


BMJ Open Efficacy of systemic lidocaine in postoperative delirium in elderly patients undergoing laparoscopic colorectal surgery: study protocol for a multicentre, prospective, double-blind, randomised, parallel-group, superiority, 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 in cognitive function has not been established. This study protocol is designed to clarify the effectiveness of lidocaine in 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, followed by an infusion of 1.5 mg/kg/hour 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 5 postoperative days. Secondary outcomes include emergence agitation, the area under the curve of the Numeric Rating Scale pain scores over 48 hours, postoperative 48-hour cumulative opioid consumption, postoperative nausea and vomiting (PONV), recovery of bowel function, quality of recovery, and patient satisfaction with postoperative analgesia.

Ethics and dissemination The Ethical Committee of the 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 number ChiCTR2100050314.

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study design will be multicentre, prospective, randomised, double-blind, superiority and placebo-controlled.
- ⇒ This is the first study to evaluate the efficacy of systemic lidocaine in postoperative delirium 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 affect the results.

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 risk of morbidity and mortality. Furthermore, the development of POD 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 length of stay.⁵ In addition, previous clinical research has reported a beneficial effect of lidocaine on neurological 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 in 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 in the prevalence of POD in elderly patients undergoing laparoscopic colorectal surgery.

Objectives

Our goal is to evaluate the efficacy of systemic lidocaine in 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 5 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 the 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 the 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 (ie, study purpose, procedures, time commitment, potential risks and benefits associated with participation in the survey). Each participant will have enough time to consider participating in this trial. Participants will be recruited for this study after signing an informed consent. The enrolment period will extend to over 24 months.

Inclusion criteria

Participants need to fulfil the following criteria:

- ▶ Age 65 years or older.
- ▶ Undergoing laparoscopic colorectal surgery.
- ▶ American Society of Anesthesiologists physical status I–III.

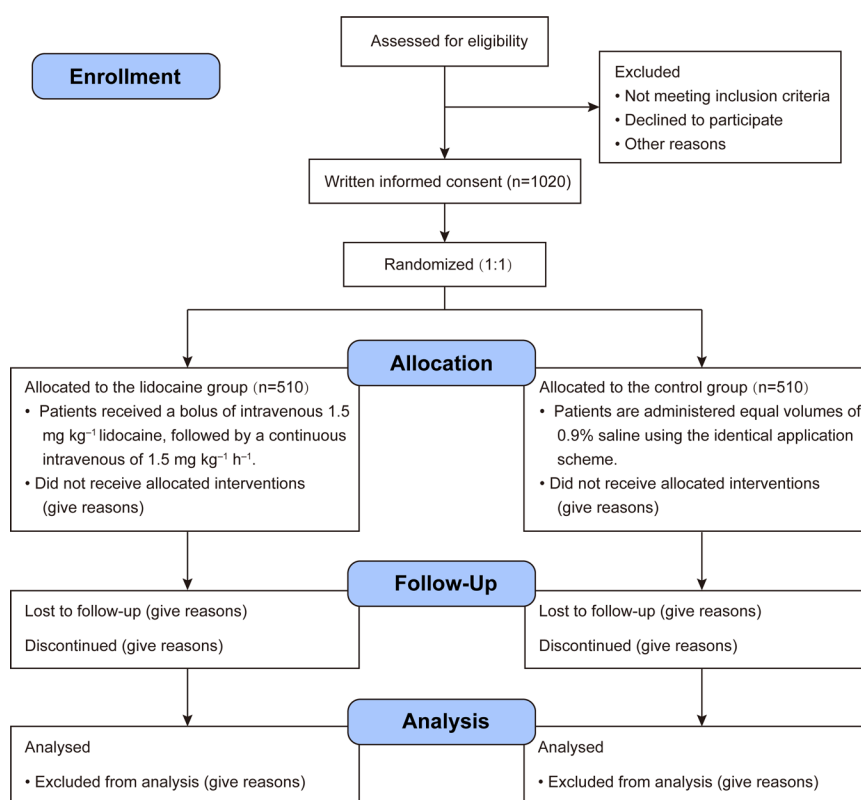


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram describing patients' progress throughout the study.

Exclusion criteria

Patients with the following conditions will be excluded:

- ▶ History of mental illness or scoring less than 27 on the baseline Mini-Mental State Examination before operation.
- ▶ Patients weighing <40 kg.
- ▶ Severe cardiac arrhythmias including Adams-Stokes syndrome, sick sinus syndrome, second-degree and third-degree atrioventricular block, double-bundle branch block, and severe bradycardia.
- ▶ Symptomatic cerebrovascular disease (eg, prior stroke).
- ▶ Severe renal dysfunction (serum creatinine more than 2 mg/dL).
- ▶ Severe hepatic dysfunction (liver function test more than 1.5 times the upper limit of normal).
- ▶ Scheduled for admission to the intensive care unit.
- ▶ Unable to communicate or other situations that are not appropriate for this study.

Study locations

We will conduct this trial in four hospitals, namely Fujian Provincial Hospital (primary centre), People's Hospital Affiliated with Fujian University of Traditional Chinese Medicine (subcentre), 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 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, anaesthesiologists 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 intravenous lidocaine over 10 min before induction of anaesthesia. A continuous infusion of 1.5 mg/kg/hour of 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

On arrival at the operating room, all patients will be monitored with pulse oximetry, invasive blood pressure and ECG. We will induce general anaesthesia using 2 mg/kg propofol and 0.6 µg/kg sufentanil. A bolus injection of rocuronium 0.6 mg/kg will be administered to facilitate cuffed endotracheal tube intubation. We will maintain an end-tidal carbon dioxide partial pressure of 35–45 mm Hg using pressure-controlled mechanical ventilation. Anaesthesia will be held by inhalation of sevoflurane, aiming for a bispectral index of 40–60. Intravenous remifentanyl infusion will be adjusted to maintain the haemodynamic parameter (mean arterial pressure and heart rate) fluctuation within 20% of baseline. 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/hour of sufentanil. If the Numeric Rating Scale (NRS) for pain exceeds 3 or if the patient requires, 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/hour.

Outcomes

Primary outcome

The primary outcome is the occurrence of POD during the first 5 postoperative days. The Confusion Assessment Method (CAM) is a screening instrument for non-psychiatrically trained clinicians designed to evaluate POD according to the 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 two times per day (between 08:00 and 10:00 and between 18:00 and 20:00). If criteria 1 and 2 and either of 3 or 4 are present, delirium is diagnosed.¹⁰

Secondary outcomes

The secondary outcomes are as follows:

- ▶ Area under the curve (AUC) 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 hours postoperatively.
- ▶ Emergence agitation will be assessed within stay in the postanesthesia care unit (PACU) using the Riker Sedation-Agitation Scale.¹¹ A score of >4 is defined as emergence agitation.
- ▶ Severity of POD will be evaluated using CAM-Severity (CAM-S).¹² CAM-S scores range from 0 to 7, with 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).

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

Participant timeline

The participant timeline is demonstrated in [table 1](#).

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 Committee of the Fujian Provincial Hospital will complete the responsibility of monitoring the conduct of the research and the quality of the data. Data analyses performed by the study investigator will be supervised by an independent statistician (not involved in the surgery) from the Ethical Committee of the 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 5 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 a study investigator. Considering lidocaine's toxicity, we will avoid plasma lidocaine concentrations reaching 5 µg/mL. 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 Committee of the Fujian Provincial Hospital as soon as possible, with the intention of a resolution or even termination of the study if necessary.

Follow-up and withdrawal

All participants will complete a 5-day follow-up. Any participants who do not meet the entire 5-day follow-up process due to deviation from intervention, discontinuation for personal reasons, admission to the intensive care unit 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 enrol 1020 participants in this study.

Data analysis

All statistical analyses will be conducted using IBM SPSS Statistics V.25.0. 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 (SD) or median (IQR). Categorical variables will be expressed as numbers (proportions). Independent t-test or Mann-Whitney U test 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% CI is given for each statistical comparison. χ^2 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 to compare groups at each time

Table 1 Participant timeline

Time point	Study period													
	Enrolment				Allocation				Postallocation					
	Preoperative	0 day	Surgery	0.5 hour	1 hour	2 hours	4 hours	8 hours	12 hours	24 hours	2 days	3 days	4 days	5 days
Enrolment	X													
Eligibility screen	X													
Informed consent	X													
Random allocation		X												
Interventions														
Baseline data		X												
Systemic lidocaine			X											
Intraoperative data			X											
Assessments														
POD and severity								X	X	X	X	X	X	X
NRS pain score				X	X	X	X	X	X	X	X	X	X	X
Emergence agitation				X	X									
Postoperative opioid consumption									X	X				
QoR-15							X		X	X				
Patient satisfaction											X			
PONV				X	X	X	X	X	X	X	X	X	X	X
Dizziness				X	X	X	X	X	X	X	X	X	X	X
Time to first bowel movement				X	X	X	X	X	X	X	X	X	X	X
Time to first passage of flatus				X	X	X	X	X	X	X	X	X	X	X
Time of first analgesia demand				X	X	X	X	X	X	X	X	X	X	X

NRS, Numeric Rating Scale; POD, postoperative delirium; PONV, postoperative nausea and vomiting; QoR-15, 15-item quality of recovery questionnaire.

point, with p values adjusted by multiplying the nominal p value by the number of tests. Additionally, the AUC of NRS pain scores over 48 hours will be calculated using GraphPad Prism V.8 (GraphPad Software, San Diego, California, 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 re-estimate 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. Neither patients nor public parties were involved in the design or conduct 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 research data pertinent to the clinical investigation will be recorded on the eCRF. Data will be entered and double-checked for accuracy. The final data set 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 length of stay 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 non-cardiac 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 due to 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 tumor necrosis factor- α , interleukin (IL) 6 and IL-8, which are 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, for example, 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. Neurotoxicity due to accumulation of lidocaine remains a concern 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 trial, which may limit the generalisability of the 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 two times per day is an accepted method of diagnosing delirium.²⁸

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

ETHICS AND DISSEMINATION

The Ethical Committee of the Fujian Provincial Hospital approved the study protocol version 2.0 on 24 June 2021 (ref: K2021-06-018). Other participating subcentres must also obtain ethics committee approval documents prior to the start of the clinical trial. The study period is planned from March 2022 to March 2024, and the clinical trial will be completed within 24 months. This trial was registered with the Chinese Clinical Trials Registry (www.chictr.org.cn; trial identifier: ChiCTR2100050314) on 26 August 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 and probably benefit patients' or affect patients' safety, including changes in study design, sample size and study procedures, will be submitted to the Ethical Committee of the Fujian Provincial Hospital. The ethical committee will communicate for amendment approval.

Trial status

This study has not been started.

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Competing interests None declared.

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