Efficacy and Safety of Propofol combined with different doses of Remifentanyl for gastroscopy: A-randomized controlled trial

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Abstract

Background Propofol is used to induce sedation or general anesthesia for procedures. Adjuvants, such as remifentanyl characterized by a rapid onset of analgesia and a very short duration of action, which was proved to be an effective opioid receptor agonist considering its effective inhibition of autonomic nervous reflex during endoscopy. Meanwhile, it brings respiratory depression and hypoxia in particular, but there is few reports to explore the optimal dose of remifentanyl during gastroscopy so far. So we design this randomized controlled trial (RCT) to identify an optimal remifentanyl dosage in patients receiving gastroscopy.

Methods A total of 200 patients were recruited and randomly assigned to receive one of four doses of remifentanyl: 0 (control group), 1.25µg/ml (PR1 group), 2.5µg/ml (PR2 group), 5µg/ml (PR3 group) combined with propofol anesthesia. The primary outcome is the incidence of hypoxia. The secondary outcomes are the dosage of propofol, patients' awakening time, and perioperative adverse reactions such as hypotension, hypertension, bradycardia, tachycardia, body movements, nausea and vomiting.

Results The onset time of PR2 (19 ± 2 s) and PR3(18 ± 4 s) group were shorter than control group (21 ± 3 s). Awakening time in PR2 (1.6 ± 0.4 min) and PR3 (1.7 ± 0.6 min) groups were significantly less than control group (4.1 ± 1.1 min). The dose of propofol in PR2(90 ± 11 mg) and PR3(87 ± 12 mg) groups were also significantly less than control group(180 ± 20 mg)

The incidence of hypoxia and increase the flow of oxygen and jaw lift in PR2 group were significantly decreased from 38% to 14% and 32% to 10% compared with the control group, respectively ($p < 0.01$). While the incidence of hypoxia in PR3 group was increased to 46%, higher than other groups ($p < 0.01$). Total number of Sedation-related adverse events in PR2 was significantly decreased from 32% to 8% ($p = 0.03$).

Conclusions Both 2.5µg/ml (PR2) and 5µg/ml (PR3) remifentanyl combined with propofol used in gastroscopy can reduce the onset time, awakening time and the amount of propofol. But the incidence of hypoxia and total number of sedation-related adverse events in PR2 group were significantly decreased compared with other groups. In our study, 2.5µg/ml remifentanyl combined with propofol in gastroscopy is an optimal remifentanyl dosage.

Trial registration: ClinicalTrials.gov, ChiCTR2000029216.

Background

According to chinese statistics, by 2018, about 50 million patients were undergoing gastroscopy every year in China¹. Given the shortage of anesthesiologists and concerning about costs, only 10% patients choose painless gastroscopy. But with the continuous development of comfortable diagnosis and treatment and the improvement of patients' economic conditions, the proportion of painless examination is increasing. Therefore, anesthesiologists need to improve every aspect of their practice to speed up the efficiency of the consulting room on the basis of ensuring the safety of patients.

Although gastroscopy can also be performed in an unsedated condition², However, due to extreme nausea, vomiting or throat bleeding, the patient usually has a severe body movement response, which makes it difficult for endoscopic doctors to successfully complete the examination or treatment³. Thus, intravenous sedation or anesthesia such as propofol has been recommended in the international guidelines for gastroscopy⁴.

We found that although propofol can meet the needs of painless gastroscopy, some patients still have a cough response that cannot be suppressed by the clinical dose of propofol. Therefore, finding a suitable way to enhance patient compliance is very important. The use of propofol in combination with opioids has been reported to improve sedation and analgesia with regard to sedative effect, pain, and discomfort⁵. Remifentanyl is a kind of opioids, which has been widely used in clinical because of its quickly onset, short half-life and metabolism independent of liver and kidney function³. It was proved to be a safe and effective opioid receptor agonist during endoscopy because of its effective inhibition of autonomic nervous reflex in the upper respiratory tract and rare adverse effects on the cardiovascular and respiratory systems. However, few reports explore the optimal dose of remifentanyl during gastroscopy.

Hypoxia is the most common complication of gastroscopy with sedation⁶, and this event is caused by airway obstruction, decreased compliance of the chest wall, and respiratory depression. The incidence of hypoxia during gastroscopy with sedation has been reported to range from 1.8–69%^{7–9}. In most cases, hypoxia is caused by airway obstruction, and lifting the jaw and increasing oxygen flow can improve hypoxia. Severe hypoxia requires pausing the gastroscopy procedure, mask ventilation, or even tracheal intubation. Studies have shown that when propofol is used alone as a sedative for gastroscopy, the side effect such as apnea or hypoxia appears to be dose and injection speed related¹⁰. As research progressed, it was reported that combination of remifentanyl and propofol not only can effectively reduce the incidence of propofol-induced pain but also can reduce the dosage of propofol¹¹. As both propofol and remifentanyl may cause dose-dependent respiratory depression, leading to hypoxia, it is important to choose an optimal dose of remifentanyl combined with propofol. We hypothesized that a better performance may be achieved with a combination of propofol and one dose of remifentanyl in the study. We observed the incidence of hypoxia and the dosage of propofol, patients' awakening time, and perioperative adverse reactions such as hypotension, hypertension, bradycardia, tachycardia, body movements, nausea and vomiting when using propofol alone or combined with different doses of remifentanyl.

Methods/design

Trial design

The study is a single-center, randomized, controlled clinical trial with the aim of assessing the possible benefits or disadvantages of propofol combined with different doses of remifentanyl anesthesia during gastroscopy. The protocol has been approved by the Ethics Committee of Affiliated hospital of Nantong

university, China (Ethics Committee number:2019-K072) and is registered at ClinicalTrial.gov with ID number ChiCTR2000029216. (<http://www.chictr.org.cn>). This work has been reported in accordance with the guidelines of the Consolidated Standards of Reporting Trials (CONSORT).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The trial flow chart is shown in Fig. 1. The patients were recruited from the gastroscopy clinic of affiliated hospital of Nantong university. All patients who participate in the study must provide their written informed consent.

Setting

Gastroscopy clinic of affiliated hospital of Nantong university, Jiangsu province, China.

Participants

The inclusion criteria were male patients aged 18–60 years, ASA physical classification I-II, BMI $\leq$ 30 kg / m². The exclusion criteria were: coagulation disorder or epistaxis; serious heart, lung, liver or kidney disease; allergy to propofol; patients with recent respiratory tract infection.

Randomization, blinding and sample size calculation

According to a random number table generated by a computer, patients are randomly assigned to receive one of four doses of remifentanyl including 0 (control group), 1.25 µg/ml (PR1 group), 2.5 µg/ml (PR2 group) or 5 µg/ml (PR3 group) combined with propofol who undergoing gastroscopy. Random numbers and group allocations are generated with a 1:1:1:1 ratio. Outcome assessment and statistical analysis will be performed by independent researchers who are from the affiliated hospital of Nantong university and are blind to the group assignment.

The calculation of the sample size in this research was based on the literature reports related to remifentanyl used in gastroscopy. The average cases were about 32 to 42 in each group. Thus, we decided to enroll 50 cases in each group. Considering the possible loss of cases in the study, we recruited a total of 246 patients (Figure. 1).

Procedures

All patients are fasted for 8 h and no water for 4 hours before gastroscopy. A topical anesthesia of oral cavity and pharynx is performed by gargling 2% lidocaine gel (10g: 0.2 g; Jumpcan Pharmaceutical Group, China). After patients enter into the examination room, the nurse opened the peripheral vein using a 24-G intravenous needle for intravenous anesthesia. After establishing an intravenous access, patient is placed at the lateral position as is the routine practice of our hospital for gastroscopy. Patients in all groups receive oxygen at 2L/min through the cannula for approximately 1 minute before they are sedated with propofol or propofol combined with different dose of remifentanyl. A propofol intravenous push strategy, and not an infusion pump, is used, because Riphaus et al demonstrated that bolus and

continuous propofol infusion allowed almost identical good controllability of propofol sedation. The anesthesiologist continually evaluated the depth of sedation with the Ramsay Sedation Scale (RSS). Once the RSS score was > 4, the endoscopist inserted the gastroscope and started the procedure. Intermittent administration maintained the depth of anesthesia (RSS > 4) until the procedure was completed.

Electrocardiogram (ECG), non-invasive blood pressure (NIBP), and pulse oxygen saturation (SpO₂) are constantly monitored and recorded in all patients. When hypoxia (SpO₂ < 90% for < 1 min) occurred, the flow of oxygen was increased from 2 to 5L/min, and the airway was opened using the jaw-thrust maneuver at the same time. Mask ventilation or even tracheal intubation was performed when severe hypoxia could not be corrected through the above method. The anesthesiologist dealt with other adverse reactions occurred during the operation if necessary.

Main study endpoint

The main study endpoint was the incidence of hypoxia.

Secondary endpoints and adverse events

These were total dose of propofol, onset time (The time from the beginning of administration to the RSS > 4), awaking time, adverse events including hypotension, hypertension, bradycardia, tachycardia, body movements, nausea, vomiting, intra-operative awareness.

Statistical analysis

All data were analyzed by using the SPSS 23.0 statistical package (IBM, Armonk, NY) and were presented as mean ± standard deviation, median (minimum, maximum; or interquartile range) or percentage. Group comparisons about age, weight, operation time, onset time, awaking time and propofol dosage were analyzed by using one-way analysis of variance (ANOVA). Categorical data were compared by using the chi-squared test or Fisher's exact test. A P value of less than 0.05 was considered statistically significant.

Results

From February 2020 to June 2020, 246 patients were enrolled; 46 of them were excluded (8 due to the absence of fasting, 4 due to acute-phase asthma, 7 due to COPD, 21 due to refused to participate in the study, and 6 due to unstable angina pectoris). Finally, 200 patients were randomized into 4 groups. A total of 200 patients were finally analyzed (Fig. 1).

General characteristics

Table 1 lists the characteristics of patients from each group, including age, sex, weight, body mass index, ASA grade, medical history, airway classification and baseline SpO₂. The duration of the gastroscopic

procedure were not significantly among four groups. The onset time of PR2 and PR3 group were faster than control group. Awakening time and dose of propofol in PR2 and PR3 groups were significantly less than control group (Fig. 2).

Table 1
General characteristics of the patients

Charateristic	Control group no. (%) (n = 50)	PR1 group no. (%) (n = 50)	PR2 group no. (%) (n = 50)	PR3 group no. (%) (n = 50)
Age(years),mean(SD)	45(19,72)	44(18,71)	46(20,74)	45(18,73)
Sex,male/female	34/16	31/19	33/17	33/17
Weight(kg),mean(SD)	60.5(10.8)	62.1(10.6)	61.7(10.4)	60.9(10.9)
BMI(kg/m ²),mean(SD)	23.3(3.3)	22.9(3.1)	23.1(3.4)	23.1(3.1)
ASA grade I/II	38/12	40/10	39/11	40/10
History of hypertension	6(12)	5(10)	6(12)	5(10)
History of diabetes	3(6)	4(8)	3(6)	3(6)
History of heart disease	1(2)	2(4)	1(2)	1(2)
Mallampati class I/II/III/IV	21/18/8/3	22/18/7/3	20/19/9/2	23/18/6/3
Mouth opening 1/2/3*	0/2/48	0/1/49	0/0/50	0/1/49
OSAHS	2(4)	4(8)	3(6)	3(6)
Baseline Spo ₂ (%),mean(SD)	98(1.2)	98(1.4)	97(2.1)	98(1.5)
The qualitative data are presented as no. (%), and the numerical data are presented as the mean (SD). There were no significant difference between the 2 groups in any of the characteristics listed.SD, standard deviation; BMI, body mass index; OSAHS, obstructive sleep apnea-hypopnea syndrome.				
*Mounth opening 1/2/3: 1,1finger, 2,2 fingers; 3, 3fingers				

Adverse events

Table 2 lists the respiratory-related adverse events and interventions. The incidence of adverse events was significantly lower in the PR2 group than other groups. The incidence of hypoxia and increase the flow of oxygen and jaw lift were significantly decreased from 38–14% and 32–10% compared with the control group, respectively ($p < 0.001$).

Table 2
Respiratory-related adverse events and interventions

Adverse events	Control group no. (%) (n = 50)	PR1 group no. (%) (n = 50)	PR2 group no. (%) (n = 50)	PR3 group no. (%) (n = 50)	<i>P</i> value
Total number of events	19(38)	14(28)	7(14)*	23(46)	< 0.001
Hypoxia	19(38)	14(28)	7(14)*	23(46)	< 0.001
Increase the flow of oxygen and Jaw lift	16(32)	13(26)	5(10)*	23(46)	< 0.001
Mask ventilation	4(8)	5(10)	3(6)	8(16)	0.37
intubation	0	0	0	0	NS

The incidence of hypoxia and increase the flow of oxygen and jaw lift were significantly decreased from 38–14% and 32–10%, respectively. ($p < 0.001$). Compared with control group, * $p < 0.05$. NS, not significant

Table 3 lists the sedation-related adverse events. The incidence of adverse events and the incidence of tachycardia were significantly lower in the PR2 group than other groups. The frequency of paradoxical responses, including unpredictable moves, overexcitement, delirium after sedation was significantly lower in PR2 group than other groups ($p < 0.05$). (Table 3). No other adverse events were observed in this study.

Table 3
Sedation-related adverse events

Adverse events	Control group no.(%)(n = 50)	PR1 group no. (%) (n = 50)	PR2 group no. (%) (n = 50)	PR3 group no. (%) (n = 50)	P value
Total number of events	16(32)	12(24)	4(8)*	9(18)	0.03
Nausea/vomit	2(4)	0	1(2)	1(2)	0.56
Bradycardia	1(2)	2(4)	2(4)	5(10)	0.29
Tachycardia	7(14)	4(8)	1(2)*	0*	0.01
Hypotension	0	0	1(2)	3(6)	0.11
Hypertension	5(10)	2(4)	1(2)	0	0.06
Recovery delay	0	0	0	0	NS
Paradoxical response	11(22)	7(14)	1(2)*	0*	< 0.001
intra-operative awareness	2(4)	0	0	0	0.11
NS,not significant. Paradoxical response: patients displayed unpredictable movement, overexcitement, and delirium after sedation with propofol. *p < 0.05 compared with control group					

Discussion

The medication used for sedation during endoscopy procedures varies among different countries¹². In recent years, propofol combined with opioids has become more widely used for endoscopy. With the development of painless diagnosis and treatment, remifentanyl, a synthetic opioid agonist, is increasing used in gastroscopy for its rapid, short-term, and potent analgesic effect. However, few reports explore the optimal dose of remifentanyl during gastroscopy.

In this study, propofol combined with remifentanyl for painless gastroscopy was shown to reduce the dosage of propofol and shorten the onset and recovery time, which was consistent with the results of previous studies¹³⁻¹⁴. In addition, our research found the combination of 2.5 mg/ml (PR2) and 5 mg/ml (PR3) of remifentanyl with propofol significantly reduced the onset time and recovery time, as well as the dosage of propofol, compared with the combination of 1.25 mg/ml (PR1) of remifentanyl with propofol. But we did not observed significant difference between PR2 and PR3 in onset time—awaking time and the dosage of propofol.

The above research results show that remifentanyl has obvious advantages for painless gastroscopy, and with the increase of dose, the advantageous effect tends to be significant, but it also seems to have a capping effect. Since the amount of propofol in the PR2 and PR3 groups is less than that in the control

group and the PR1 group, and there is no difference in the amount of propofol between the PR2 group and the PR3 group, we infer that the advantages brought by remifentanyl mainly come from reduction in the amount of propofol. So far, it seems that 2.5 mg/ml or 5 mg /ml remifentanyl can be used for painless gastroscopy, Subsequently, we studied the side effects associated with hypoxia and sedation in order to determine the appropriate dose of remifentanyl.

The study showed that the incidence of hypoxia in the PR2 group was only 14%, significantly lower than that in the control group (38%) and PR1 group (28%). Surprisingly, the incidence of hypoxia in the PR3 group was as high as 46%, indicating that the low concentration of remifentanyl can reduce the amount of propofol and reduce the respiratory depression caused by high dose propofol, but the high concentration of remifentanyl produced respiratory depression also increased the incidence of hypoxia. In addition, for patients with hypoxia, the method of increasing oxygen flow and lifting the jaw can basically improve hypoxia, but we found that compared with the PR2 group, the PR3 group requires a higher proportion of mask ventilation, although there is no statistical significance, it can be seen that the proportion of hypoxia and the degree of hypoxia in the PR3 group are higher than those in the PR2 group.

For the discussion of the results of this study, we believe that propofol combined with remifentanyl for painless gastroscopy has the advantage of reducing the side effects of the drug. First, lager dose of propofol alone is required to suppress choking caused by gastroscopy entering the throat, but large doses of propofol can cause airway obstruction, reduce thoracic compliance, and then respiratory depression occurs¹². Second, previous studies have shown that small doses of remifentanyl can significantly inhibit choking reflex, so remifentanyl exerts a choking inhibition effect, and propofol exerts a sedative effect and reduces the amount of drugs. And remifentanyl has a fast onset and metabolism, so the patient's recovery time is also short, which is consistent with our findings. Third, although high-dose remifentanyl can also reduce the amount of propofol and reduce the recovery time, its side effects of respiratory depression are significantly increased. Large-dose remifentanyl can produce central respiratory depression, despite its metabolism is fast and the resulting respiratory depression is transient, but the risk is high during the operation of the gastroscopy, and it is not appropriate to use.

But our research also has its limitations. First, this study is a single-center study, which still needs to be confirmed by multi-center research results. Second, the several doses selected in this study are in a multiple relationship, but it is not clear whether there is a better dose between the 2.5 mg/ml and 5 mg/ml doses, and further research is needed.

Conclusions

In this study, 2.5 mg/ml remifentanyl combined with propofol was shown to the optimal dose during gastroscopy, which has a fast onset, short recovery time, and low incidence of adverse reactions such as hypoxia and body movement reactions. This provides a new method of anesthesia for gastroscopy and is worthy of clinical application.

Abbreviations

ASA: American society of anesthesiology; RSS: Ramsay Sedation Scale; ECG: Electrocardiogram; NIBP: non-invasive blood pressure; SpO2: pulse oxygen saturation

Declarations

Ethics Approval and Consent to Participate

Approval for this study was obtained from the ethics committee of the Affiliated Hospital of Nantong University (approval number: 2019-K072), and each patient provided a written informed consent.

Consent to publish

We acknowledge that upon the publication, the ownership of copyright for this work will be transferred to the journal “BMC Gastroenterology”. We declare that this work was original research, and all authors participated in drafting, revising, and approving the submitted manuscript.

Availability of data and materials

We presented all necessary supporting data in the paper. Upon request, the datasets used in this study can be available from the corresponding author.

Competing interests

The authors declare that no competing interests exist in the paper.

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Authors' contributions

CCZ performed the clinical trials, and wrote the manuscript. YBQ and HHM conducted the statistical analysis as well as working in the data collection. CCZ and XCH worked in revising the manuscript. All authors have read and approved the manuscript.

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Not applicable

References

1. Liu, Q; Ding, L; Qiu, X; et al. Updated evaluation of endoscopic submucosal dissection versus surgery for early gastric cancer: A systematic review and meta-analysis.[J].*Int J Surg*.2020,73(2):28-41
2. Nishizawa T, Suzuki H. Propofol for gastrointestinal endoscopy. *United European Gastroenterol J* 2018;6;801-805.
3. Uliana GN, Tambara EM, Baretta GA. Use of remifentanyl to reduce propofol injection pain and the required propofol dose in upper digestive tract endoscopy diagnostic tests. *Braz J Anesthesiol*. 2015;65(6):437-444.
4. Wang D, Chen C, Chen J, et al. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. *PLos One* 2013;8;e53311.
5. Borrat X, Valencia JF, Magrans R, et al. sedation-analgesia with propofol and remifentanyl: concentrations required to avoid gag reflex in upper gastrointestinal endoscopy. *Anesth Analg*, 2015;121(1):90-96.
6. Amornyotin S. Sedation-related complications in gastrointestinal endoscopy. *World J Gastrointest Endosc* 2103;5:527-33.
7. Xiao Q, Yang Y, Zhou Y, et al. Comparison of nasopharyngeal airway device and nasal oxygen tube in obese patients undergoing intravenous anesthesia for gastroscopy: a prospective and randomized study. *Gastroenterol Res Pract* 2016;2016:2641257.
8. Cai G, Huang Z, Zou T, et al. Clinical application of novel endoscopic mask: A randomized controlled trial in aged patients undergoing painless gastroscopy. *Int J Med Sci* 2017;14;167-72.
9. Gouda B, Gouda G, Borle A, et al. Safety of non-anesthesia provider administered propofol sedation in non-advanced gastrointestinal endoscopic procedures: a meta-analysis. *Saudi J Gastroenterol* 2017;23;133-43.
10. Wadhwa V, Issa D, Garg S, et al. Similar risk of cardiopulmonary adverse events between propofol and traditional anesthesia for gastrointestinal endoscopy: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2017;15(2):194-206.
11. Madan HK, Singh R, Sodhi GS. Comparison of intravenous lignocaine, Tramadol and keterolac for attenuation of propofol injection pain. *J Clin Diagn Res*. 2016;10(7):UC05-08.
12. Shahidi N, Schoeman S, Bourke MJ. Acute Epigastric Pain after Gastric Endoscopic Submucosal Dissection. *J Gastroenterology*.2020,158(4):e2-e3.
13. Sajedi P, Rahimian A, Khalili G. Comparative evaluation between two methods of induced hypotension with infusion of remifentanyl and labetalol during sinus endoscopy. *J Res Pharm Pract*. 2016;5(4):264-271.
14. Abu-Shahwan I, Mack D. Propofol and remifentanyl for deep sedation in children undergoing gastrointestanal endoscopy. *Paediatr Anaesth*. 2007;17(5):460-463.

Figures

Figure 1

Flow diagram of included participants

Figure 2

Data on the gastroscopy procedure. The duration of the gastroscopic procedure were not significantly among four groups. The onset time of PR2 and PR3 group were faster than control group. Awakening time and dose of propofol in PR2 and PR3 groups were significantly less than control group

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