

Comparison of propofol vs. propofol/remifentanyl anesthesia in upper GI endoscopic ultrasound examination (EUS)

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Abstract

Aim: To examine whether there is any benefit from adding remifentanyl to propofol during anesthesia for EUS.

Methods: Anesthesia conditions and the incidence of complications were compared when propofol vs propofol/remifentanyl anesthesia were used for EUS.

Results: There was a trend for better anesthesia conditions and lower incidence of complications when propofol was used alone. The difference between the two groups, however, was not statistically significant.

Conclusion: Combining remifentanyl with propofol during anesthesia for EUS does not produce better conditions or lower incidence of complications than using propofol alone.

Keywords: Anesthesia; Upper gastrointestinal endoscopy; propofol; remifentanyl.

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Introduction

As gastrointestinal (GI) endoscopies increase in both number and complexity, propofol anesthesia for these procedures has gained wide popularity because of its desirable pharmacologic profile as an ultrashort-acting sedative-hypnotic. Propofol is often used as the sole anesthetic for GI endoscopy, but has also been used in combination with opioids during upper GI endoscopy where opioids confer the added advantage of suppressing some of the airway reflexes [2]. The opioid remifentanyl is a potent but short-acting synthetic mu-opioid agonist. Similar to that of propofol, the kinetic profile of remifentanyl is ideal for procedures such as upper GI endoscopy where the stimulus is intense but brief and intermittent, and where no post-procedural pain is anticipated. Therefore, combining the two drugs could potentially improve patient tolerance of the procedure.

Synergy between remifentanyl and propofol in blunting response to noxious stimuli has been demonstrated [3]. However, this synergy also increases the risk of respiratory and cardiovascular depression necessitating the use of a smaller dose of propofol when used in combination with remifentanyl compared to when propofol is used alone. The benefits of propofol/remifentanyl over propofol alone in upper GI endoscopy have not been demonstrated prospectively. As a result, this randomized, double-blinded study sought to test the working hypothesis that propofol/remifentanyl combination provides superior conditions than propofol alone during anesthesia for upper GI endoscopic ultrasound (EUS). In addition, this study aimed to compare the incidence of hypoxia and hypotension between the two techniques.

Methods

One hundred ASA physical status I-III patients age 18 to 65, scheduled for EUS were enrolled in the study. The study was approved by the Institutional Review Board of our hospital. Informed consent was obtained from participating patients. Exclusion criteria included history of allergic reactions to any of the study drugs, chronic opioid

use, morbid obesity (BMI > 40), and pregnancy.

Patients were randomly assigned to Group P (propofol) or Group P/R (propofol/remifentanyl) using a web-based program (www.randomizer.org). Group P patients received plain propofol 10 mg/ml, and Group P/R patients received propofol diluted with normal saline to a 5 mg/ml concentration + remifentanyl 1 mcg/ml. All medications were prepared by the OR pharmacist. Both the endoscopist and the anesthesia provider were blinded to the treatment drug(s) by preparing the syringes such that the appearance of both propofol and propofol/remifentanyl was identical. In addition, regardless of group designation, identical drug volumes were delivered using the same drug administration protocol.

After intravenous access was established, the patients received routine supplemental oxygen (3 L/min) by nasal cannula. Vital signs (non-invasive blood pressure, heart rate, respiratory rate, pulse oximetry, and capnography) were monitored before and every 3 minutes until the conclusion of the procedure. All patients were given intravenous glycopyrrolate 0.2 mg before the start of the procedure to decrease salivary secretions. Group P patients received propofol 1.5 mg/kg for induction followed by propofol infusion of 200 mcg/kg/min for maintenance of anesthesia. Group P/R patients received propofol 0.75 mg/kg + remifentanyl 0.15 mcg/kg for induction followed by an infusion of propofol 100 mcg/kg/min + remifentanyl 0.02 mcg/kg/min for maintenance of anesthesia. Additional boluses of propofol 200 mcg/kg in Group P, or propofol 100 mcg/kg + remifentanyl 0.02 mcg/kg in Group P/R were administered at 30-45 second intervals until the patients were unresponsive to stimulation by a Yankauer suction catheter inserted into the oropharynx. The infusion rate and bolus delivery were adjusted based upon the clinical judgment of the anesthesia provider. Conditions during the procedure were deemed appropriate when the patient exhibited minimal movement but was able to maintain spontaneous respirations.

During the procedure, the following data were recorded: total induction time (start of anesthesia to endoscope insertion), total induction drug(s) dose, total procedure time

(endoscope insertion to endoscope removal), and total procedure drug dose. The quality of anesthesia, as determined by patient response, was rated by the blinded endoscopist using a 4-point scale (1 = minimal response, 2 = mild response, 3 = moderate response, 4 = severe response). Episodes of hypoxia (arterial O₂ saturation <85%) or hypotension (systolic blood pressure <90 mmHg) were also noted. Apnea was managed by decreasing or discontinuing the treatment and with positive pressure ventilation, if necessary. Airway obstruction was managed with standard airway maneuvers such as chin lift, jaw thrust, and the use of oral or nasal airways, if necessary. Hypotension was treated with intravenous fluid boluses and/or pharmacologic agents such as phenylephrine or ephedrine, as appropriate. At the conclusion of the procedure, patients were monitored at the post-anesthesia care unit. Patients were discharged when appropriate criteria were met including stable vital signs, lack of post-procedure nausea and vomiting, ability to tolerate oral intake and return of mental status and ambulation to baseline.

The study's primary endpoint was quality of sedation and secondary endpoints were the incidence of hypoxia and hypotension. A sample size of 50 per group was chosen for simple feasibility in the single-site clinical setting of the study. This sample size was sufficient to detect a significant difference for the primary endpoint with 80% power and an overall experiment-wise error rate of alpha = 0.05. The quality of sedation was analyzed using nonparametric Wilcoxon test and the incidence of hypoxia and hypotension were analyzed using Student's t-test.

Results

Ninety-six out of 100 enrolled patients were included in the analysis. One patient underwent the procedure and enrolled in the study twice, receiving different treatment each time. One patient was excluded from the study because of procedure change. One patient assigned to the P/R group was excluded from the study because he required very large induction dose that was not possible to deliver using the study protocol. Two patients were excluded because of incomplete data collection. Patients were similar with respect to demographic data and procedure time except for a higher number of females in the P group and a higher number of males in the P/R group (Table 1). As expected, remifentanyl had a dose-sparing effect on propofol (Table 1).

Table 1 Patient Characteristics.

	P	P/R
Total Number	49	47
Sex (M/F)	19/30	29/18
Age	51.0 (23-65)	51.6 (27-65)
BMI	26.1 (19.1-37.0)	25.5 (18.2-37.1)
ASA Class (I/II/III)	1/37/11	3/37/7
Total Anesthesia Time (min:sec)	19:52	20:24
Total Dose Propofol (mg/kg)	5.9 ± 2.4	3.6 ± 1.7
Total Dose Remifentanyl (mcg/kg)	N/A	0.7 ± 0.3

P = propofol group, P/R = propofol/remifentanyl group

Overall, the quality of sedation as rated by the endoscopist was similar in both groups. The number of patients with anesthesia score of 1, 2, 3 and 4 was 35, 11, 2, 1 in the P group and 27, 16, 4, 0 in the P/R group, respectively (Table 2). The average anesthesia score was 1.37 and 1.51 for P and P/R, respectively (p-value = 0.15) (Table 2). Hypoxia occurred in 4/49 (8%) and 6/47 (13%) of patients in the P and P/R groups, respectively (Table 2). Most of the hypoxia was caused by airway obstruction and responded to standard maneuvers such as chin lift and jaw thrust. One patient in the P group developed apnea that required management by mask-bag ventilation. Hypotension occurred in 2/49 (4%) and 6/47 (13%) of patients in the P and P/R groups, respectively (Table 2). All episodes of hypotension resolved after administration of IV fluid bolus and/or phenylephrine or ephedrine. Although there was a trend for better anesthesia scores and lower incidence of hypoxia and hypotension in the P group, the difference between the two groups was not statistically significant (Table 2).

Table 2 Patient Outcomes.

	P	P/R	p-value
Quality of Anesthesia	1.37	1.51	0.15
Hypoxia	4/49 (8%)	6/47 (13%)	0.46
Hypotension	2/49 (4%)	6/47 (13%)	0.12

P = propofol group, P/R = propofol/remifentanyl group

Discussion

Propofol has gained wide acceptance for anesthesia in upper GI endoscopy because of its rapid onset and short duration of action. However, propofol has a narrow therapeutic index and lacks intrinsic analgesic properties. Therefore, when propofol is used alone, relatively large doses are needed to provide optimal conditions for insertion of the upper endoscope, increasing the possibility of adverse events [5]. Indeed, this level of sedation can rapidly reach the depth of general anesthesia, and can result in dose-dependent hypotension, respiratory depression, and airway obstruction [4]. Remifentanyl, unlike other mu-opioid receptor agonists, is metabolized by nonspecific plasma esterases through enzymatic hydrolysis, resulting in an extremely rapid clearance that is independent of excretory organ function [6]. Numerous studies have evaluated the use of remifentanyl to supplement propofol during colonoscopy with mixed results [7,8].

However, findings from these studies may not be extrapolated for GI endoscopy because of the difference in the intensity and pattern of stimulation between the two procedures. As a result, our study compared propofol/remifentanyl and propofol in upper GI endoscopy, a procedure considered more stimulating than colonoscopy. Because of the similar pharmacokinetics of both drugs and the known synergy between propofol and remifentanyl, we hypothesized that the combination of propofol/remifentanyl will provide better anesthesia compared to propofol alone. Our findings suggest that the combination of propofol/remifentanyl does not improve the quality of sedation and confers no benefit compared with the use of propofol alone.

In the current study, the dose of remifentanyl used was comparable to the dose recommended for spontaneously breathing patients [9]. In addition, the dose of propofol used was within the range used to produce general anesthesia. All routine requirements for care of patients undergoing general anesthesia were applied to the study

patients. Anesthesia was induced slowly and the drugs were given enough time to reach peak plasma levels before the start of the procedure. In addition, adequate depth of anesthesia was confirmed before insertion of the endoscope. Consequently, we postulate that these steps were helpful in achieving generally favorable sedation conditions and low incidence of complications in most of the study patients regardless of treatment regimen.

As expected, patients in the P/R group required a smaller dose of propofol during the procedure than patients in the P group. Unfortunately, the trend for better conditions and lower incidence of hypoxia and hypotension when propofol was used alone did not reach statistical significance because the study was powered to detect relatively large, clinically meaningful differences. However, our results suggest that using propofol alone during anesthesia for EUS may be preferable to using a smaller dose of propofol combined with remifentanyl.

A major limitation of our study is that post-procedure data about recovery and discharge times as well as the incidence of complications such as nausea and vomiting were not collected. Propofol is known to have antiemetic properties while remifentanyl has the potential for causing nausea and vomiting.

In conclusion, when anesthesia induction and maintenance during EUS is carried out slowly according to the described protocol, there is a trend for better anesthesia conditions and lower incidence of hypoxia and hypotension when propofol is used alone compared to when a smaller dose of propofol is used combined with remifentanyl. However, the difference between the two groups was not statistically significant.

Additional studies using a larger group of patients are warranted to detect the small but potentially clinically-significant differences between the two groups.

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