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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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4 **Effect of propofol combined with opioids on cough reflex suppression in**
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6 **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.

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4 **Ethics and dissemination:** This study has been approved by the Institutional Ethics
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6 Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast
7
8 University (No. 2015ZDSYLL033.0). The results of the trial will be published in an
9
10 international peer-reviewed journal.
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12

13
14 **Trial registration:** This study was registered with the Chinese Clinical Trial Center
15
16 (No. ChiCTR-ICR-15006952).
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21 **Keywords:** sedation, endoscopy, propofol, opioids
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24 25 26 **Strengths and limitations of this study** 27

28 Double-blinded randomized placebo-controlled study design
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30 Aiming to find adequate regimen of sedation and analgesia for gastroscopy
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33 Evaluated a wide range of opioids
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36 Single-center study
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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

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4 respiratory depression and hypoxemia, and the workload of recovery management.

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6 Use of propofol in combination with opioids has been proposed to improve sedation
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8 and analgesia regarding aspects such as recovery time, sedative effect, pain and other
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10 discomfort [18-22].

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14 Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to
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16 both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effect
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18 on airway reflex. However, propofol may still have chance to cause cough [23 24].

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21 Moreover, stimulation of the larynx during propofol anesthesia can cause various
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23 types of reflex responses [25]. Although opioids exert favorable analgesic and
24
25 sedative effects [20 26], and can inhibit pharyngeal reflex and stress response,
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27 intravenous fentanyl and sufentanil-induced coughing is not uncommon [27 28]. The
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29 induced cough, can be reduced by reduced by propofol [29] and interestingly, by
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31 another opioid, dezocine [30]. Dezocine is an opioid analgesic acting on μ -, δ - and
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33 κ -opioid receptors and has been used in propofol sedation [31-33]. Oxycodone is an
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35 opioid alkaloid also known to depress cough reflex. Unlike fentanyl and sufentanil,
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37 dezocine and oxycodone have rarely been studied in combination with propofol for
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39 gastroscopy.
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46 The best methods for analgesia and sedation for gastroscopy are still in debate and
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48 finding adequate regimen of sedation/analgesia is important, which can influence the
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50 quality of the examination, the patient's cooperation and the patient's and physician's
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52 satisfaction with the sedation [5 16 34]. Based on our preliminary observation in
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54 clinical practice, we hypothesize that combination of propofol and low-dose dezocine,
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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 fentanyl 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.

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4 Exclusion criteria:

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6 1. Body mass index (BMI) ≥ 30 kg/m²,
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9 2. Patients with preoperative circulatory, respiratory or nervous system diseases,
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11 3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
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14 4. Patients with sleep apnea syndrome.

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16 ***Randomization and blinding***

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

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35 A total of 350 subjects were planned to be involved. The subjects will be randomly
36
37 divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil
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39 and the control group, 70 cases in each group. The sample size was estimated
40
41 according to the chi-square test of the incidence of the primary categorical outcome,
42
43 incidence of cough within 5 min after endoscope insertion. The above total number of
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45 observations makes it possible to detect small to moderate effective size
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47 (approximately 0.20) with Type I error 5% and power of test 90%. The test of power
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49 will remain 80% or higher when up to 20% of the subjects dropout from the study.
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56 ***Statistical analysis***

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

13 ***Sedation***

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16 Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken
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18 10 minutes prior to sedation. The right upper extremity venous access will be
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20 established before the patients enter the operation room. After entering the operation
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22 room, the patients will lie in the left-lateral position, with the blood pressure cuff tied
23
24 to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min).
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26 After placement of bite block, blood pressure, heart rate, and SpO₂ will be measured
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28 noninvasively (Philips MP50, Germany) to set up baselines and will be monitored
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30 throughout the operation afterwards. Blood pressure will be measured at an interval of
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32 1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius
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34 Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China),
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36 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical,
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38 China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg dezocine (Yangtze River
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40 Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg oxycodone
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42 (Monti Pharmaceutical, China), or 2.4-3 mg/kg propofol plus 2-2.5 ml saline. All
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44 drugs will be diluted with saline. The doses of dezocine and oxycodone are defined
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46 according to our preliminary study. The 2 ml of normal saline is for subjects weighing
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48 ≤ 70 kg, and the 2.5 ml of normal saline is for subjects weighing > 70 kg. Fentanyl will
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4 be diluted to 20 ug/ml, sufentanil to 2.5ug/ml, dezocine and oxycodone each to 1
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6 mg/ml. Drugs will be delivered by the Aespire 7900 anesthesia delivery system (GE
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8 Healthcare, USA).

11 *Adverse events*

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13 All adverse events will be recorded and closely monitored. Medical strategy will be
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15 adjusted if necessary. Unexpected severe adverse events will be reported to the ethics
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17 committee.
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21 *Data collection and management*

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23 Demographic variables and clinical data will be collected from all patients.
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25 Furthermore, outcome related variables as well as variables that may influence the
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27 outcome will be collected. All data will be collected throughout the study and will be
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29 securely managed in confidential conditions. The participants will be referred by the
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31 participant number rather than names, throughout the study unless otherwise specified.
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34 All relevant documents and files will be archived for five years. Data can be only
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36 accessed by the investigators who sign the confidential disclosure agreement and
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38 institutional or governmental auditors during the study. Data without patient
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40 identification will be publicly accessible after the study. The process will be
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42 monitored by the Institutional Ethics Committee (ICE) for Clinical Research of
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44 Zhongda Hospital.
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51 *Endpoints*

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53 The primary endpoint is the incidence and reflex degree of cough, which will be
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55 recorded within 5 min after endoscope insertion and throughout the procedure. The
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4 secondary endpoints include (1) the occurrence of swallowing, body movement, and
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6 other discomfort or side effects and whether jaw thrust, assistant ventilation, and
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8 additional propofol is used, which will be recorded within five minutes after
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10 endoscope insertion and throughout the procedure, and (2) duration of calls for eyes
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12 open, the duration of procedure and Steward score [35] after eyes open. Blood
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14 pressure, heart rate and SpO₂ will be monitored throughout the process
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18 ***Protocol amendments***

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20 Any changes of the protocol during the trial that may affect the conduct of the trial,
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22 the safety and the benefit of the patients will require a formal amendment to the
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24 protocol.
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31 **Discussion**

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33 It is important to improve analgesia and sedation for gastroscopy. Opioids, which
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35 exert favorable analgesic, sedative effect and inhibit the stress response, are an
36
37 important part of surgical anesthesia. The combination of opioids and propofol is the
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39 most commonly used regimen for general anesthesia. Currently, a small dose of
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41 fentanyl combined with propofol in sedation for gastroscopy have been used in
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43 clinical practice. However, fentanyl has the potential risks of respiratory depression,
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45 choking and the stiffness of chest wall muscles. Clinical study on other opioids for
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47 gastroscopy, such as oxycodone, dezocine and sufentanil, is inadequate. Finding an
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49 adequate regimen is essential. Herein, we conduct this trial to evaluate the
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51 combination of small doses of dezocine, oxycodone or sufentanil for gastroscopy.
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4 This study observes the incidence and reflex degree of cough under sedation. This
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6 trial compares propofol combined the above drugs to propofol alone and to propofol
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8 with fentanil, allowing a broad screen for feasible regimen. There are limitations of
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10 this study. This is a single-center, which may limit the generalization of this study.
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12 Future multiple-center large-sample size study will be needed. The result of this
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14 clinical trial can confirm the favorable effects of combination of propofol with
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16 small-dose opioids, and can contribute to finding satisfying regimens for sedation for
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18 gastroscopy.
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26 **Trial status**

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28 At the time of manuscript submission, the study is in the recruitment phase.
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34 **Ethics and dissemination**

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36 This study has been approved by the Institutional Ethics Committee (ICE) for Clinical
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38 Research of Zhongda Hospital, Affiliated to Southeast University (No.
39
40 2015ZDSYLL033.0) and is registered with the Chinese Clinical Trial Center
41
42 (ChiCTR-ICR-15006952). Only patients who give written informed consent will be
43
44 recruited. The results of the trial will be published in an international peer-reviewed
45
46 journal.
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54 **Authors' contributions**

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56 NY conceived of the study. NY and JX participated in its design and coordination. NY,
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3 JX, XL, JY and JX collected references and figured out the protocol. XL, JY and JX
4
5 performed statistics analysis. NY and JX drafted the manuscript. All authors read and
6
7 approved the final manuscript.
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21 22 23 **Competing interests**

24
25 The authors declare that they have no competing interests. The committee mentioned
26
27 is independent from the sponsor and competing interests
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3 **Figure Legend**
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5 Figure 1. Follow chart of the study.
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For peer review only

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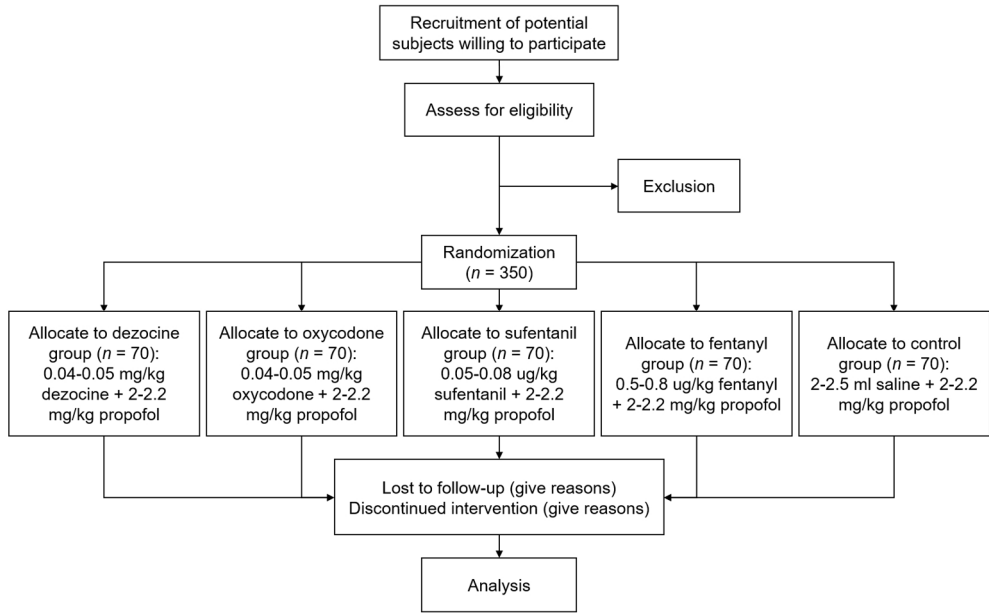


Figure 1. Follow chart of the study.

292x182mm (150 x 150 DPI)

Review only



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 ___

1	Introduction			
2				
3	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 ____
4		6b	Explanation for choice of comparators	____ 5 ____
5	Objectives	7	Specific objectives or hypotheses	____ 5-6 ____
6		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 ____
7				
8	Methods: Participants, interventions, and outcomes			
9	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 ____
10		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 ____
11	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____ 8 ____
12		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 ____
13		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____ 8 ____
14		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____ NA ____
15	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 ____
16		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 ____
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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____7_____
 2 clinical and statistical assumptions supporting any sample size calculations

3
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____6_____
 5
 6

7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

9
 10
 11 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____7_____
 12 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 13 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 14 or assign interventions
 15

16
 17 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____7_____
 18 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 19 mechanism
 20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____7_____
 22 interventions
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____7_____
 25 assessors, data analysts), and how
 26

27
 28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____NA_____
 29 allocated intervention during the trial
 30

31 **Methods: Data collection, management, and analysis**

32
 33
 34 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____9_____
 35 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 37 Reference to where data collection forms can be found, if not in the protocol
 38

39
 40 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____9_____
 41 collected for participants who discontinue or deviate from intervention protocols
 42
 43
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1	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_____
2				
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5	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_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA_____
9				
10		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_____
11				
12				
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15	Methods: Monitoring			
16				
17	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_____
18				
19				
20				
21				
22		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_____
23				
24				
25				
26	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_____
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____9_____
30				
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33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____11_____
36				
37				
38	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_____
39				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 11 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
5				
6				
7	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 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 11 _____
11				
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13				
14	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 _____
15				
16				
17	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 _____
18				
19				
20	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 _____
21				
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24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ 9 _____
28				
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ NA _____
33				
34				
35	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 _____
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*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

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

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Manuscript ID	bmjopen-2016-014881.R1
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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Gastroenterology and hepatology
Keywords:	sedation, propofol, opioids, Endoscopy < GASTROENTEROLOGY, cough

SCHOLARONE™
Manuscripts

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4 **Effect of propofol combined with opioids on cough reflex suppression in**
5
6 **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 gagging 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 gagging. 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.

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4 **Ethics and dissemination:** This study has been approved by the Institutional Ethics
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6 Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast
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8 University (No. 2015ZDSYLL033.0). The results of the trial will be published in an
9
10 international peer-reviewed journal.
11

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14 **Trial registration:** This study was registered with the Chinese Clinical Trial Center
15
16 (No. ChiCTR-ICR-15006952).
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21 **Keywords:** sedation, endoscopy, propofol, opioids, cough
22

23 24 25 26 **Strengths and limitations of this study** 27

28 Double-blinded randomized placebo-controlled study design

29 Aiming to find adequate regimen of sedation and analgesia for gastroscopy

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32 Evaluated the antitussive effects of a wide range of opioids
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36 Single-center study
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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

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4 respiratory depression and hypoxemia, and the workload of recovery management.

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6 Use of propofol in combination with opioids has been proposed to improve sedation
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8 and analgesia regarding aspects such as recovery time, sedative effect, pain and other
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10 discomfort [18-22].

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14 Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to
15
16 both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effect
17
18 on airway reflex. However, propofol may still have chance to cause cough [23 24].

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21 Moreover, stimulation of the larynx during propofol anesthesia can cause various
22
23 types of reflex responses [25]. Although opioids exert favorable analgesic and
24
25 sedative effects [20 26], and can inhibit pharyngeal reflex and stress response,
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27 intravenous fentanyl and sufentanil-induced coughing is not uncommon [27 28]. The
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29 induced cough, can be reduced by reduced by propofol [29] and interestingly, by
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31 another opioid, dezocine [30]. Dezocine is an opioid analgesic acting on μ -, δ - and
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33 κ -opioid receptors and has been used in propofol sedation [31-33]. Oxycodone is an
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35 opioid alkaloid acting on μ - and κ -opioid receptors. It shows a good performance on
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37 relieving visceral pain with small respiratory depression and is known to depress
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39 cough reflex. Unlike fentanyl and sufentanil, dezocine and oxycodone have rarely
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41 been studied in combination with propofol for gastroscopy.
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49 The best methods for analgesia and sedation for gastroscopy are still in debate and
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51 finding adequate regimen of sedation/analgesia is important, which can influence the
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53 quality of the examination, the patient's cooperation and the patient's and physician's
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55 satisfaction with the sedation [5 16 34]. Based on our preliminary observation in
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4 clinical practice, we hypothesize that combination of propofol and low-dose dezocine,
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6 oxycodone or sufentanil for gastroscopy may decrease the incidence of cough and that
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8 specifically, combination of propofol and oxycodone may have a better performance
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10 than others.

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13 In order to verify our hypothesis, we designed this clinical study, aiming to investigate
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15 the effect of combination of propofol and opioids on cough reflex suppression in
16
17 gastroscopy.
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23 **Methods and analysis**

24 ***Study objective***

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26
27 The primary objective of this study is to investigate the incidence and reflex degree of
28
29 cough and giggling under sedation with combination of propofol and fentanyl
30
31 sufentanil, dezocine, or oxycodone during gastroscopy. The secondary objective is to
32
33 assess effect of the combination regimens on sedative performance.
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38 ***Study location***

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41 A prospective, single-center, randomized, double-blinded, controlled trial will be
42
43 conducted in patients undergoing gastroscopy in the Affiliated Zhongda Hospital of
44
45 Southeast University, China.
46
47

48 ***Study population***

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51 Participants will be recruited voluntarily according to the inclusion and exclusion
52
53 criteria below.
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55

56
57 Inclusion criteria:
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4 Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years, willing to
5
6 participate after reading and sign an informed consent.
7

8
9 Exclusion criteria:

- 10
11 1. Body mass index (BMI) ≥ 30 kg/m²,
- 12
13 2. Patients with preoperative circulatory, respiratory or nervous system diseases,
- 14
15 3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
- 16
17 4. Patients with sleep apnea syndrome.
- 18
19 5. Patients with URI symptom.
- 20
21 6. Patients with dry cough history.
- 22
23 7. Patients with drug allergy.
- 24
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26
27

28 29 ***Randomization and blinding***

30
31 Stratified randomization will be used to assign the candidate subjects to five groups
32
33 according to sex and BMI (two groups or three groups). Computer-generated random
34
35 group numbers will be printed and placed into different sealed envelope in turn. When
36
37 receiving a subject who met the inclusion criteria, the anesthesiologist determined the
38
39 grouping of the newly recruited subject according to different group numbers in the
40
41 envelopes. The regimen will be blind to both anesthesiologists and patients. The drugs
42
43 will be prepared by nurse anesthetists and labeled with numbers. Then the
44
45 anesthesiologist will inject the medication. The nurse anesthetists will be responsible
46
47 for recoding. The anesthesiologist will be notified the study group by the nurse
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49 anesthetists in case of emergency.
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55 56 ***Current sample size justification***

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4 A total of 500 subjects were planned to be involved. The subjects will be randomly
5
6 divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil
7
8 and the control group, 100 cases in each group. The sample size was estimated
9
10 according to the chi-square test of the incidence of the primary categorical outcome,
11
12 incidence of cough (30%) within 5 min after endoscope insertion. The above total
13
14 number of observations makes it possible to detect small to moderate effective size
15
16 (approximately 0.20) with Type I error 5% and power of test 90%. The test of power
17
18 will remain 80% or higher when up to 20% of the subjects dropout from the study.
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22

23 ***Statistical analysis***

24
25 All data will be analyzed using SAS 9.3 or other statistical software packages as
26
27 needed. The statistical methods included descriptive statistics, t-test, χ^2 test, analysis
28
29 of variance, univariate unconditional logistic regression analysis, multivariate linear
30
31 regression analysis. A significance level is set at 5%.
32
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35

36 ***Sedation***

37
38 Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken
39
40 10 minutes prior to sedation. The right upper extremity venous access will be
41
42 established before the patients enter the operation room. After entering the operation
43
44 room, the patients will lie in the left-lateral position, with the blood pressure cuff tied
45
46 to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min).
47
48 After placement of bite block, blood pressure, heart rate, and SpO₂ will be measured
49
50 noninvasively (Philips MP50, Germany) to set up baselines and will be monitored
51
52 throughout the operation afterwards. Blood pressure will be measured at an interval of
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4 1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius
5
6 Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China),
7
8 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical,
9
10 China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg dezocine (Yangtze River
11
12 Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg oxycodone
13
14 (Monti Pharmaceutical, China), or 2.4-3 mg/kg propofol plus 2-2.5 ml saline. All
15
16 drugs except Propofol will be diluted with saline. The doses of dezocine and
17
18 oxycodone are defined according to our preliminary study. The 2 ml of normal saline
19
20 is for subjects weighing ≤ 70 kg, and the 2.5 ml of normal saline is for subjects
21
22 weighing >70 kg. Fentanyl will be diluted to 20 ug/ml, sufentanil to 2.5ug/ml,
23
24 dezocine and oxycodone each to 1 mg/ml. Drugs will be delivered by the Aespire
25
26 7900 anesthesia delivery system (GE Healthcare, USA). We will insert the probe
27
28 when BIS is 40-60. Jaw thrust will be done in case of respiratory depression and
29
30 oxygen desaturation. If jaw thrust is not working, assistant ventilation will be used.
31
32 For severe situation, tracheal intubation assisted respiration will performed. After
33
34 gastroscopy, all the patients will stay PACU. Patients will be followed up until
35
36 discharge of PACU.
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45 46 *Adverse events*

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48 All adverse events, such as nausea, vomiting, dyspnea, hypopnea, apnea, hypotension,
49
50 oxygen desaturation and bradycardia, will be recorded and closely monitored.
51
52 Medical strategy will be adjusted if necessary. Unexpected severe adverse events will
53
54 be reported to the ethics committee.
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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 giggling, 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 giggling, 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

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4 swallowing, body movement, and adverse events and whether jaw thrust, assistant
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6 ventilation, and additional propofol is used, which will be recorded within five
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8 minutes after endoscope insertion and throughout the procedure, and (2) duration of
9
10 calls for eyes open, the duration of procedure and Steward score [35] after eyes open.
11
12 Blood pressure, heart rate and SpO₂ will be monitored throughout the process.
13
14 "Patient satisfaction" is not included as a secondary outcome since patient can not
15
16 recall coughing or gagging.
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20 21 ***Protocol amendments*** 22

23
24 Any changes of the protocol during the trial that may affect the conduct of the trial,
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26 the safety and the benefit of the patients will require a formal amendment to the
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28 protocol.
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32 33 **Discussion** 34

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36 It is important to improve analgesia and sedation for gastroscopy. Opioids, which
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38 exert favorable analgesic, sedative effect and inhibit the stress response, are an
39
40 important part of surgical anesthesia. The combination of opioids and propofol is the
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42 most commonly used regimen for general anesthesia. Currently, a small dose of
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44 fentanyl combined with propofol in sedation for gastroscopy have been used in
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46 clinical practice. However, fentanyl has the potential risks of respiratory depression,
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48 choking and the stiffness of chest wall muscles. Clinical study on other opioids for
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50 gastroscopy, such as oxycodone, dezocine and sufentanil, is inadequate. Finding an
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52 adequate regimen is essential. Herein, we conduct this trial to evaluate the
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4 combination of small doses of dezocine, oxycodone or sufentanil for gastroscopy.
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6 This study observes the incidence and reflex degree of cough under sedation. This
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8 trial compares propofol combined the above drugs to propofol alone and to propofol
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10 with fentanil, allowing a broad screen for feasible regimen. There are limitations of
11
12 this study. This is a single-center, which may limit the generalization of this study.
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14 Future multiple-center large-sample size study will be needed. The result of this
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16 clinical trial can confirm the favorable effects of combination of propofol with
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18 small-dose opioids, and can contribute to finding satisfying regimens for sedation for
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20 gastroscopy.
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29 **Trial status**

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31 At the time of manuscript submission, the study is in the recruitment phase.
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36 **Ethics and dissemination**

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38 This study has been approved by the Institutional Ethics Committee (ICE) for Clinical
39
40 Research of Zhongda Hospital, Affiliated to Southeast University (No.
41
42 2015ZDSYLL033.0) and is registered with the Chinese Clinical Trial Center
43
44 (ChiCTR-ICR-15006952). Only patients who give written informed consent will be
45
46 recruited. The results of the trial will be published in an international peer-reviewed
47
48 journal.
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55 **Authors' contributions**

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4 NY conceived of the study. NY and JX participated in its design and coordination. NY,
5
6 JX, YZC, XL, JY and JX collected references and figured out the protocol. XL, YZC,
7
8 JY and JX performed statistics analysis. NY and JX drafted the manuscript. All
9
10 authors read and approved the final manuscript.
11
12
13

14 15 16 **Funding**

17
18 This research received no specific grant from any funding agency in the public,
19
20 commercial or not-for-profit sectors.
21
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23

24 25 26 **Competing interests**

27
28 The authors declare that they have no competing interests. The committee mentioned
29
30 is independent from the sponsor and competing interests
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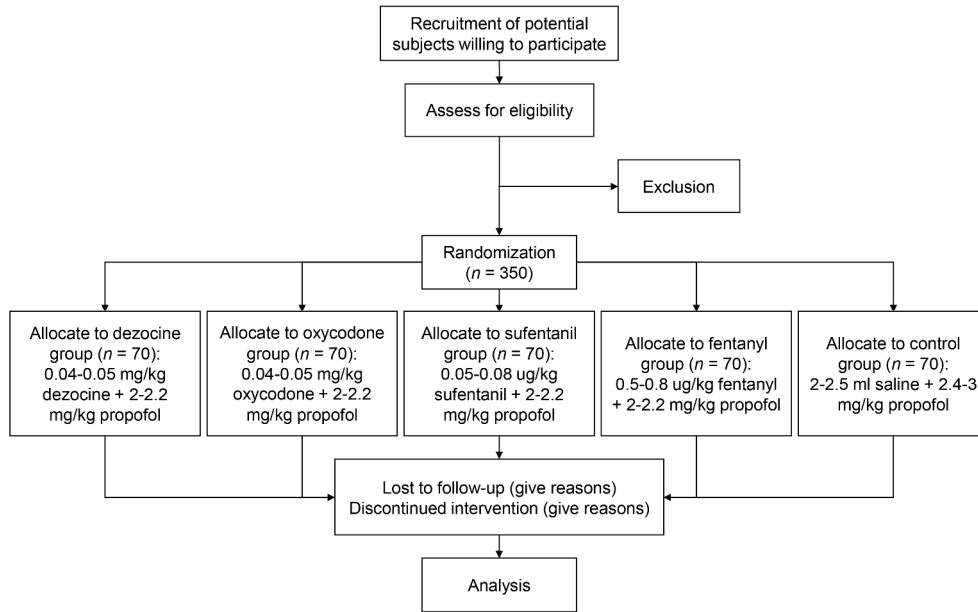
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Figure Legend

Figure 1. Follow chart of the study.

For peer review only



Follow chart of the study.

292x182mm (300 x 300 DPI)

Review only



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 ___

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant _____ 4-5 _____

4 rationale studies (published and unpublished) examining benefits and harms for each intervention

5

6 6b Explanation for choice of comparators _____ 5 _____

7

8 Objectives 7 Specific objectives or hypotheses _____ 5-6 _____

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), _____

11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____ 6 _____

12

13

14

15 **Methods: Participants, interventions, and outcomes**

16

17 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will _____ 6 _____

18 be collected. Reference to where list of study sites can be obtained

19

20 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and _____ 6 _____

21 individuals who will perform the interventions (eg, surgeons, psychotherapists)

22

23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be _____ 8 _____

24 administered

25

26 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose _____ 9 _____

27 change in response to harms, participant request, or improving/worsening disease)

28

29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence _____ 8 _____

30 (eg, drug tablet return, laboratory tests)

31

32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ NA _____

33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood _____ 9 _____

35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, _____

36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen _____

37 efficacy and harm outcomes is strongly recommended

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40

41 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for _____ Figure 1

42 participants. A schematic diagram is highly recommended (see Figure)

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____7_____
 2 clinical and statistical assumptions supporting any sample size calculations

3
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____6_____
 5
 6

7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

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 10
 11 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____7_____
 12 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 13 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 14 or assign interventions

15
 16
 17 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____7_____
 18 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 19 mechanism

20
 21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____7_____
 22 interventions

23
 24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____7_____
 25 assessors, data analysts), and how

26
 27
 28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____NA_____
 29 allocated intervention during the trial

30 31 32 **Methods: Data collection, management, and analysis**

33
 34 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____9_____
 35 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 37 Reference to where data collection forms can be found, if not in the protocol

38
 39
 40 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____9_____
 41 collected for participants who discontinue or deviate from intervention protocols

1	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_____
2				
3				
4				
5	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_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA_____
9				
10		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_____
11				
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14				
15	Methods: Monitoring			
16				
17	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_____
18				
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22		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_____
23				
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25				
26	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_____
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____9_____
30				
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33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____11_____
36				
37				
38	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_____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 11 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
5				
6				
7	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 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 11 _____
11				
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14	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 _____
15				
16				
17	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 _____
18				
19				
20	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 _____
21				
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ 9 _____
28				
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30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ NA _____
33				
34				
35	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 _____
36				
37				

38
39 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
40 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014881.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Jun-2017
Complete List of Authors:	Yin, Ning; Sir Run Run Hospital, Najing Medical University, Department of Anesthesiology Xia, Jiangyan ; Zhongda Hospital, School of Medicine, Southeast University, Department of Anesthesiology Cao, Yi-Zhi; Nanjing Medical University, School of Basic Medical Sciences Lu, Xinjian ; Zhongda Hospital, School of Medicine, Southeast University, Department of Anesthesiology Yuan, Jing ; Zhongda Hospital, School of Medicine, Southeast University, Department of Anesthesiology Xie , Jue ; Zhongda Hospital, School of Medicine, Southeast University, Department of Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Gastroenterology and hepatology
Keywords:	sedation, propofol, opioids, Endoscopy < GASTROENTEROLOGY, cough

SCHOLARONE™
Manuscripts

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4 **Effect of propofol combined with opioids on cough reflex suppression in**
5
6 **gastroscopy: study protocol for a double-blind randomized controlled trial**
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11 Ning Yin¹, Jiangyan Xia², Yi-Zhi Cao³, Xinjian Lu², Jing Yuan², Jue Xie²
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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 gagging 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 gagging. 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.

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4 **Ethics and dissemination:** This study has been approved by the Institutional Ethics
5
6 Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast
7
8 University (No. 2015ZDSYLL033.0). The results of the trial will be published in an
9
10 international peer-reviewed journal.
11

12
13
14 **Trial registration:** This study was registered with the Chinese Clinical Trial Center
15
16 (No. ChiCTR-ICR-15006952).
17

18
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20
21 **Keywords:** sedation, endoscopy, propofol, opioids, cough
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23 24 25 26 **Strengths and limitations of this study** 27

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

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

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

31 The dose of propofol for this study is still high.

32 This is a single-center study.
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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

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4 respiratory depression and hypoxemia, and the workload of recovery management.

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6 Use of propofol in combination with opioids has been proposed to improve sedation
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8 and analgesia regarding aspects such as recovery time, sedative effect, pain and other
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10 discomfort [18-22].

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14 Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to
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16 both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory effect
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18 on airway reflex. However, propofol may still have chance to cause cough [23 24].

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21 Moreover, stimulation of the larynx during propofol anesthesia can cause various
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23 types of reflex responses [25]. Although opioids exert favorable analgesic and
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25 sedative effects [20 26], and can inhibit pharyngeal reflex and stress response,
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27 intravenous fentanyl and sufentanil-induced coughing is not uncommon [27 28]. The
28
29 induced cough, can be reduced by propofol [29] and interestingly, by another opioid,
30
31 dezocine [30]. Dezocine is an opioid analgesic acting on μ -, δ - and κ -opioid receptors
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33 and has been used in propofol sedation [31-33]. Oxycodone is an opioid alkaloid
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35 acting on μ - and κ -opioid receptors. It shows a good performance on relieving visceral
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37 pain with small respiratory depression and is known to depress cough reflex. Unlike
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39 fentanyl and sufentanil, dezocine and oxycodone have rarely been studied in
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41 combination with propofol for gastroscopy.
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49 The best methods for analgesia and sedation for gastroscopy are still in debate and
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51 finding adequate regimen of sedation/analgesia is important, which can influence the
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53 quality of the examination, the patient's cooperation and the patient's and physician's
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55 satisfaction with the sedation [5 16 34]. Based on our preliminary observation in
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4 clinical practice, we hypothesize that combination of propofol and low-dose dezocine,
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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 giggling under sedation with combination of propofol and fentanyl, 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:

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4 Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years, willing to
5
6 participate after reading and sign an informed consent.
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9 Exclusion criteria:

- 10
11 1. Body mass index (BMI) ≥ 30 kg/m²,
- 12
13 2. Patients with preoperative circulatory, respiratory or nervous system diseases,
- 14
15 3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
- 16
17 4. Patients with sleep apnea syndrome.
- 18
19 5. Patients with URI (upper respiratory tract infection) symptom.
- 20
21 6. Patients with dry cough history.
- 22
23 7. Patients with drug allergy.
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28 29 ***Randomization and blinding***

30
31 Stratified randomization will be used to assign the candidate subjects to five groups
32
33 according to sex and BMI (two groups or three groups). Computer-generated random
34
35 group numbers will be printed and placed into different sealed envelope in turn. When
36
37 receiving a subject who met the inclusion criteria, the anesthesiologist determined the
38
39 grouping of the newly recruited subject according to different group numbers in the
40
41 envelopes. The regimen will be blind to both anesthesiologists and patients. The drugs
42
43 will be prepared by nurse anesthetists and labeled with numbers. Then the
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45 anesthesiologist will inject the medication. The nurse anesthetists will be responsible
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47 for recoding. The anesthesiologist will be notified the study group by the nurse
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49 anesthetists in case of emergency.
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55 56 ***Current sample size justification***

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4 A total of 500 subjects were planned to be involved. The subjects will be randomly
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6 divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil
7
8 and the control group, 100 cases in each group. The sample size was estimated
9
10 according to the chi-square test of the incidence of the primary categorical outcome,
11
12 incidence of cough (30%) within 5 min after endoscope insertion. The above total
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14 number of observations makes it possible to detect small to moderate effective size
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16 (approximately 0.20) with Type I error 5% and power of test 90%. The test of power
17
18 will remain 80% or higher when up to 20% of the subjects dropout from the study.
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23 ***Statistical analysis***

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25 All data will be analyzed using SAS 9.3 or other statistical software packages as
26
27 needed. The statistical methods included descriptive statistics, t-test, χ^2 test, analysis
28
29 of variance, univariate unconditional logistic regression analysis, multivariate linear
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31 regression analysis. A significance level is set at 5%.
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36 ***Sedation***

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38 Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken
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40 10 minutes prior to sedation. The right upper extremity venous access will be
41
42 established before the patients enter the operation room. After entering the operation
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44 room, the patients will lie in the left-lateral position, with the blood pressure cuff tied
45
46 to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min).
47
48 After placement of bite block, blood pressure, heart rate, and SpO₂ will be measured
49
50 noninvasively (Philips MP50, Germany) to set up baselines and will be monitored
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52 throughout the operation afterwards. Blood pressure will be measured at an interval of
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4 1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius
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6 Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China),
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8 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical,
9
10 China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg dezocine (Yangtze River
11
12 Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg oxycodone
13
14 (Monti Pharmaceutical, China), or 2.4-3 mg/kg propofol plus 2-2.5 ml saline. All
15
16 drugs except Propofol will be diluted with saline. The doses of dezocine and
17
18 oxycodone are defined according to our preliminary study. The 2 ml of normal saline
19
20 is for subjects weighing ≤ 70 kg, and the 2.5 ml of normal saline is for subjects
21
22 weighing >70 kg. Fentanyl will be diluted to 20 ug/ml, sufentanil to 2.5ug/ml,
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24 dezocine and oxycodone each to 1 mg/ml. Drugs will be delivered by the Aespire
25
26 7900 anesthesia delivery system (GE Healthcare, USA). We will insert the probe
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28 when BIS (bispectral index) is 40-60. A BIS of 40-60 is usually considered as
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30 sufficient depth of general anesthesia. Jaw thrust will be done in case of respiratory
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32 depression and oxygen desaturation. If jaw thrust is not working, assistant ventilation
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34 will be used. For severe situation, tracheal intubation assisted respiration will
35
36 performed. After gastroscopy, all the patients will stay PACU (post-anesthesia care
37
38 unit). Patients will be followed up until discharge of PACU.

49 *Adverse events*

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51 All adverse events, such as nausea, vomiting, dyspnea, hypopnea, apnea, hypotension,
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53 oxygen desaturation and bradycardia, will be recorded and closely monitored.
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55 Medical strategy will be adjusted if necessary. Unexpected severe adverse events will
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3
4 be reported to the ethics committee.

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6 ***Data collection and management***
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9 Demographic variables and clinical data will be collected from all patients.
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11 Furthermore, during operation, blood pressure, heart rate, oxygen saturation, blood
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13 pressure will be monitored. The occurrence of swallowing, cough and giggling, body
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15 movement, adverse events, whether jaw thrust, assistant ventilation, and additional
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17 propofol is used and the duration of endoscopy will be recorded. Then, duration of
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19 calls for eyes open and the Steward score after eyes open will be recorded. All data
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21 will be collected throughout the study and will be securely managed in confidential
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23 conditions. Data will be recorded automatically by the vital signs monitor and
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25 anesthesia information system, and manually by a nurse anesthetist. The participants
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27 will be referred by the participant number rather than names, throughout the study
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29 unless otherwise specified. All relevant documents and files will be archived for five
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31 years. Data can be only accessed by the investigators who sign the confidential
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33 disclosure agreement and institutional or governmental auditors during the study. Data
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35 without patient identification will be publicly accessible after the study. The process
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37 will be monitored by the Institutional Ethics Committee (ICE) for Clinical Research
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39 of Zhongda Hospital.
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49 ***Endpoints***
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52 The primary endpoint is the incidence and reflex degree of cough and giggling, which
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54 will be recorded within 5 min after endoscope insertion and throughout the procedure.
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56 The severity of cough is defined according to cough intensity and whether leading to
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4 failure of endoscope insertion. The secondary endpoints include (1) the occurrence of
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6 swallowing, body movement, and adverse events and whether jaw thrust, assistant
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8 ventilation, and additional propofol is used, which will be recorded within five
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10 minutes after endoscope insertion and throughout the procedure, and (2) duration of
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12 calls for eyes open, the duration of procedure and Steward score [35] after eyes open.
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14 Blood pressure, heart rate and SpO₂ will be monitored throughout the process.
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16 "Patient satisfaction" is not included as a secondary outcome since patient can not
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18 recall coughing or gagging.
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23 ***Protocol amendments***

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

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38 It is important to improve analgesia and sedation for gastroscopy. Opioids, which
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40 exert favorable analgesic, sedative effect and inhibit the stress response, are an
41
42 important part of surgical anesthesia. The combination of opioids and propofol is the
43
44 most commonly used regimen for general anesthesia. Currently, a small dose of
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46 fentanyl combined with propofol in sedation for gastroscopy have been used in
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48 clinical practice. However, fentanyl has the potential risks of respiratory depression,
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50 choking and the stiffness of chest wall muscles. Clinical study on other opioids for
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52 gastroscopy, such as oxycodone, dezocine and sufentanil, is inadequate. Finding an
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4 adequate regimen is essential. Herein, we conduct this trial to evaluate the
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6 combination of small doses of dezocine, oxycodone or sufentanil for gastroscopy.
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8 This study observes the incidence and reflex degree of cough under sedation. This
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10 trial compares propofol combined the above drugs to propofol alone and to propofol
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12 with fentanil, allowing a broad screen for feasible regimen. There are limitations of
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14 this study. This is a single-center, which may limit the generalization of this study.
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16 Future multiple-center large-sample size study will be needed. The result of this
17
18 clinical trial can confirm the favorable effects of combination of propofol with
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20 small-dose opioids, and can contribute to finding satisfying regimens for sedation for
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22 gastroscopy.
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31 **Trial status**

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34 At the time of manuscript submission, the study is in the recruitment phase.
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39 **Ethics and dissemination**

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41 This study has been approved by the Institutional Ethics Committee (ICE) for Clinical
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43 Research of Zhongda Hospital, Affiliated to Southeast University (No.
44
45 2015ZDSYLL033.0) and is registered with the Chinese Clinical Trial Center
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47 (ChiCTR-ICR-15006952). Only patients who give written informed consent will be
48
49 recruited. A model informed consent has been provided. The results of the trial will be
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51 published in an international peer-reviewed journal.
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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

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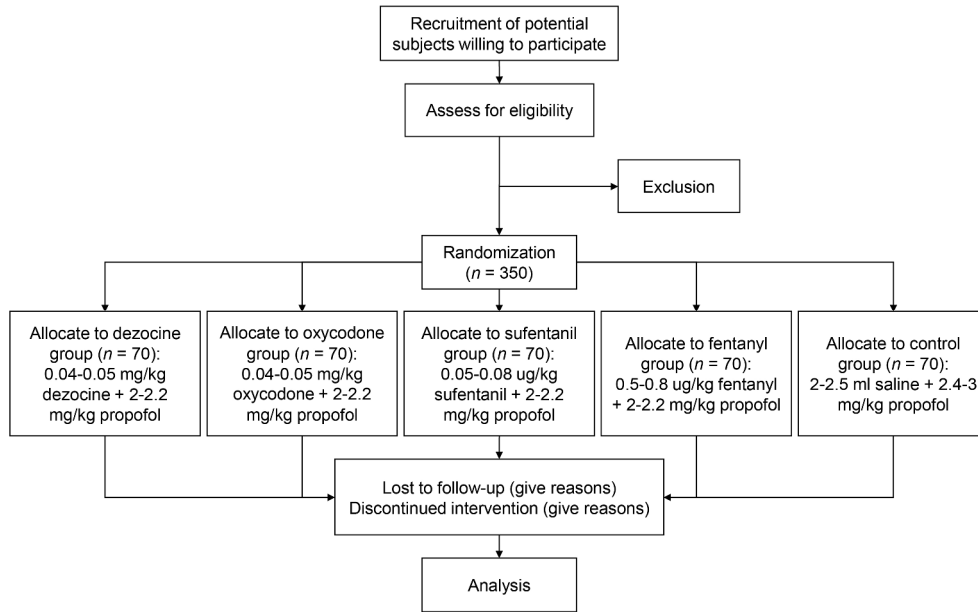
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Figure Legend

Figure 1. Follow chart of the study.

For peer review only



Follow chart of the study.

292x182mm (300 x 300 DPI)

Review only



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 ___

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 4-5
4 rationale studies (published and unpublished) examining benefits and harms for each intervention

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6 6b Explanation for choice of comparators 5

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8 Objectives 7 Specific objectives or hypotheses 5-6

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),
11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 6
12
13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will
17 be collected. Reference to where list of study sites can be obtained 6
18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and
20 individuals who will perform the interventions (eg, surgeons, psychotherapists) 6-7
21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be
23 administered 8-9
24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose
26 change in response to harms, participant request, or improving/worsening disease) 9
27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence
29 (eg, drug tablet return, laboratory tests) 8
30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial NA
32

33 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
34 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
35 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
36 efficacy and harm outcomes is strongly recommended 10-11
37

38 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for
39 participants. A schematic diagram is highly recommended (see Figure) Figure 1
40
41
42
43
44

1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____7_____
 2 clinical and statistical assumptions supporting any sample size calculations

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____6_____
 5

7 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

11 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____7_____
 12 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 13 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 14 or assign interventions

17 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____7_____
 18 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 19 mechanism

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____7_____
 22 interventions

25 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____7_____
 26 assessors, data analysts), and how

28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____7_____
 29 allocated intervention during the trial

32 **Methods: Data collection, management, and analysis**

34 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____10_____
 35 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 37 Reference to where data collection forms can be found, if not in the protocol

40 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____10_____
 41 collected for participants who discontinue or deviate from intervention protocols

1	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_____
2				
3				
4				
5	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_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA_____
9				
10		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_____
11				
12				
13				
14				
15	Methods: Monitoring			
16				
17	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_____
18				
19				
20				
21				
22		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_____
23				
24				
25				
26	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_____
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____9_____
30				
31				
32				
33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____12_____
36				
37				
38	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_____
39				
40				
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47				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 12 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
5				
6				
7	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 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 12 _____
11				
12				
13				
14	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 _____
15				
16				
17	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 _____
18				
19				
20	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 _____
21				
22				
23				
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ 10 _____
28				
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ 12 _____
33				
34				
35	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 _____
36				
37				

38
39 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
40 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
41 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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BMJ Open

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

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Manuscripts

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4 **Effect of propofol combined with opioids on cough reflex suppression in**
5
6 **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 giggling 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 giggling. 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.

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4 **Ethics and dissemination:** This study has been approved by the Institutional Ethics
5
6 Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast
7
8 University (No. 2015ZDSYLL033.0). The results of the trial will be published in an
9
10 international peer-reviewed journal.
11

12
13
14 **Trial registration:** This study was registered with the Chinese Clinical Trial Center
15
16 (No. ChiCTR-ICR-15006952).
17

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19
20
21 **Keywords:** sedation, endoscopy, propofol, opioids, cough
22

23 24 25 26 **Strengths and limitations of this study** 27

- 28
29 ▪ This study is the first randomized controlled trial investigating the effect of
30
31 dezocine and oxycodone on cough reflex suppression when combining propofol
32
33 during gastroscopy.
34
- 35
36 ▪ This study focuses on the antitussive effects of a wide range of opioids, which
37
38 few previous studies have addressed.
39
- 40
41 ▪ Mythological strengths include appropriate sample size, stratified randomization
42
43 and double-blind placebo-controlled design.
44
- 45
46 ▪ This is a single-center, which could be a limitation of this study.
47
- 48
49 ▪ The dose of propofol for this study could be a limitation, which is relatively high
50
51 and may have a risk to abolish the effects of the opioids examined in this study.
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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

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3
4 respiratory depression and hypoxemia, and the workload of recovery management.

5
6 The use of propofol in combination with opioids has been proposed to improve
7
8 sedation and analgesia regarding the aspects such as recovery time, sedative effect,
9
10 pain and other discomfort [18-22].

11
12
13 Cough is a defensive airway reflex. The epithelium cough receptors are sensitive to
14
15 both mechanical and chemical stimuli. Sedatives and analgesics have inhibitory
16
17 effects on airway reflex. However, propofol may still have the chance to cause cough
18
19 [23 24]. Moreover, stimulation of the larynx during propofol anesthesia can cause
20
21 various types of reflex responses [25]. Although opioids exert favorable analgesic and
22
23 sedative effects [20 26], and can inhibit the pharyngeal reflex and stress response,
24
25 intravenous fentanyl- and sufentanil-induced coughing is not uncommon [27 28]. The
26
27 induced cough, can be reduced by propofol [29] and interestingly, by another opioid,
28
29 dezocine [30]. Dezocine is an opioid analgesic acting on μ -, δ - and κ -opioid receptors
30
31 and has been used in propofol sedation [31-33]. Oxycodone is an opioid alkaloid
32
33 acting on μ - and κ -opioid receptors. It shows a good performance on relieving visceral
34
35 pain with small respiratory depression and is known to depress cough reflex. Unlike
36
37 fentanyl or sufentanil, dezocine and oxycodone have rarely been studied in
38
39 combination with propofol for gastroscopy.

40
41
42 The best methods for analgesia and sedation for gastroscopy are still in debate and
43
44 finding an adequate regimen of sedation/analgesia is important, which can influence
45
46 the quality of the examination, the patient's cooperation, and the patient's and
47
48 physician's satisfaction with the sedation [5 16 34]. Based on our preliminary
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4 observation in clinical practice, we hypothesize that combination of propofol and
5
6 low-dose dezocine, oxycodone or sufentanil for gastroscopy may decrease the
7
8 incidence of cough and that specifically, combination of propofol and oxycodone may
9
10 have a better performance than others.
11

12
13 In order to verify our hypothesis, we designed this clinical study, aiming to investigate
14
15 the effect of combination of propofol and opioids on cough reflex suppression in
16
17 gastroscopy.
18
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22

23 **Methods and analysis**

24 ***Study objective***

25
26 The primary objective of this study is to investigate the incidence and reflex degree of
27
28 cough and giggling under sedation with combination of propofol and fentanil
29
30 sufentanil, dezocine, or oxycodone during gastroscopy. The secondary objective is to
31
32 assess the effect of the combination regimens on sedative performance.
33
34
35
36
37

38 ***Study location***

39
40 A prospective, single-center, randomized, double-blinded, controlled trial will be
41
42 conducted in patients undergoing gastroscopy in the Affiliated Zhongda Hospital of
43
44 Southeast University, China.
45
46
47

48 ***Study population***

49
50 Participants will be recruited voluntarily according to the inclusion and exclusion
51
52 criteria below.
53
54

55
56 Inclusion criteria:
57
58
59
60

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3
4 Patients scheduled for gastroscopy, ASA I-II level, aged 18-65 years, and willing to
5
6 participate after reading and signing an informed consent.
7

8
9 Exclusion criteria:

- 10
11 1. Body mass index (BMI) ≥ 30 kg/m²,
- 12
13 2. Patients with preoperative circulatory, respiratory or nervous system diseases,
- 14
15 3. Preoperative hemoglobin level less than 70 g/L or albumin level less than 30 g/L
- 16
17 4. Patients with sleep apnea syndrome.
- 18
19 5. Patients with URI (upper respiratory tract infection) symptom.
- 20
21 6. Patients with dry cough history.
- 22
23 7. Patients with drug allergy.
- 24
25
26
27

28 29 ***Randomization and blinding***

30
31 Stratified randomization will be used to assign the candidate subjects to five groups
32
33 according to sex and BMI (two groups or three groups). Computer-generated random
34
35 group numbers will be printed and placed into different sealed envelopes in turn.
36
37
38 When receiving a subject who meets the inclusion criteria, the anesthesiologist
39
40 determined the grouping of the newly recruited subject according to the different
41
42 group numbers in the envelopes. The regimen will be blind to both anesthesiologists
43
44 and patients. The drugs will be prepared by nurse anesthetists and labeled with
45
46 numbers. Then the anesthesiologist will inject the medication. The nurse anesthetists
47
48 will be responsible for recoding. The anesthesiologist will be notified the study group
49
50 by the nurse anesthetists in case of emergency.
51
52
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55 56 ***Current sample size justification***

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4 A total of 500 subjects are planned to be involved. The subjects will be randomly
5
6 divided into 5 groups: dezocine group, fentanyl group, oxycodone group, sufentanil
7
8 and control group, with 100 cases in each group. The sample size was estimated
9
10 according to the chi-square test of the incidence of the primary categorical outcome,
11
12 incidence of cough (30%) within 5 min after endoscope insertion. The above total
13
14 number of observations made it possible to detect small to moderate effective size
15
16 (approximately 0.20) with the Type I error 5% and power of test 90%. The test of
17
18 power will remain 80% or higher when up to 20% of the subjects dropout from the
19
20 study.
21
22
23
24

25 26 *Statistical analysis*

27
28 All data will be analyzed using SAS 9.3 or other statistical software packages as
29
30 needed. The statistical methods will include descriptive statistics, t-test, χ^2 test,
31
32 analysis of variance, univariate unconditional logistic regression analysis, multivariate
33
34 linear regression analysis. A significance level is set at 5%.
35
36
37
38

39 40 *Sedation*

41
42 Patients will fast for twelve hours before gastroscopy. Dyclonine will be orally taken
43
44 10 minutes prior to sedation. The right upper extremity venous access will be
45
46 established before the patients enter the operation room. After entering the operation
47
48 room, the patients will lie in the left-lateral position, with the blood pressure cuff tied
49
50 to the left upper arm, and receive oxygen inhalation via nasal cannula (3-5 L/min).
51
52 After the placement of bite block, blood pressure, heart rate, and SpO₂ will be
53
54 measured noninvasively (Philips MP50, Germany) to set up baselines and will be
55
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3
4 monitored throughout the operation. Blood pressure will be measured at an interval of
5
6 1 minute. Then patients will intravenously receive 2-2.2 mg/kg propofol (Fresenius
7
8 Kabi AB, Germany) plus 0.5-0.8 ug/kg fentanyl (Humanwell Pharmaceutical, China),
9
10 2-2.2 mg/kg propofol plus 0.05-0.08 ug/kg sufentanil (Humanwell Pharmaceutical,
11
12 China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg dezocine (Yangtze River
13
14 Pharmaceutical, China), 2-2.2 mg/kg propofol plus 0.04-0.05 mg/kg oxycodone
15
16 (Monti Pharmaceutical, China), or 2.4-3 mg/kg propofol plus 2-2.5 ml saline. All
17
18 drugs except Propofol will be diluted with saline. The doses of dezocine and
19
20 oxycodone are defined according to our preliminary study. The 2 ml of normal saline
21
22 is for subjects weighing ≤ 70 kg, and the 2.5 ml of normal saline is for subjects
23
24 weighing >70 kg. Fentanyl will be diluted to 20 ug/ml, sufentanil to 2.5ug/ml,
25
26 dezocine and oxycodone each to 1 mg/ml. Drugs will be delivered by the Aespire
27
28 7900 anesthesia delivery system (GE Healthcare, USA). We will insert the probe
29
30 when the BIS (bispectral index) is 40-60. A BIS of 40-60 is usually considered as
31
32 sufficient depth of general anesthesia. Jaw thrust will be done in case of respiratory
33
34 depression and oxygen desaturation. If jaw thrust is not working, assistant ventilation
35
36 will be used. For severe situation, tracheal intubation assisted respiration will
37
38 performed. After gastroscopy, all the patients will stay PACU (post-anesthesia care
39
40 unit). Patients will be followed up until discharge of PACU.

51 *Adverse events*

52
53 All adverse events, such as nausea, vomiting, dyspnea, hypopnea, apnea, hypotension,
54
55 oxygen desaturation and bradycardia, will be recorded and closely monitored.
56
57
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4 Medical strategy will be adjusted if necessary. Unexpected severe adverse events will
5
6 be reported to the ethics committee.
7

8 ***Data collection and management***

9
10 Demographic variables and clinical data will be collected from all patients.
11
12 Furthermore, during operation, blood pressure, heart rate, oxygen saturation, blood
13
14 pressure will be monitored. The occurrence of swallowing, cough and giggling, body
15
16 movement, adverse events, whether jaw thrust, assistant ventilation, and additional
17
18 propofol is used and the duration of endoscopy will be recorded. Then, duration of
19
20 calls for eyes open and the Steward score after eyes open will be recorded. All data
21
22 will be collected throughout the study and will be securely managed in confidential
23
24 conditions. Automatic data collection will be performed by the vital signs monitor and
25
26 anesthesia information system. Manual data collection will be performed by a nurse
27
28 anesthetist. The participants will be referred by the participant number rather than
29
30 names throughout the study unless otherwise specified. All relevant documents and
31
32 files will be archived for five years. Data can be only accessed by the investigators
33
34 who sign the confidential disclosure agreement and by the institutional or
35
36 governmental auditors during the study. Data without patient identification will be
37
38 publicly accessible after the study. The process will be monitored by the Institutional
39
40 Ethics Committee (ICE) for Clinical Research of Zhongda Hospital.
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50 ***Endpoints***

51
52 The primary endpoint is the incidence and reflex degree of cough and giggling, which
53
54 will be recorded within 5 min after endoscope insertion and throughout the procedure.
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4 The severity of cough is defined according to cough intensity and whether leading to
5
6 failure of endoscope insertion. The secondary endpoints include (1) the occurrence of
7
8 swallowing, body movement, and adverse events and whether jaw thrust, assistant
9
10 ventilation, and additional propofol is used, which will be recorded within five
11
12 minutes after endoscope insertion and throughout the procedure, and (2) duration of
13
14 calls for eyes open, the duration of procedure and Steward score [35] after eyes open.
15
16 Blood pressure, heart rate and SpO₂ will be monitored throughout the process.
17
18 "Patient satisfaction" is not included as a secondary outcome since patient can not
19
20 recall coughing or gagging.
21
22
23
24

25 26 *Protocol amendments*

27
28 The current protocol version is v1.5 (11 June 2017). Any changes of the protocol
29
30 during the trial that may affect the conduct of the trial, the safety and the benefit of the
31
32 patients will require a formal amendment to the protocol.
33
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39 **Discussion**

40
41 It is important to improve analgesia and sedation for gastroscopy. Opioids, which
42
43 exert favorable analgesic, sedative effect and inhibit the stress response, are an
44
45 important part of surgical anesthesia. The combination of opioids and propofol is the
46
47 most commonly used regimen for general anesthesia. Currently, a small dose of
48
49 fentanyl combined with propofol in sedation for gastroscopy has been used in clinical
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51 practice. However, fentanyl has the potential risks of respiratory depression, choking
52
53 and the stiffness of chest wall muscles. Clinical study on other opioids for gastroscopy,
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4 such as oxycodone, dezocine and sufentanil, is rare. Finding an adequate regimen is
5
6 essential. Herein, we conduct this trial to evaluate the combination of small doses of
7
8 dezocine, oxycodone or sufentanil for gastroscopy. This study observes the incidence
9
10 and reflex degree of cough under sedation. There are limitations of this study. This is
11
12 a single-center, which may limit the generalization of this study. Future
13
14 multiple-center large-sample size study will be needed. The dose of propofol for this
15
16 study is relatively high and may have a risk to abolish the effects of the opioids
17
18 examined in this study. The result of this clinical trial can confirm the favorable
19
20 effects of combination of propofol with small-dose opioids, and can contribute to
21
22 finding satisfying regimens for sedation for gastroscopy.
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31 **Trial status**

32
33
34 At the time of manuscript submission, the study is in the recruitment phase.
35
36
37
38

39 **Ethics and dissemination**

40
41 This study has been approved by the Institutional Ethics Committee (ICE) for Clinical
42
43 Research of Zhongda Hospital, Affiliated to Southeast University (No.
44
45 2015ZDSYLL033.0) and is registered with the Chinese Clinical Trial Center
46
47 (ChiCTR-ICR-15006952). Only patients who give written informed consent will be
48
49 recruited. A model informed consent has been provided. The results of the trial will be
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51 published in an international peer-reviewed journal.
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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

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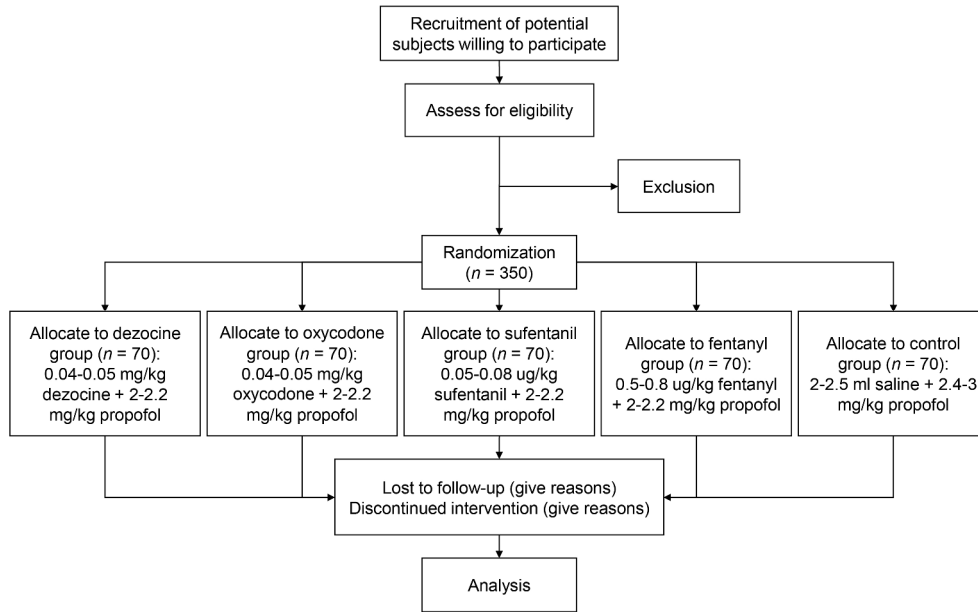
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Figure Legend

Figure 1. Follow chart of the study.

For peer review only



Follow chart of the study.

292x182mm (300 x 300 DPI)

Review only



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 ___

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 4-5
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention
 5
 6 6b Explanation for choice of comparators 5
 7
 8 Objectives 7 Specific objectives or hypotheses 5-6
 9
 10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),
 11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 6
 12
 13
 14

15 **Methods: Participants, interventions, and outcomes**

16

17 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 6
 18 be collected. Reference to where list of study sites can be obtained
 19
 20 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 6-7
 21 individuals who will perform the interventions (eg, surgeons, psychotherapists)
 22
 23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 8-9
 24 administered
 25
 26 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 9
 27 change in response to harms, participant request, or improving/worsening disease)
 28
 29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 8
 30 (eg, drug tablet return, laboratory tests)
 31
 32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial NA
 33
 34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood 10-11
 35 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
 36 efficacy and harm outcomes is strongly recommended
 37
 38 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for Figure 1
 39 participants. A schematic diagram is highly recommended (see Figure)
 40
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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____7_____
 2 clinical and statistical assumptions supporting any sample size calculations

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____6_____

7 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

11 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____7_____
 12 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 13 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 14 or assign interventions

17 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____7_____
 18 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 19 mechanism

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____7_____
 22 interventions

25 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____7_____
 26 assessors, data analysts), and how

28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____7_____
 29 allocated intervention during the trial

32 **Methods: Data collection, management, and analysis**

34 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____10_____
 35 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 37 Reference to where data collection forms can be found, if not in the protocol

40 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____10_____
 41 collected for participants who discontinue or deviate from intervention protocols

1	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_____
2				
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5	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_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA_____
9				
10		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_____
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15	Methods: Monitoring			
16				
17	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_____
18				
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22		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_____
23				
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26	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_____
27				
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____9_____
30				
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33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____12_____
36				
37				
38	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_____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 12 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
5				
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7	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 _____
8				
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 12 _____
11				
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14	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 _____
15				
16				
17	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 _____
18				
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20	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 _____
21				
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ 10 _____
28				
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30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ 12 _____
33				
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35	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 _____
36				
37				

38
39 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
40 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
41 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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