

BMJ Open Effect of propofol combined with opioids on cough reflex suppression in gastroscopy: study protocol for a double-blind randomized controlled trial

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To cite: Yin N, Xia J, Cao Y-Z, *et al.* Effect of propofol combined with opioids on cough reflex suppression in gastroscopy: study protocol for a double-blind randomized controlled trial. *BMJ Open* 2017;**7**:e014881. doi:10.1136/bmjopen-2016-014881

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2016-014881>).

Received 24 October 2016
Revised 18 July 2017
Accepted 3 August 2017



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ABSTRACT

Introduction The best methods for inducing analgesia and sedation for gastroscopy are still debated but finding an adequate regimen of sedation/analgesia is important. Stimulation of the larynx under sedation can cause reflex responses. Propofol with opioids has been recommended for gastroscopy sedation but the effects on cough reflex suppression remain unclear. This trial will evaluate the effects of propofol combined with small doses of dezocine, oxycodone, sufentanil or fentanyl for gastroscopy. We hypothesise that better performance may be obtained with a combination of propofol and oxycodone. We will observe the incidence and degree of reflex coughing and gagging under sedation when using propofol combined with one of the above drugs or propofol alone.

Methods and analysis This will be a prospective, randomised, double-blind, controlled trial. ASA I–II level patients aged 18–65 years and scheduled for gastroscopy will be included. It is planned that 500 subjects will be randomised to intravenously receive 2–2.2 mg/kg propofol plus 0.5–0.8 µg/kg fentanyl (fentanyl group), 2–2.2 mg/kg propofol plus 0.05–0.08 µg/kg sufentanil (sufentanil group), 2–2.2 mg/kg propofol plus 0.04–0.05 mg/kg dezocine (dezocine group), 2–2.2 mg/kg propofol plus 0.04–0.05 mg/kg oxycodone (oxycodone group), or 2.4–3 mg/kg propofol plus 2–2.5 mL saline (control group) for sedation. The primary endpoint is the incidence and degree of reflex coughing and gagging. The secondary endpoints include the occurrence of discomfort or side effects, the use of jaw thrust, assisted ventilation or additional propofol, recovery time, duration of procedure and Steward score.

Ethics and dissemination This study has been approved by the Institutional Ethics Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (No. 2015ZDSYLL033.0). The results of the trial will be published in an international peer-reviewed journal.

Trial registration This study has been registered with the Chinese Clinical Trial Register (No. ChiCTR-ICR-15006952).

Trial status At the time of manuscript submission, the study was in the recruitment phase.

INTRODUCTION

Gastroscopy is an important and common endoscopic method for the diagnosis and

Strengths and limitations of this study

- This study is the first randomised controlled trial investigating the effect of dezocine and oxycodone on cough reflex suppression when combined with propofol during gastroscopy.
- This study focuses on the antitussive effects of a range of opioids which few previous studies have examined.
- Study strengths include an appropriate sample size, stratified randomization and the double-blind placebo-controlled design.
- This is a single-centre trial, which could be a limitation of this study.
- The dose of propofol for this study could be a limitation, as it is relatively high and might abolish the effects of the opioids examined.

treatment of digestive disease. However, during gastroscopy, patient anxiety and discomfort such as throat irritation, cough and nausea may result in low examination quality and consequently decreased patient willingness to undergo a repeat procedure. Pharyngeal anaesthesia and sedation/anaesthesia ranging from minimal sedation to general anaesthesia have been used to relieve anxiety and discomfort, resulting in a successful procedure.^{1–5}

Endoscopic sedation is widely used in routine practice, with propofol sedation being endorsed.^{5–12} Propofol is an intravenously administered sedative with a rapid onset and short duration of action.¹³ It has a favourable sedative effect and a wide range of inhibition effects on the central nervous system.¹⁴ It also strongly inhibits the contraction of gastrointestinal smooth muscle, antagonises the vomiting reflex and reduces cough and physical movement.^{5 15 16} Postoperative headache occurs infrequently

and in addition propofol reduces nausea and vomiting, so their incidence is also low.¹⁷ Therefore, propofol has been widely used for sedation for gastroscopic procedures. Propofol is often used as a single agent but has a short duration of clinical effect. Inadequate sedation with propofol alone occurs sometimes and requires additional doses. The duration of gastroscopy is relatively short, usually lasting for about 10 min, but repeated addition of propofol can significantly prolong the recovery time, increasing the risk of post-procedure respiratory depression and hypoxaemia, and the workload of recovery management. The use of propofol in combination with opioids has been proposed to improve sedation and analgesia regarding recovery time, sedative effect, pain and discomfort.^{18–22}

Cough is a defensive airway reflex. The cough receptors in the epithelium are sensitive to both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effects on airway reflexes, but propofol may still cause cough.^{23–24} Moreover, stimulation of the larynx during propofol anaesthesia can cause various types of reflex responses.²⁵ Although opioids exert favourable analgesic and sedative effects,^{20–26} and can inhibit the pharyngeal reflex and stress response, intravenous fentanyl- and sufentanil-induced coughing is not uncommon.^{27–28} Induced cough can be reduced by propofol²⁹ and interestingly, by another opioid, dezocine.³⁰ Dezocine is an opioid analgesic acting on μ -, δ - and κ -opioid receptors and has been used in propofol sedation.^{31–33} Oxycodone is an opioid alkaloid acting on μ - and κ -opioid receptors. It shows good performance for relieving visceral pain with slight respiratory depression and is known to depress the cough reflex. Unlike fentanyl or sufentanil, dezocine and oxycodone have rarely been studied in combination with propofol for gastroscopy.

The best methods to induce analgesia and sedation for gastroscopy are still debated, so finding an adequate regimen of sedation/analgesia is important as it can influence the quality of the examination, patient cooperation, and the patient's and physician's satisfaction with the sedation.^{5–16–34} Based on our preliminary observations in clinical practice, we hypothesise that a combination of propofol and low-dose dezocine, oxycodone or sufentanil for gastroscopy may decrease the incidence of cough and that specifically, the combination of propofol and oxycodone may show the best performance.

In order to verify our hypothesis, we designed this clinical study, aiming to investigate the effect of a combination of propofol and opioids on cough reflex suppression in gastroscopy.

METHODS AND ANALYSIS

Study objective

The primary objective of this study is to investigate the incidence and degree of reflex coughing and gagging under sedation with a combination of propofol and fentanyl, sufentanil, dezocine or oxycodone during

gastroscopy. The secondary objective is to assess the effect of the combination regimens on sedative performance.

Study location

A prospective, single-centre, randomised, double-blinded, controlled trial will be conducted in patients undergoing gastroscopy in the Affiliated Zhongda Hospital of Southeast University, China.

Study population

Participants will be recruited voluntarily according to the inclusion and exclusion criteria below.

Inclusion criteria

ASA I–II level patients scheduled for gastroscopy, aged 18–65 years, and willing to participate after reading and signing an informed consent form.

Exclusion criteria

1. Body mass index (BMI) ≥ 30 kg/m²
2. Patients with preoperative circulatory, respiratory or nervous system disease
3. Preoperative haemoglobin level less than 70 g/L or albumin level less than 30 g/L
4. Patients with sleep apnoea
5. Patients with upper respiratory tract infection symptoms
6. Patients with a history of dry cough
7. Patients with a drug allergy.

Randomization and blinding

Stratified randomization will be used to assign the candidate subjects to five groups (figure 1) according to sex and BMI (two groups). Computer-generated random group numbers will be printed and placed in separate sealed envelopes. When receiving a subject who meets the inclusion criteria, the anaesthesiologist will assign the newly recruited subject to a group according to the number in the envelope. Both anaesthesiologists and patients will be blinded to the regimen. The drugs will be prepared by nurse anaesthetists, labelled with numbers and then injected by the anaesthesiologist. The nurse anaesthetists will be responsible for recording patients' physiological characteristic. The anaesthesiologist will be notified of the study group by the nurse anaesthetist in case of emergency.

Current sample size justification

It is planned that a total of 500 subjects will be recruited. The subjects will be randomly divided into five groups: a dezocine group, fentanyl group, oxycodone group, sufentanil group and control group, with 100 cases in each group. The sample size was estimated according to the χ^2 test of the incidence of the primary categorical outcome, incidence of cough (30%) within 5 min after endoscope insertion. The number of observations will allow detection of a small to moderate effective size (approximately 0.20) with a 5% chance of a type I error and 90% power.

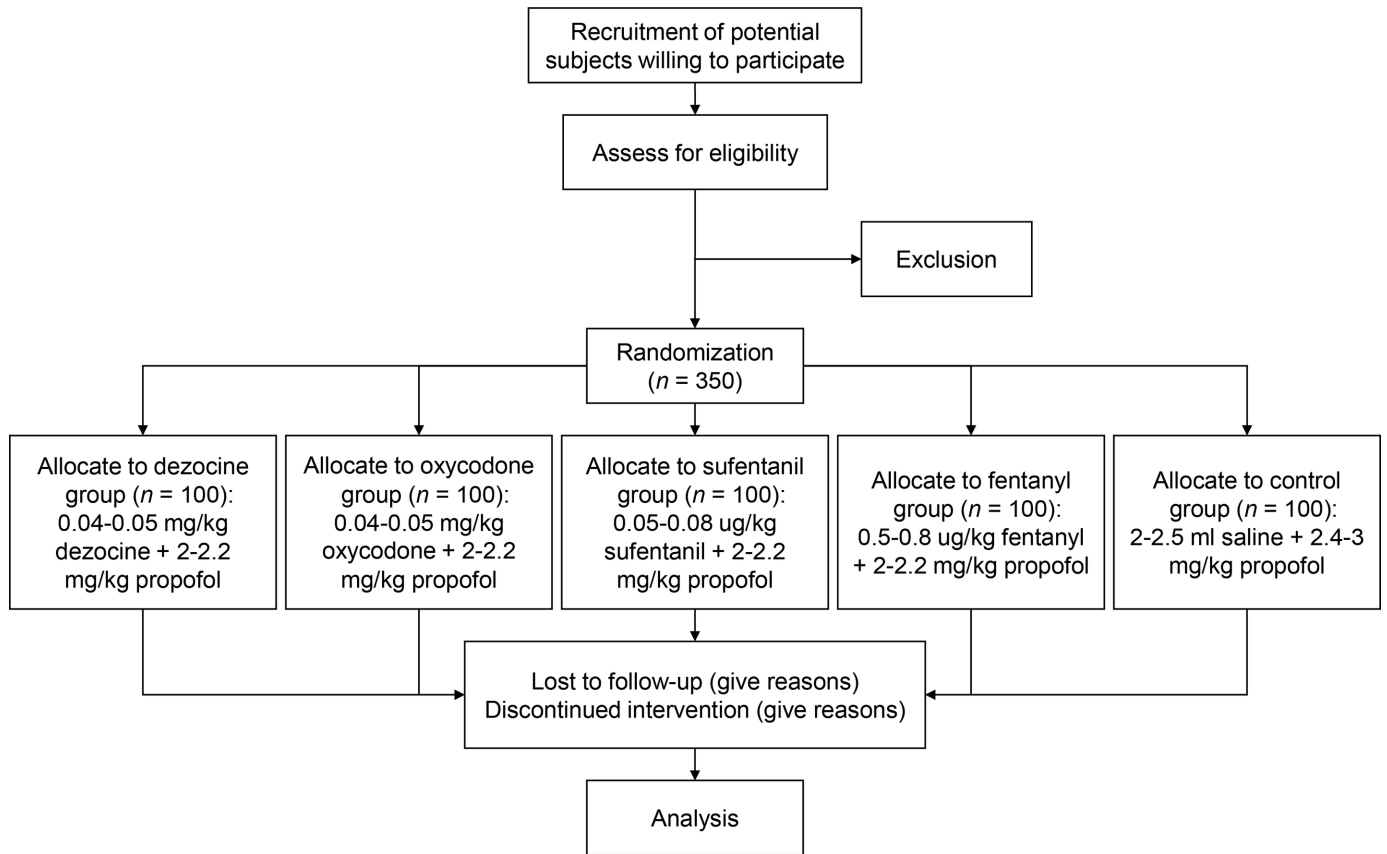


Figure 1 Flow chart of the study.

The test of power will remain at 80% or higher if up to 20% of subjects drop out from the study.

Statistical analysis

All data will be analysed using SAS 9.3 or other statistical software packages as needed. The statistical methods will include descriptive statistics, the t-test, χ^2 test, analysis of variance, univariate unconditional logistic regression analysis and multivariate linear regression analysis. The significance level will be set at 5%.

Sedation

Patients will fast for 12 hours before gastroscopy. Dyclonine will be administered orally 10 min before sedation. Right upper extremity venous access will be established before the patients enter the operating room. In the operating theatre, the patients will lie in the left-lateral position, with a blood pressure cuff fitted around the left upper arm, and receive oxygen via a nasal cannula (3–5 L/min). After placement of a bite block, blood pressure, heart rate and SpO₂ will be measured non-invasively (Philips MP50, Germany) to establish baselines and will be monitored throughout the procedure. Blood pressure will be measured at 1 min intervals. Patients will then intravenously receive 2–2.2 mg/kg propofol (Fresenius Kabi AB, Germany) plus 0.5–0.8 µg/kg fentanyl (Humanwell Pharmaceutical, China), 2–2.2 mg/kg propofol plus 0.05–0.08 µg/kg sufentanil (Humanwell Pharmaceutical), 2–2.2 mg/kg propofol plus 0.04–0.05 mg/kg dezocine (Yangtze River Pharmaceutical, China), 2–2.2 mg/kg

propofol plus 0.04–0.05 mg/kg oxycodone (Monti Pharmaceutical, China), or 2.4–3 mg/kg propofol plus 2–2.5 mL saline (figure 1). All drugs except propofol will be diluted with saline. The doses of dezocine and oxycodone have been defined according to our preliminary study. Subjects weighing ≤70 kg will be administered 2 mL of normal saline, while subjects weighing >70 kg will receive 2.5 mL of normal saline. Fentanyl will be diluted to 20 µg/mL, sufentanil to 2.5 µg/mL, and dezocine and oxycodone to 1 mg/mL. Drugs will be delivered by the Aespire 7900 anaesthesia delivery system (GE Healthcare, USA). We will insert the probe when the bispectral index (BIS) reaches 40–60. A BIS of 40–60 is usually considered to indicate sufficient depth of general anaesthesia. The jaw thrust manoeuvre will be performed in case of respiratory depression and oxygen desaturation. If this is not effective, assisted ventilation will be used. In severe situations, tracheal intubation assisted respiration will be performed. After gastroscopy, all patients will remain in the post-anaesthesia care unit (PACU) and will be followed up until discharge from the PACU.

Adverse events

All adverse events, such as nausea, vomiting, dyspnoea, hypopnoea, apnoea, hypotension, oxygen desaturation and bradycardia, will be recorded and closely monitored. The medical strategy will be adjusted if necessary. Unexpected severe adverse events will be reported to the ethics committee.

Data collection and management

Demographic variables and clinical data will be collected from all patients. Furthermore, during the procedure, blood pressure, heart rate and oxygen saturation will be monitored. Any swallowing, coughing or gagging, physical movements, adverse events, jaw thrust manoeuvre, assisted ventilation, additional propofol use and duration of endoscopy will be recorded. The duration of calls for eyes to open and the Steward score after eyes open will also be recorded. Data will be collected throughout the study and will be securely managed under conditions of confidentiality. Automatic data collection will be performed by the vital signs monitor and anaesthesia information system. Manual data collection will be performed by a nurse anaesthetist. The participants will be referred to by their participant number rather than their name throughout the study unless otherwise specified. All relevant documents and files will be archived for 5 years. Data can be only accessed by the investigators who sign the confidential disclosure agreement and by institutional or governmental auditors during the study. Data without patient identifiers will be publicly accessible after the study. The process will be monitored by the Institutional Ethics Committee (ICE) for Clinical Research of Zhongda Hospital.

Endpoints

The primary endpoint is the incidence and degree of reflex coughing and gagging, which will be recorded within 5 min after endoscope insertion and throughout the procedure. The severity of cough is defined according to cough intensity and whether it causes failure of endoscope insertion. The secondary endpoints include (1) the occurrence of swallowing, physical movement and adverse events, and whether the jaw thrust manoeuvre, assisted ventilation or additional propofol is used, which will be recorded within 5 min after endoscope insertion and throughout the procedure, and (2) duration of calls for eyes to open, the duration of the procedure and the Steward score³⁵ after eyes open. Blood pressure, heart rate and SpO₂ will be monitored throughout the procedure. 'Patient satisfaction' is not included as a secondary outcome since patients can not recall coughing or gagging.

Protocol amendments

The current protocol is version 1.5 (11 June 2017). Any changes in the protocol during the trial that may affect the conduct of the trial, the safety and the benefit to patients will require a formal amendment to the protocol.

DISCUSSION

It is important to improve analgesia and sedation for gastroscopy. Opioids, which exert a favourable analgesic and sedative effect and inhibit the stress response, are an important part of surgical anaesthesia. A combination of opioids and propofol is the most commonly

used regimen for general anaesthesia. Currently, a small dose of fentanyl combined with propofol is used for sedation for gastroscopy, but fentanyl may cause respiratory depression, choking and stiff chest wall muscles. Clinical studies of other opioids for gastroscopy, such as oxycodone, dezocine and sufentanil, are rare. As it is essential to find an adequate regimen, we will conduct a trial to evaluate the combination of small doses of dezocine, oxycodone or sufentanil with propofol for gastroscopy. This study will observe the incidence and degree of reflex coughing under sedation. However, the study has some limitations. It is a single-centre study, which may limit its generalisability so a future multiple-centre large-sample size study will be needed. Also the dose of propofol for this study is relatively high and may abolish the effects of the examined opioids. The result of this clinical trial may confirm the favourable effects of a combination of propofol with small-dose opioids, and may identify a satisfactory regimen for sedation for gastroscopy.

Contributors NY conceived of the study. NY and JXia participated in its design and coordination. NY, JX, Y-ZC, XL, JY and JX collected references and developed the protocol. XL, Y-ZC, JY and JX performed statistics analysis. NY and JXia drafted the manuscript. All authors read and approved the final manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests The authors declare that they have no competing interests. The committee mentioned is independent from the sponsor and competing interests.

Ethics approval This study has been approved by the Institutional Ethics Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (No. 2015ZDSYLL033.0) and is registered with the Chinese Clinical Trial Registry (ChiCTR-ICR-15006952). Only patients who give written informed consent will be recruited. An informed consent form has been provided. The results of the trial will be published in an international peer-reviewed journal.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Not applicable.

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