Capnographic monitoring reduces the incidence of hypoxia in elderly patients undergoing gastrointestinal endoscopy under propofol sedation: study protocol for a multicenter randomized controlled trial

Qiuyue Lian
Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University, School of Medicine
Shaoyi Chen
Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University, School of Medicine
Xiangyang Cheng
Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University, School of Medicine
Jie Zhang
Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University, School of Medical
Weifeng Yu
Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University, School of Medicine
Renlong Zhou
Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University, School of Medicine
Diansan Su (diansansu@yahoo.com)
Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University, School of Medicine
https://orcid.org/0000-0001-9755-1025

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Title

Capnographic monitoring reduces the incidence of hypoxia in elderly patients undergoing gastrointestinal endoscopy under propofol sedation: study protocol for a multicenter randomized controlled trial

Authors

Qiuyue Lian*, Shaoyi Chen*, Xiangyang Cheng, Jie Zhang, Weifeng Yu, Renlong Zhou, Diansan Su.

Department of Anesthesiology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

*： These authors contribute equally to this work.

Corresponding author

Diansan Su.

Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University School of Medicine, 160 Pujian Road, Shanghai, 200127, China.

E-mail: diansansu@yahoo.com

Co-corresponding author

Renlong Zhou

Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University School of Medicine, 160 Pujian Road, Shanghai, 200127, China.

E-mail: renlongzhou@shsmu.edu.cn

Abstract

Background

Hypoxia is an extremely common adverse event occurring during a sedated gastrointestinal endoscopy procedure, especially in elderly patients, because of the limited reservation. Prolonged or severe hypoxia can cause ischemia of coronary artery, permanent nervous system damage, or even result in death. Hence, it is extremely important to reduce or prevent hypoxia during sedated gastrointestinal endoscopy in elderly patients. Although several oxygen methods would reduce hypoxia during this procedure, early detection of respiratory depression and early administration of intervention would be the best method to reduce or even confirm the hypoxia. Capnographic monitoring is found to be more sensitive to respiratory depression in patients before the onset of hypoxia than the current clinical routine monitoring of pulse oxygen saturation (SpO_2); however, there exists a controversy regarding its effect. Therefore, this study was designed to improve the security of sedated gastrointestinal endoscopy in elderly patients.

Methods: A multicenter, randomized, single-blind, two-arm parallel-group, controlled with active comparator, interventional clinical trial will be conducted to evaluate the impact of an intervention based on additional capnographic monitoring on the incidence of hypoxia in elderly patients. Patients (n = 1800) scheduled for gastrointestinal endoscopy with propofol sedation will be

randomly assigned to either a control arm with standard monitoring or an interventional arm in which additional capnographic monitoring is available.

Discussion: This research project is primarily intended to examine whether an intervention based on additional capnographic monitoring would reduce the incidence of hypoxia in elderly patients during propofol and sufentanil sedation for gastrointestinal endoscopy. The results of this study may have a extensive impact on sedated gastrointestinal endoscopy practice and the development of guidelines.

Trial registration: ClinicalTrials.gov, NCT05030870. Registered on September 1, 2021.

Keywords

capnographic monitoring, hypoxia, gastrointestinal endoscopy, elderly patients, propofol

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Capnographic monitoring reduces the incidence of hypoxia in elderly patients undergoing gastrointestinal endoscopy under propofol sedation: study protocol for a multicenter randomized controlled trial
Trial registration {2a and 2b}.	ClinicalTrials.gov, NCT05030870. Registered on September 1, 2021.
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Author details {5a}	Authors Qiuyue Lian, Shaoyi Chen, Xiangyang Cheng, Jie Zhang, Weifeng Yu, Renlong Zhou, Diansan Su Department of Anesthesiology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China Email address: Qiuyue Lian: l18724464815@163.com Shaoyi Chen: docteurchensy@163.com Xiangyang Cheng: 1647384344@qq.com Jie Zhang: q150981@qq.com Weifeng Yu: ywf808@yeah.net Renlong Zhou: renlongzhou@shsmu.edu.cn

	Diansan Su: diansansu@yahoo.com Corresponding author Diansan Su Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University School of Medicine, 160 Pujian Road, Shanghai, 200127, China Email address: Diansan Su: +862168383702, Email:diansansu@yahoo.com Co-corresponding author Renlong Zhou Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University School of Medicine, 160 Pujian Road, Shanghai, 200127, China Email address: Renlong Zhou: +862168383702, Email:renlongzhou@shsmu.edu.cn
Name and contact information for the trial sponsor {5b}	Sponsor： The National Nature Science Foundation of China (Nos. U21A20357) Grant recipient: Diansan Su Address： Department of Anesthesiology, Renji Hospital, Shanghai Jiaotong University School of Medicine, 160 Pujian Road, Shanghai, 200127, China Tel：+862168383702

Role of sponsor {5c}	The funder had no role in the analyses and interpretation of the results or writing of the manuscript.

Introduction

Background and rationale{6a}

The sedation rate of gastrointestinal endoscopy varies in different countries. In China, the overall sedation rate was only approximately 50%[1], whereas in the United States, >98% of gastrointestinal endoscopy procedures are sedated[2,3]. Cardiopulmonary complications, especially hypoxia, are most common during sedated gastrointestinal endoscopy. Prolonged or severe hypoxia can cause ischemia of coronary artery, permanent nervous system damage, or even result in death[4,5], and hence, determining a method to reduce the incidence of hypoxia has become a vital problem in the field of sedated gastrointestinal endoscopy.

Compared with the current clinical routine monitoring of pulse oxygen saturation (SpO_2), capnographic monitoring can detect hypoventilation and respiratory depression earlier, which could help in providing earlier intervention[6]. Therefore, it is believed that capnographic monitoring would reduce the incidence of hypoxia. Nevertheless, a controversy exists regarding whether capnographic monitoring should be routinely performed during the sedated gastrointestinal endoscopy procedure.

In this regard, there are two major investigations, but a discrepancy was noted in their results. The first investigation, which was a randomized, controlled study (ColoCap Study) conducted by Beltz et al., confirmed that additional capnographic monitoring of ventilatory activity in ASA I–III patients reduces the incidence of hypoxia during propofol sedation for colonscopy[7]. However, the second investigation, which was a cohort study, demonstrated that the addition of capnographic monitoring did not improve safety or patient satisfaction, but it did increase the cost[8]. The fundamental problem was that the initial oxygen flow in the ColoCap Study was only 2 L/min, which is not consistent with clinical practice, wherein it is generally 3–4 L/min. This inconsistency resulted in an incidence of hypoxia of >50% in the controlled group. Another limitation of the ColoCap Study was that the depth of sedation between the two groups may have been inconsistent. Although the cohort study was designed closer to clinical practice, it did not yield positive results. These conflicting results suggest that there is insufficient evidence for routine capnographic monitoring in all patients.

The elderly patients comprise a vulnerable group and are more susceptible to hypoxia during gastrointestinal endoscopy performed under drug sedation[9,10]. However, whether this vulnerable group needs to be routinely monitored for capnography has not been investigated. Therefore, this study was designed to improve the security of sedated gastrointestinal endoscopy in elderly patients.

Objectives {7}

Our aim is to investigate whether an intervention based on additional capnographic monitoring would reduce the incidence of hypoxia in elderly patients undergoing sedated gastrointestinal endoscopy. Our primary objective is to measure the incidence of hypoxia (75% ≤ SpO_2 < 90% for < 60 s). Our secondary objective is to measure the incidence of subclinical respiratory depression (90% ≤ SpO_2 < 95%), the incidence of severe hypoxia (SpO_2 < 75% or 75% ≤ SpO_2 < 90% for ≥60 s), the incidence of capnography curve decreased by half or more than the baseline and even disappeared without hypoxia (SpO_2 > 90%), and the incidence of other adverse events recorded by tools proposed by the World Society of Intravenous Anesthesia International Sedation Task Force. We predict that additional capnographic monitoring of ventilatory activity would reduce the incidence of hypoxia during propofol sedation for gastrointestinal endoscopy in elderly patients. Our aim is to provide credible evidence of a reduction in the incidence of hypoxia in elderly patients.

Trial design {8}

Our study is a multicenter, randomized, single-blind, two-arm parallel-group, controlled with active comparator, interventional clinical trial. We intend to

evaluate the impact of an intervention based on additional capnographic monitoring on the incidence of hypoxia in elderly patients.

This trial was conducted under the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (supplemental file, SPIRIT checklist). On September 1, 2021, the trial was registered on ClinicalTrials.gov (No. NCT05030870). We presented the trial registration data in the form of supplemental data.

Methods: Participants, interventions, and outcomes

Study setting {9}

Approximately 1800 participants will be enrolled in this study from the Renji Hospital Shanghai Jiao Tong University School of Medicine, Henan Provincial People's Hospital, and Qilu Hospital of Shandong University. The ethics committee of the Renji Hospital Shanghai Jiao Tong University School of Medicine approved and supported this clinical trial (KY-2021014).

Eligibility criteria {10}

This clinical trial has three centers recruited patients. A summary of the inclusion and exclusion criteria is presented in Table 1.

Who will take informed consent? {26a}

Potential participants will be explained this trial in detail by trained anesthesiologists and will be provided the informed consent form. After take enough time to deliberate, participants can decide whether they wish to participate in the trial. Then the participant or his/her trustee or guardian sign the informed consent form, and they can withdraw at any time during the trial. We collected baseline data from patients and randomize allocation using the central random system. Furthermore, participants can contact our team if they have any health concerns during the trial. The entire process of recruitment and consenting of study participants by members of the research team will be consistent with good clinical practice (GCP). If any serious adverse events occurs during the clinical trial, the researchers will immediately report to the director in charge of the clinical trial of the research institution and contact Professor Diansan Su, whether related to the procedure under study or not.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable as no participant data and biological specimens were collected or used in ancillary studies.

Interventions

Explanation for the choice of comparators {6b}

For the choice of comparators, the central randomization system will be used for each study site. Following randomization, subjects will receive either (Arm2) standard monitoring or (Arm1) with additional capnography. The comparator in this trial is standard monitoring alone (Arm2).

Intervention description {11a}

The interventions for participants in this trial are capnography-blinded arm (Arm2) and capnography-open arm (Arm1). Capnography-blinded arm with standard monitoring, and the capnography-open arm with additional capnography.

In both groups, standard monitoring will include heart rate, SpO_2, electrocardiogram, and noninvasive blood pressure in selected patients. In the capnography-open arm, a sampling line will be connected to a bedside portable monitor (Capnostream 20; Medtronic, Inc.), so that the capnographic data of the patients are available for additional noninvasive assessment of ventilation. In the capnography-blinded arm, no sampling line will be connected to the bedside portable monitor, and the capnographic data of the patients will not be visible, so that only the integrated pulse oximetric readout of the monitor will be visible.

Table 2 lists the adverse events of anesthesia and sedation.

Criteria for discontinuing or modifying allocated interventions {11b}

If participants request to withdraw from the trial, we will discontinue the allocated intervention for a given trial participant.

Strategies to improve adherence to interventions {11c}

Adherence to interventions primarily refers to patient self-management adherence.

Relevant concomitant care permitted or prohibited during the trial {11d}

No concomitant care or interventions will be permitted during this trial.

Provisions for posttrial care {30}

If a participant suffers harm from this trial, he/she will receive financial compensation accordingly. The amount of compensation is determined jointly by the consultation of relevant departments and the participant.

Outcomes {12}

Primary outcome measures. The primary outcome of this study is the incidence of hypoxia (75% ≤ SpO_2 < 90% for <60 s) in the two groups.

Secondary outcome measures. The secondary outcomes comprise the following:

1. The incidence of subclinical respiratory depression (90% ≤ SpO_2 < 95%).

2. The incidence of severe hypoxia (SpO_2 < 75% or 75% ≤ SpO_2 < 90% for ≥60 s).

3. The incidence of capnography curve decreased by half or more than the baseline and even disappeared without hypoxia (SpO_2 > 90%).

4. The incidence of other adverse events recorded by tools proposed by the World Society of Intravenous Anesthesia International Sedation Task Force.

Participant timeline {13}

Figure 1 shows the schedule for enrollment, interventions, assessments, and visit for participants.

When patients enter the gastrointestinal endoscopic operating room, they will be screened for eligibility by the investigator. If they meet the inclusion criteria but not the exclusion criteria, the investigator will provide them the fully informed consent form. After signing the informed consent form, the patients will be allocated to the capnographic monitoring group or the control group by the central randomization system.

In the capnographic monitoring group, the criteria for apnea will be the absence of exhaled CO_2; altered ventilation will be defined as a reduction of end-tidal CO_2 of more than half of baseline as shown by the capnogram; and the definition of hypoxia will be SpO_2 < 90%. In the control group, the definition of hypoxia will be SpO_2 < 90%.

In both groups, any sign of apnea, altered ventilation, or hypoxia that prompts an intervention will consist of (i) increasing oxygen supplementation, (ii) a chin lift or jaw thrust maneuver, (iii) insert the oropharyngeal airway or nasopharyngeal airway with a chin lift or jaw thrust maneuver, (iv) artificial mask ventilation, and (v) tracheal intubation.

Sample size {14}

Our previous study showed that the incidence of hypoxia during gastrointestinal endoscopy with propofol sedation in patients was approximately 8%. The anticipated effect size of additional capnographic monitoring was 50%, implying that the hypoxia incidence power analysis assumes a reduction from 8% to 4%. Between the capnography-open and capnography-blinded groups, the results of a conventional analysis to detect differences in proportions (hypoxia). We use PASS 11.0, randomization 1:1, power of $1 - \beta = 0.90$ and a two-sided α level of 5%. We assume a 10% dropout rate. This results in a requirement of approximately 1800 patients.

Recruitment {15}

The schedule of the major study events for each study visit was shown in Figure 1. In this study, Elderly patients who are scheduled to undergo gastrointestinal endoscopy with propofol sedation will be included. The entire process of recruitment and consenting of study participants by members of the

research team will be consistent with GCP.

Assignment of interventions: allocation

Sequence generation {16a}

In this trial, we used stratified blocked randomization to design the central randomization system. Complete baseline data will be collected from participants, including name, gender, date of birth, etc. After assessing the patient's eligibility for inclusion, his/her informed consent will be obtained. We randomly assigned the participants in a ratio of 1:1 to the standard monitoring group or the additional capnographic monitoring group according to the allocation sequence of the central randomization system. The length of a random sequence is not fixed, and 4, 6, and 8 are random.

Concealment mechanism {16b}

After obtaining the signed informed consent, participants will be randomly assigned to the standard monitoring group or the additional capnographic monitoring group according to the central randomization system. Random results, random number, and their relationship with groups will be maintained confidential to the participants throughout the trial. The same nasal cannula with a carbon dioxide-collecting device will be used in both groups and connected to the capnographic monitoring device. Participants will not be aware of their own and others' grouping before, during, and after the

gastrointestinal endoscopy procedure.

Implementation {16c}

Designated doctors will generate the allocation sequence, enroll participants, and assign participants to interventions.

Assignment of interventions: Blinding

Who will be blinded {17a}

After assignment to the interventions, only the trial participants will be blinded. The results in the central randomized system will be maintained confidential to the participants throughout the entire process. The same nasal cannula will be used in both the standard monitoring group and the additional capnographic monitoring group, and the sampling line will be connected to a portable beside monitor. The researcher will ensure that participants are not aware of their own or other’s information of assignment.

Procedure for unblinding if needed {17b}

As the trial is single-blind, patients interested in knowing their group could be informed by the investigator after the analysis of results.

Data collection and management

Plans for assessment and collection of outcomes {18a}

This study is an internal multicenter clinical trial. All data collection physicians will be specially trained by assessors. We will conduct online meetings regularly to share the progress of the trial and discuss the problems that we encounter during the project. Moreover, we will conduct field visits to subcenters for quality control. We shall also organize the trial data regularly to check for any data missing, and to promote data quality, we intend to apply other methods and call the participants as well.

Plans to promote participant retention and complete follow-up {18b}

Not applicable as the trial did not involve follow-up, so we have no plans to promote participant retention and complete the follow-up.

Data management {19}

The respective patients' case report form (CRF) entered and/or filled in all patient data collected during this clinical trial. The study number, subject number, date of subject information and informed consent will be documented appropriately in the patient CRF. We will archive the source data in accordance with GCP guidelines. According to the sponsor's standard operating procedures, the data manager will be responsible for data processing, and will conduct regular monitoring to ensure that the dates are adequate, accurate, and complete. Only after the completion of quality

assurance procedures, the database lock will occur.

Confidentiality {27}

Participants information will be confidential and managed according to the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee (REC) approval.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable as no biological specimens were collected as part of this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Data selection for statistical analysis

1. Full analysis set (FAS): According to the principle of intention-to-treat analysis, the full analysis set will include all subjects who are enrolled in the study.

2. Per-protocol set (PPS): The PPS population will include all FAS patients without major protocol deviations that influence the evaluation of primary outcome. The efficacy analysis will be performed on the FAS and PPS.

3. Safety analysis set (SAS): The safety population will consist of all subjects. Analyses of safety data in the study will be based on the safety population.

Statistical analysis plan

All statistical analyses in this trial will be programed and calculated using SPSS 23.0 (IBM Inc., Armonk, NY, USA). We intend to use the unpaired *t*-test or Mann–Whitney U test for the main efficacy outcome. When the P value of ≤0.05 will be considered as statistically significant. We will using the χ^2 test, continuity correction χ^2 test, or Fisher's exact test to analyse categorical variavles. Besides, we will compare the patients' incidence of hypoxia, subclinical hypoxia, and severe hypoxia during the sedated gastrointestinal endoscopy procedure. Fishers' exact test will be conducted to analyze primary and secondary outcomes.

Additional analyzes

Safety analysis: General safety evaluations will be based on the incidence and type of adverse events (AEs). Safety variables will be tabulated and presented for all patients in safety sets. Adverse events will be coded using the tools proposed by the World Society of Intravenous Anesthesia International Sedation Task Force. The number (%) of subjects with any AEs will be summarized.

Interim analyzes {21b}

Not applicable as we have no plans to conduct any interim analyzes, and no

one has rights to access to these interim results and decides to terminate the trial.

Methods for additional analyzes (e.g., subgroup analyzes) {20b}

The methods used for statistical analyzes will also be used for additional analyzes for primary and secondary outcomes.

Methods in the analysis to handle protocol nonadherence and any statistical methods to handle missing data

Intention-to-treat (ITT) basis conducts the statistical analysis. Regardless of protocol adherence, the results of the outcome analyzes will be analyzed as randomised. The frequency and type of missingness of all variables will be screened. If missingness is >5% in any variable, we will use multiple imputation. Complete case analysis will be performed as a sensitivity analysis, in case of missing data and imputation.

Plans to provide access to the full protocol, participant-level data, and statistical code {31c}

Not applicable as we have no plans to provide access to the full protocol, participant-level data, and statistical code.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

Diansan Su is responsible for preparing and revising the protocol and

disseminating any changes. Renlong Zhou and Weifeng Yu are responsible for overseeing the study design and protocol, and interpretation of the findings. Qiuyue Lian and Shaoyi Chen are responsible for coordinating data collection and analyzes and writing the scientific manuscript. Xiangyang Cheng and Jie Zhang are responsible for overseeing any statistical analyzes and the study implementation on the floor follows the protocol.

Composition of the data monitoring committee, its role, and reporting structure {21a}

We do not have composition of the data monitoring committee (DMC).

Adverse event reporting and harms {22}

The nasal cannula with a port for collecting exhaled carbon dioxide samples used for capnographic monitoring is similar to the original nasal cannula and does not have additional risks. To date, there has been no evidence that this study may cause any risk or discomfort to participants.

We will record any adverse events that occur during the clinical trial, regardless of whether these events were associated with the the intervention. And all these expected and unexpected trial-related adverse events will be reported in trial publications.

Frequency and plans for auditing trial conduct {23}

The investigators shall maintain all study data according to GCP requirements. The original study data and information will be retained for at least 5 years after the completion of the trial. Data security and monitoring reports will be submitted to the ethical committee every 3 months.

Plans for communicating important protocol amendments to relevant parties (e.g.,., trial participants, ethical committees) {25}

This clinical trial will be conducted according to ethical committee approval. Any problem or protocol modifications during the trial will be communicated to the ethical committees, trial participants, trial registries, journals, and regulators in a timely manner. Ethical committee's consent will be required to change the protocol.

Dissemination plans {31a}

The participants, healthcare professionals, the public, and other relevant groups in the form of articles will communicate the results of this trial.

Discussion

Worldwide, the number of sedated gastrointestinal endoscopy procedures is increasing. In China, the overall number of gastrointestinal endoscopies is high and will continue to increase[1]. The sedation rate was 48.3%, with 47.9% attributed to gastroscopies and 49.3% to colonscopies[1]. With the worldwide aging population, the safety of sedated gastrointestinal endoscopy in elderly patients is becoming increasingly important. Hypoxia is the most common and severe complication during sedated gastrointestinal endoscopy procedure. Therefore, reducing the occurrence of hypoxia remains an extremely important problem.

The primary course of hypoxia in sedated gastrointestinal endoscopy procedure is hypoventilation caused by respiratory depression. Early detection

of respiratory depression and early intervention are vital to prevent hypoxia. The routine monitoring index SpO_2 cannot completely reflect the real-time ventilation of patients. As a more sensitive, more real-time monitoring indicator, capnographic monitoring may be used to reflect respiratory depression before the onset of hypoxia[11,12].

Capnographic monitoring provides quantitative digital readings of the patient's exhaled and inhaled carbon dioxide levels and graphically display the carbon dioxide levels over time[13]. It is more sensitive than SpO_2 and can reflect patient's ventilation in real-time [6].

Studies have demonstrated that there can be a lag of up to 2 min between apnea and a change in breathing pattern and hypoxia[6]. Effective interventions provided within this time interval can reduce the incidence and mortality of sedation-related complications. Early detection of respiratory depression in patients and timely and effective intervention measures can reduce the occurrence of severe hypoxia, hypercapnia, and even cardiac arrest, thus improving the prognosis of patients[14].

The capnographic monitoring device used in the present study (Capnostream 20； Medtronic, Inc.) is connected to the nasal cannula, which has a carbon dioxide sampling port and allows breathing through the mouth. It can provide 0–5 L/min oxygen to the patient and offer real-time monitoring of wave form and the level of patients' exhaled carbon dioxide. We can also obtain the patient's breath rate. The capnographic monitoring device can also be connected to a pulse oximeter to monitor the patient's SPO_2 value. Capnographic monitoring of waveform can intuitively evaluate ventilation in the experimental group. In this trial, the capnographic criterion for apnea will be

the absence of exhaled CO_2. Altered ventilation will be defined as a reduction of end-tidal CO_2 of more than half of baseline as shown by the capnogram. Oxygen desaturation will be defined as a decrease of SaO_2 level to <90%[2]. Currently, no unified conclusion has been drawn on whether end-tidal CO_2 monitoring can effectively reduce the occurrence of hypoxia during endoscopy. In 2011, the American Society of Anesthesiologists' Standards for Basic Anesthetic Monitoring recommended that capnographic should be monitored in addition to pulse oximetry in moderate sedation cases[15]. However, a joint statement from the major gastroenterology societies did not recommend routine capnographic monitoring for patients undergoing moderate sedated gastrointestinal endoscopy[16]. Recently, standards advocated by the American Society of Anesthesiologists along with a multisociety task force updated their practice guidelines for moderate sedation; they go on to suggest that continuous capnographic monitoring should be used to evaluated the adequancy of ventilation[17]. In the same year, the American Society for Gastrointestinal Endoscopy advocated that integrating capnography into patient monitoring protocols for endoscopic procedures with moderate sedation has not been shown to improve patient safety[18]. There are also standards suggesting the need to assess the clinical usefulness of capnography in patients considered to be at high risk for morbidity from hypoxemia, such as those with severe cardiovascular disease[19,20]. These guidelines indicate that there is insufficient evidence for routine capnographic monitoring in all patients during sedated gastrointestinal endoscopy.

Elderly patients comprise a vulnerable group different from adult patients. They are more susceptible to respiratory depression and hypoxia. Our previous

study showed that the incidence of hypoxia during upper gastrointestinal endoscopy in patients of all ages who were sedated with propofol was 9% in China[21], whereas the incidence of hypoxia during sedated gastrointestinal endoscopy in elderly patients was 15.9%[22]. Hence, capnographic monitoring may be more valuable during sedated gastrointestinal endoscopy in elderly patients.

Based on existing data, whether end-tidal CO_2 must be routinely monitored during sedated gastrointestinal endoscopy remains no consesus be reached; however, there have been few recent studies to add to the scant literature on this topic. There are also a few clinical trials on capnographic monitoring in elderly patients. To our knowledge, our trial is the first randomized controlled study designed to confirm capnographic monitoring in elderly patients during gastrointestinal endoscopy procedure with sedation. Our study design avoids some of the limitations of other studies, indicating its more closeness to clinical practice. We expect that our study would provide a higher level of evidence and improve the safety of sedated gastrointestinal endoscopy in elderly patients.

Trial status

Trial registration: ClinicalTrials.gov, NCT05030870. Registered on September 1, 2021. The protocol version is 2.2, which was approved in November 22, 2021. This study was started on September 1, 2021, and the recruitment phase will last until December 2023.

Abbreviations

SpO_2: hemoglobin oxygen saturation; CRF: case report form; GCP: good clinical practice; REC: Research Ethics Committee; FAS: full analysis set; PPS: per-protocol set; SAS: safety analysis set; AEs: adverse events; ITT: intention-to-treat; DMC: data monitoring committee; CO_2: carbon dioxide; RCT: randomized controlled study.

Declarations

Acknowledgments

Our team would like to thank the patients who have participated in the trial to date and all the staff at all participating sites.

Authors' contributions {31b}

Diansan Su is the principal investigator of this clinical trial, came up with the idea of the study. Renlong Zhou is the senior investigator of this clinical trial. They were both responsible for the conception and design of the study. Weifeng Yu is the academic director, led the proposal and design of study. Qiuyue Lian and Shaoyi Chen contributed equally to this work and they shared first authorship and contributed to the final manuscript. Qiuyue Lian participated in the development of the protocol, the trial database and case report forms. Shaoyi Chen contributed to statistical design of the RCT and sample size estimations. Qiuyue Lian, Xiangyang Cheng, and Jie Zhang participated in conducting the experiment and collection of data. All authors have approved the final manuscript and agree with submission. We will assigned the authorship for future trial publications according to the

contribution. Professional writers will not be used by us.

Funding {4}

The National Nature Science Foundation of China (Nos. U21A20357) supported this study. The funder was not interfere with the analyzes and interpretation of the trial results or writing of the protocol manuscript.

Availability of data and materials {29}

Because of Chinese data protection rules and regulations, the participant-level data set cannot be made publicly available. If request, the statistical code is available.

Ethics approval and consent to participate {24}

The Ethics Commission of Renji Hospital Shanghai Jiaotong University School of Medicine approved and supported this clinical trial (KY2021-014).

Consent for publication {32}

Not applicable as we are not intend to publish personal information about an individual.

Competing interests {28}

The authors declare that they have no competing interests.

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650 **Table 1 Inclusion/exclusion criteria**

Inclusion criteria	Exclusion criteria
1) Aged ≥65 and <80 years	1) Coagulation disorders or a tendency of nose bleeding
2) Scheduled to undergo gastrointestinal endoscopy procedure with sedation	2) An episode/exacerbation of congestive heart failure that requires a change in medication, diet, or hospitalization from any cause in the past 6 months
3) Signed the informed consent form	3) Severe aortic stenosis or mitral stenosis
4) American Society of Anesthesiologists (ASA) classification I-II	4) Cardiac surgery involving thoracotomy (e.g., coronary artery bypass graft, valve replacement surgery) in the past 6 months
	5) Acute myocardial infarction in the past 6 months
	6) Acute arrhythmia (including any tachycardia or bradycardia) with fluid of hemodynamics instability
	7) Diagnosed with chronic obstructive pulmonary disease or current other acute or chronic lung disease requiring supplemental chronic or intermittent oxygen therapy
	8) Preexisting bradycardia (heart rate <50/min), or hypoxia (SaO_2 < 90%)
	9) Need supplemental oxygen because of preexisting diseases
	10) Emergency procedure or surgery
	11) Multiple trauma
	12) Upper respiratory tract infection
	13) Allergy to propofol or tape and adhesives

651 **Table 2 Adverse events of anesthesia and sedation**

Step 1:Was there one or more adverse events associated with this sedation encounter?				
❍ No, this form is now complete.	❍ Yes, fill out remainder of form below.			
Step 2: Please DESCRIBE the adverse event(s). Check all that apply.				
Minimal risk descriptors	**Minor risk descriptors**		**Sentinel risk descriptors**	
❍ Vomiting/Retching	❍ Oxygen desaturation (75-90%) for < 60s		❍ Oxygren desaturation, severe (<75% at any time) or prolonged(<90% for >60s)	Other, specify below
❍ Sub-clinical respiratory depression	❍ Apnoea not prolonged		❍Apnoea, prolonged (>60s)	
❍Muscle rigidity, Myoclonus	❍ Airway obstruction		❍Cardiovascular collapse/shock	
❍ Hypersalivation	❍ Failed sedation		❍Cardiac arrest/absent pulse	
❍ Paradoxical response	❍ Allergic reaction without anaphylaxis			
❍ Recovery agitationc	❍ Bradycardiatf			
❍ Prolonged recovery	❍ Tachycardiaf			
	❍ Hypotensionf			
	❍ Hypertensionf			
	❍ Seizure			
Step 3: Please note the INTERVENTIONS performed to treat the adverse events(s). Check all that apply.				
Minimal risk	**Minor risk**	**Moderate risk**	**Sentinel intervention**	
❍ No intervention performed	❍ Airway repositioni	❍ Bag valve mask-assisted	❍ Chest compressions	Other, specify

	ng	ventilation		below
❍ Tactile stimulation	❍ Tactile stimulatio n	❍ Laryngeal mask airway	❍Tracheal intubation	
❍ Additional sedative(s)	or the administra tion of:	❍ Ora/nasal airway	or the administration of:	
❍ Antiemetic	❍ Supple mental oxygen, new or increased	❍ CPAP	❍ Neuromuscular block	
❍ Antihistamine	❍ Antisial ogogue	or the administration of:	❍Pressor/epinephrine	
		❍ Reversal agents	❍ Atropine to treat bradycardia	
		❍ Rapid i.v.fluids		
		❍ Anticonvulsanti.v .		
Step 4: Please note the OUTCOME of the adverse events(s). Check all that apply.				
Minimal risk outcome	**Moderate risk outcome**	**Sentinel outcome**		
❍No adverse outcome	❍ Unplanned hospitalisation or escalation of care	❍ Death		Other, specify below
		❍Permanent neurological deficit		
		❍Pulmonary aspiration syndromei		
Step 5: Assign a SEVERITY rating to the adverse event(s) associated with this sedation encounter.				
If there are any options checked in the Sentinel columns above, then this is a Sentinel adverse event.				

If the most serious option(s) checked above are Moderate risk, then this is a Moderate risk adverse event.
If the most serious option(s) checked above are Minor risk, then this is a Minor risk adverse event.
If the most serious option(s) checked above are Minimal risk, then this is a Minimal risk adverse event.

Footnotes:

a. “Sub-clinical respiratory depression” is defined as capnographic abnormalities suggesting respiratory depression that do not manifest clinically.

b. “Paradoxical response” is defined as unanticipated restlessness or agitation in response to sedatives.

c. “Recovery agitation” is defined as abnormal patient affect or behaviors during the recovery phase that can include crying, agitation, delirium, dysphoria, hallucinations, or nightmares.

d. “Prolonged recovery” is defined as failure to return to baseline clinical status within 2 hours.

e. “Failed sedation” is defined as inability to attain suitable conditions to humanely perform the procedure.

f. Alteration in vitals signs (bradycardia, tachycardia, hypotension, hypertension) is defined as a change of >25% from baseline.

g. “Cardiovascular collapse/shock” is defined as clinical evidence of inadequate perfusion.

h. Examples of “escalation of care” include transfer from ward to intensive care, and prolonged hospitalisation.

i. “Pulmonary aspiration syndrome” is defined as known or suspected inhalation of foreign material such as gastric contents into the respiratory tract associated with new or worsening respiratory signs.

j. “Sentinel” adverse events are those critical enough to represent real or serious imminent risk of serious and major patient injury. Once recognized, they warrant immediate and aggressive rescue interventions. Once clinically concluded, they warrant immediate reporting within sedation care systems, and the highest level of peer scrutiny for continuous quality improvement.

k. “Moderate” adverse events are those that, while not sentinel, are serious enough to quickly endanger the patient if not promptly managed. Once clinically concluded, they warrant timely reporting within sedation care systems, and periodic peer scrutiny for continuous quality improvemet.

l. “Minor” adverse events are those encountered periodically in most sedation settings, and that pose little threat given appropriate sedationist skills and monitoring.

m. “Minimal” adverse events are those that alone present no danger of permanent harm to the patient.

687 **Figure1 Schedule of the major study events**

Project	Gastroscopy diagnosis and treatment period（Visit 1）					
	Arrive the examination room	sedative induction	Procedure start	Procedure over	participants wakes up	Leave the examination room
Baseline data						
informed consent	×					
medical history	×					
inclusion / exclusion criteria	×					
demographic data	×					
Vital signs	×	×	×	×	×	×
physical examination	×					
Research outcome measures						
hypoxia		×	×	×		
Sub-clinical hypoxia		×	×	×		
Severe hypoxia		×	×	×		
Adverse event		×	×	×		
Research drug						
Study randomization	×					
Calculate drug dosage						×
Others						
Gastroscope procedure time				×		
Combined medication	×	×	×	×	×	×

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Supplementary Files

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