



Comparison of the Incidence of Postoperative Nausea and Vomiting between Ciprofol and Propofol in Patients Undergoing Painless Gastroscopy

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Abstract

Background: Ciprofol is a new anaesthetic sedative drug independently developed in China, and its chemical structure is derived from the classical sedative drug Propofol. The aim of this trial was to compare the incidence of anaesthetic PONV in patients undergoing painless gastroscopy with that of Propofol, and to analyze and evaluate the antiemetic effect, one of the non-sedative effects of cyclobenzaprine, in comparison with that of Propofol.

Methods: In this trial, 112 patients undergoing elective painless gastroscopy were included and divided into two groups: Group C for Ciprofol (0.4 mg/kg of Ciprofol) and Group P for Propofol (1.5 mg/kg of Propofol). The patients were also given 7 µg/kg alfentanil. At the end of the examination and after complete awakening, the patients were discharged after observing no special conditions. The assistant physician made a telephone follow-up after 24 hours. The PONV impact scale was used as a reference, and the patients were asked whether they had developed PONV. A chi-square test was used to count the occurrence of PONV in Group C and Group P and to compare the incidence rates of the two. Statistical significance was defined by a Pearson's chi-squared P value < 0.05.

Results: The incidence of PONV in Ciprofol (Group C) was 26%; the incidence of PONV in Propofol (Group P) was 11.3%. The Pearson's chi-square test results of Group C and Group P = 0.042, indicating that both Ciprofol and Propofol could prevent the occurrence of PONV.

Conclusion: Both Ciprofol and Propofol can prevent PONV when used for anaesthesia in patients undergoing painless gastroscopy, with Propofol's antiemetic effect being superior to that of Ciprofol. Propofol has a better antiemetic effect than Ciprofol, and both can be safely used for anaesthesia in patients undergoing gastroscopy.

Keywords

Ciprofol, Propofol, Anaesthesia Sedation, Postoperative Nausea and Vomiting, Gastroscopy, Antiemetic Effect

Introduction

Ciprofol is a new type of anaesthesia sedation drug independently developed by China, which has been

widely used in patients' anaesthesia sedation after multi-centre clinical studies in various medical centres around the world [1,2].

Propofol is a classical anaesthesia and sedation drug; the scope of application is not only limited to the induction and maintenance of surgical anaesthesia but also widely used in short and small diagnostic operations for painless sedation. The chemical structure of Ciprofol is based on Propofol, and the modification of the side chain of Propofol's effective core group has changed the original structure of Propofol and optimised the whole chemical structure, which has been proved to be better than Ciprofol after a large number of basic and clinical multi-centre researches [1,3]. After a lot of basic research and clinical multi-centre studies, it has been proved that Ciprofol is a safer drug than Propofol, with a lower incidence of adverse reactions such as respiratory depression, circulatory depression, and injection pain in patients.

Postoperative nausea and vomiting (PONV) is a common perioperative complication of anaesthetic sedation. The occurrence of PONV is a fatal complication in patients with poor quality of anaesthetic awakening. It can cause acute respiratory obstruction in patients, resulting in aspiration pneumonia, destruction of alveolar surface cells by acid in the stomach, acute respiratory insufficiency, and further hypoxic acute cardiac arrest [4]. Studies have shown that the use of opioid analgesics increases the incidence of PONV in patients [5], but in the early days of Propofol's market launch, it was shown that Propofol at subanaesthetic doses significantly reduces the incidence of PONV [6,7]. Ciprofol, as a sedative based on the chemical structure of Propofol, validation of its antiemetic effect is crucial for the drug's long-term clinical application.

The aim of this trial is to compare the incidence of PONV between Ciprofol and Propofol in gastroscopy with opioids, where the antiemetic effect of Ciprofol has been demonstrated. The strength of its antiemetic effect will also be compared.

Methods

Study Design and Patient Recruitment:

This trial was a prospective randomized controlled trial, ethically approved by the Second Clinical College of Hainan Medical University (approval

number: LW202051) and registered with the China Drug Clinical Trial Centre (<http://www.chinadrugtrials.org.cn/>, registration number: ChiCTR2200061727). All patients signed an informed consent form. After obtaining permission, we recruited 120 patients who requested painless gastroscopy, aged 21-55 years old, and were visited by an outpatient anaesthesiologist the day before the examination for a pre-anaesthetic visit to assess their physiological status and decide whether to include them in the trial.

Inclusion criteria were: ASA classification (American Society of Anaesthesiologists physical status classification) of 1-2, and BMI of 18-25 kg/m². Exclusion criteria were: patients who did not meet the criteria for the outpatient examination, comorbidities with multiple organ diseases assessed by the anaesthesiologist, patients with difficult airway, hypertension, coronary artery disease and other cardiorespiratory abnormalities, patients with psychiatric abnormalities, patients with drug, alcohol, and other psychotropic substance abuse, patients with abnormalities in liver and renal function in laboratory tests, patients with abnormalities in cardiac and pulmonary structures in imaging tests, and patients who refused to participate in the study.

Exclusion criteria also included severe complications of intrathecal anaesthesia, such as decreased blood pressure, slowed heart rate, and respiratory depression.

Randomization and Study Group Allocation:

The patients were divided into Ciprofol (group C) and Propofol (group P) by a physician assistant using the coin toss method. The shape of the test drug (Ciprofol and Propofol) was indistinguishable to the naked eye, and the results of the grouping were not known to the participants. Twenty-four hours after the patient's clinic visit, the participant contacted the subject by phone to ask if the patient had developed PONV, using the PONV impact scale (**Fig-1**) as a reference [8].

Perioperative Management:

On the day of the trial, the anaesthesiologist will

Q1. Have you vomited or had dry-retching*?

- o. No
- 1. Once
- 2. Twice
- 3. Three or more times

Q2. Have you experienced a feeling of nausea (“an unsettled feeling in the stomach and slight urge to vomit”)? If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally, or eating and drinking?

- o. Not at all
- 1. Sometimes
- 2. Often or most of the time
- 3. All of the time.

To calculate the PONV Impact Scale score, add the numerical responses to questions 1 and 2. A PONV Impact Scale score of ≥ 5 defines clinically important PONV.

*count distinct episodes: several vomits or retching events occurring over a short time frame, say 5min, should be counted as one vomiting/dry-retching episode; multiple episodes require distinct time periods without vomiting/dry-retching.

Fig-1: The PONV impact scale

prepare for the anaesthesia by checking that the anaesthesia machine and monitors are functioning properly and preparing the trial medications alfentanil, Ciprofol, and Propofol. Emergency medications will include atropine sulphate injection, ephedrine hydrochloride injection, and norepinephrine. For safety reasons, an emergency endotracheal intubation device was ensured, and an artificial ventilation device was readily available for application.

Before the patient enters the operating theatre, it is confirmed that the patient has not taken any sedative or other drugs that may interfere with the operation, anaesthesia, or tests. The patient is also fasted from food and water for 8 hours or more. After confirming that there are no abnormalities, connect the cardiac monitor, open the peripheral venous access, and leave the intravenous catheter for the intravenous infusion of compound sodium chloride injection. Observe the patient's basic vital signs, such as blood pressure, heart rate, and oxygen saturation.

The patient inhaled 50% O₂ through a nasal cannula at a rate of 3 L/min. After 15 minutes of observation, the patient's vital signs were assessed to be stable, and the test drug was administered if there were no special conditions.

Conduct of the Study:

After the patient was placed in the lateral position, anaesthesia was administered. Firstly, 7 µg/kg alfentanil was given and observed for 1 minute, then the assistant physician gave the test drug according to the group: group C: 0.4 mg/kg Ciprofol; group P: 1.5 mg/kg Propofol. After confirming that the patient's eyelash reflex disappeared and the vital signs were stable, the endoscopist inserted the gastroscope to examine the patient. During the examination, remedial drugs were given if any patient showed somatic reaction, choking, or awakening. The remedial drug was Propofol 0.5 mg/kg, while the case was nullified and not entered into the subsequent statistical analysis. At the end of the examination and after

complete awakening of the patient, the subject was discharged after observing no special conditions. Twenty-four hours later, the assistant physician made a telephone follow-up.

The patient was interviewed by telephone with reference to the items covered in the PONV impact scale. It is worth pointing out that we do not count the total score to confirm whether a patient has developed PONV or not. If a patient experiences any one of the symptoms in the table (vomited, dry-retching, nausea, or feeling of nausea interfering with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally, or eating and drinking), we consider that the patient has developed PONV. The data were collected and then statistically analysed.

Statistical Analysis and Sample Size Calculations:

Statistical analysis was performed using SPSS Statistics 25™ (SPSS Inc., Chicago, IL, U.S.A.). Values were expressed as the mean $\pm$ standard deviation (SD), mean (95% C.I.), or as numbers. The chi-square test was used to statistically compare the incidence of PONV in group C with that in group P. Statistical significance was defined by a Pearson's chi-square P value < 0.05 . Sample size was calculated according to the minimum criteria for the total sample of the chi-square test, while meeting the requirement of a single cell frequency ≥ 5 . The chi-square test statistic requires a sample size of no less than 30 per group and a frequency of more than 5 per cell, so we included a total of 112 subjects to make our statistics more accurate [9].

Results

Comparative data on the general conditions of the final included patients are shown in **Table-1**. The incidence of PONV in Ciprofol (group C) versus Propofol (group P) is shown in **Table-2**. Positive indicates the presence of PONV, while negative indicates the absence of PONV. There was a 26% incidence of PONV in group C and an 11.3% incidence in group P. The results of Pearson's chi-square test between group C and group P are shown in **Table-3**.

Table-1: Demographic Characteristics of Patients

Characteristics	n=112
Age (year)	38.47 $\pm$ 5.64
Height (cm)	165.75 $\pm$ 4.68
Weight (kg)	59.98 $\pm$ 6.59
BMI (kg/m ²)	22.39 $\pm$ 1.42
Sex	Male 59
	Female 53

Table-2: Occurrence of PONV in Ciprofol (Group C) and Propofol (Group P)

		Negatives	Positives	Total
Groups	Ciprofol	13	37	50
	Propofol	7	55	62
Total		20	92	112

Table-3: Results of Pearson's chi-square test for Ciprofol (Group C) and Propofol (Group P)

	Value	Degree of freedom	Asymptotic significance (two-sided)
Pearson's chi-square	4.083	1	0.043

The results of Pearson's chi-square test ($P=0.042$) for group C and group P indicate that both Ciprofol and Propofol prevented the occurrence of PONV.

Discussion

Through our experiments, we have found that Ciprofol, as an anaesthetic drug structurally homologous to Propofol, also has an antiemetic effect, but its antiemetic efficacy is not as good as that of Propofol. The analgesic effect of Propofol was discovered in the 1990s, and domestic and foreign researchers have tried to study this non-sedative function of Propofol, but so far the antiemetic effect of Propofol at a sub-sedative dose has not been confirmed. It is known that Propofol is able to inhibit the central nervous system widely and uniformly, whereas conventional antiemetic drugs exert their efficacy through subcortical structures. Thus, some scholars believe that Propofol acts on the patient's subcortical structures and thus produces an antiemetic effect.

P. Ewalanko et al. used a subhypnotic dose of Propofol in patients undergoing thyroid surgery in an

attempt to further verify the analgesic effect of Propofol, and this study further confirmed the antiemetic effect of Propofol. P. Ewalanko et al. mentioned that due to the stimulation of the cervical vagus nerves, patients, especially females, who underwent thyroid surgery were particularly prone to PONV. They considered that the antiemetic effect of Propofol might not be significant in laparoscopic gynaecological surgery, where the stimulation of the cervical vagus nerve is lost [10]. However, with the wide application of Propofol and subsequent studies, it was found that the antiemetic effect of Propofol is not only limited to thyroid surgery, but also to short surgeries [11,12], which also has an antiemetic effect.

Ciprofol is a new anaesthetic sedative drug developed in China, which is highly homologous to Propofol. The chemical structure of Ciprofol is (R)-2-(1-cyclopropyl ethyl)-6-isopropylphenol. The core structure of classic short-acting intravenous anaesthetics is 2,6-disubstituted phenol, which binds to the GABAA receptor to produce an anaesthetic effect. Propofol is the most widely used of these drugs. Ciprofol adds a cyclopropyl group to the side chain of the core structure. The addition of this crucial structure reduces the lipophilicity of the parent structure by increasing the spatial effect. Substitution also breaks the symmetry of the original structure and forms a chiral center, generating a stereoselective product. These changes lead to a higher receptor affinity for Ciprofol than for Propofol. Furthermore, compared with the S-isomer of Ciprofol, the R-enantiomer possesses better stereoselectivity for the GABAA receptor and is more potent than the S-isomer. Ciprofol has superior advantages over Propofol in terms of target selectivity, as shown in a radioligand-binding assay indicating a higher intensity of action.

Like Propofol, Ciprofol is a positive allosteric modulator and direct agonist of the GABAA receptor. Competitive binding assays and whole-cell patch-clamp experiments demonstrated that Ciprofol could trigger chloride influx by competitive binding to butylbicyclophosphorothionate and t-butylbicycloorthobenzoate targets in the chloride channels of GABAA receptors. The influx of chloride can cause hyperpolarization of nerve cell membranes by increasing the intracellular chloride concentration

and further activating GABAergic neurons to achieve central nerve inhibition, producing sedative and anaesthetic effects [1,13,14].

From the structural analysis, modification of the side chain of the chemical structure of Propofol did not change the core function of Propofol, and even increased the affinity of the drug to the cell membrane, which led to the enhancement of the drug efficacy, and to a certain extent reduced the common side effects of the drug, including respiratory depression, circulatory inhibition, and injection pain. Therefore, since Propofol has been shown to have antiemetic effects of unknown mechanism, we designed the trial to validate the antiemetic efficacy of Ciprofol in order to further optimise the guidelines for the clinical use of Ciprofol. Our results show that Ciprofol at sedative doses is as antiemetic as Propofol with satisfactory efficacy, but Ciprofol is still slightly less antiemetic compared to Propofol. In gastroenteroscopy, the manipulation of instruments through the mouth and throat and the inflation of the stomach inevitably stimulate the vagus nerve to a certain extent, so this manipulation will undoubtedly increase the reflexes of the vagus nerve leading to nausea and vomiting. We also used an opioid analgesic, alfentanil, in our study, which has been shown to recruit β -arrestin during G-protein activation of the pathway, thus producing nausea and vomiting [15]. Therefore, we designed this prospective randomised controlled trial to verify the antiemetic effect of Ciprofol and attempted to compare its effect with that of Propofol.

The clinical indications for intraoperative sedation with Ciprofol have been gradually improved with the completion of phase I clinical trials both at home and abroad, and clinicians are now using Ciprofol for continuous intraoperative intravenous pumping. Therefore, anaesthesiologists using total intravenous anaesthesia (TIVA) should not only consider the risk of intraoperative awareness, but also consider the advantages of suppressing nausea and vomiting. Etomidate, as an anaesthetic sedative drug, has been widely used for induction of anaesthesia in severe cardiac insufficiency due to its outstanding advantage of mild degree of circulatory depression. However, its significant inhibition of adrenocortical function has led to severe PONV in patients, limiting subsequent

research and treatment of its sustained administration [16]. Therefore, Ciprofol, as a novel drug, to verify whether it has antiemetic effects, can provide anaesthesiologists and ICU physicians with different clinical ideas to better treat patients.

This trial has limitations. Firstly, we cannot determine the exact dose of Ciprofol for its antiemetic effect. Combined with the previous study of Propofol subhypnotic dose of antiemetic, the study cannot derive the exact dose of Propofol as antiemetic. Therefore, we need to continue to study, which is also the direction of our subsequent research. Secondly, the sample size of our study and the limitation of the surgical procedure limits the scope of the study, so we look forward to more different types of operations to further validate our conclusions. Thirdly, we were unable to standardize the proficiency of different endoscopists, which would have affected our trial drug dosage. At the same time, the characteristics of the patient's own condition, gender, level of disease, and other circumstances that affect the results of the test should not be ignored. We are also following up on the patient's condition in order to obtain more convincing results.

Conclusion

Both Ciprofol and Propofol prevent PONV when used for anaesthesia in patients undergoing painless gastroscopy, with Propofol having a better antiemetic effect than Ciprofol. Both can be safely used for anaesthesia in patients undergoing gastroscopy.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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