Clinical Critical Care

E-ISSN 2774-0048

VOLUME 32 NUMBER 1

JANUARY-DECEMBER 2024

Clinical Critical Care
eISSN 2774-0048

Clinical Critical Care
Volume 32, Article ID e240011, 6 pages
https://doi.org/10.54205/ccc.v32.267521

RESEARCH PROTOCOL

Dexmedetomidine versus propofol on intestinal barrier function in patients undergoing major gastrointestinal tract surgery: A prospective randomized comparative trial protocol

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OPEN ACCESS

Citation:
Wisawachaiwat J, Assawaroongsakul P, Payongsri T, Sirilaksanamanon P, Chokengarmwong N, Thawitsri T. Dexmedetomidine versus propofol on intestinal barrier function in patients undergoing major gastrointestinal tract surgery: A prospective randomized comparative trial protocol. Clin Crit Care 2024; 32: e240011.

Received: January 28, 2024
Revised: April 11, 2024
Accepted: May 13, 2024

Data Availability Statement:
The data and code were available upon reasonable request (Thammasak Thawitsri, email address: thawitsri@gmail.com)

Funding:
Ratchadapiseksompotch fund, Graduate Affairs, Faculty of Medicine, Chulalongkorn University

Competing interests:
No potential conflict of interest relevant to this article was reported.

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ABSTRACT:

Background: Dexmedetomidine and propofol are recommended as sedatives for agitation management in critically ill adults. However, sedative agents always have a diversity of adverse effects, including gastrointestinal recovery. Delayed recovery of gastrointestinal motility results in prolonged hospital stays and increased medical costs for critically ill patients. The study is intended to compare the effects of dexmedetomidine and propofol on intestinal barrier function and clinical benefits in patients undergoing major gastrointestinal surgery.

Methods: In an experimental prospective randomized comparative trial, 60 patients who undergo major gastrointestinal tract surgery will be randomized into the dexmedetomidine group (n=30) and the propofol group (n=30). In the dexmedetomidine group, dexmedetomidine will be commenced at an initial concentration of 0.3 to 0.7 mcg/kg/h. In the propofol group, propofol will be commenced at an initial dose of 1.0 mg/kg/h to 4.0 mg/kg/h. Sedation is targeted at RAAS (-1)-0. Epidural analgesia will be used for pain control in both groups. The blood pressure, mean arterial pressure, heart rate, length of stay in the intensive care unit, postoperative endotracheal intubation time, and time to postoperative first defecation will be recorded. Serum D-lactate levels will be detected before the start of sedation (0 hour) and after sedation at 12, 24 hours, respectively.

Hypothesis: We hypothesize that dexmedetomidine and propofol, with optimal use for sedation, will have different effects on gastrointestinal recovery.

Ethics and dissemination: This study protocol was developed by investigators and approved by the Institutional Review Board of Faculty of Medicine of Chulalongkorn University (COA No. 0139/2023)

Trial registration: TCTR20230118002

Keywords: Dexmedetomidine; Propofol; Major gastrointestinal surgery; Intestinal barrier function; D-lactate; Randomized

INTRODUCTION

Major gastrointestinal surgery, such as esophageal, gastric, and intestinal surgeries, often encounters challenges in the delayed recovery of intestinal function postoperatively. Various factors contribute to delayed intestinal recovery, including immobility, electrolyte imbalance, intra-abdominal hematoma, use of anesthetic, sedative, and analgesic medications, prolonged mechanical ventilation, and extended hospital length of stay [1,3], associated with an increased risk of intra-abdominal infection and sepsis, as bacteria from the intestines may translocate into the bloodstream (bacterial translocation) [2]. Patients undergoing major gastrointestinal surgery are also at an elevated risk of developing pneumonia, with rates ranging from 10-30%. All complications add to the overall healthcare costs associated with prolonged hospitalization.[1]

Postoperative pain due to inadequate pain control is the major cause of delayed immobility. When patients experience discomfort, either from pain or inflammation, it stimulates the body's immune system to respond by releasing cytokines. This process collectively contributes to a reduction in intestinal motility.[4] Opioid analgesics such as morphine and fentanyl are most commonly used in postoperatively critically ill patients to control pain.[5] Systemic opioid analgesics result in decreased gastrointestinal motility.[6] Therefore, delayed immobility from inadequate pain control and decreased motility of the gastrointestinal tract from opioid analgesics led to delayed recovery of gastrointestinal function.

Furthermore, agitation is one of the observable symptoms in critically ill patients, arising from many factors and leading to patient non-cooperation with treatment, potentially resulting in complications like dislodgement of endotracheal tubes, dislodgement of intravenous lines, etc. Effectively managing agitation involves addressing the underlying causes and symptoms to relieve patient anxiety, promote relaxation, facilitate sleep, and decrease the complications from uneventful effects of sedation, such as over/underdose and inappropriate types of sedative drugs.[7] According to the 2018 PADIS guidelines: Standard neurological sedative medications used to control agitation in critically ill patients include propofol and dexmedetomidine. Propofol and dexmedetomidine are widely used for sedation in critically ill patients due to their lower delirium compared to benzodiazepine. Besides its sedative effect, propofol also has anti-inflammatory properties and protects multiple organs by reducing the production of cytokines, which result in activating inflammation and inhibiting neutrophils's functions[8]. Dexmedetomidine exerts an anti-inflammatory effect, inhibits pro-inflammatory cytokine production (interleukin-6, tumor necrotic factor alpha), and increases the production of anti-inflammatory cytokines (interleukin-10) [9]. The activation of the inflammatory process results in a delay in the recovery of intestinal function. In previous studies, Lui KX and colleagues [11] investigated the efficacy of propofol in preventing intestinal mucosal injury in mice. The study involved comparing mice that received propofol with a control group that did not receive the medication. The results revealed a significant reduction in intestinal mucosal injury in the group treated with propofol compared to the untreated group. This finding suggests that propofol may have a protective effect against intestinal mucosal injury. In another study by Yu-Peng Qi and colleagues[10], a comparative study between dexmedetomidine and midazolam regarding postoperative gastrointestinal recovery in patients undergoing gastrointestinal surgery was investigated. The findings revealed that patients administered dexmedetomidine exhibited faster restoration of bowel function, including earlier flatus passage and bowel movements, when compared to those who received midazolam. Additionally, the dexmedetomidine group showed lower levels of postoperative delirium compared to the midazolam group.

The major complication of a malfunctioning gastrointestinal tract is bacterial translocation into the bloodstream. Serum D-lactate is the byproduct of unabsorbed carbohydrate metabolism by intestinal bacteria. These bacteria can produce the enzyme D-lactate dehydrogenase, which is not only found in mammals but also humans.[12,13] Unabsorbed carbohydrates will be fermented by intestinal bacteria into short chain fatty acids. Overproduction of short chain fatty acids results in a decrease in intraluminal pH, which leads to the overgrowth of acid-resistant D-lactate-producing bacteria. Overproducing these bacteria will displace healthy gut microbiota and cause dysbiosis, which contributes to impairments of the intestinal barrier, which then allow the translocation of D-lactate into the bloodstream.

KEY MESSAGES:

- Serum D-lactate has been demonstrated to be one of the potential biomarkers reflecting the degree of damage to the intestinal mucosal barrier and the change in intestinal permeability.
- 2018 PADIS guidelines suggest using propofol and dexmedetomidine as standard sedation in critically ill patients.
- This study compares the efficacy of dexmedetomidine to propofol on intestinal function in patients undergoing gastrointestinal surgery. It's a single-center prospective randomized comparative trial. The primary outcome is the comparison of D-lactate levels at 24 hours.

OBJECTIVES

Primary objective

The primary objective of this study is to compare the effect of dexmedetomidine versus propofol on intestinal barrier function in patients undergoing major gastrointestinal tract surgery by measuring the level of D-lactate in the first 24 hours.

Secondary objective

The secondary objective is to compare the clinical benefits of dexmedetomidine and propofol on improvement of intestinal function, postoperative nausea and vomiting in the first 24 hours, time to first defecation, and time to first flatus.

MATERIALS AND METHODS

Study design

This study is a single-centered, experimental, prospective, randomized, comparative trial conducted at the surgical intensive care units (SICU) of King Chulalongkorn Memorial Hospital. The study protocol was approved by the Med Chula Institutional Review Board. The investigators obtain written informed consent from all patients.

Study populations

We will recruit all patients who are scheduled for major gastrointestinal tract surgery with the following criteria 1. Patients who have planned to receive mechanical ventilation with an estimated ventilation time of at least 12 hours in the SICU 2. Patients who have received epidural analgesia for postoperative pain control 3. Patients who give informed consent to participating in this study. Exclusion criteria are women who are pregnant or lactating, age younger than 18 years old, patients who have previously been diagnosed with delirium or dementia, patients with a diagnosis of cerebrovascular accident, patients with a diagnosis of acute liver failure, patients with a heart rate less than 55 bpm or high atrioventricular block without a pacemaker, patients with organ transplants, and patients who are allergic to either dexmedetomidine or propofol.

Intervention

Using the computer-generated random number table with a block size of 4 to assign patients in a 1:1 ratio. Eligible patients who fulfill the criteria will be informed and consented to, then allocated to sequentially numbered sealed envelopes. Each envelope will contain a study arm allocation. On the day of surgery, after arrival in the surgical ICU, the investigator will hand the patient's enrollment number to randomization. After randomization, patients will be allocated to either the dexmedetomidine group or the propofol group. This trial is for evaluators and patients.

Study protocol

After arrival at intensive care, vital signs, the Richmond Agitation-Sedation Scale (RASS), and the Numeric Rating Scale (NRS) will be recorded. Also collecting the patient's blood sample for D-lactate level. The epidural analgesia drug will be adjusted until the resting NRS is less than 3, then patients will be induced by a sedative drug with either dexmedetomidine or propofol. In the dexmedetomidine group, dexmedetomidine will be infused without a loading dose at a rate of 0.3 mcg/kg/h. The infusion rate will be increased up to 0.7 mcg/kg/h. or decreased to 0.2 mcg/kg/h. via protocol. In the propofol group, propofol will be infused at a rate of 1 mg/kg/h. The infusion rate will be increased up to 4 mg/kg/h. or decreased to 0.5 mg/kg/h. via a protocol. Analgesia and sedation are performed according to the following procedure: RASS is maintained at -1 to 0.

Dexmedetomidine or propofol will be continued until sedation is no longer needed: extubation, discharge from the intensive care unit, postoperative 24 hours. Dexmedetomidine or propofol boluses are disallowed for rescue purposes. This is achieved with midazolam 2 mg, which could be administered when the maximum infusion rate has been reached. (Figure 1)

DATA ANALYSIS PLAN

Sample size

On the basis of retrospective data from the Yu-Peng Qi et al. study [10], the primary outcome mean D-lactate levels in plasma of the dexmedetomidine group at 24 h: 34 μmol/mL, and the standard deviation (SD): 5.68 μmol/mL. The primary outcome the mean D-lactate levels in plasma of control group at 24 h: 39.13 μmol/mL, and the standard deviation (SD): 7.39 μmol/mL. A power analysis will be performed using mean D-lactate level at 24 hours. Twenty-six patients are required in each group to detect a difference of 5.13 between the groups at a level of 0.05, with a power of 80%, expecting a SD of 6.54. Considering 10% lost up, 30 patients will be enrolled in each group.

DATA MANAGEMENT AND DATA MONITORING

Data collection

The patient's demographics and clinical characteristic, including sex, age, body mass index, underlying disease, diagnosis, type of epidural analgesia, operation, duration of operation, and anesthesia, will be recorded. Systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, respiratory rate, saturation of peripheral oxygen (SpO_2), RASS, and NRS, will be recorded at the beginning of intensive care unit administration and at 4, 8, 12, 16, 20 and 24 hours after surgery. Adverse effects potentially related to dexmedetomidine and propofol, such as bradycardia, hypotension, and bradypnea, will be recorded. (Table 1)

Blood will be collected before sedation (0 hour), 12 hours, and 24 hours after sedation. The blood will be centrifuged at 2000 rpm for 10 minutes. The supernatant will be absorbed to detect D-lactate. The plasma D-lactate levels will be measured by a colorimetric D-lactate commercial assay kit (Abcam, UK) in accordance with the manufacturer's protocol.

The postoperative clinical variables, including first defecation time, first flatus time, postoperative nausea and vomiting, duration of postoperative mechanical ventilator hours, and length of ICU stays, will be recorded.

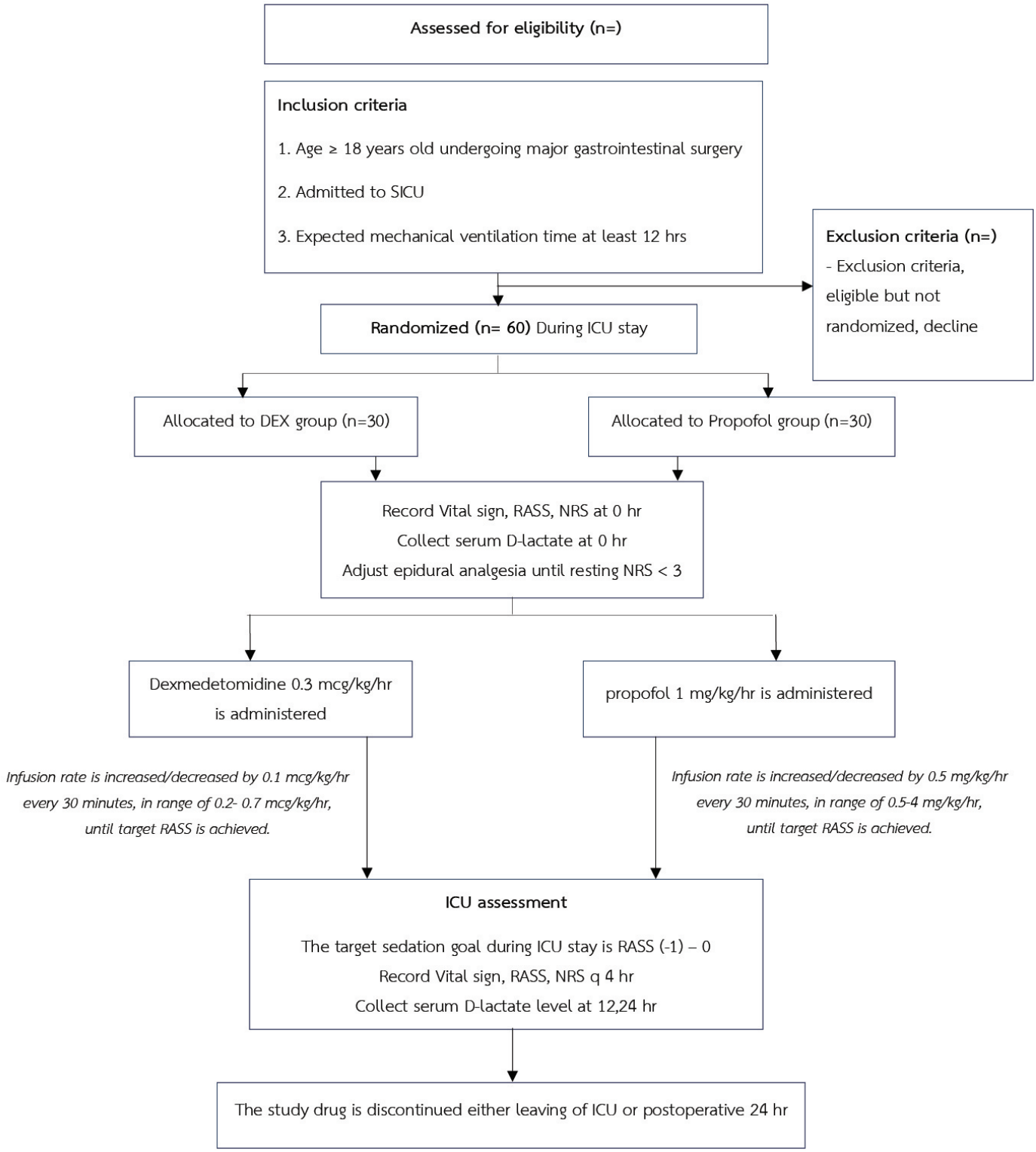

Figure 1. Flow chart of study protocol.

OUTCOME

The primary outcome includes the D-lactate level at 24 hours.

The secondary outcomes include the first defecation time, the first flatus time, postoperative nausea and vomiting, the duration of postoperative mechanical ventilator hours, and the length of the ICU stay. (Table 2)

OUTCOME ANALYSIS PLAN

Statistical analysis

Data analysis will be performed with SPSS software version 27. Demographics and clinical variables of participants will be obtained and reported as descriptive statistics. Categorical variables will be presented as the frequency (percentage). Continuous variables will be presented as the mean ± standard deviation or median (in-

Table 1. Demographic and clinical characteristics.

Demographic and clinical characteristics	Dexmedetomidine (N=30)	Propofol (N=30)
Age		
Sex		
Male		
Female		
BMI		
Underlying disease		
HT		
DM		
DLP		
CKD		
None		
Others		
Operation		
CRS with HIPEC		
Gastrectomy		
Whipple's		
Cystostomy with ileal conduit		
Epidural analgesia		
Local anesthetic agent		
Local + opioids		
Opioids		
NRS at 0 hour		
RASS at 0 hour		
Operative times (hours)		
Anesthesia times (hours)		

Table 2. Outcome variables.

Outcome variables	Dexmedetomidine (N=30)	Propofol (N=30)	P-value
D-lactate level			
0 hour			
12 hours			
24 hours			
Time of first defecation			
Time to first flatus			
Postoperative nausea & vomiting (N %)			
Mechanical ventilator (hours)			
Length of ICU stay (hours)			

terquartile range). The comparison of two groups will use the Chi-square test to analyze. We evaluate the primary outcome of D-lactate level between the two groups by an unpaired t-test. To compare intervention and D-lactate levels at 0, 12, and 24 hours will use the repeated ANOVA to be analyzed. The comparison of D-lactate levels and first defecation time uses the mixed model analysis to be analyzed. Significance levels were established at a p-value of <0.05.

DISCUSSION

Currently, there is a lack of definitive data pointing to the standard effectiveness of sedative drugs in the treatment of patients in the intensive care unit, with implications for gastrointestinal function. This gap in knowledge has prompted research efforts to investigate the efficacy of dexmedetomidine and propofol on gastrointestinal function in postoperative patients with digestive system surgeries.

The strengths of this study are, first, that it is a randomized comparative controlled trial protocol-based study of the effect of propofol vs. dexmedetomidine on intestinal barrier function in postoperative patients in a surgical intensive care unit. The drugs in the study, which are propofol and dexmedetomidine, are recommended as per the PADIS guidelines and are widely used worldwide. The second strength is that the study intends to select patients who have postoperative epidural analgesia to maximize optimal pain control and minimize the side effects of under- and overuse of systemic analgesia drugs on gastrointestinal function.

There are also several limitations to this study. The first is that it's a single center with a small sample size, which may limit the generalizability of the findings. The results may need to be confirmed by large samples from a multicenter study. The second is that it's an unblinded trial, so bias may be expected. The third limitation is the possible hemodynamic and respiratory instability from the drug. The fourth limitation is that serum D-lactate measurement is not available in many countries.

CONFIDENTIALITY

The informed consent is obtained by the investigator only within the private room before patient's go under surgery. Patient's information was recorded by using a code number instead of using patient's name or hospital number or admission number. Data collection will be recorded in recorded form and investigator's personal computer. After the trial, all data information will be permanently erased and recorded form will be destroyed.

ACKNOWLEDGEMENT

Grateful acknowledgment are made to Prof. Dr. Nattachai Srisawat , who gave me supportive facilities for blood analysis, my fellow colleagues and nurses in the surgical intensive care unit, Department of anesthesia, Faculty of Medicine, Chulalongkorn University, Critical Care Excellent Center, King Chulalongkorn Memorial Hospital, who participated in this study.

AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Jantarat Wisawachaiwat, Thammasak Thawitsri; (II) Data curation: Jantarat Wisawachaiwat, Thammasak Thawitsri, Pimpisa Assawaroongsakul; (III) Formal analysis: Jantarat Wisawachaiwat, Thammasak Thawitsri, Pimpisa Assawaroongsakul; (IV) Funding acquisition: Thammasak Thawitsri; (V) Methodology: Jantarat Wisawachaiwat, Pimpisa Assawaroongsakul, Titipon Payongsri, Pongpol Sirilaksanamanon, Nalin Chokengarmwong; (VI) Project administration: Jantarat Wisawachaiwat; (VII) Visualization: Jantarat Wisawachaiwat; (VIII)Writing – original draft: Jantarat Wisawachaiwat; (IX) Writing – review & editing: Thammasak Thawitsri.

ETHICS APPROVAL

This study protocol was developed by investigators and approved by the Institutional Review Board of Faculty of Medicine of Chulalongkorn University (COA No. 0139/2023) and has been registered with Thai Clinical Trials Registry (TCTR20230118002).

SUPPLEMENTARY MATERIALS

None

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