Discussion

In Japan as well as in Western countries, the number of elderly patients who need gastrointestinal endoscopy has rapidly increased in recent years [16, 17]. Non-anesthesiologist administration of propofol has been widely accepted as an effective and safe sedation choice for gastrointestinal endoscopy and other interventional procedures [18, 19]. In contrast to diagnostic endoscopy, therapeutic endoscopy requires adequate sedation irrespective of age and ASA classification. However, there has been limited information on the outcome of therapeutic endoscopic procedures and sedation used in elderly patients. In this case-series study, we found that gastric ESD under monitored propofol sedation by gastroenterologist could be achieved with acceptable safety in the elderly population with ASA classification I/II.

Propofol is a phenolic derivative with satisfactory sedative, hypnotic, antiemetic, and amnesic properties. This sedative-hypnotic drug is also highly lipophilic, and can rapidly cross the blood–brain barrier resulting in an early onset of action and a shorter recovery profile [20]. Sedation with propofol can be achieved both by bolus administration and continuous infusion. Concerning side effects, propofol is generally associated with good hemodynamic stability, although it can induce a dose-dependent decrease in blood pressure and heart rate. Transient decreases in blood pressure are more prominent during bolus administration. Thus, slow initial infusions have been recommended. There are also other disadvantages to propofol, including its lack of a pharmacological antagonist.

Although gastrointestinal endoscopy with sedation in elderly patients is increasingly being performed, data on the outcomes and side effects of sedation are limited. Age-related pharmacokinetic changes and their co-morbidities complicate drug therapy. Consequently, lipophilic drugs may have a prolonged half-life. When combined with reduced hepatic and renal clearance mechanisms, this prolonged half-life can prolong the recovery of elderly patients after sedation [21]. Hepatic drug clearance of some drugs can be reduced, and renal excretion is decreased in most elderly individuals because of the presence of hypertension and coronary heart disease. Thus, sedation should be modified by the administration of fewer agents at a slower rate and with a lower cumulative dose.

A recent study also showed that elderly patients who underwent endoscopy required lower mean propofol doses for sedation without any major complications compared with patients aged <70 years [22]. A study indicated the safety of sedation with propofol in patients 90 years of age and older for upper gastrointestinal endoscopy, percutaneous endoscopic gastrostomy, colonoscopy, and ERCP [23]. Another report indicated that continuous propofol sedation in patients >80 years of age is generally as safe as it is in younger patients, although patients >80 years showed a greater tendency to develop severe oxygen desaturation during the colonoscopy and endoscopic

ultrasonography procedures [24]. However, there is limited information on the outcome of therapeutic endoscopic procedures and sedation used in elderly patients.

In our case-series study, we assessed the safety of gastroenterologist-guided sedation with propofol in elderly patients who underwent time-consuming gastric ESD. The rates of co-morbidity were also same among groups. Consequently, the frequency of ASA classification I/II was similarly found in all 3 groups. Furthermore, the average maintenance dose (mg/kg/h) of propofol infusion in the elderly patients is managed same as in younger patients. Recent study concluding higher level of endoscopist satisfaction without cardiopulmonary complications and better patient cooperation under balanced propofol sedation with conventional sedation (midazolam and meperidine) included approximately 10 % of patients with ASA classification III [25]. A meta-analysis indicated that propofol sedation was not associated with an increased risk of complications [26]. Another meta-analysis comparing propofol-based sedation with traditional sedative agents found that they had similar rates of adverse effects [27]. However, a recent study showed deep sedation in elderly men under continuous propofol infusion with opioid injection such as fentanyl by anesthesiologist during gastric ESD might be a risk factor for pneumonia because of less gag reflex [28, 29]. Thus, we could consider that the reasons of low incidence of severe complication were excluding patients with ASA classification III after careful assessment for cardiopulmonary function and managing propofol sedation without opioid injection. Propofol administration in elderly patients should be promising that no re-sedation cases were found in the ward; this is because propofol is easier and safer to maintain than midazolam [30]. In our study, all adverse events were resolved by reducing the continuous infusion dose, and no patients developed a re-sedated condition.

Medication used for endoscopic sedation should be determined effectively and safely by the type and length of procedure and the patient's condition including their age and ASA classification. We conclude that lengthy propofol sedation could be safely managed in the elderly population with less co-morbidity, however we have to pay more careful attention with tight monitoring to this group. The best methods for sedation during digestive endoscopy are also controversial. Since our study was retrospective analysis conducted in a single center, considering clinical features in elderly patients, further investigation is required.

Limitations

This case-series study was completed at a single institution in Japan.

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Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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