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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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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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Abstract

Introduction: The best methods for analgesia and sedation for gastroscopy are still in debate and finding 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 their effects on cough reflex suppression remain to be investigated.

Objective: This trial will evaluate the effects of propofol combined with small doses of dezocine, oxycodone, sufentanil, or fentanil for gastroscopy. This study will observe the incidence and reflex degree of cough under sedation and will compare propofol combined with the above drugs to propofol alone and to each other, allowing a broad screen for feasible regimen.

Methods and analysis: This will be a prospective, randomized, double-blinded, controlled trial. Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years will be included. A total of 350 subjects are planned to be randomized to intravenously receive 2-2.2 mg/kg propofol plus 0.5-0.8 ug/kg fentanyl (fentanyl group), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/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 reflex degree of cough. The secondary endpoints include occurrence of discomfort or side effects, whether jaw thrust, assistant ventilation, and additional propofol is used, 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 was registered with the Chinese Clinical Trial Center (No. ChiCTR-ICR-15006952).

Keywords: sedation, endoscopy, propofol, opioids

Strengths and limitations of this study

Double-blinded randomized placebo-controlled study design

Aiming to find adequate regimen of sedation and analgesia for gastroscopy

Evaluated a wide range of opioids

Single-center study

Introduction

Gastroscopy is an important and common endoscopic method of diagnosis and treatment of digestive diseases. However, during gastroscopy, patients' anxiety and discomfort such as throat irritation, cough, and nausea usually occur, which may affect the endoscopic operation, result in low examination quality, and consequently decrease the willingness of patients to undergo a repeated procedure. Pharyngeal anesthesia and sedation/anesthesia ranging from minimal sedation to general anesthesia have been used to relieve anxiety and discomfort, allowing a successful procedure [1-5].

Currently, endoscopic sedation has been widely applied 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]. Propofol has a favorable sedative effect and a wide range of inhibition effect on the central nervous system [14]. Propofol also strongly inhibits the contraction of gastrointestinal smooth muscles, antagonizes the vomiting reflex and reduce cough and body movement [5 15 16]. The incidences of postoperative headache, nausea and vomiting are low, and propofol even reduces nausea and vomiting [17]. Therefore, it has been widely used for sedation for gastroscopic procedures. Propofol is often used as a single agent. However, it has short duration of clinical effect, and inadequate sedation with propofol alone is seen, which requires additional doses. The duration of gastroscopy is relatively short, generally lasting for 10 minutes, but repeated addition of propofol can significantly prolong the recovery duration, increasing the risk of post-procedure

respiratory depression and hypoxemia, and the workload of recovery management. Use of propofol in combination with opioids has been proposed to improve sedation and analgesia regarding aspects such as recovery time, sedative effect, pain and other discomfort [18-22].

Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effect on airway reflex. However, propofol may still have chance to cause cough [23 24]. Moreover, stimulation of the larynx during propofol anesthesia can cause various types of reflex responses [25]. Although opioids exert favorable analgesic and sedative effects [20 26], and can inhibit pharyngeal reflex and stress response, intravenous fentanyl and sufentanil-induced coughing is not uncommon [27 28]. The induced cough, can be reduced by reduced by propofol [29] 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 also known to depress cough reflex. Unlike fentanyl and sufentanil, dezocine and oxycodone have rarely been studied in combination with propofol for gastroscopy.

The best methods for analgesia and sedation for gastroscopy are still in debate and finding adequate regimen of sedation/analgesia is important, which can influence the quality of the examination, the patient's cooperation and the patient's and physician's satisfaction with the sedation [5 16 34]. Based on our preliminary observation in clinical practice, we hypothesize that combination of propofol and low-dose dezocine,

oxycodone or sufentanil for gastroscopy may decrease the incidence of cough.

In order to verify our hypothesis, we designed this clinical study, aiming to investigate the effect of 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 reflex degree of cough under sedation with combination of propofol and fentanil sufentanil, dezocine, or oxycodone during gastroscopy. The secondary objective is to assess effect of the combination regimens on sedative performance, relieving stress and discomfort, and reducing side effects.

Study location

A prospective, single-center, randomized, 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:

Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years, willing to participate after reading and sign an informed consent.

Exclusion criteria:

1. Body mass index (BMI) ≥30 kg/m^2,
2. Patients with preoperative circulatory, respiratory or nervous system diseases,
3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
4. Patients with sleep apnea syndrome.

Randomization and blinding

Stratified randomization will be used to assign the candidate subjects to five groups according to sex and BMI (two groups or three groups). Computer-generated random group numbers will be printed and placed into different sealed envelope in turn. When receiving a subject who met the inclusion criteria, the anesthesiologist determined the grouping of the newly recruited subject according to different group numbers in the envelopes. The regimen will be blind to both anesthesiologists and patients.

Current sample size justification

A total of 350 subjects were planned to be involved. The subjects will be randomly divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil and the control group, 70 cases in each group. The sample size was estimated according to the chi-square test of the incidence of the primary categorical outcome, incidence of cough within 5 min after endoscope insertion. The above total number of observations makes it possible to detect small to moderate effective size (approximately 0.20) with Type I error 5% and power of test 90%. The test of power will remain 80% or higher when up to 20% of the subjects dropout from the study.

Statistical analysis

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

Sedation

Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken 10 minutes prior to sedation. The right upper extremity venous access will be established before the patients enter the operation room. After entering the operation room, the patients will lie in the left-lateral position, with the blood pressure cuff tied to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min). After placement of bite block, blood pressure, heart rate, and SpO_2 will be measured noninvasively (Philips MP50, Germany) to set up baselines and will be monitored throughout the operation afterwards. Blood pressure will be measured at an interval of 1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical, China), 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. All drugs will be diluted with saline. The doses of dezocine and oxycodone are defined according to our preliminary study. The 2 ml of normal saline is for subjects weighing ≤70 kg, and the 2.5 ml of normal saline is for subjects weighing >70 kg. Fentanyl will

be diluted to 20 ug/ml, sufentanil to 2.5ug/ml, dezocine and oxycodone each to 1 mg/ml. Drugs will be delivered by the Aespire 7900 anesthesia delivery system (GE Healthcare, USA).

Adverse events

All adverse events will be recorded and closely monitored. 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, outcome related variables as well as variables that may influence the outcome will be collected. All data will be collected throughout the study and will be securely managed in confidential conditions. The participants will be referred by the participant number rather than names, throughout the study unless otherwise specified. All relevant documents and files will be archived for five years. Data can be only accessed by the investigators who sign the confidential disclosure agreement and institutional or governmental auditors during the study. Data without patient identification 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 reflex degree of cough, which will be recorded within 5 min after endoscope insertion and throughout the procedure. The

secondary endpoints include (1) the occurrence of swallowing, body movement, and other discomfort or side effects and whether jaw thrust, assistant ventilation, and additional propofol is used, which will be recorded within five minutes after endoscope insertion and throughout the procedure, and (2) duration of calls for eyes open, the duration of procedure and Steward score [35] after eyes open. Blood pressure, heart rate and SpO_2 will be monitored throughout the process

Protocol amendments

Any changes of the protocol during the trial that may affect the conduct of the trial, the safety and the benefit of the patients will require a formal amendment to the protocol.

Discussion

It is important to improve analgesia and sedation for gastroscopy. Opioids, which exert favorable analgesic, sedative effect and inhibit the stress response, are an important part of surgical anesthesia. The combination of opioids and propofol is the most commonly used regimen for general anesthesia. Currently, a small dose of fentanyl combined with propofol in sedation for gastroscopy have been used in clinical practice. However, fentanyl has the potential risks of respiratory depression, choking and the stiffness of chest wall muscles. Clinical study on other opioids for gastroscopy, such as oxycodone, dezocine and sufentanil, is inadequate. Finding an adequate regimen is essential. Herein, we conduct this trial to evaluate the combination of small doses of dezocine, oxycodone or sufentanil for gastroscopy.

This study observes the incidence and reflex degree of cough under sedation. This trial compares propofol combined the above drugs to propofol alone and to propofol with fentanil, allowing a broad screen for feasible regimen. There are limitations of this study. This is a single-center, which may limit the generalization of this study. Future multiple-center large-sample size study will be needed. The result of this clinical trial can confirm the favorable effects of combination of propofol with small-dose opioids, and can contribute to finding satisfying regimens for sedation for gastroscopy.

Trial status

At the time of manuscript submission, the study is in the recruitment phase.

Ethics and dissemination

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

Authors' contributions

NY conceived of the study. NY and JX participated in its design and coordination. NY,

JX, XL, JY and JX collected references and figured out the protocol. XL. JY and JX performed statistics analysis. NY and JX drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests

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

References

1. Standards of Practice Committee of the American Society for Gastrointestinal E, Lichtenstein DR, Jagannath S, et al. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008;**68**:815-26.
2. Soma Y, Saito H, Kishibe T, Takahashi T, Tanaka H, Munakata A. Evaluation of topical pharyngeal anesthesia for upper endoscopy including factors associated with patient tolerance. *Gastrointest Endosc* 2001;**53**:14-8.
3. Froehlich F, Schwizer W, Thorens J, Kohler M, Gonvers JJ, Fried M. Conscious sedation for gastroscopy: patient tolerance and cardiorespiratory parameters. *Gastroenterology* 1995;**108**:697-704.
4. Evans LT, Saberi S, Kim HM, Elta GH, Schoenfeld P. Pharyngeal anesthesia during sedated EGDs: is "the spray" beneficial? A meta-analysis and systematic review. *Gastrointest Endosc* 2006;**63**:761-6.
5. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol* 2013;**19**:463-81.
6. Porostocky P, Chiba N, Colacino P, Sadowski D, Singh H. A survey of sedation practices for colonoscopy in Canada. *Can J Gastroenterol* 2011;**25**:255-60.
7. Fanti L, Agostoni M, Gemma M, et al. Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. *Dig Liver Dis* 2011;**43**:726-30.
8. Paspatis GA, Manolaraki MM, Tribonias G, et al. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of

gastroenterology and nutrition. *Dig Liver Dis* 2009;**41**:807-11.

9. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006;**101**:967-74.

10. Riphaus A, Rabofski M, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: results from the first nationwide survey. *Z Gastroenterol* 2010;**48**:392-7.

11. Baudet JS, Borque P, Borja E, et al. Use of sedation in gastrointestinal endoscopy: a nationwide survey in Spain. *Eur J Gastroenterol Hepatol* 2009;**21**:882-8.

12. Wehrmann T, Triantafyllou K. Propofol sedation in gastrointestinal endoscopy: a gastroenterologist's perspective. *Digestion* 2010;**82**:106-9.

13. Byrne MF, Chiba N, Singh H, Sadowski DC, Clinical Affairs Committee of the Canadian Association of G. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. *Can J Gastroenterol* 2008;**22**:457-9.

14. Inada T, Murao K, Shingu K, Yamada K, Nakao S, Nagata A. Effects of propofol and thiopental on the central nervous system during nociceptive stimulation in cats. *J Anesth* 2001;**15**:159-63.

15. Lee TL, Ang SB, Dambisya YM, Adaikan GP, Lau LC. The effect of propofol on human gastric and colonic muscle contractions. *Anesth Analg* 1999;**89**:1246-9.

16. Fanti L, Testoni PA. Sedation and analgesia in gastrointestinal endoscopy: what's new? *World J Gastroenterol* 2010;**16**:2451-7.

17. Cohen LB, Delegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007;**133**:675-701.

18. Ho WM, Yen CM, Lan CH, et al. Comparison between the recovery time of alfentanil and fentanyl in balanced propofol sedation for gastrointestinal and colonoscopy: a prospective, randomized study. *BMC Gastroenterol* 2012;**12**:164.

19. Poulos JE, Kalogerinis PT, Caudle JN. Propofol compared with combination propofol or midazolam/fentanyl for endoscopy in a community setting. *AANA J* 2013;**81**:31-6.

20. Zhang L, Bao Y, Shi D. Comparing the pain of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy. *Acta Cir Bras* 2014;**29**:675-80.

21. Xu ZY, Wang X, Si YY, et al. Intravenous remifentanil and propofol for gastroscopy. *J Clin Anesth* 2008;**20**:352-5.

22. LaPierre CD, Johnson KB, Randall BR, Egan TD. A simulation study of common propofol and propofol-opioid dosing regimens for upper endoscopy: implications on the time course of recovery. *Anesthesiology* 2012;**117**:252-62.

23. Yamamoto S, Motokawa K, Toyooka H. Propofol may cause coughing when used as a sedative in patients undergoing orthopedic surgery under spinal anesthesia. *Anesthesia & Analgesia* 1998;**86**:529S.

24. Mitra S, Sinha PK, Anand LK, Gombar KK. Propofol-induced violent coughing.

Anaesthesia 2000;**55**:707-8.

25. Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anesthesia. *The Journal of the American Society of Anesthesiologists* 1998;**88**:1459-66.

26. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 2000;**95**:1476-9.

27. Yemen TA. Small doses of sufentanil will produce violent coughing in young children. *Anesthesiology* 1998;**89**:271-2.

28. Bohrer H, Fleischer F, Werning P. Tussive effect of a fentanyl bolus administered through a central venous catheter. *Anaesthesia* 1990;**45**:18-21.

29. Sedighinejad A, Naderi Nabi B, Haghighi M, et al. Propofol is Effective to Depress Fentanyl-Induced Cough during Induction of Anesthesia. *Anesth Pain Med* 2013;**2**:170-3.

30. Liu XS, Xu GH, Shen QY, et al. Dezocine prevents sufentanil-induced cough during general anesthesia induction: A randomized controlled trial. *Pharmacol Rep* 2015;**67**:52-5.

31. Ramirez-Ruiz M, Smith I, White PF. Use of analgesics during propofol sedation: a comparison of ketorolac, dezocine, and fentanyl. *J Clin Anesth* 1995;**7**:481-5.

32. Lu Y, Ye Z, Wong GT, Dong C, Yu J. Prevention of injection pain due to propofol by dezocine: a comparison with lidocaine. *Indian J Pharmacol* 2013;**45**:619-21.

33. Zheng M, Guo Y, Shan S, Yang S. Dezocine for anesthesia and stress reduction in induced abortion. *Patient Prefer Adherence* 2015;**9**:369-72.

34. Bell GD. Preparation, premedication, and surveillance. *Endoscopy* 2004;**36**:23-31.

35. Steward DJ. A simplified scoring system for the post-operative recovery room. *Can Anaesth Soc J* 1975;**22**:111-3.

Figure Legend

Figure 1. Follow chart of the study.

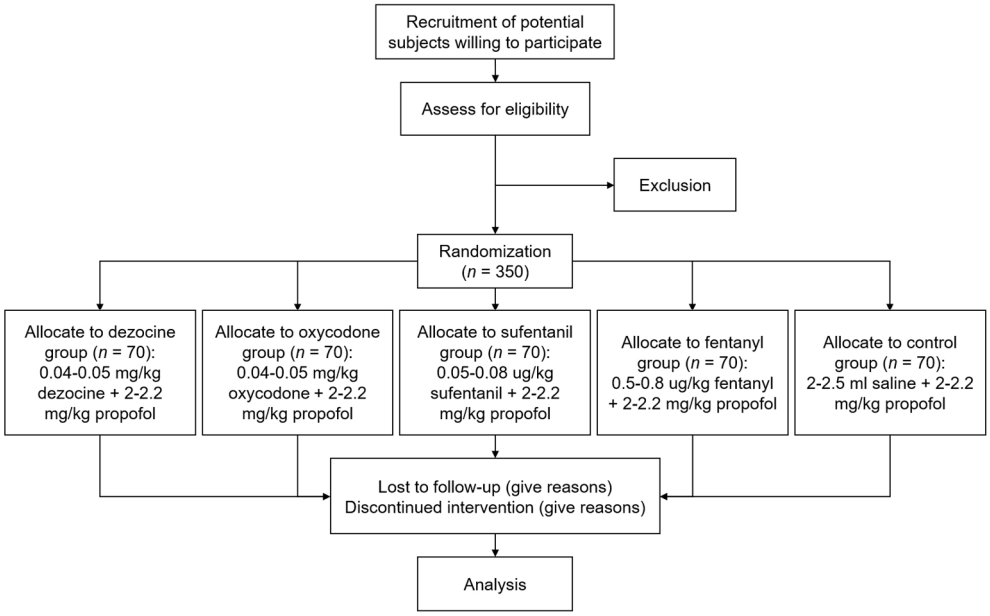

Figure 1. Follow chart of the study.

292x182mm (150 x 150 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	NA
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9, 11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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Keywords:	sedation, propofol, opioids, Endoscopy < GASTROENTEROLOGY, cough

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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Abstract

Introduction: The best methods for analgesia and sedation for gastroscopy are still in debate and finding 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 their 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 hypothesize that combination of propofol and oxycodone may have better performance. We will observe the incidence and reflex degree of cough and gigging under sedation and will compare propofol combined with the above drugs to propofol alone and to each other, allowing a broad screen for feasible regimen.

Methods and analysis: This will be a prospective, randomized, double-blinded, controlled trial. Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years will be included. A total of 500 subjects are planned to be randomized to intravenously receive 2-2.2 mg/kg propofol plus 0.5-0.8 ug/kg fentanyl (fentanyl group), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/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 reflex degree of cough and gigging. The secondary endpoints include occurrence of discomfort or side effects, whether jaw thrust, assistant ventilation, and additional propofol is used, 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 was registered with the Chinese Clinical Trial Center (No. ChiCTR-ICR-15006952).

Keywords: sedation, endoscopy, propofol, opioids, cough

Strengths and limitations of this study

Double-blinded randomized placebo-controlled study design

Aiming to find adequate regimen of sedation and analgesia for gastroscopy

Evaluated the antitussive effects of a wide range of opioids

Single-center study

Introduction

Gastroscopy is an important and common endoscopic method of diagnosis and treatment of digestive diseases. However, during gastroscopy, patients' anxiety and discomfort such as throat irritation, cough, and nausea usually occur, which may affect the endoscopic operation, result in low examination quality, and consequently decrease the willingness of patients to undergo a repeated procedure. Pharyngeal anesthesia and sedation/anesthesia ranging from minimal sedation to general anesthesia have been used to relieve anxiety and discomfort, allowing a successful procedure [1-5].

Currently, endoscopic sedation has been widely applied 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]. Propofol has a favorable sedative effect and a wide range of inhibition effect on the central nervous system [14]. Propofol also strongly inhibits the contraction of gastrointestinal smooth muscles, antagonizes the vomiting reflex and reduce cough and body movement [5 15 16]. The incidences of postoperative headache, nausea and vomiting are low, and propofol even reduces nausea and vomiting [17]. Therefore, it has been widely used for sedation for gastroscopic procedures. Propofol is often used as a single agent. However, it has short duration of clinical effect, and inadequate sedation with propofol alone is seen, which requires additional doses. The duration of gastroscopy is relatively short, generally lasting for 10 minutes, but repeated addition of propofol can significantly prolong the recovery duration, increasing the risk of post-procedure

respiratory depression and hypoxemia, and the workload of recovery management. Use of propofol in combination with opioids has been proposed to improve sedation and analgesia regarding aspects such as recovery time, sedative effect, pain and other discomfort [18-22].

Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effect on airway reflex. However, propofol may still have chance to cause cough [23 24]. Moreover, stimulation of the larynx during propofol anesthesia can cause various types of reflex responses [25]. Although opioids exert favorable analgesic and sedative effects [20 26], and can inhibit pharyngeal reflex and stress response, intravenous fentanyl and sufentanil-induced coughing is not uncommon [27 28]. The induced cough, can be reduced by reduced by propofol [29] 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 a good performance on relieving visceral pain with small respiratory depression and is known to depress cough reflex. Unlike fentanyl and sufentanil, dezocine and oxycodone have rarely been studied in combination with propofol for gastroscopy.

The best methods for analgesia and sedation for gastroscopy are still in debate and finding adequate regimen of sedation/analgesia is important, which can influence the quality of the examination, the patient's cooperation and the patient's and physician's satisfaction with the sedation [5 16 34]. Based on our preliminary observation in

clinical practice, we hypothesize that combination of propofol and low-dose dezocine, oxycodone or sufentanil for gastroscopy may decrease the incidence of cough and that specifically, combination of propofol and oxycodone may have a better performance than others.

In order to verify our hypothesis, we designed this clinical study, aiming to investigate the effect of 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 reflex degree of cough and gigging under sedation with combination of propofol and fentanil sufentanil, dezocine, or oxycodone during gastroscopy. The secondary objective is to assess effect of the combination regimens on sedative performance.

Study location

A prospective, single-center, randomized, 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:

Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years, willing to participate after reading and sign an informed consent.

Exclusion criteria:

1. Body mass index (BMI) ≥30 kg/m^2,
2. Patients with preoperative circulatory, respiratory or nervous system diseases,
3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
4. Patients with sleep apnea syndrome.
5. Patients with URI symptom.
6. Patients with dry cough history.
7. Patients with drug allergy.

Randomization and blinding

Stratified randomization will be used to assign the candidate subjects to five groups according to sex and BMI (two groups or three groups). Computer-generated random group numbers will be printed and placed into different sealed envelope in turn. When receiving a subject who met the inclusion criteria, the anesthesiologist determined the grouping of the newly recruited subject according to different group numbers in the envelopes. The regimen will be blind to both anesthesiologists and patients. The drugs will be prepared by nurse anesthetists and labeled with numbers. Then the anesthesiologist will inject the medication. The nurse anesthetists will be responsible for recoding. The anesthesiologist will be notified the study group by the nurse anesthetists in case of emergency.

Current sample size justification

A total of 500 subjects were planned to be involved. The subjects will be randomly divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil and the control group, 100 cases in each group. The sample size was estimated according to the chi-square test of the incidence of the primary categorical outcome, incidence of cough (30%) within 5 min after endoscope insertion. The above total number of observations makes it possible to detect small to moderate effective size (approximately 0.20) with Type I error 5% and power of test 90%. The test of power will remain 80% or higher when up to 20% of the subjects dropout from the study.

Statistical analysis

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

Sedation

Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken 10 minutes prior to sedation. The right upper extremity venous access will be established before the patients enter the operation room. After entering the operation room, the patients will lie in the left-lateral position, with the blood pressure cuff tied to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min). After placement of bite block, blood pressure, heart rate, and SpO_2 will be measured noninvasively (Philips MP50, Germany) to set up baselines and will be monitored throughout the operation afterwards. Blood pressure will be measured at an interval of

1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical, China), 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. All drugs except Propofol will be diluted with saline. The doses of dezocine and oxycodone are defined according to our preliminary study. The 2 ml of normal saline is for subjects weighing ≤70 kg, and the 2.5 ml of normal saline is for subjects weighing >70 kg. Fentanyl will be diluted to 20 ug/ml, sufentanil to 2.5ug/ml, dezocine and oxycodone each to 1 mg/ml. Drugs will be delivered by the Aespire 7900 anesthesia delivery system (GE Healthcare, USA). We will insert the probe when BIS is 40-60. Jaw thrust will be done in case of respiratory depression and oxygen desaturation. If jaw thrust is not working, assistant ventilation will be used. For severe situation, tracheal intubation assisted respiration will performed. After gastroscopy, all the patients will stay PACU. Patients will be followed up until discharge of PACU.

Adverse events

All adverse events, such as nausea, vomiting, dyspnea, hypopnea, apnea, hypotension, oxygen desaturation and bradycardia, will be recorded and closely monitored. 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 operation, blood pressure, heart rate, oxygen saturation, blood pressure will be monitored. The occurrence of swallowing, cough and gigging, body movement, adverse events, whether jaw thrust, assistant ventilation, and additional propofol is used and the duration of endoscopy will be recorded. Then, duration of calls for eyes open and the Steward score after eyes open will be recorded. All data will be collected throughout the study and will be securely managed in confidential conditions. Data will be recorded automatically by the vital signs monitor and anesthesia information system, and manually by a nurse anesthetist. The participants will be referred by the participant number rather than names, throughout the study unless otherwise specified. All relevant documents and files will be archived for five years. Data can be only accessed by the investigators who sign the confidential disclosure agreement and institutional or governmental auditors during the study. Data without patient identification 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 reflex degree of cough and gigging, 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 leading to failure of endoscope insertion. The secondary endpoints include (1) the occurrence of

swallowing, body movement, and adverse events and whether jaw thrust, assistant ventilation, and additional propofol is used, which will be recorded within five minutes after endoscope insertion and throughout the procedure, and (2) duration of calls for eyes open, the duration of procedure and Steward score [35] after eyes open. Blood pressure, heart rate and SpO_2 will be monitored throughout the process. “Patient satisfaction" is not included as a secondary outcome since patient can not recall coughing or gagging.

Protocol amendments

Any changes of the protocol during the trial that may affect the conduct of the trial, the safety and the benefit of the patients will require a formal amendment to the protocol.

Discussion

It is important to improve analgesia and sedation for gastroscopy. Opioids, which exert favorable analgesic, sedative effect and inhibit the stress response, are an important part of surgical anesthesia. The combination of opioids and propofol is the most commonly used regimen for general anesthesia. Currently, a small dose of fentanyl combined with propofol in sedation for gastroscopy have been used in clinical practice. However, fentanyl has the potential risks of respiratory depression, choking and the stiffness of chest wall muscles. Clinical study on other opioids for gastroscopy, such as oxycodone, dezocine and sufentanil, is inadequate. Finding an adequate regimen is essential. Herein, we conduct this trial to evaluate the

combination of small doses of dezocine, oxycodone or sufentanil for gastroscopy. This study observes the incidence and reflex degree of cough under sedation. This trial compares propofol combined the above drugs to propofol alone and to propofol with fentanil, allowing a broad screen for feasible regimen. There are limitations of this study. This is a single-center, which may limit the generalization of this study. Future multiple-center large-sample size study will be needed. The result of this clinical trial can confirm the favorable effects of combination of propofol with small-dose opioids, and can contribute to finding satisfying regimens for sedation for gastroscopy.

Trial status

At the time of manuscript submission, the study is in the recruitment phase.

Ethics and dissemination

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

Authors' contributions

NY conceived of the study. NY and JX participated in its design and coordination. NY, JX, YZC, XL, JY and JX collected references and figured out the protocol. XL, YZC, JY and JX performed statistics analysis. NY and JX drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests

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

References

1. Standards of Practice Committee of the American Society for Gastrointestinal E, Lichtenstein DR, Jagannath S, et al. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008;**68**:815-26.

2. Soma Y, Saito H, Kishibe T, Takahashi T, Tanaka H, Munakata A. Evaluation of topical pharyngeal anesthesia for upper endoscopy including factors associated with patient tolerance. *Gastrointest Endosc* 2001;**53**:14-8.

3. Froehlich F, Schwizer W, Thorens J, Kohler M, Gonvers JJ, Fried M. Conscious sedation for gastroscopy: patient tolerance and cardiorespiratory parameters. *Gastroenterology* 1995;**108**:697-704.

4. Evans LT, Saberi S, Kim HM, Elta GH, Schoenfeld P. Pharyngeal anesthesia during sedated EGDs: is "the spray" beneficial? A meta-analysis and systematic review. *Gastrointest Endosc* 2006;**63**:761-6.

5. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol* 2013;**19**:463-81.

6. Porostocky P, Chiba N, Colacino P, Sadowski D, Singh H. A survey of sedation practices for colonoscopy in Canada. *Can J Gastroenterol* 2011;**25**:255-60.

7. Fanti L, Agostoni M, Gemma M, et al. Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. *Dig Liver Dis* 2011;**43**:726-30.

8. Paspatis GA, Manolaraki MM, Tribonias G, et al. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of

gastroenterology and nutrition. *Dig Liver Dis* 2009;**41**:807-11.

9. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006;**101**:967-74.

10. Riphaus A, Rabofski M, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: results from the first nationwide survey. *Z Gastroenterol* 2010;**48**:392-7.

11. Baudet JS, Borque P, Borja E, et al. Use of sedation in gastrointestinal endoscopy: a nationwide survey in Spain. *Eur J Gastroenterol Hepatol* 2009;**21**:882-8.

12. Wehrmann T, Triantafyllou K. Propofol sedation in gastrointestinal endoscopy: a gastroenterologist's perspective. *Digestion* 2010;**82**:106-9.

13. Byrne MF, Chiba N, Singh H, Sadowski DC, Clinical Affairs Committee of the Canadian Association of G. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. *Can J Gastroenterol* 2008;**22**:457-9.

14. Inada T, Murao K, Shingu K, Yamada K, Nakao S, Nagata A. Effects of propofol and thiopental on the central nervous system during nociceptive stimulation in cats. *J Anesth* 2001;**15**:159-63.

15. Lee TL, Ang SB, Dambisya YM, Adaikan GP, Lau LC. The effect of propofol on human gastric and colonic muscle contractions. *Anesth Analg* 1999;**89**:1246-9.

16. Fanti L, Testoni PA. Sedation and analgesia in gastrointestinal endoscopy: what's new? *World J Gastroenterol* 2010;**16**:2451-7.

17. Cohen LB, Delegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007;**133**:675-701.

18. Ho WM, Yen CM, Lan CH, et al. Comparison between the recovery time of alfentanil and fentanyl in balanced propofol sedation for gastrointestinal and colonoscopy: a prospective, randomized study. *BMC Gastroenterol* 2012;**12**:164.

19. Poulos JE, Kalogerinis PT, Caudle JN. Propofol compared with combination propofol or midazolam/fentanyl for endoscopy in a community setting. *AANA J* 2013;**81**:31-6.

20. Zhang L, Bao Y, Shi D. Comparing the pain of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy. *Acta Cir Bras* 2014;**29**:675-80.

21. Xu ZY, Wang X, Si YY, et al. Intravenous remifentanil and propofol for gastroscopy. *J Clin Anesth* 2008;**20**:352-5.

22. LaPierre CD, Johnson KB, Randall BR, Egan TD. A simulation study of common propofol and propofol-opioid dosing regimens for upper endoscopy: implications on the time course of recovery. *Anesthesiology* 2012;**117**:252-62.

23. Yamamoto S, Motokawa K, Toyooka H. Propofol may cause coughing when used as a sedative in patients undergoing orthopedic surgery under spinal anesthesia. *Anesthesia & Analgesia* 1998;**86**:529S.

24. Mitra S, Sinha PK, Anand LK, Gombar KK. Propofol-induced violent coughing.

Anaesthesia 2000;**55**:707-8.

25. Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anesthesia. *The Journal of the American Society of Anesthesiologists* 1998;**88**:1459-66.

26. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 2000;**95**:1476-9.

27. Yemen TA. Small doses of sufentanil will produce violent coughing in young children. *Anesthesiology* 1998;**89**:271-2.

28. Bohrer H, Fleischer F, Werning P. Tussive effect of a fentanyl bolus administered through a central venous catheter. *Anaesthesia* 1990;**45**:18-21.

29. Sedighinejad A, Naderi Nabi B, Haghighi M, et al. Propofol is Effective to Depress Fentanyl-Induced Cough during Induction of Anesthesia. *Anesth Pain Med* 2013;**2**:170-3.

30. Liu XS, Xu GH, Shen QY, et al. Dezocine prevents sufentanil-induced cough during general anesthesia induction: A randomized controlled trial. *Pharmacol Rep* 2015;**67**:52-5.

31. Ramirez-Ruiz M, Smith I, White PF. Use of analgesics during propofol sedation: a comparison of ketorolac, dezocine, and fentanyl. *J Clin Anesth* 1995;**7**:481-5.

32. Lu Y, Ye Z, Wong GT, Dong C, Yu J. Prevention of injection pain due to propofol by dezocine: a comparison with lidocaine. *Indian J Pharmacol* 2013;**45**:619-21.

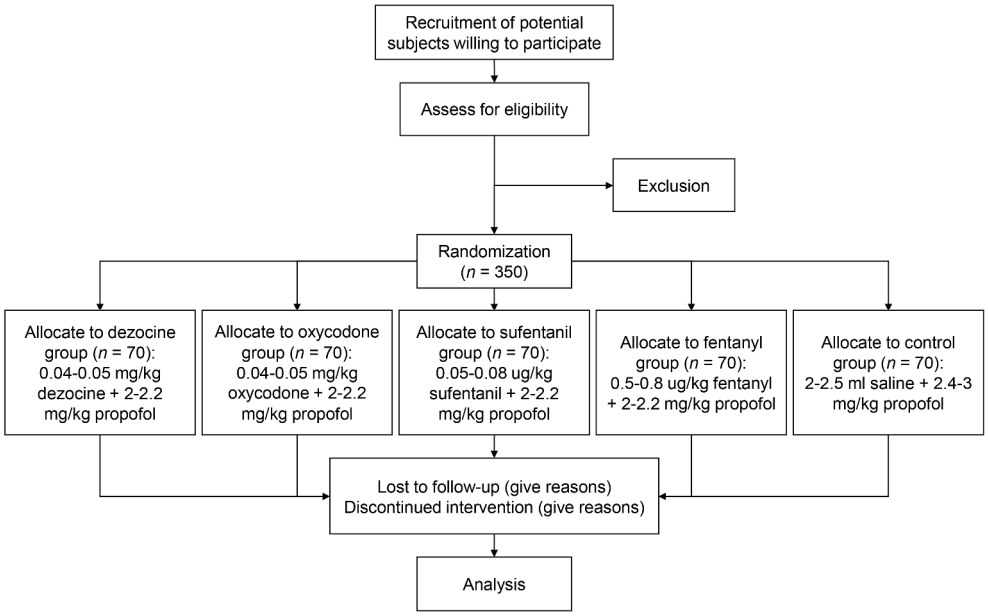
33. Zheng M, Guo Y, Shan S, Yang S. Dezocine for anesthesia and stress reduction in induced abortion. *Patient Prefer Adherence* 2015;**9**:369-72.

34. Bell GD. Preparation, premedication, and surveillance. *Endoscopy* 2004;**36**:23-31.

35. Steward DJ. A simplified scoring system for the post-operative recovery room. *Can Anaesth Soc J* 1975;**22**:111-3.

Figure Legend

Figure 1. Follow chart of the study.



Follow chart of the study.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	NA
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9, 11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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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Keywords:	sedation, propofol, opioids, Endoscopy < GASTROENTEROLOGY, cough

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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Abstract

Introduction: The best methods for analgesia and sedation for gastroscopy are still in debate and finding 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 their 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 hypothesize that combination of propofol and oxycodone may have better performance. We will observe the incidence and reflex degree of cough and gigging under sedation and will compare propofol combined with the above drugs to propofol alone and to each other, allowing a broad screen for feasible regimen.

Methods and analysis: This will be a prospective, randomized, double-blinded, controlled trial. Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years will be included. A total of 500 subjects are planned to be randomized to intravenously receive 2-2.2 mg/kg propofol plus 0.5-0.8 ug/kg fentanyl (fentanyl group), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/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 reflex degree of cough and gigging. The secondary endpoints include occurrence of discomfort or side effects, whether jaw thrust, assistant ventilation, and additional propofol is used, 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 was registered with the Chinese Clinical Trial Center (No. ChiCTR-ICR-15006952).

Keywords: sedation, endoscopy, propofol, opioids, cough

Strengths and limitations of this study

This is a double-blinded randomized placebo-controlled study design

This study aims to find adequate regimen of sedation and analgesia for gastroscopy

This study will evaluate the antitussive effects of a wide range of opioids

The dose of propofol for this study is still high.

This is a single-center study.

Introduction

Gastroscopy is an important and common endoscopic method of diagnosis and treatment of digestive diseases. However, during gastroscopy, patients' anxiety and discomfort such as throat irritation, cough, and nausea usually occur, which may affect the endoscopic operation, result in low examination quality, and consequently decrease the willingness of patients to undergo a repeated procedure. Pharyngeal anesthesia and sedation/anesthesia ranging from minimal sedation to general anesthesia have been used to relieve anxiety and discomfort, allowing a successful procedure [1-5].

Currently, endoscopic sedation has been widely applied 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]. Propofol has a favorable sedative effect and a wide range of inhibition effect on the central nervous system [14]. Propofol also strongly inhibits the contraction of gastrointestinal smooth muscles, antagonizes the vomiting reflex and reduce cough and body movement [5 15 16]. The incidences of postoperative headache, nausea and vomiting are low, and propofol even reduces nausea and vomiting [17]. Therefore, it has been widely used for sedation for gastroscopic procedures. Propofol is often used as a single agent. However, it has short duration of clinical effect, and inadequate sedation with propofol alone is seen, which requires additional doses. The duration of gastroscopy is relatively short, generally lasting for 10 minutes, but repeated addition of propofol can significantly prolong the recovery duration, increasing the risk of post-procedure

respiratory depression and hypoxemia, and the workload of recovery management. Use of propofol in combination with opioids has been proposed to improve sedation and analgesia regarding aspects such as recovery time, sedative effect, pain and other discomfort [18-22].

Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effect on airway reflex. However, propofol may still have chance to cause cough [23 24]. Moreover, stimulation of the larynx during propofol anesthesia can cause various types of reflex responses [25]. Although opioids exert favorable analgesic and sedative effects [20 26], and can inhibit pharyngeal reflex and stress response, intravenous fentanyl and sufentanil-induced coughing is not uncommon [27 28]. The induced cough, can be reduced by propofol [29] 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 a good performance on relieving visceral pain with small respiratory depression and is known to depress cough reflex. Unlike fentanyl and sufentanil, dezocine and oxycodone have rarely been studied in combination with propofol for gastroscopy.

The best methods for analgesia and sedation for gastroscopy are still in debate and finding adequate regimen of sedation/analgesia is important, which can influence the quality of the examination, the patient's cooperation and the patient's and physician's satisfaction with the sedation [5 16 34]. Based on our preliminary observation in

clinical practice, we hypothesize that combination of propofol and low-dose dezocine, oxycodone or sufentanil for gastroscopy may decrease the incidence of cough and that specifically, combination of propofol and oxycodone may have a better performance than others.

In order to verify our hypothesis, we designed this clinical study, aiming to investigate the effect of 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 reflex degree of cough and gigging under sedation with combination of propofol and fentanil sufentanil, dezocine, or oxycodone during gastroscopy. The secondary objective is to assess effect of the combination regimens on sedative performance.

Study location

A prospective, single-center, randomized, 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:

Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years, willing to participate after reading and sign an informed consent.

Exclusion criteria:

1. Body mass index (BMI) ≥30 kg/m^2,
2. Patients with preoperative circulatory, respiratory or nervous system diseases,
3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
4. Patients with sleep apnea syndrome.
5. Patients with URI (upper respiratory tract infection) symptom.
6. Patients with dry cough history.
7. Patients with drug allergy.

Randomization and blinding

Stratified randomization will be used to assign the candidate subjects to five groups according to sex and BMI (two groups or three groups). Computer-generated random group numbers will be printed and placed into different sealed envelope in turn. When receiving a subject who met the inclusion criteria, the anesthesiologist determined the grouping of the newly recruited subject according to different group numbers in the envelopes. The regimen will be blind to both anesthesiologists and patients. The drugs will be prepared by nurse anesthetists and labeled with numbers. Then the anesthesiologist will inject the medication. The nurse anesthetists will be responsible for recoding. The anesthesiologist will be notified the study group by the nurse anesthetists in case of emergency.

Current sample size justification

A total of 500 subjects were planned to be involved. The subjects will be randomly divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil and the control group, 100 cases in each group. The sample size was estimated according to the chi-square test of the incidence of the primary categorical outcome, incidence of cough (30%) within 5 min after endoscope insertion. The above total number of observations makes it possible to detect small to moderate effective size (approximately 0.20) with Type I error 5% and power of test 90%. The test of power will remain 80% or higher when up to 20% of the subjects dropout from the study.

Statistical analysis

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

Sedation

Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken 10 minutes prior to sedation. The right upper extremity venous access will be established before the patients enter the operation room. After entering the operation room, the patients will lie in the left-lateral position, with the blood pressure cuff tied to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min). After placement of bite block, blood pressure, heart rate, and SpO_2 will be measured noninvasively (Philips MP50, Germany) to set up baselines and will be monitored throughout the operation afterwards. Blood pressure will be measured at an interval of

1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical, China), 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. All drugs except Propofol will be diluted with saline. The doses of dezocine and oxycodone are defined according to our preliminary study. The 2 ml of normal saline is for subjects weighing ≤70 kg, and the 2.5 ml of normal saline is for subjects weighing >70 kg. Fentanyl will be diluted to 20 ug/ml, sufentanil to 2.5ug/ml, dezocine and oxycodone each to 1 mg/ml. Drugs will be delivered by the Aespire 7900 anesthesia delivery system (GE Healthcare, USA). We will insert the probe when BIS (bispectral index) is 40-60. A BIS of 40-60 is usually considered as sufficient depth of general anesthesia. Jaw thrust will be done in case of respiratory depression and oxygen desaturation. If jaw thrust is not working, assistant ventilation will be used. For severe situation, tracheal intubation assisted respiration will performed. After gastroscopy, all the patients will stay PACU (post-anesthesia care unit). Patients will be followed up until discharge of PACU.

Adverse events

All adverse events, such as nausea, vomiting, dyspnea, hypopnea, apnea, hypotension, oxygen desaturation and bradycardia, will be recorded and closely monitored. 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 operation, blood pressure, heart rate, oxygen saturation, blood pressure will be monitored. The occurrence of swallowing, cough and gigging, body movement, adverse events, whether jaw thrust, assistant ventilation, and additional propofol is used and the duration of endoscopy will be recorded. Then, duration of calls for eyes open and the Steward score after eyes open will be recorded. All data will be collected throughout the study and will be securely managed in confidential conditions. Data will be recorded automatically by the vital signs monitor and anesthesia information system, and manually by a nurse anesthetist. The participants will be referred by the participant number rather than names, throughout the study unless otherwise specified. All relevant documents and files will be archived for five years. Data can be only accessed by the investigators who sign the confidential disclosure agreement and institutional or governmental auditors during the study. Data without patient identification 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 reflex degree of cough and gigging, 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 leading to

failure of endoscope insertion. The secondary endpoints include (1) the occurrence of swallowing, body movement, and adverse events and whether jaw thrust, assistant ventilation, and additional propofol is used, which will be recorded within five minutes after endoscope insertion and throughout the procedure, and (2) duration of calls for eyes open, the duration of procedure and Steward score [35] after eyes open. Blood pressure, heart rate and SpO_2 will be monitored throughout the process. “Patient satisfaction" is not included as a secondary outcome since patient can not recall coughing or gagging.

Protocol amendments

The current protocol version is v1.5 (11 June 2017). Any changes of the protocol during the trial that may affect the conduct of the trial, the safety and the benefit of the patients will require a formal amendment to the protocol.

Discussion

It is important to improve analgesia and sedation for gastroscopy. Opioids, which exert favorable analgesic, sedative effect and inhibit the stress response, are an important part of surgical anesthesia. The combination of opioids and propofol is the most commonly used regimen for general anesthesia. Currently, a small dose of fentanyl combined with propofol in sedation for gastroscopy have been used in clinical practice. However, fentanyl has the potential risks of respiratory depression, choking and the stiffness of chest wall muscles. Clinical study on other opioids for gastroscopy, such as oxycodone, dezocine and sufentanil, is inadequate. Finding an

adequate regimen is essential. Herein, we conduct this trial to evaluate the combination of small doses of dezocine, oxycodone or sufentanil for gastroscopy. This study observes the incidence and reflex degree of cough under sedation. This trial compares propofol combined the above drugs to propofol alone and to propofol with fentanil, allowing a broad screen for feasible regimen. There are limitations of this study. This is a single-center, which may limit the generalization of this study. Future multiple-center large-sample size study will be needed. The result of this clinical trial can confirm the favorable effects of combination of propofol with small-dose opioids, and can contribute to finding satisfying regimens for sedation for gastroscopy.

Trial status

At the time of manuscript submission, the study is in the recruitment phase.

Ethics and dissemination

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

Authors' contributions

NY conceived of the study. NY and JX participated in its design and coordination. NY, JX, YZC, XL, JY and JX collected references and figured out the protocol. XL, YZC, JY and JX performed statistics analysis. NY and JX drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests

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

References

1. Standards of Practice Committee of the American Society for Gastrointestinal E, Lichtenstein DR, Jagannath S, et al. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008;**68**:815-26.

2. Soma Y, Saito H, Kishibe T, Takahashi T, Tanaka H, Munakata A. Evaluation of topical pharyngeal anesthesia for upper endoscopy including factors associated with patient tolerance. *Gastrointest Endosc* 2001;**53**:14-8.

3. Froehlich F, Schwizer W, Thorens J, Kohler M, Gonvers JJ, Fried M. Conscious sedation for gastroscopy: patient tolerance and cardiorespiratory parameters. *Gastroenterology* 1995;**108**:697-704.

4. Evans LT, Saberi S, Kim HM, Elta GH, Schoenfeld P. Pharyngeal anesthesia during sedated EGDs: is "the spray" beneficial? A meta-analysis and systematic review. *Gastrointest Endosc* 2006;**63**:761-6.

5. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol* 2013;**19**:463-81.

6. Porostocky P, Chiba N, Colacino P, Sadowski D, Singh H. A survey of sedation practices for colonoscopy in Canada. *Can J Gastroenterol* 2011;**25**:255-60.

7. Fanti L, Agostoni M, Gemma M, et al. Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. *Dig Liver Dis* 2011;**43**:726-30.

8. Paspatis GA, Manolaraki MM, Tribonias G, et al. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of

gastroenterology and nutrition. *Dig Liver Dis* 2009;**41**:807-11.

9. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006;**101**:967-74.

10. Riphaus A, Rabofski M, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: results from the first nationwide survey. *Z Gastroenterol* 2010;**48**:392-7.

11. Baudet JS, Borque P, Borja E, et al. Use of sedation in gastrointestinal endoscopy: a nationwide survey in Spain. *Eur J Gastroenterol Hepatol* 2009;**21**:882-8.

12. Wehrmann T, Triantafyllou K. Propofol sedation in gastrointestinal endoscopy: a gastroenterologist's perspective. *Digestion* 2010;**82**:106-9.

13. Byrne MF, Chiba N, Singh H, Sadowski DC, Clinical Affairs Committee of the Canadian Association of G. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. *Can J Gastroenterol* 2008;**22**:457-9.

14. Inada T, Murao K, Shingu K, Yamada K, Nakao S, Nagata A. Effects of propofol and thiopental on the central nervous system during nociceptive stimulation in cats. *J Anesth* 2001;**15**:159-63.

15. Lee TL, Ang SB, Dambisya YM, Adaikan GP, Lau LC. The effect of propofol on human gastric and colonic muscle contractions. *Anesth Analg* 1999;**89**:1246-9.

16. Fanti L, Testoni PA. Sedation and analgesia in gastrointestinal endoscopy: what's new? *World J Gastroenterol* 2010;**16**:2451-7.

17. Cohen LB, Delegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007;**133**:675-701.

18. Ho WM, Yen CM, Lan CH, et al. Comparison between the recovery time of alfentanil and fentanyl in balanced propofol sedation for gastrointestinal and colonoscopy: a prospective, randomized study. *BMC Gastroenterol* 2012;**12**:164.

19. Poulos JE, Kalogerinis PT, Caudle JN. Propofol compared with combination propofol or midazolam/fentanyl for endoscopy in a community setting. *AANA J* 2013;**81**:31-6.

20. Zhang L, Bao Y, Shi D. Comparing the pain of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy. *Acta Cir Bras* 2014;**29**:675-80.

21. Xu ZY, Wang X, Si YY, et al. Intravenous remifentanil and propofol for gastroscopy. *J Clin Anesth* 2008;**20**:352-5.

22. LaPierre CD, Johnson KB, Randall BR, Egan TD. A simulation study of common propofol and propofol-opioid dosing regimens for upper endoscopy: implications on the time course of recovery. *Anesthesiology* 2012;**117**:252-62.

23. Yamamoto S, Motokawa K, Toyooka H. Propofol may cause coughing when used as a sedative in patients undergoing orthopedic surgery under spinal anesthesia. *Anesthesia & Analgesia* 1998;**86**:529S.

24. Mitra S, Sinha PK, Anand LK, Gombar KK. Propofol-induced violent coughing.

Anaesthesia 2000;**55**:707-8.

25. Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anesthesia. *The Journal of the American Society of Anesthesiologists* 1998;**88**:1459-66.

26. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 2000;**95**:1476-9.

27. Yemen TA. Small doses of sufentanil will produce violent coughing in young children. *Anesthesiology* 1998;**89**:271-2.

28. Bohrer H, Fleischer F, Werning P. Tussive effect of a fentanyl bolus administered through a central venous catheter. *Anaesthesia* 1990;**45**:18-21.

29. Sedighinejad A, Naderi Nabi B, Haghighi M, et al. Propofol is Effective to Depress Fentanyl-Induced Cough during Induction of Anesthesia. *Anesth Pain Med* 2013;**2**:170-3.

30. Liu XS, Xu GH, Shen QY, et al. Dezocine prevents sufentanil-induced cough during general anesthesia induction: A randomized controlled trial. *Pharmacol Rep* 2015;**67**:52-5.

31. Ramirez-Ruiz M, Smith I, White PF. Use of analgesics during propofol sedation: a comparison of ketorolac, dezocine, and fentanyl. *J Clin Anesth* 1995;**7**:481-5.

32. Lu Y, Ye Z, Wong GT, Dong C, Yu J. Prevention of injection pain due to propofol by dezocine: a comparison with lidocaine. *Indian J Pharmacol* 2013;**45**:619-21.

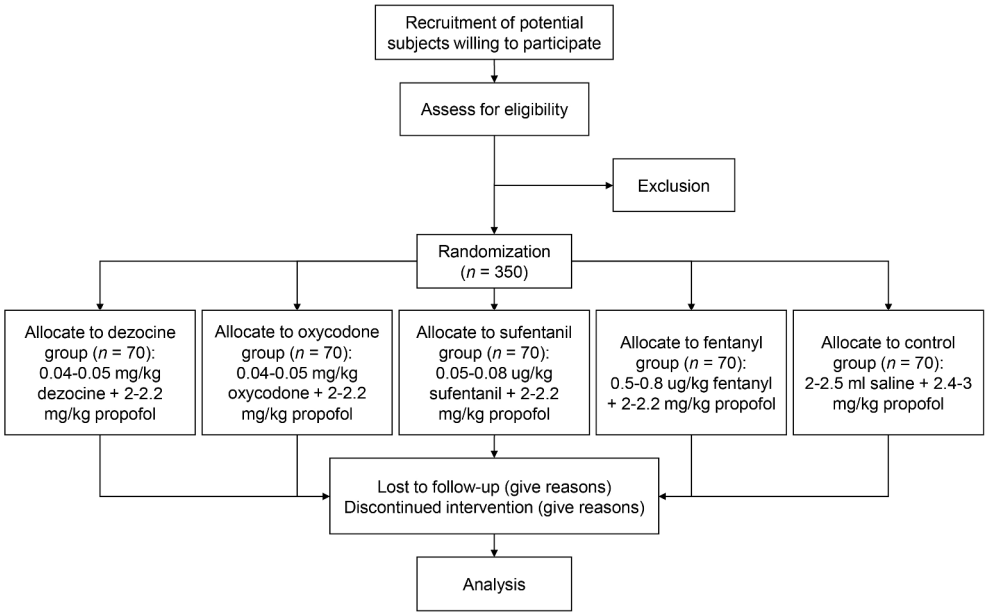
33. Zheng M, Guo Y, Shan S, Yang S. Dezocine for anesthesia and stress reduction in induced abortion. *Patient Prefer Adherence* 2015;**9**:369-72.

34. Bell GD. Preparation, premedication, and surveillance. *Endoscopy* 2004;**36**:23-31.

35. Steward DJ. A simplified scoring system for the post-operative recovery room. *Can Anaesth Soc J* 1975;**22**:111-3.

Figure Legend

Figure 1. Follow chart of the study.



Follow chart of the study.

292x182mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	11
Funding	4	Sources and types of financial, material, and other support	NA
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	12
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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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Keywords:	sedation, propofol, opioids, Endoscopy < GASTROENTEROLOGY, cough

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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Abstract

Introduction: The best methods for analgesia and sedation for gastroscopy are still in debate and 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 remains unclear. This trial will evaluate the effects of propofol combined with small doses of dezocine, oxycodone, sufentanil, or fentanyl for gastroscopy. We hypothesize that combination of propofol and oxycodone may have better performance. We will observe the incidence and reflex degree of cough and gigging under sedation when using propofol combined with the above drugs or propofol alone. This study will allow a broad screen for feasible regimen.

Methods and analysis: This will be a prospective, randomized, double-blind, controlled trial. Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years will be included. A total of 500 subjects are planned to be randomized to intravenously receive 2-2.2 mg/kg propofol plus 0.5-0.8 ug/kg fentanyl (fentanyl group), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/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 reflex degree of cough and gigging. The secondary endpoints include occurrence of discomfort or side effects, whether jaw thrust, assistant ventilation, and additional propofol is used, 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 was registered with the Chinese Clinical Trial Center (No. ChiCTR-ICR-15006952).

Keywords: sedation, endoscopy, propofol, opioids, cough

Strengths and limitations of this study

- This study is the first randomized controlled trial investigating the effect of dezocine and oxycodone on cough reflex suppression when combining propofol during gastroscopy.
- This study focuses on the antitussive effects of a wide range of opioids, which few previous studies have addressed.
- Mythological strengths include appropriate sample size, stratified randomization and double-blind placebo-controlled design.
- This is a single-center, which could be a limitation of this study.
- The dose of propofol for this study could be a limitation, which is relatively high and may have a risk to abolish the effects of the opioids examined in this study.

Introduction

Gastroscopy is an important and common endoscopic method of diagnosis and treatment of digestive diseases. However, during gastroscopy, patients' anxiety and discomfort such as throat irritation, cough, and nausea usually occur, which may affect the endoscopic operation, resulting in low examination quality, and consequently decrease the willingness of patients to undergo a repeated procedure. Pharyngeal anesthesia and sedation/anesthesia ranging from minimal sedation to general anesthesia have been used to relieve anxiety and discomfort, allowing a successful procedure [1-5].

Currently, endoscopic sedation has been widely applied 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]. Propofol has a favorable sedative effect and a wide range of inhibition effects on the central nervous system [14]. Propofol also strongly inhibits the contraction of gastrointestinal smooth muscles, antagonizes the vomiting reflex and reduces cough and body movement [5 15 16]. The incidences of postoperative headache, nausea and vomiting are low, and propofol even reduces nausea and vomiting [17]. Therefore, it has been widely used for sedation for gastroscopic procedures. Propofol is often used as a single agent. However, it has short duration of clinical effect. Inadequate sedation with propofol alone is seen, which requires additional doses. The duration of gastroscopy is relatively short, usually lasting for 10 minutes, but repeated addition of propofol can significantly prolong the recovery time, increasing the risk of post-procedure

respiratory depression and hypoxemia, and the workload of recovery management. The use of propofol in combination with opioids has been proposed to improve sedation and analgesia regarding the aspects such as recovery time, sedative effect, pain and other discomfort [18-22].

Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effects on airway reflex. However, propofol may still have the chance to cause cough [23 24]. Moreover, stimulation of the larynx during propofol anesthesia can cause various types of reflex responses [25]. Although opioids exert favorable 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]. The induced cough, can be reduced by propofol [29] 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 a good performance on relieving visceral pain with small respiratory depression and is known to depress cough reflex. Unlike fentanyl or sufentanil, dezocine and oxycodone have rarely been studied in combination with propofol for gastroscopy.

The best methods for analgesia and sedation for gastroscopy are still in debate and finding an adequate regimen of sedation/analgesia is important, which can influence the quality of the examination, the patient's cooperation, and the patient's and physician's satisfaction with the sedation [5 16 34]. Based on our preliminary

observation in clinical practice, we hypothesize that combination of propofol and low-dose dezocine, oxycodone or sufentanil for gastroscopy may decrease the incidence of cough and that specifically, combination of propofol and oxycodone may have a better performance than others.

In order to verify our hypothesis, we designed this clinical study, aiming to investigate the effect of 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 reflex degree of cough and gigging under sedation with combination of propofol and fentanil 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-center, randomized, 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:

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

Exclusion criteria:

1. Body mass index (BMI) ≥30 kg/m^2,
2. Patients with preoperative circulatory, respiratory or nervous system diseases,
3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
4. Patients with sleep apnea syndrome.
5. Patients with URI (upper respiratory tract infection) symptom.
6. Patients with dry cough history.
7. Patients with drug allergy.

Randomization and blinding

Stratified randomization will be used to assign the candidate subjects to five groups according to sex and BMI (two groups or three groups). Computer-generated random group numbers will be printed and placed into different sealed envelopes in turn. When receiving a subject who meets the inclusion criteria, the anesthesiologist determined the grouping of the newly recruited subject according to the different group numbers in the envelopes. The regimen will be blind to both anesthesiologists and patients. The drugs will be prepared by nurse anesthetists and labeled with numbers. Then the anesthesiologist will inject the medication. The nurse anesthetists will be responsible for recoding. The anesthesiologist will be notified the study group by the nurse anesthetists in case of emergency.

Current sample size justification

A total of 500 subjects are planned to be involved. The subjects will be randomly divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil and control group, with 100 cases in each group. The sample size was estimated according to the chi-square test of the incidence of the primary categorical outcome, incidence of cough (30%) within 5 min after endoscope insertion. The above total number of observations made it possible to detect small to moderate effective size (approximately 0.20) with the Type I error 5% and power of test 90%. The test of power will remain 80% or higher when up to 20% of the subjects dropout from the study.

Statistical analysis

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

Sedation

Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken 10 minutes prior to sedation. The right upper extremity venous access will be established before the patients enter the operation room. After entering the operation room, the patients will lie in the left-lateral position, with the blood pressure cuff tied to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min). After the placement of bite block, blood pressure, heart rate, and SpO_2 will be measured noninvasively (Philips MP50, Germany) to set up baselines and will be

monitored throughout the operation. Blood pressure will be measured at an interval of 1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical, China), 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. All drugs except Propofol will be diluted with saline. The doses of dezocine and oxycodone are defined according to our preliminary study. The 2 ml of normal saline is for subjects weighing ≤70 kg, and the 2.5 ml of normal saline is for subjects weighing >70 kg. Fentanyl will be diluted to 20 ug/ml, sufentanil to 2.5ug/ml, dezocine and oxycodone each to 1 mg/ml. Drugs will be delivered by the Aespire 7900 anesthesia delivery system (GE Healthcare, USA). We will insert the probe when the BIS (bispectral index) is 40-60. A BIS of 40-60 is usually considered as sufficient depth of general anesthesia. Jaw thrust will be done in case of respiratory depression and oxygen desaturation. If jaw thrust is not working, assistant ventilation will be used. For severe situation, tracheal intubation assisted respiration will performed. After gastroscopy, all the patients will stay PACU (post-anesthesia care unit). Patients will be followed up until discharge of PACU.

Adverse events

All adverse events, such as nausea, vomiting, dyspnea, hypopnea, apnea, hypotension, oxygen desaturation and bradycardia, will be recorded and closely monitored.

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 operation, blood pressure, heart rate, oxygen saturation, blood pressure will be monitored. The occurrence of swallowing, cough and gigging, body movement, adverse events, whether jaw thrust, assistant ventilation, and additional propofol is used and the duration of endoscopy will be recorded. Then, duration of calls for eyes open and the Steward score after eyes open will be recorded. All data will be collected throughout the study and will be securely managed in confidential conditions. Automatic data collection will be performed by the vital signs monitor and anesthesia information system. Manual data collection will be performed by a nurse anesthetist. The participants will be referred by the participant number rather than names throughout the study unless otherwise specified. All relevant documents and files will be archived for five years. Data can be only accessed by the investigators who sign the confidential disclosure agreement and by the institutional or governmental auditors during the study. Data without patient identification 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 reflex degree of cough and gigging, 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 leading to failure of endoscope insertion. The secondary endpoints include (1) the occurrence of swallowing, body movement, and adverse events and whether jaw thrust, assistant ventilation, and additional propofol is used, which will be recorded within five minutes after endoscope insertion and throughout the procedure, and (2) duration of calls for eyes open, the duration of procedure and Steward score [35] after eyes open. Blood pressure, heart rate and SpO_2 will be monitored throughout the process. “Patient satisfaction" is not included as a secondary outcome since patient can not recall coughing or gagging.

Protocol amendments

The current protocol version is v1.5 (11 June 2017). Any changes of the protocol during the trial that may affect the conduct of the trial, the safety and the benefit of the patients will require a formal amendment to the protocol.

Discussion

It is important to improve analgesia and sedation for gastroscopy. Opioids, which exert favorable analgesic, sedative effect and inhibit the stress response, are an important part of surgical anesthesia. The combination of opioids and propofol is the most commonly used regimen for general anesthesia. Currently, a small dose of fentanyl combined with propofol in sedation for gastroscopy has been used in clinical practice. However, fentanyl has the potential risks of respiratory depression, choking and the stiffness of chest wall muscles. Clinical study on other opioids for gastroscopy,

such as oxycodone, dezocine and sufentanil, is rare. Finding an adequate regimen is essential. Herein, we conduct this trial to evaluate the combination of small doses of dezocine, oxycodone or sufentanil for gastroscopy. This study observes the incidence and reflex degree of cough under sedation. There are limitations of this study. This is a single-center, which may limit the generalization of this study. Future multiple-center large-sample size study will be needed. The dose of propofol for this study is relatively high and may have a risk to abolish the effects of the opioids examined in this study. The result of this clinical trial can confirm the favorable effects of combination of propofol with small-dose opioids, and can contribute to finding satisfying regimens for sedation for gastroscopy.

Trial status

At the time of manuscript submission, the study is in the recruitment phase.

Ethics and dissemination

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

Consent

Each participant will be asked to carefully read the informed consent by the doctors of the research team. The doctors are responsible for explaining all relevant information of this study. Participants must sign the informed consent voluntarily. The signed informed consent will be obtained by the doctors of the research team and bring to the nurse anesthetist responsible for the management of those files.

Authors' contributions

NY conceived of the study. NY and JX participated in its design and coordination. NY, JX, YZC, XL, JY and JX collected references and figured out the protocol. XL, YZC, JY and JX performed statistics analysis. NY and JX drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests

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

References

1. Standards of Practice Committee of the American Society for Gastrointestinal E, Lichtenstein DR, Jagannath S, et al. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008;**68**:815-26.

2. Soma Y, Saito H, Kishibe T, Takahashi T, Tanaka H, Munakata A. Evaluation of topical pharyngeal anesthesia for upper endoscopy including factors associated with patient tolerance. *Gastrointest Endosc* 2001;**53**:14-8.

3. Froehlich F, Schwizer W, Thorens J, Kohler M, Gonvers JJ, Fried M. Conscious sedation for gastroscopy: patient tolerance and cardiorespiratory parameters. *Gastroenterology* 1995;**108**:697-704.

4. Evans LT, Saberi S, Kim HM, Elta GH, Schoenfeld P. Pharyngeal anesthesia during sedated EGDs: is "the spray" beneficial? A meta-analysis and systematic review. *Gastrointest Endosc* 2006;**63**:761-6.

5. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol* 2013;**19**:463-81.

6. Porostocky P, Chiba N, Colacino P, Sadowski D, Singh H. A survey of sedation practices for colonoscopy in Canada. *Can J Gastroenterol* 2011;**25**:255-60.

7. Fanti L, Agostoni M, Gemma M, et al. Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. *Dig Liver Dis* 2011;**43**:726-30.

8. Paspatis GA, Manolaraki MM, Tribonias G, et al. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of

gastroenterology and nutrition. *Dig Liver Dis* 2009;**41**:807-11.

9. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006;**101**:967-74.

10. Riphaus A, Rabofski M, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: results from the first nationwide survey. *Z Gastroenterol* 2010;**48**:392-7.

11. Baudet JS, Borque P, Borja E, et al. Use of sedation in gastrointestinal endoscopy: a nationwide survey in Spain. *Eur J Gastroenterol Hepatol* 2009;**21**:882-8.

12. Wehrmann T, Triantafyllou K. Propofol sedation in gastrointestinal endoscopy: a gastroenterologist's perspective. *Digestion* 2010;**82**:106-9.

13. Byrne MF, Chiba N, Singh H, Sadowski DC, Clinical Affairs Committee of the Canadian Association of G. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. *Can J Gastroenterol* 2008;**22**:457-9.

14. Inada T, Murao K, Shingu K, Yamada K, Nakao S, Nagata A. Effects of propofol and thiopental on the central nervous system during nociceptive stimulation in cats. *J Anesth* 2001;**15**:159-63.

15. Lee TL, Ang SB, Dambisya YM, Adaikan GP, Lau LC. The effect of propofol on human gastric and colonic muscle contractions. *Anesth Analg* 1999;**89**:1246-9.

16. Fanti L, Testoni PA. Sedation and analgesia in gastrointestinal endoscopy: what's new? *World J Gastroenterol* 2010;**16**:2451-7.

17. Cohen LB, Delegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007;**133**:675-701.

18. Ho WM, Yen CM, Lan CH, et al. Comparison between the recovery time of alfentanil and fentanyl in balanced propofol sedation for gastrointestinal and colonoscopy: a prospective, randomized study. *BMC Gastroenterol* 2012;**12**:164.

19. Poulos JE, Kalogerinis PT, Caudle JN. Propofol compared with combination propofol or midazolam/fentanyl for endoscopy in a community setting. *AANA J* 2013;**81**:31-6.

20. Zhang L, Bao Y, Shi D. Comparing the pain of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy. *Acta Cir Bras* 2014;**29**:675-80.

21. Xu ZY, Wang X, Si YY, et al. Intravenous remifentanil and propofol for gastroscopy. *J Clin Anesth* 2008;**20**:352-5.

22. LaPierre CD, Johnson KB, Randall BR, Egan TD. A simulation study of common propofol and propofol-opioid dosing regimens for upper endoscopy: implications on the time course of recovery. *Anesthesiology* 2012;**117**:252-62.

23. Yamamoto S, Motokawa K, Toyooka H. Propofol may cause coughing when used as a sedative in patients undergoing orthopedic surgery under spinal anesthesia. *Anesthesia & Analgesia* 1998;**86**:529S.

24. Mitra S, Sinha PK, Anand LK, Gombar KK. Propofol-induced violent coughing.

Anaesthesia 2000;**55**:707-8.

25. Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anesthesia. *The Journal of the American Society of Anesthesiologists* 1998;**88**:1459-66.

26. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 2000;**95**:1476-9.

27. Yemen TA. Small doses of sufentanil will produce violent coughing in young children. *Anesthesiology* 1998;**89**:271-2.

28. Bohrer H, Fleischer F, Werning P. Tussive effect of a fentanyl bolus administered through a central venous catheter. *Anaesthesia* 1990;**45**:18-21.

29. Sedighinejad A, Naderi Nabi B, Haghighi M, et al. Propofol is Effective to Depress Fentanyl-Induced Cough during Induction of Anesthesia. *Anesth Pain Med* 2013;**2**:170-3.

30. Liu XS, Xu GH, Shen QY, et al. Dezocine prevents sufentanil-induced cough during general anesthesia induction: A randomized controlled trial. *Pharmacol Rep* 2015;**67**:52-5.

31. Ramirez-Ruiz M, Smith I, White PF. Use of analgesics during propofol sedation: a comparison of ketorolac, dezocine, and fentanyl. *J Clin Anesth* 1995;**7**:481-5.

32. Lu Y, Ye Z, Wong GT, Dong C, Yu J. Prevention of injection pain due to propofol by dezocine: a comparison with lidocaine. *Indian J Pharmacol* 2013;**45**:619-21.

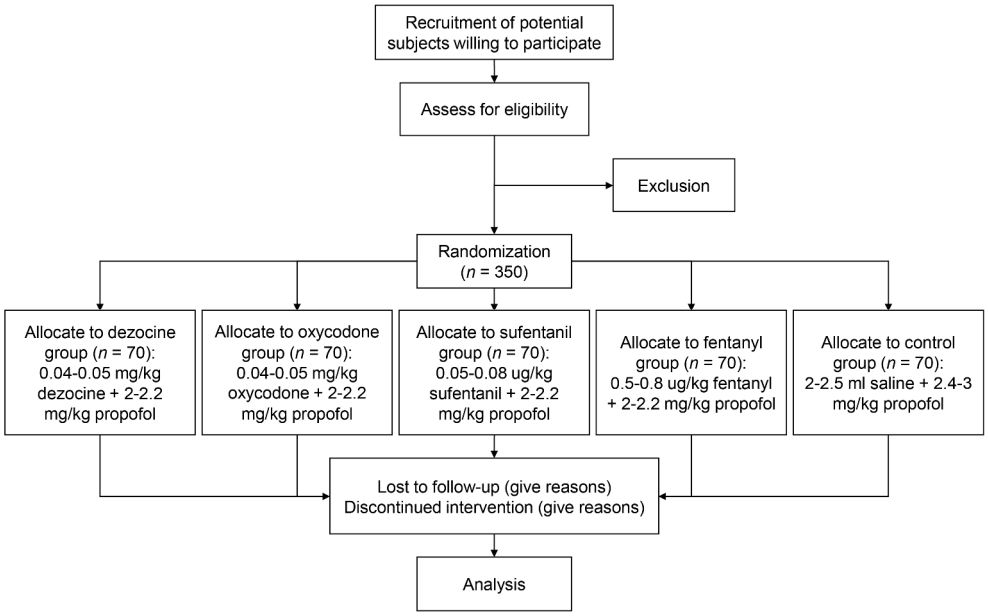
33. Zheng M, Guo Y, Shan S, Yang S. Dezocine for anesthesia and stress reduction in induced abortion. *Patient Prefer Adherence* 2015;**9**:369-72.

34. Bell GD. Preparation, premedication, and surveillance. *Endoscopy* 2004;**36**:23-31.

35. Steward DJ. A simplified scoring system for the post-operative recovery room. *Can Anaesth Soc J* 1975;**22**:111-3.

Figure Legend

Figure 1. Follow chart of the study.



Follow chart of the study.

292x182mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	11
Funding	4	Sources and types of financial, material, and other support	NA
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	12
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.