A RETROSPECTIVE STUDY OF RISK FACTORS FOR CARDIOPULMONARY EVENTS DURING PROPOFOL-MEDIATED GASTROINTESTINAL ENDOSCOPY IN PATIENTS AGED OVER 70 YEARS

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Abstract

Background: Because of its rapid onset and recovery profile, propofol-mediated sedation is predominantly used during endoscopy.

Objective: To examine procedure-specific occurrence and risk factors for cardiopulmonary events during propofol-mediated gastrointestinal endoscopy in patients aged over 70 years.

Methods: Retrospective study with the anesthesia recorder system was performed to determine the occurrence and frequency of cardiopulmonary events. We enrolled 660 elderly outpatients who had undergone gastrointestinal endoscopies in our hospital between May 2006 and May 2007. Multivariate logistic regression analysis was performed using variables, including age, body mass, American Society of Anesthesiologists (ASA) classification, anddifferent anesthetic method either by monitored anesthesia care or intravenously administered propofol, to determine the risks of cardiopulmonary events.

Results: Slight adverse effects occurred in 88 patients during gastro-intestinal endoscopy, and no severe cardiopulmonary events occurred. There was no significant correlation between the adverse effects and sex or anesthetic methods ($p = 0.95$ and $p = 0.053$, respectively). There was a significant correlation between the occurrence of cardiopulmonary events and both age and body mass ($p = 0.022$ and $p = 0.009$, respectively).

Conclusion: The procedure-specific risk factors for cardiopulmonary events during propofol-mediated gastrointestinal endoscopy in patients aged over 70 years include age and body mass. These factors should be taken into account during future comparative trials.

Key words: Cardiopulmonary events (CP), Propofol-mediated gastro-intestinal endoscopy, Digestive System, Hypotics and sedatives Administration & dosage/adverse effects.

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Introduction

Intravenous sedation with benzodiazepines is a standard practice in interventional endoscopic procedures including therapeutic esophago-gastro-duodenoscopy or endoscopic retrograde cholangiopancreatography. Midazolam is frequently selected because it has powerful amnesic properties, some anxiolytic effects, and a short elimination half-life. However, the sedative and amnesic effects of benzodiazepines sometimes do not provide adequate patient comfort during more sophisticated interventional procedures. Propofol (2,6-di-isopropylphenol) is classified as an ultra-short acting sedative-hypnotic agent with a short duration of action (t1/2 distribution, 2–4 min). Consequently, propofol has a more rapid recovery time for the patient (10–20 min) compared with the available benzodiazepines, which provide amnesia, but affords minimal levels of analgesia[1-2]. Currently, propofol is used for sedation during gastrointestinal endoscopy. Proponents of propofol indicate its superior recovery and patient satisfaction parameters when compared with the standard combination of a narcotic agent and benzodiazepine[3-4]. However, propofol is relatively expensive and may lead to respiratory arrest when used in higher doses. The successful performance of endoscopic procedures can be achieved with patients in either moderate or deep sedation or under general anesthesia. The use of sedation or anesthesia can relieve the patients' anxiety and discomfort and improve the outcome of examination. Elderly patients with chronic diseases who are more vulnerable to complications are an exception. The most important issue is to guarantee the patients' safety and ensure vital signs stability during the examination.

In a previous study, more than 140,000 cases of gastroenterologist or nurse-administered propofol sedation (NAPS) for endoscopic procedures were reported with no instances of significant adverse events (SAEs) such as endotracheal intubation or death[5]. Despite the size of the study, the comparative safety of propofol is still unknown. The objective of this retrospective study was to compare the morbidity of cardiopulmonary events with or without propofol among septuagenarians, octogenarians, and nonagenarians, and determine the risk factors for cardiopulmonary events of propofol-mediated gastro-intestinal endoscopy.

Materials and Methods

Study design

This study was approved by the People's Liberation Army General Hospital Ethics Committee, and got all of the subjects' written consent 660 ASA physiological status □~□ cases that had scheduled gastrointestinal endoscopy between May 2006 and May 2007 were included in our study. Inclusion criteria: Healthy, aged over 70 years, and no prior endoscopic examinations. Exclusion criteria: Prior gastrectomy, psychiatric diseases or long-term psychiatric drug addiction, presence of neoplastic or other serious concomitant diseases, history of intolerance to propofol, obesity (body mass index >30), and severe cardiopulmonary disease. Patient demographics were as follows male/female ratio was389/271, 592 patients aged 70–79 years, 61 patients aged 80–89 years, and 7 patients aged more than 90 years. 293 patients underwent gastroduodenoscopy, 277 patients underwent colonoscopy, and 90 cases underwent gastro-intestinoscopy. The patients were divided into two groups according to propofol used or not: Group A (control group, propofol not used) and Group B (propofol used).

No premedication or intravenous solution was given before examination. An intravenous cannula was placed in the right antecubital vein for the infusion of anesthetics and analgesics. Cardiopulmonary (CP) events included: (1) chest pain, (2) transient hypoxaemia, (3) prolonged hypoxaemia, (4) bradycardia, (5) wheezing, (6) dysrhythmia, (7) tachycardia, (8) tracheal compression, (9) hypertension, (10) hypotension, (11) respiratory distress, and (12) pulmonary edema and vasovagal reaction. The majority of quantitative CP events were not given threshold values, which includes transient and prolonged hypoxaemia, dysrhythmia, hypertension and hypotension. Noninvasive blood pressure, heart rate and pulse oxygen saturation were recorded routinely. Supplemental oxygen was given by endoscopy mask with O_2 at 2 L/min. Patients with three minutes of persistent oxygen saturation nadir <90% were defined as having respiratory depression and

needed respiratory assistance or controlled breathing. If hypotension (<90 mmHg systolic arterial pressure) or bradycardia (<45 beats/min) persisted for more than 5 minutes, this was defined as circulatory depression, and was restored by a combination of intravenously administered fluid, ephedrine, and atropine.

Anesthetic method

Neuroleptanalgesia (NLA) with midazolam (1.0–2.0 mg) and fentanyl (50–150 μg) was given intravenously in the group A that we called monitored anesthesia care (MAC). Propofol (1–1.5 mg/kg; 30–40s) was given slowly after the administration of midazolam (1.0 mg) and fentanyl (50 μg) in the Group B. The endoscope was inserted when the patients lost consciousness and exhibited no eyelash reflex. Propofol at 10–20 mg was added intermittently according to the patient's reaction and the duration of examination.

Statistical analysis

The data analysis was performed using SPSS 11.0 for Windows (SPSS China Inc, Beijing). Logistic regression analyses were performed to determine cardiopulmonary (CP) events during gastro-intestinal endoscopy. Predictors from univariate analyses with P values less than 0.5 were included in the multivariate models. Stepwise elimination of predictors was used to arrive at a parsimonious model and interaction testing (NLA versus plus propofol) was conducted on an intention-to-treat basis. A p value <0.05 was considered to be statistically significant.

Results

A total of 660 gastro-intestinal endoscopies were performed. In 455 of these, propofol was utilized while the remainder received MAC (Table 1). The most common CP event for both groups was transient hypoxaemia. When comparing MAC to propofol usage during colonoscopy, no significant statistical differences were seen between the two groups for age distribution, gender, dichotomized ASA classification, and the setting in which the colonoscopy was performed (Table 1). There was no significant difference between the demographics of two groups (Table 1).

Table 1
Demographic data of the study

	Group A	Group B
Age(years) (mean ± sd)	78.95±6.71	77.98±6.15
Body weight(kg)(mean ± sd)	65.16±8.07	66.35±9.46
Gender(male/female)	122/83	267/188
ASA		
□~□(n(%))	180(87.9)	414(90.9)
□(n(%))	25(12.1)	41(9.1)
Procedure(n)		
Gastroscopy	97	196
Colonoscopy	73	204
Gastro-intestinal scopy	35	55
Duration of examination(min) (mean ± sd)	26.87±9.07	29.48±8.49

The patients were divided into 3 different groups according to their age: 70–79 years old, 80–89 years old, and over 90 years old. We observed respiratory events in 9.83% of patients in the 80–89 years old group and circulatory events were also observed in 9.83% of the 80–89 year olds. The 80–89 years old group had significantly higher rates of respiratory and circulatory events than the 70–79 years old group, which had respiratory events in 6.93% of patients and circulatory events in 5.74% of these patients (p = 0.024). However, there was no significant difference between the two groups using different anesthetic methods (Table 2).

Table 2
Occurrence of cardiopulmonary events in patients over 70 years old

	Group A	Group B	Total
Respiratory events(n(%))	13(6.34)	34(5.74)	
70–79 yrs			41(6.93)
80–89 yrs			6(9.83)*
≥90 yrs			-
Circulatory events(n(%))	9(4.29)	31(6.81)	
70–79 yrs			34(5.74)
80–89 yrs			6(9.83)*
≥90 yrs			-
Body mass(kg) (mean ± sd)	64.15±10.24	65.25±11.01	
Gender (male/female)	53/35	343/229	

* P<0.05

Table 3
Results of univariate logistic analysis of risk factors for CP events

Characteristic	Sig (B)	Exp (B)	95% CI for Exp(B) Lower	Upper
ASA□	0.721	1.881	0.783	1.164
Procedure	0.882	1.682	0.864	1.232
Anesthetic method	0.196	1.404	0.841	2.306
Body weight	0.416	0.914	0.725	1.136
Gender	0.953	0.986	0.624	1.560
Age	0.330	1.332	0.748	2.337
Duration of examination	0.820	0.958	0.596	1.062

A univariate logistic analysis of risk factors for CP events was performed while controlling for potential confounders, and the characteristics include ASA III, procedure, anesthetic methods, body weight, gender age, and duration of examination (Table 3). The different anesthetic method was one of the most critical factors, and exp (B) is 1.404. Then a multivariate logistic regression model was set up for gastrointestinal endoscopy to estimate the ARR of CP events when controlling for potential confounders (Table 4). However, no significant difference was found among different anesthetic methods. Age and body weight in different groups are two critical factors that affect CP events, as both showed significant difference for CP events ($p < 0.05$).

Table 4
Results of multivariate logistic analysis of risk factors for CP events

Characteristic	Sig.	Exp(B)	95% CI for Exp(B) Lower	Upper
Age	0.022*			
70–79 yrs	0.99		0.000	…
≥80 yrs	0.99		0.000	..
Anesthetic method	0.053	0.577	0.331	1.006
Body weight	0.009*			
<50 kg	0.544	1.897	0.239	15.035
50–59 kg	0.189	3.979	0.506	31.274
60–69 kg	0.696	1.552	0.171	14.084
≥70 kg	0.894	0.858	0.90	8.178

* $p < 0.05$

Discussion

Propofol is a potent hypnotic agent with an unclear mechanism of action, a rapid onset and offset of sedation, and marked cardiorespiratory depressant effects[6]. Despite these effects, several empirical statements and reports have favored the use of propofol for sedation during gastrointestinal endoscopy-one of the most widely performed procedures throughout the world. Endoscopy has proved to be safe; although bloating and mild throat discomfort can occur after the procedure, severe complications are rare. Endoscopy gives a high diagnostic yield in elderly people[7-8]. Jia et al[9] reported the incidence of digestive tract carcinoma in the elderly Chinese population (aged more than 80 years) as 46.6%, and that of pre-carcinoma as 63.6%. These rates are much higher than reported previously[10-12]. Therefore, age is one of the most critical risk factors.

Although sedation is intended to facilitate endoscopy, it may cause slight adverse effect, even severe adverse cardiopulmonary events, especially in elderly patients. There is a paradox in using NLA in the elderly population, as small doses of midazolam and fentanyl can cause purposeful movement of body and complicate the examination. Furthermore, Padmanabhan et al[13] reported the administration of >2 mg of midazolam as a predictor of impaired cognitive function at discharge after colonoscopy. In patients undergoing routine endoscopy procedures, the rapid action and short half-life of propofol offers an excellent sedative state and early recovery[5,14-16]. Gangi et al. reported, in an analysis of 31,039 endoscopic procedures utilizing either standard sedation or propofol, cardiovascular complications rate was of 3.08%[17]. In this study, CP events were mainly cardiac in nature, including dysrhythmia, chest pain, angina, hypotension, and myocardial infarction. Risk factors

for these cardiopulmonary events include male sex, modified Goldman score, and the use of propofol. In our study, the rates of cardiocirculatory and pulmonary events were 6.06% and 7.12%, respectively, which are significantly different from the reported morbidity rates. This difference between the 2 studies may be due to the difference in study population of ours and Gangi's; in their study, the subjects were middle-aged adults, and theoretically they may have an increased tolerance for the sedation drug.

In randomized controlled trials, it is difficult to comment on safety, as the sample sizes were powered to detect differences in recovery profiles and patient or endoscopist satisfaction. Rex et al[18] reported a large multicenter case series of 36,473 endoscopic procedures employing nurse/endoscopy team-administered propofol. In our study, propofol was not the independent predictor for the cardiopulmonary events ($p = 0.053$). However, in clinical practice, the elderly people exhibit greater sensitivity to propofol than other adults. We considered the possibility that this difference might be due to the small number of patients in our study. If additional patients were included, our results would have been consistent with the previous report. Further, different propofol concentrations that are safe for gastrointestinal endoscopy are also crucial[19,20]. Patterson et al[21] reported the plasma propofol concentration for different age groups in which 50% of patients do not respond to gastrointestinal endoscopy stimuli and do not have hemodynamic disordance. The results demonstrated that the propofol concentration necessary for gastroscopy decreased with increasing age (Cp50 endo at 2.87 mg/ml, 2.34 mg/ml, and 1.64 mg/ml in ages 17–49 years, 50–69 years, and 70–89 years, respectively), and systolic blood pressure decreased significantly with increasing propofol concentrations. In the present study, heart rate response to endoscopy was minimal when compared with systolic blood pressure response. In previous reports, propofol was associated with a significantly slower heart rate than midazolam. In addition, a recent study by Padmanabhan et al[13] concluded that significant cognitive impairment was common at discharge from elective outpatient colonoscopy. However, the addition of midazolam and/or fentanyl to propofol sedation did not result in increased cognitive impairment when compared to the use of propofol alone. Furthermore, the use of adjuvants improved the ease of colonoscopy without increasing the rate of complications or prolonging early recovery time. Post-procedure patient satisfaction ratings with sedation were excellent in 86%, good in 12% and fair in 2%. The results indicate that the very low dose of benzodiazepine allows successful titration of propofol to moderate levels of sedation. The percentage of sedation level assessments at the deep sedation level compares quite favorably with the study on the percentage of deep sedation assessments using only midazolam[22].

The risk of arrhythmias may be increased during periods of arterial desaturation[23-25]. According to the results of Lieberman[26], if sedation is necessary for elderly patients with marginal arterial oxygen saturation, supplemental oxygen should be used. Therefore, in our study, all the patients breathed oxygen using an endoscopy mask with O_2 at 2L/min.

In our retrospective study, a higher ASA physiologic classification was associated with an increased ARR of a CP event. MAC was associated with a lower ARR of CP events when compared with Group B. During gastro-intestinal endoscopy, ASA class I and II patients receiving MAC exhibited a significantly lower ARR for CP events when compared with Group B. In addition, age and body mass were also independent risk factors for CP events during gastrointestinal endoscopy. It has been well recognized that with the increasing age, the incidence rate of systemic complications increases sharply whether the patients received diagnostic checking or surgical procedures. That coincides with Xu's study[27], in which to maintain the target plasma concentration of propofol, the infusion rate decreased with decreasing body weight and increasing age. The reason for this may be that healthier patients require deeper sedation with propofol due to the absence of an analgesic effect, predisposing the patient to central and/or obstructive apnea. There also may be a preconceived, albeit unfounded, notion that younger patients are healthier and therefore, can be taken to deeper levels of sedation without difficulty. However, the true relationship between body mass and cardiopulmonary events still need preceding prospective, random, and control study in the future.

Our study showed an association between ASA

classification and CP events for gastro-intestinal endoscopy. Additionally, the ARR for CP events was significantly less for MAC when compared to propofol administration. However, there are several limitations of this study that are inherent to its design. Since this is a cohort study, there are no randomization and inclusion/exclusion criteria for propofol-mediated endoscopy that may have been center- and operator-specific. In a recent study, a randomized, controlled, double blind trial of patient-controlled sedation with propofol/Remifentanil versus midazolam/fentanyl for colonoscopy demonstrated that patient-controlled sedation with propofol/Remifentanil yields superior facility throughout compared to midazolam/fentanyl when used in an appropriate care setting[28]. However, we hypothesized that higher risk patients would be more likely to have MAC. Therefore, this bias may increase the likelihood of adverse events in the propofol administration group. It is unlikely that a truly independent and unbiased observer was recording the physiological outcomes. The definition of the CP event contains elements such as tracheal compression that may be open to variable interpretation. Tinker et al[29] performed a closed claim analysis of anesthetic mishaps and utilized subjective findings, such as cyanosis and hypotension as a quantifiable variable without specific threshold value.

Conclusion

In conclusion, a spectrum of adverse side effects occurs during gastrointestinal endoscopy via MAC or propofol administration. In the elderly people, the risk factors for adverse events are related to age and body mass. Although the majority of adverse events are most likely a minor clinical consequence, we hypothesize that they may potentially lead to serious events, such as respiratory and cardiac arrest, even death. The risk factors for the CP events are procedure-specific, and they need to be critically appraised in any future comparative sedation trial. However, this study was a retrospective investigation, and we await further randomized-controlled studies that may give us a clear glimpse of the risk factors for complications in the elderly people using meta-analytic or meta-regressive modeling.

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