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Anaesthesia

Protocol

Efficacy of systemic lidocaine on postoperative delirium in patients undergoing laparoscopic colorectal surgery: study protocol for a multicentre, prospective, double-blind, randomised, parallel-group, equivalence, placebo-controlled trial

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ABSTRACT

Introduction: Systemic lidocaine may reduce pain intensity and accelerate postoperative recovery. But the efficacy of systemic lidocaine on cognitive function has not been established. This study protocol is designed to clarify the effectiveness of lidocaine on postoperative delirium (POD) in elderly patients scheduled for elective laparoscopic colorectal surgery.

Methods and analysis: This is a prospective, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial. One thousand and twenty elderly patients will be randomly allocated in a ratio of 1:1 to receive either systemic lidocaine (a bolus of 1.5 mg kg^{-1}, followed by an infusion of 1.5 mg kg^{-1} h^{-1} until the end of the surgery) or identical volumes and rates of 0.9% saline. The primary outcome measure is the prevalence of POD during the first five postoperative days. Secondary outcomes include emergence agitation, the area under the curve of the Numerical Rating Scale pain scores over 48 h, postoperative 48-h cumulative opioid consumption, postoperative nausea and vomiting, recovery of bowel function, quality of recovery, and patient satisfaction with postoperative analgesia.

Ethics and dissemination: The Ethical Committees of Fujian Provincial Hospital has approved the study protocol (Ref: K2021-06-018). We will obtain written informed consent from each patient before they are randomised. The result of this study will be presented at scientific conferences and submitted to international journals.

Trial registration details: This study has been registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn, identifier number: ChiCTR2100050314).

Keywords: postoperative delirium; lidocaine; elderly patients; laparoscopic colorectal surgery

Article Summary

Strengths and limitations of this study

- The study design will be multicentre, prospective, randomised, double-blinded, equivalent and placebo-controlled.
- This is the first study to evaluate the efficacy of systemic lidocaine on postoperative delirium (POD) in geriatric patients undergoing laparoscopic colorectal surgery.
- Only elderly patients following laparoscopic colorectal surgery are included, which will limit the generalisability of the results.
- The anaesthetic-sparing effects of lidocaine might weaken the efficiency of blindness to the treating anesthesiologist.
- Several confounding factors such as anxiety, distress probably influence the prevalence of POD.

INTRODUCTION

Background

Postoperative delirium (POD) is a debilitating postoperative neurological complication, which often starts in the post-anaesthesia care unit and appears up to 5 days after surgery. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) has defined POD as an acute and fluctuating alteration of the mental state of reduced awareness and disturbance of attention.[2] Advanced age is one of the significant predisposing factors for POD. The prevalence of delirium varies from 20% to 45% in geriatric surgical patients.[3] POD is associated with several adverse clinical consequences, including prolonged hospitalisation, additional healthcare costs, increased morbidity and mortality risks. Furthermore, POD development may induce cognitive impairment after surgery, resulting in significant loss of functional independence and long-term cognitive decline.[4]

Systemic lidocaine is widely used for its beneficial effects on postoperative analgesia and recovery, including alleviating visceral pain, accelerating gastrointestinal recovery, and

reducing hospital stay length.[5] In addition, previous clinical research has reported a beneficial effect of lidocaine on neurologic injury after major surgeries.[6-8] Because lidocaine's therapeutic index is relatively low, central nervous system toxicity may start when plasma levels are only slightly higher than therapeutic levels. Consequently, Lidocaine might be fatal to elderly patients when misused.[9] To date, the efficacy of systemic lidocaine on POD in older patients undergoing major surgery remains elusive. We hypothesise that the administration of systemic lidocaine intraoperatively will reduce the prevalence of POD in elderly patients. The proposed clinical trial aims to establish evidence for the efficacy of lidocaine on the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery.

Objectives

Our goal is to evaluate the efficacy of systemic lidocaine on POD in elderly patients undergoing laparoscopic colorectal surgery. Therefore, we test the primary hypothesis that patients receiving systemic lidocaine are associated with a lower prevalence of POD within the first five postoperative days. Secondly, we test the hypotheses that systemic lidocaine alleviates postoperative pain, reduces postoperative opioid consumption, enhances the quality of recovery, and further improves patients' satisfaction.

Trial design

This study is a prospective, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial. The Ethical Committees of Fujian Provincial Hospital has approved the protocol. A total of 1020 participants will be randomly assigned to the lidocaine group or saline group in a ratio of 1:1. The study schema is presented in **Figure 1**.

METHODS

Recruitment and study setting

Participants scheduled for elective laparoscopic colorectal surgery under general anaesthesia will be enrolled by a researcher (Dr Bingbing Fu). Patients participating in the study will be screened according to inclusion and exclusion criteria. Dr Bingbing Fu will visit patients scheduled for laparoscopic colorectal surgery who meet the eligibility criteria and express

interest in participating in this trial. Dr Bingbing Fu will provide a verbal explanation of written consent and answer any questions about the study in detail (i.e., the study purpose, procedures, time commitment, the potential risks and benefits associated with participation in the survey.) There will be enough time for each participant to consider whether participating in this trial. The participants are recruited in this study after signing separate informed consents. The enrollment period will extend over twelve months.

Inclusion criteria

Participants need to fulfil the following criteria:

- Aged 65 years or older.
- Undergoing laparoscopic colorectal surgery.
- American Society of Anesthesiologists (ASA) physical status I to III.

Exclusion criteria

Patients with the following conditions are excluded:

- History of mental illness or scored less than 27 on the baseline Mini-Mental State examination before operation.
- Patients weighing < 40 kg.
- Severe cardiac arrhythmias.
- Symptomatic cerebrovascular disease (e.g., prior stroke).
- Severe renal dysfunction (serum creatinine more than 2 mg dL^{-1}).
- Severe hepatic dysfunction (liver function tests more than 1.5 times the upper limit of normal).
- Unable to communicate or other situations that are not appropriate for this study.

Study locations

We will conduct this trial in four hospitals, including Fujian Provincial Hospital, People's Hospital Affiliated with Fujian University of Traditional Chinese Medicine, the 900th Hospital of Joint Service Support Force of People's Liberation Army of China, and Sanming First Hospital.

Randomisation, allocation concealment, and blinding

Allocation sequence has been generated using a computer-generated randomisation list followed by obtaining written informed consent. And participants will be randomised to receive a continuous intravenous infusion of lidocaine or 0.9% saline in a ratio of 1:1. This study is a simple allocation with no stratifications and blocks. Group assignments will be concealed in sequentially numbered opaque envelopes opened on the day of surgery. The study medications will be prepared by an independent research nurse who is not involved in the patient's care. All participants, surgeons, anesthesiologists, and research personnel will not be informed of the group assignments during the study period.

Intervention

After patients in the lidocaine group received a bolus of 1.5 mg kg^{-1} intravenous lidocaine over 10 min before induction of anaesthesia, and then a continuous infusion of 1.5 mg kg^{-1} h^{-1} systemic lidocaine is administered until the end of the surgery. Ideal body weight will be used for lidocaine dose calculation. Patients in the control group will be administered equal volumes of 0.9% saline using the identical application scheme. The study medications will be prepared in two syringes: a 20 mL syringe for the bolus injection and a 50 mL syringe for the continuous intravenous infusion. This approach will result in both groups receiving an equal volume per unit of time.

General anaesthesia and postoperative analgesia protocol

Upon arrival at the operating room, all patients will be monitored with pulse oximetry, invasive blood pressure and electrocardiogram. We will induce general anaesthesia using propofol 2 mg kg^{-1} and sufentanil 0.6 μg kg^{-1}. A bolus injection of rocuronium 0.6 mg kg^{-1} will be administered to facilitate laryngeal mask airway (LMA) insertion. We will maintain the end-tidal carbon dioxide partial pressure ($PaCO_2$) of 35 to 45 mmHg using pressure-controlled mechanical ventilation. Anaesthesia will be maintained by inhalation of sevoflurane, aiming for a bispectral index of 40–60. Intravenous remifentanil infusion will be adjusted to maintain the hemodynamic parameters (mean arterial pressure and heart rate) fluctuation within 20% of baseline. The neuromuscular blockade will be achieved by intermittent injections of cisatracurium 5 mg as needed. After the surgical procedure, the surgeon will infiltrate the wounds with 10 mL of 0.25% ropivacaine. For postoperative analgesia, all patients will receive

patient-controlled intravenous analgesia (PCIA) with sufentanil. The PCIA pump (REHN II; Renxian Medical Corporation, Jiangsu, China) will be set to deliver 1 μg h^{-1} sufentanil. If the numeric rating scale (NRS) for pain exceeded three or the patient required, a bolus injection of sufentanil 2 μg would be administrated as a rescue analgesic, with a 10-min lockout interval via the PCIA pump, and the maximum dose of sufentanil will be set at 10 μg h^{-1}. The PCIA will be discontinued 48 h after surgery.

Patient and public involvement

Patients and the public are not involved in the study design and conduct. The study results will not be disseminated to study participants.

OUTCOMES

Primary outcome

The primary outcome is the occurrence of POD during the first five postoperative days. The Confusion Assessment Method (CAM) is a screening instrument for non-psychiatrically trained clinicians to evaluate POD according to the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) criteria. Delirium can be diagnosed via interview using the CAM algorithm following four criteria: (1) acute onset or fluctuating course; (2) inattention; (3) disorganised thinking; and (4) altered level of consciousness. The research member will assess POD twice daily (between 8 and 10 am and between 6 and 8 pm). If criteria 1 and 2 and either of 3 or 4 are present, delirium is diagnosed. [10] Meanwhile, POD severity will be rated daily using CAM-Severity (CAM-S).

Secondary outcomes

Secondary outcomes are as follows:

1. The AUCs of the NRS pain scores over time: The postoperative pain at rest and on movement will be assessed using self-reported NRS score (no pain=0; maximum pain=10) at 0.5, 1, 2, 4, 8, 24 and 48h postoperatively.
2. The emergence agitation will be assessed within stay in the PACU using the Riker Sedation-Agitation Scale. [11] A score＞of 4 is defined as emergence agitation.

3. Postoperative cumulative opioid consumption over 48 h postoperatively will be recorded.
4. Postoperative nausea and vomiting (PONV) will be assessed within 48h postoperatively. PONV score are assessed using a 4-point scale (1 = absent; 2 = mild nausea; 3 = severe nausea; and 4 = vomiting).[12]
5. The occurrence of dizziness will be assessed within 48 h after surgery.
6. Quality of recovery will be assessed 24 h and 48 h postoperatively using the Chinese version of the global 15-item QoR questionnaire (QoR-15).[13]
7. Patient satisfaction with pain management will be assessed 48 h after surgery using an 11-point Likert scale (0 = entirely unsatisfied; 10 = fully satisfied).
8. Time to first bowel movement and time to first passage of flatus will be recorded to assess bowel function. Recovery of bowel function between two groups will be compared.

Participant timeline

The participant timeline is demonstrated in **Table 1**

Table 1 **Participant timeline**

STUDY PERIOD														
	Enrolment	Allocation	Post-allocation											
TIMEPOINT**	*preoperative*	0 day	*surgery*	*0.5h*	*1h*	*2h*	*4h*	*8h*	*12h*	*24h*	*2d*	*3d*	*4d*	*5d*
ENROLMENT:	X													
Eligibility screen	X													
Informed consent	X													
Random allocation		X												
INTERVENTIONS:														
Baseline data	X	X												
Systemic lidocaine		X												
Intraoperative data			X											
ASSESSMENTS:														
CAM										X	X	X	X	
NRS score				X	X	X	X	X		X	X			
Emergence Agitation				X	X									
Postoperative opioid consumption											X			
QoR-15	X									X	X			
patient satisfaction											X			
PONV				♦	—	—	—	—	—	—	♦			
Dizziness				♦	—	—	—	—	—	—	♦			
Time to first bowel movement				♦	—	—	—	—	—	—	—	—	—	♦
Time to first passage of flatus				♦	—	—	—	—	—	—	—	—	♦	
Time of first analgesia demand				♦	—	—	—	—	—	—	♦			

Study monitoring

Data monitoring and quality assurance

All assessments will be carried out by study team members blinded to the treatment allocation. All investigators will receive standardised training for neurocognitive and delirium assessments before study initiation. The completed CRFs will be checked by a qualified study coordinator. Severe adverse events will be monitored so that patients could be discontinued from the study. The Ethical Committees of Fujian Provincial Hospital have complete responsibility for monitoring the conduct of the research and the quality of data. Data analyses performed by the primary investigator (Dr Xincheng Liao) will be supervised by an independent statistician (not involved in the surgery) from the Ethical Committees of Fujian Provincial Hospital. Missing intraoperative data, if any, will be obtained from the electronic medical record. The postoperative data will be received during the first five postoperative days via interview.

Harm

We do not expect that the study would expose participants to any severe hazards. Lidocaine-related adverse events, including central nervous system toxicity, such as central nervous system depression, dizziness and convulsions during the trial, will be recorded and assessed by Dr Yusheng Yao. Considering lidocaine's toxicity, we will avoid plasma lidocaine concentrations reaching 5 μg mL^{-1}. Lipid emulsion 20% will be readily prepared in case of local anaesthetic toxicity.[9] The study will be stopped if there is a clinical suspicion of harm of the intervention. All serious and unexpected adverse events during the study will be recorded, closely monitored, and reported to the Ethical Committees of Fujian Provincial Hospital as soon as possible, with the intentions of a resolution or even termination of the study if necessary.

Follow-up and withdrawal

All the participants will complete a five days' follow-up. Any participants who do not meet the entire five-day follow-up process due to deviation from intervention, discontinuation for personal

reasons, or contact failure will not be replaced by other patients. All patients can decide to withdraw at any time.

Patient and public involvement

None.

Statistics

Loss to follow-up

Although we expect a negligible loss of patients to follow-up, we have accounted for up to 10% loss to follow-up in our sample size calculation. If a patient withdraws from the study prematurely, data will be collected under the informed consent up to a consent withdrawal point. Analyses of all outcomes will be performed according to the intention-to-treat principle, and once enrolled, all participants will be analysed.

Sample size

Our sample size calculation for testing the efficacy of systemic lidocaine is based on the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery. Based on our institution's retrospective medical record, the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery is approximate 21%. According to power analysis (a type I error rate of 5% and a power of 0.8), we need 458 participants per group to detect a reduction in the prevalence of POD by one-third. Allowing for 10% of withdrawal or drop out, we will enroll 1020 participants in this study.

Data analysis

All statistical analyses will be conducted using the IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA). We will use Shapiro-Wilk test and the Q-Q plot to assess the normality distribution of the continuous data. Normal distribution and Skewed distribution variables will be presented as mean (standard deviation, SD) or median (interquartile range, IQR). Categorical variables will be expressed as numbers (proportion). Independent t-tests or Mann-Whitney U-tests will be used to analyse the global QoR-15 score, postoperative cumulative opioid consumption, bowel function and patient satisfaction between the groups. For

each statistical comparison, the 95% confidence interval (CI) of the difference is given. Chi-Square test or Fisher's exact test will be used to compare the prevalence of postoperative delirium, the incidence of dizziness and PONV between the lidocaine group and the control group. Additionally, the area under the curve (AUC) of NRS pain scores over 48 h will be calculated using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). A two-tailed *P* value of less than 0.05 is considered statistically significant.

Data management

Before initiating the study, an electronic case report form (eCRF) is established and available online at a dedicated website with password-protected access for each participating centre. Each enrolled patient will be assigned an identification number. Participants' identification data will be kept confidential until the results of the study are published. All the research data pertinent to the clinical investigation will be recorded into the e-CRF. Data are entered and double-checked for accuracy. The final dataset is encrypted and stored on the secure Research Electronic Data Capture to protect confidentiality before, during, and after the trial.

DISCUSSION

Perioperative lidocaine infusion is widely used in pain control and offers beneficial clinical efficacy, especially in colorectal surgery. The 2018 edition of a Cochrane review concluded that systemic lidocaine could improve postoperative outcomes, including gastrointestinal recovery, hospital stay length, opioid requirements and suggested that perioperative systemic lidocaine could benefit colorectal surgery patients[14] Moreover, preclinical trials suggest that systemic lidocaine might have neuroprotective effects in elderly patients undergoing noncardiac surgery such as spine and orthopaedic surgery.[7] With the increasing number of elderly patients undergoing colorectal surgery and the growing incidence of postoperative delirium, the management of geriatric patients has become the forefront of colorectal surgery. We hypothesise that administering systemic lidocaine perioperatively would reduce the prevalence of postoperative delirium in elderly patients undergoing laparoscopic colorectal surgery.

Elderly patients are exposed to a higher risk of POD because of predisposing risk factors such as impaired functional status, comorbidity, malnutrition, cognitive impairment and feeble brain.[1] Today the common explanation for the development of POD is increased neuroinflammatory activity and immuno-hormonal response due to perioperative stress.[15] Proof of the role of neuroinflammation in this process is the excessive production of generally proinflammatory chemokine such as TNF, interleukin (IL)-6 and IL-8, which is found in elderly patients with delirium.[16] To date, the anti-inflammatory properties of lidocaine have been well characterised.[17,18] Several clinical studies show that perioperative administration of lidocaine is significantly associated with attenuation of the surgery-induced release of proinflammatory cytokines, e.g. IL-6 and IL-8, and/or decreased C-reactive protein levels.[19-25] Thus, lidocaine may be a candidate for preventing POD in elderly patients.

This study is subject to several limitations. First, we do not assess plasma lidocaine levels. After a loading dose of 1.5 mg kg^{-1} is given as an injection over 10 min, an infusion of 1.5 mg kg^{-1} h^{-1} until the end of the surgery is administered. Which is recommended by the international consensus statement of the use of intravenous lidocaine for postoperative pain and recovery.[9] This dosage results typically in plasma concentrations < 5 µg mL^{-1} (toxic level). But the accumulation of lidocaine is still a concern for neurotoxicity with continuous infusion, especially in elderly patients. We will prepare Lipid emulsion 20% wherever systemic lidocaine is used in case of an adverse incident when elderly patients receive an intravenous lidocaine infusion. Secondly, only elderly surgical patients undergoing laparoscopic colorectal surgery are enrolled in our trials, which may limit the generalisability of this study. Thirdly, it is possible that during daily delirium assessments, some periods of acute-onset inattention, disorganised thinking, or altered level of consciousness may be missed, potentially leading to misclassification of these outcomes. Despite this, routine testing once per day is an accepted method of diagnosing delirium.[26]

In the present project, we expect to definitively clarify the efficacy of systemic lidocaine on postoperative delirium in elderly patients scheduled for laparoscopic colorectal surgery. This study results may support systemic lidocaine reducing POD prevalence in elderly patients.

Ethical approval and dissemination

The Ethical Committees of Fujian Provincial Hospital approved the study protocol version 2.0 on June 24th, 2021 (Ref: K2021-06-018). The study period is designed to be from October 2021 to October 2022, and the clinical trial will be completed within 12 months. This trial was registered at the Chinese Clinical Trials Registry（www.chictr.org.cn, trial identifier： ChiCTR2100050314） on August 26th, 2021. The result of this study will be disseminated via manuscript publication and peer-reviewed journals.

Protocol amendments

Any modifications of the protocol which may impact the implementation of the study, probably benefit the patients, or affect patients' safety, including changes in study design, sample size, and study procedures, will be submitted to the Ethical Committees of Fujian Provincial Hospital. And the Ethical Committees will communicate for the amendment approval.

Trial status

This study has not been started.

Author contributions

LC, FB and YY designed the study. LC and FB drafted the manuscript of the protocol. YY critically revised the manuscript. LC, FB, YJ, LH, and QB participated in the conduct of the study. All authors have read and given consent to the final manuscript.

Data sharing statement

The individual participant data are available upon reasonable request from the principal investigator (Yusheng Yao, ORCID: 0000-0001-8488-8876) after publication. The study protocol, statistical analysis plan, and clinical study report will also be available.

Patient consent for publication

Obtained.

Competing interests

The authors have no conflicts of interest.

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Provenance and peer review

Not commissioned; externally peer-reviewed.

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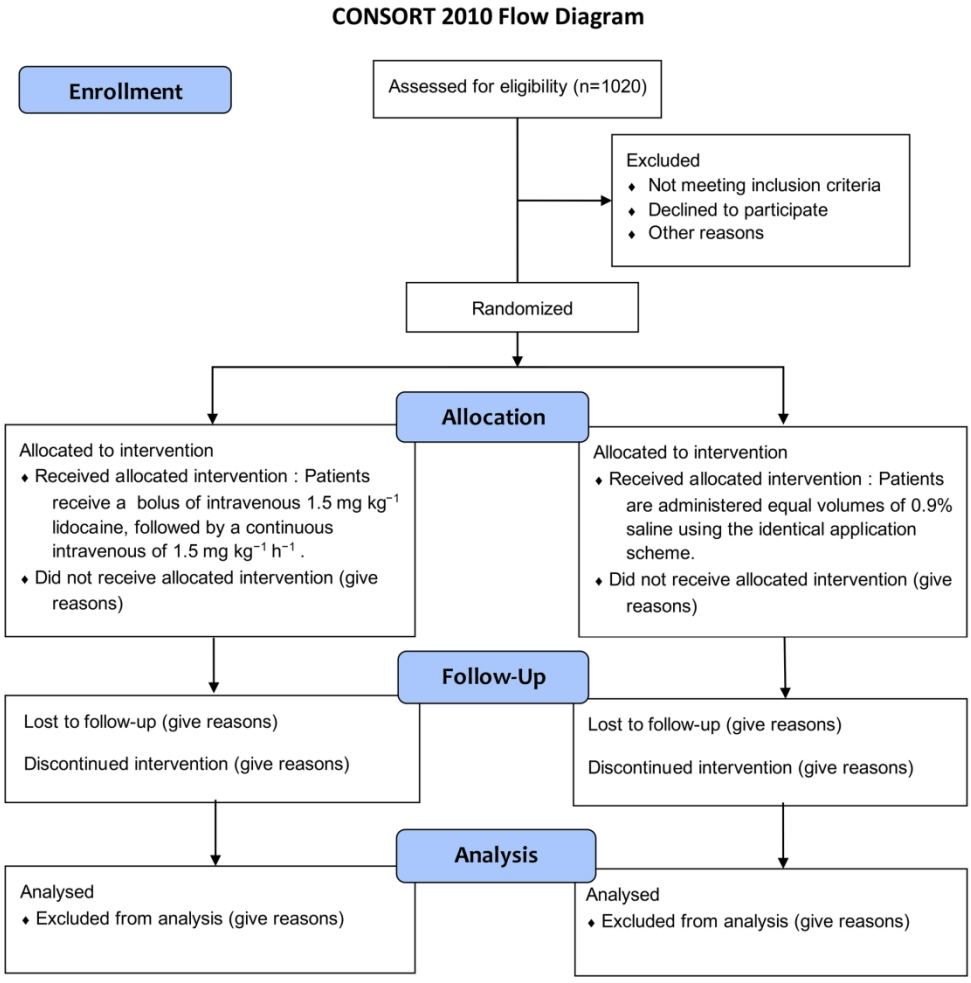
Figure legends

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram describing patient progress through the study.

Abbreviations: POD, postoperative delirium.



Consolidated Standards of Reporting Trials (CONSORT) flow diagram describing patient progress through the study.

90x90mm (600 x 600 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1 line 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 line 19
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	Page 15 line 2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 14 line 8
	5b	Name and contact information for the trial sponsor	n/a
	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	n/a
	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)	n/a
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3 line 16
	6b	Explanation for choice of comparators	Page 4 line 3
Objectives	7	Specific objectives or hypotheses	Page 4 line 11
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 4 line 18
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 5 line 24
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 line 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 6 line 10
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	Page 7 line 12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 8 line 12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 11 line 13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 6 line 1
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 6 line 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 4 line 25

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 6 line 7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 10 line 4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10 line 25
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	Page 12 line 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 11 line 21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	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)	n/a
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	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	n/a
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	Page 10 line 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14 line 1
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)	Page 14 line 8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 5 line 1
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	Page 12 line 12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14 line 25

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	n/a
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	n/a
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	Page 7 line 8
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a

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

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Efficacy of systemic lidocaine on postoperative delirium in elderly patients undergoing laparoscopic colorectal surgery: study protocol for a multicentre, prospective, double-blind, randomised, parallel-group, equivalence, placebo-controlled trial

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Anaesthesia

Protocol

Efficacy of systemic lidocaine on postoperative delirium in elderly patients undergoing laparoscopic colorectal surgery: study protocol for a multicentre, prospective, double-blind, randomised, parallel-group, equivalence, placebo-controlled trial

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ABSTRACT

Introduction: Systemic lidocaine may reduce pain intensity and accelerate postoperative recovery. However, the efficacy of systemic lidocaine on cognitive function has not been established. This study protocol is designed to clarify the effectiveness of lidocaine on postoperative delirium (POD) in elderly patients scheduled for elective laparoscopic colorectal surgery.

Methods and analysis: This is a prospective, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial. One thousand and twenty elderly patients will be randomly allocated in a ratio of 1:1 to receive either systemic lidocaine (a bolus of 1.5 mg kg^{-1}, followed by an infusion of 1.5 mg kg^{-1} h^{-1} until the end of the surgery) or identical volumes and rates of 0.9% saline. The primary outcome measure is the prevalence of POD during the first five postoperative days. Secondary outcomes include emergence agitation, the area under the curve of the Numerical Rating Scale pain scores over 48 h, postoperative 48-h cumulative opioid consumption, postoperative nausea and vomiting, recovery of bowel function, quality of recovery, and patient satisfaction with postoperative analgesia.

Ethics and dissemination: The Ethical Committees of Fujian Provincial Hospital approved the study protocol (Ref: K2021-06-018). Other participating subcentres must also obtain ethics committee approval before the start of the study. We will obtain written informed consent from each patient before they are randomised. This study will be presented at scientific conferences and submitted to international journals.

Trial registration details: This study has been registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn, identifier number: ChiCTR2100050314).

Keywords: postoperative delirium; lidocaine; elderly patients; laparoscopic colorectal surgery

Article Summary

Strengths and limitations of this study

- The study design will be multicentre, prospective, randomised, double-blinded, equivalent and placebo-controlled.
- This is the first study to evaluate the efficacy of systemic lidocaine on postoperative delirium (POD) in geriatric patients undergoing laparoscopic colorectal surgery.
- Only elderly patients following laparoscopic colorectal surgery will be included, limiting the generalisability of the results.
- The anaesthetic-sparing effects of lidocaine might weaken the efficiency of blindness to the treating anaesthesiologist.
- Lidocaine will be administered only until the end of the surgery, not postoperatively, which may have affected the results.

INTRODUCTION

Background

Postoperative delirium (POD) is a debilitating postoperative neurological complication that often starts in the postanesthesia care unit and appears up to 5 days after surgery. [1] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) has defined POD as an acute and fluctuating alteration of the mental state of reduced awareness and disturbance of attention. [2] Advanced age is one of the significant predisposing factors for POD. The prevalence of delirium varies from 20% to 45% in geriatric surgical patients. [3] POD is associated with several adverse clinical consequences, including prolonged hospitalisation, additional healthcare costs, and increased morbidity and mortality risks. Furthermore, POD development may induce cognitive impairment after surgery, resulting in significant loss of functional independence and long-term cognitive decline. [4]

Systemic lidocaine is widely used for its beneficial effects on postoperative analgesia and recovery, including alleviating visceral pain, accelerating gastrointestinal recovery, and

reducing hospital stay length. [5] In addition, previous clinical research has reported a beneficial effect of lidocaine on neurologic injury after major surgeries. [6-8] Because lidocaine's therapeutic index is relatively low, central nervous system toxicity may start when plasma levels are only slightly higher than therapeutic levels. Consequently, Lidocaine might be fatal to elderly patients when misused. [9] To date, the efficacy of systemic lidocaine on POD in older patients undergoing major surgery remains elusive. We hypothesise that administering systemic lidocaine intraoperatively will reduce the prevalence of POD in elderly patients. The proposed clinical trial aims to establish evidence for the efficacy of lidocaine on the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery.

Objectives

Our goal is to evaluate the efficacy of systemic lidocaine on POD in elderly patients undergoing laparoscopic colorectal surgery. Therefore, we will test the primary hypothesis that patients receiving systemic lidocaine have a lower prevalence of POD within the first five postoperative days. Second, we will test the hypotheses that systemic lidocaine alleviates postoperative pain, reduces postoperative opioid consumption, enhances the quality of recovery, and further improves patient satisfaction.

Trial design

This study is a prospective, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial. A total of 1020 participants will be randomly assigned to the lidocaine group or saline group at a ratio of 1:1. The study schema is presented in **Figure 1**.

METHODS

Recruitment and study setting

Participants scheduled for elective laparoscopic colorectal surgery under general anaesthesia will be enrolled by a member of the research team. Patients participating in the study will be screened according to inclusion and exclusion criteria. A study investigator will visit patients scheduled for laparoscopic colorectal surgery who meet the eligibility criteria and express interest in participating in this trial. A research team member will verbalise written consent and

answer any questions about the study in detail (i.e., the study purpose, procedures, time commitment, the potential risks and benefits associated with participation in the survey). Each participant will have enough time to consider participating in this trial. The participants will be recruited for this study after signing informed consent. The enrollment period will extend to over twenty-four months.

Inclusion criteria

Participants need to fulfil the following criteria:

- Aged 65 years or older.
- Undergoing laparoscopic colorectal surgery.
- American Society of Anesthesiologists (ASA) physical status I to III.

Exclusion criteria

Patients with the following conditions will be excluded:

- History of mental illness or scored less than 27 on the baseline Mini-Mental State examination before operation.
- Patients weighing < 40 kg.
- Severe cardiac arrhythmias include Adams-Stokes syndrome, sick sinus syndrome, second- and third-degree atrioventricular block, double-bundle branch block, and severe bradycardia.
- Symptomatic cerebrovascular disease (e.g., prior stroke).
- Severe renal dysfunction (serum creatinine more than 2 mg dL^{-1}).
- Severe hepatic dysfunction (liver function tests more than 1.5 times the upper limit of normal).
- Being scheduled to be admitted to the intensive care unit.
- Being unable to communicate or other situations that are not appropriate for this study.

Study locations

We will conduct this trial in four hospitals, including Fujian Provincial Hospital (primary centre), People's Hospital Affiliated with Fujian University of Traditional Chinese Medicine (subcentre), the 900th Hospital of Joint Service Support Force of People's Liberation Army of China (subcentre), and Sanming First Hospital (subcentre).

Randomisation, allocation concealment, and blinding

After obtaining written informed consent, an allocation sequence will be generated using a computer-generated randomisation list. Participants will be randomised to receive a continuous intravenous infusion of lidocaine or 0.9% saline at a ratio of 1:1. This study is a simple allocation with no stratifications and blocks. Group assignments will be concealed in sequentially numbered opaque envelopes opened on the day of surgery. The study medications will be prepared by an independent research nurse who is not involved in the patient's care. All participants, surgeons, anesthesiologists, and research personnel will not be informed of the group assignments during the study period.

Intervention

Patients in the lidocaine group will receive a bolus of 1.5 mg kg^{-1} intravenous lidocaine over 10 min before anaesthesia induction. A continuous infusion of 1.5 mg kg^{-1} h^{-1} systemic lidocaine will be administered until the end of the surgery. Ideal body weight will be used for lidocaine dose calculation. Patients in the saline group will be administered equal volumes of 0.9% saline using the identical application scheme. The study medications will be prepared in two syringes: a 20 mL syringe for the bolus injection and a 50 mL syringe for the continuous intravenous infusion. This approach will result in both groups receiving an equal volume per unit of time. Blood samples from both groups will be collected to determine plasma drug concentrations at the end of surgery.

General anaesthesia and postoperative analgesia protocol

Upon arrival at the operating room, all patients will be monitored with pulse oximetry, invasive blood pressure and electrocardiogram. We will induce general anaesthesia using 2 mg kg^{-1} propofol and 0.6 μg kg^{-1} sufentanil. A bolus injection of rocuronium 0.6 mg kg^{-1} will be administered to facilitate cuffed endotracheal tube intubation. We will maintain an end-tidal carbon dioxide partial pressure ($PaCO_2$) of 35 to 45 mmHg using pressure-controlled mechanical ventilation. Anaesthesia will be held by inhalation of sevoflurane, aiming for a bispectral index of 40–60. Intravenous remifentanil infusion will be adjusted to maintain the hemodynamic parameter (mean arterial pressure and heart rate) fluctuation within 20% of baseline. The neuromuscular blockade will be achieved by intermittent injections of

cisatracurium 5 mg as needed. All patients will receive patient-controlled intravenous analgesia (PCIA) with sufentanil for postoperative analgesia. The PCIA pump (REHN II; Renxian Medical Corporation, Jiangsu, China) will be set to deliver 1 μg h^{-1} sufentanil. If the numeric rating scale (NRS) for pain exceeds three or the patients require, a bolus injection of sufentanil 2 μg will be administered as a rescue analgesic, with a 10-min lockout interval via the PCIA pump, and the maximum dose of sufentanil will be set at 10 μg h^{-1}.

OUTCOMES

Primary outcome

The primary outcome is the occurrence of POD during the first five postoperative days. The Confusion Assessment Method (CAM) is a screening instrument for nonpsychiatrically trained clinicians to evaluate POD according to the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) criteria. Delirium can be diagnosed via interview using the CAM algorithm following four criteria: (1) acute onset or fluctuating course; (2) inattention; (3) disorganised thinking; and (4) altered level of consciousness. The research members will assess POD twice daily (between 8 and 10 am and between 6 and 8 pm). If criteria 1 and 2 and either of 3 or 4 are present, delirium is diagnosed. [10]

Secondary outcomes

Secondary outcomes are as follows:

1. The AUCs of the NRS pain scores over time: The postoperative pain at rest and on movement will be assessed using a self-reported NRS score (no pain=0; maximum pain=10) at 0.5, 1, 2, 4, 8, 24 and 48 h postoperatively.
2. The emergence agitation will be assessed within stay in the PACU using the Riker Sedation-Agitation Scale. [11] A score＞of 4 is defined as emergence agitation.
3. The severity of POD will be evaluated using CAM-Severity (CAM-S). [12] CAM-S scores range from 0 to 7 (7 indicating the most severe). Inattention, disorganised thinking, and altered level of consciousness will be rated as absent (0), mild (1) or marked (2). Acute onset or fluctuation will be absent (0) or present (1).

4. Postoperative cumulative opioid consumption over 48 h postoperatively will be recorded.
5. Postoperative nausea and vomiting (PONV) will be assessed within 48 h postoperatively. PONV scores are assessed using a 4-point scale (1 = absent; 2 = mild nausea; 3 = severe nausea; and 4 = vomiting). [13]
6. The occurrence of dizziness will be assessed within 48 h after surgery.
7. Quality of recovery will be assessed 24 h and 48 h postoperatively using the Chinese version of the global 15-item QoR questionnaire (QoR-15). [14]
8. Patient satisfaction with pain management will be assessed 48 h after surgery using an 11-point Likert scale (0 = entirely unsatisfied; 10 = fully satisfied).
9. Time to first bowel movement and time to first passage of flatus will be recorded to assess bowel function. The recovery of bowel function between the two groups will be compared.
10. The plasma concentration of lidocaine will be determined by high-performance liquid chromatography (HPLC) at the end of surgery.
11. The local anaesthetic toxicity will be recorded by CRF forms, such as metallic taste, tinnitus, and abnormal vision.

Participant timeline

The participant timeline is demonstrated in **Table 1**

Table 1 Participant timeline

STUDY PERIOD														
	Enrolment	Allocation	Post-allocation											
TIMEPOINT**	*preoperative*	0 day	*surgery*	*0.5 h*	*1 h*	*2 h*	*4 h*	*8 h*	*12 h*	*24 h*	*2 d*	*3 d*	*4 d*	*5 d*
ENROLMENT:	X													
Eligibility screen	X													
Informed consent	X													
Random allocation		X												
INTERVENTIONS:														
Baseline data	X	X												
Systemic lidocaine		X												
Intraoperative data			X											
ASSESSMENTS:														
POD and severity									X	X	X	X	X	X
NRS pain score				X	X	X	X	X	X	X	X			
Emergence agitation				X	X									
Postoperative opioid consumption											X			
QoR-15	X									X	X			
Patient satisfaction											X			
PONV				♦	—	—	—	—	—	—	♦			
Dizziness				♦	—	—	—	—	—	—	♦			
Time to first bowel movement				♦	—	—	—	—	—	—	—	♦		
Time to first passage of flatus				♦	—	—	—	—	—	—	—	♦		
Time of first analgesia demand				♦	—	—	—	—	—	—	♦			

Study monitoring

Data monitoring and quality assurance

All assessments will be carried out by study team members blinded to the treatment allocation. All investigators will receive standardised neurocognitive and delirium assessment training before study initiation. A qualified study coordinator will check the completed CRFs. Severe adverse events will be monitored so that patients can be discontinued from the study. The Ethical Committees of Fujian Provincial Hospital will complete responsibility for monitoring the conduct of the research and the quality of the data. Data analyses performed by a study investigator will be supervised by an independent statistician (not involved in the surgery) from the Ethical Committees of Fujian Provincial Hospital. Missing intraoperative data, if any, will be obtained from the electronic medical record. The postoperative data will be received via interview during the first five postoperative days.

Harm

We do not expect the study to expose participants to any severe hazards. Lidocaine-related adverse events, including central nervous system toxicity, such as central nervous system depression, dizziness and convulsions during the trial, will be recorded and assessed by Dr Yusheng Yao. Considering lidocaine's toxicity, we will avoid plasma lidocaine concentrations reaching 5 μg mL^{-1}. A 20% lipid emulsion will be readily prepared in case of local anaesthetic toxicity.[9] The study will be stopped if there is a clinical suspicion of harm from the intervention. All serious and unexpected adverse events during the study will be recorded, closely monitored, and reported to the Ethical Committees of Fujian Provincial Hospital as soon as possible, with the intentions of a resolution or even termination of the study if necessary.

Follow-up and withdrawal

All the participants will complete a five-day follow-up. Any participants who do not meet the entire five-day follow-up process due to deviation from intervention, discontinuation for personal reasons, admission to the ICU involuntarily due to bleeding or shock, or contact failure will not be replaced by other patients. All patients can decide to withdraw at any time.

Statistics

Loss to follow-up

Although we expect a negligible loss of patients to follow-up, we account for up to 10% loss to follow-up in our sample size calculation. If a patient withdraws from the study prematurely, data will be collected under the informed consent up to a consent withdrawal point. Analyses of all outcomes will be performed according to the intention-to-treat principle, and once enrolled, all participants will be analysed.

Sample size

Our sample size calculation for testing the efficacy of systemic lidocaine is based on the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery. Based on our institution's retrospective medical record, the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery is approximately 21%. According to power analysis (a type I error rate of 5% and a power of 0.8), we will need 458 participants per group to detect a reduction in the prevalence of POD by one-third. Allowing for 10% withdrawal or dropout, we will enroll 1020 participants in this study.

Data analysis

All statistical analyses will be conducted using IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA). We will use the Shapiro–Wilk test and the Q-Q plot to assess the normality distribution of the continuous data. Normally, skewed distribution variables will be presented as mean (standard deviation, SD) or median (interquartile range, IQR). Categorical variables will be expressed as numbers (proportions). Independent t tests or Mann–Whitney U–tests will be used to analyse the global QoR-15 score, severity of POD, postoperative cumulative opioid consumption, bowel function and patient satisfaction between the groups. The difference's 95% confidence interval (CI) is given for each statistical comparison. The chi-square test or Fisher's exact test will be used to compare the prevalence of POD and the incidence of dizziness and PONV between the lidocaine group and the saline group. Postoperative NRS pain scores will be assessed using a two-way repeated-measures analysis of variance. Bonferroni correction

will be applied for comparing groups at each time point, with p values adjusted by multiplying the nominal p value by the number of tests. Additionally, the area under the curve (AUC) of NRS pain scores over 48 h will be calculated using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). A two-tailed p value of less than 0.05 is considered statistically significant.

Interim analysis

An interim analysis will initiate the primary outcome when the collected cases reach 50% of the target sample size. The primary purpose of the medium-term plan is to assess the safety and effectiveness of interventions and to reestimate sample sizes. We will calculate alpha expenditure by the O'Brien–Fleming method, and the final p value will be regarded as 0.048. There will be no plans to terminate the trial for futility.

Patient and public involvement

Clinicians and a medical statistician took part in the design of the study. Patients nor public parties were involved in the design or conducting of the study.

Data management

Before initiating the study, an electronic case report form (eCRF) will be established and available online at a dedicated website with password-protected access for each participating centre. Each enrolled patient will be assigned an identification number. Participants' identification data will be kept confidential until the study results are published. All the research data pertinent to the clinical investigation will be recorded in the e-CRF. Data will be entered and double-checked for accuracy. The final dataset will be encrypted and stored on the secure Research Electronic Data Capture to protect confidentiality before, during, and after the trial.

DISCUSSION

Perioperative lidocaine infusion is widely used in pain control and offers beneficial clinical efficacy, especially in colorectal surgery. The 2018 edition of a Cochrane review concluded that systemic lidocaine could improve postoperative outcomes, including gastrointestinal recovery,

hospital stay length, and opioid requirements, and suggested that perioperative systemic lidocaine could benefit colorectal surgery patients. [15] Moreover, preclinical trials suggest that systemic lidocaine might have neuroprotective effects in elderly patients undergoing noncardiac surgery such as spine and orthopaedic surgery. [7] With the increasing number of elderly patients undergoing colorectal surgery and the growing incidence of POD, the management of geriatric patients has become the forefront of colorectal surgery. We hypothesise that administering systemic lidocaine perioperatively would reduce the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery.

Elderly patients are exposed to a higher risk of POD because of predisposing risk factors such as impaired functional status, comorbidity, malnutrition and cognitive impairment. [1] Currently, the standard explanation for the development of POD is increased neuroinflammatory activity and immuno-hormonal response due to perioperative stress. [16] Proof of the role of neuroinflammation in this process is the excessive production of generally proinflammatory chemokines such as TNF, interleukin (IL)-6 and IL-8, which is found in elderly patients with delirium. [17] To date, the anti-inflammatory properties of lidocaine have been well characterised. [18,19] Several clinical studies have shown that perioperative administration of lidocaine is significantly associated with attenuation of the surgery-induced release of proinflammatory cytokines, e.g., IL-6 and IL-8, and decreased C-reactive protein levels. [20-26] Thus, lidocaine may be a candidate for preventing POD in elderly patients.

This study is subject to several limitations. First, lidocaine will only be infused for safety reasons until the end of surgery rather than postoperatively. Intravenous lidocaine outside the operating room requires close monitoring on a level 2 or higher ward, [27] which is not available in all participating centres. The accumulation of lidocaine is still a concern for neurotoxicity with continuous infusion, especially in elderly patients. We will prepare a 20% lipid emulsion wherever systemic lidocaine is used in case of an adverse incident when elderly patients receive an intravenous lidocaine infusion. Second, only elderly surgical patients undergoing laparoscopic colorectal surgery will be enrolled in our trials, which may limit the generalisability of this study. Third, it is possible that during daily delirium assessments, some periods of acute-onset inattention, disorganised thinking, or altered level of consciousness may be missed, potentially

leading to misclassification of these outcomes. Despite this, routine testing twice per day is an accepted method of diagnosing delirium. [28]

In the present project, we expect to definitively clarify the efficacy of systemic lidocaine on postoperative delirium in elderly patients scheduled for laparoscopic colorectal surgery. These study results may support the idea that systemic lidocaine reduces POD prevalence in elderly patients.

Ethics and dissemination

The Ethical Committees of Fujian Provincial Hospital approved the study protocol version 2.0 on June 24th, 2021 (Ref: K2021-06-018). Other participating subcentres must also obtain ethics committee approval documents prior to the start of clinical trials. The study period is designed to be from March 2022 to March 2024, and the clinical trial will be completed within 24 months. This trial was registered at the Chinese Clinical Trials Registry (www.chictr.org.cn, trial identifier: ChiCTR2100050314) on August 26th, 2021. The results of this study will be disseminated via manuscript publication and peer-reviewed journals.

Protocol amendments

Any modifications of the protocol that may impact the study's implementation, probably benefit the patient's, or affect patients' safety, including changes in study design, sample size, and study procedures, will be submitted to the Ethical Committees of Fujian Provincial Hospital. The Ethical Committees will communicate for the amendment approval.

Trial status

This study has not been started.

Author contributions

Xincheng Liao: conceptualisation, design, investigation, and writing-original draft. Bingbing Fu: conceptualisation, design, data curation, formal analysis, and writing-original draft. Jia Yun: conceptualisation, design, investigation, and resources. Huifen Lin: conceptualisation, design, investigation, and resources. Bin Qian: conceptualisation, design, investigation, and resources.

Yusheng Yao: conceptualisation, design, resources, supervision, validation, funding acquisition, and writing-review & editing. All authors have critically reviewed the article and approved the final submitted version of the manuscript.

Data sharing statement

After publication, the individual participant data are available upon reasonable request from the principal investigator (Yusheng Yao, ORCID: 0000-0001-8488-8876). The study protocol, statistical analysis plan, and clinical study report will also be available.

Patient consent for publication

Not applicable.

Competing interests

None declared.

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Provenance and peer review

Not commissioned; externally peer-reviewed.

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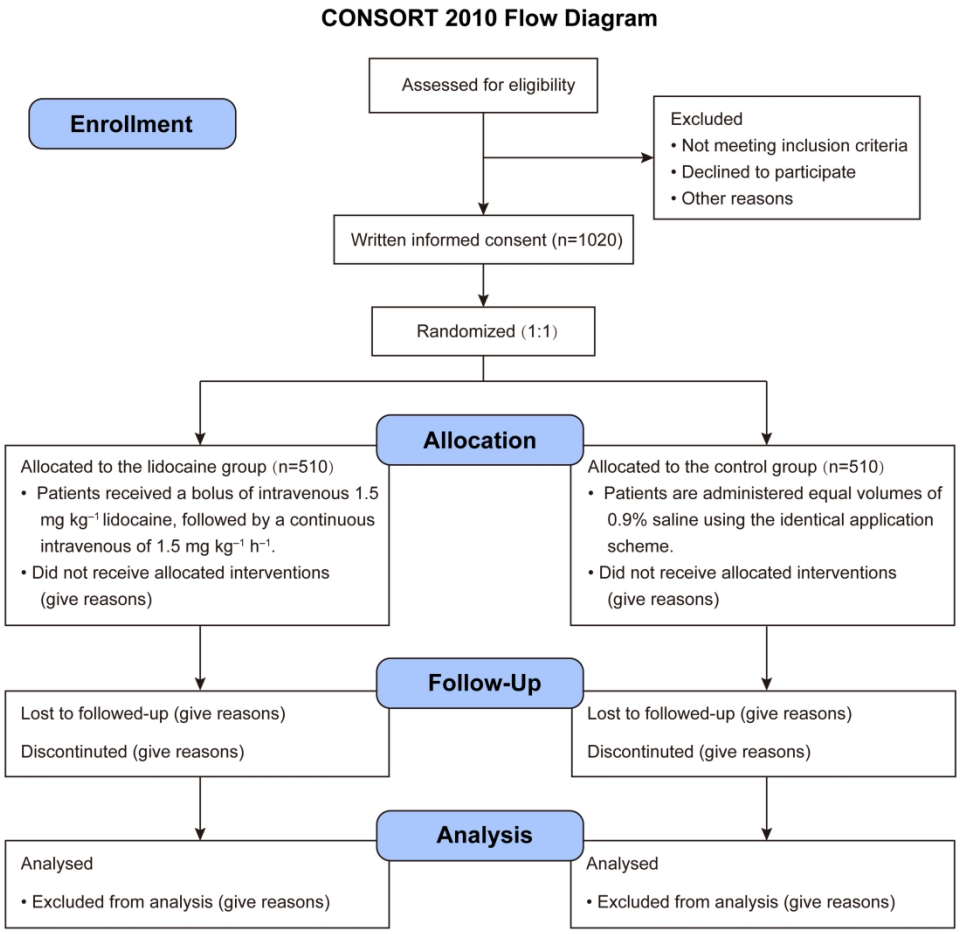
Figure legends

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram describing patient progress throughout the study.

Abbreviations: POD, postoperative delirium.



Consolidated Standards of Reporting Trials (CONSORT) flow diagram describing patient progress throughout the study.

120x120mm (600 x 600 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1 line 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 line 19
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	Page 15 line 2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 14 line 8
	5b	Name and contact information for the trial sponsor	n/a
	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	n/a
	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)	n/a
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3 line 16
	6b	Explanation for choice of comparators	Page 4 line 3
Objectives	7	Specific objectives or hypotheses	Page 4 line 11
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 4 line 18
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 5 line 24
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 line 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 6 line 10
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	Page 7 line 12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 8 line 12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 11 line 13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 6 line 1
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 6 line 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 4 line 25

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 6 line 7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 10 line 4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10 line 25
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	Page 12 line 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 11 line 21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	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)	n/a
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	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	n/a
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	Page 10 line 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14 line 1
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)	Page 14 line 8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 5 line 1
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	Page 12 line 12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14 line 25

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	n/a
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	n/a
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	Page 7 line 8
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a

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