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Effect of anaesthetic depth on primary postoperative ileus after laparoscopic colorectal surgery: protocol for and preliminary data from a prospective, randomised, controlled trial

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ABSTRACT

Introduction Primary postoperative ileus is one of the principal factors affecting in-hospital recovery after colorectal surgery. Research on the relationship between anaesthetic depth and perioperative outcomes has been attracting growing attention. However, the impact of anaesthetic depth on the recovery of gastrointestinal function after surgery is unclear. We aimed to conduct a single-centre, prospective, randomised, controlled trial to explore the effect of anaesthetic depth on primary postoperative ileus after laparoscopic colorectal surgery.

Methods and analysis In this single-centre, prospective, patient-blinded and assessor-blinded, parallel, randomised, controlled trial, a total of 854 American Society of Anesthesiologists physical status I–III patients, aged between 18 and 65 years and scheduled for laparoscopic colorectal surgery lasting ≥2 hours, will be randomly assigned to deep anaesthesia group (Bispectral Index (BIS) 30–40) or light anaesthesia group (BIS 45–55). The primary outcome is primary postoperative ileus during the hospital stay. Secondary outcomes were time to gastrointestinal function recovery, another defined postoperative ileus, 15-item quality of recovery score, length of postoperative stay, postoperative 30-day complications and serum concentrations of intestinal fatty acid-binding protein at 6 hours after surgery.

Ethics and dissemination The protocol was approved by Medical Ethics Committee of Nanfang Hospital, Southern Medical University (Approval number: NFEC-2018–107) prior to recruitment. All participants will provide written informed consent before randomisation. Findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

Trial registration number ChiCTR1800018725.

Strengths and limitations of this study

► The present study is the first to focus on the relationship between anaesthetic depth and primary postoperative ileus.
► The preliminary results demonstrate the good feasibility of our protocol and provide a good basis for our following study.
► This study was designed to recruit patients from a single centre, hence the findings will need to be further validated in a large multicentre study.
► The strict inclusion and exclusion criteria will restrict the general applicability of our study results.

vomiting (PONV), inability to tolerate oral diet, abdominal distention and delayed passage of flatus and stool.[3 4] As the most common complication following major abdominal surgery, primary postoperative ileus is intimately associated with increased patient discomfort, delayed recovery after surgery, extended hospital stay and increased healthcare costs.[5–9]

Anaesthesiologists should be recognised as important participants in attempts to improve the recovery of postoperative gastrointestinal function. Some anaesthesia-associated factors, such as intraoperative fluid management,[10] epidural anaesthesia[11] and usage of inhalation anaesthetics (particularly nitrous oxide),[12–14] opioids[15 16] and lidocaine,[17] have a considerable influence on postoperative gastrointestinal dysfunction that includes postoperative ileus. Nevertheless, no published study has prospectively evaluated the role of anaesthetic depth on postoperative gastrointestinal function.

Benefitting from the advent of processed electroencephalographic monitors such as Bispectral Index (BIS) and Narcotrend

INTRODUCTION

Primary postoperative ileus, a temporary interruption of gastrointestinal function in the absence of surgical complications, is one of the principal factors affecting in-hospital recovery after colorectal surgery.[1 2] It is characterised by postoperative nausea and

Index, anaesthesiologists are now able to formulate individualised scheme of anaesthetic depth for each patient, which is advantageous to avoid excessive anaesthetic administration and improve recovery from general anaesthesia.[18] Meanwhile, the association between anaesthetic depth and prognosis, whether short-term or long-term, has become a hotspot of clinical research. In an international, randomised controlled trial published in Lancet recently, it found no evidence indicating that light anaesthesia (BIS 50) was superior to deep anaesthesia (BIS 35) in terms of reducing all-cause mortality 1-year postoperatively among older patients after major surgery.[19] Moreover, a large number of researches focus on the relationship between anaesthetic depth and various clinical phenomena during the perioperative period, including oculocardiac reflex during operation,[20] emergence agitation,[21] postoperative delirium[22 23] and postoperative pain.[24 25] However, randomised controlled trials to explore the relationship between anaesthetic depth and postoperative gastrointestinal dysfunction are currently lacking. We aimed to investigate the effect of two levels of anaesthetic depth on primary postoperative ileus after laparoscopic colorectal surgery in a single-centre, prospective, randomised, controlled trial.

METHODS AND ANALYSIS
Study design
The study is a single-centre, prospective, patient-blinded and assessor-blinded, parallel, randomised, controlled trial, with patients randomised at a 1:1 ratio to either deep anaesthesia group (BIS 30–40) or light anaesthesia group (BIS 45–55).[26] It will be conducted in Nanfang Hospital in Guangzhou, China. Recruitment started in October 2018 and is projected to run until September 2021. In order to achieve adequate participant enrolment, screening and enrolment will be performed by trained research staff.

Inclusion criteria
1. Written informed consent (see online supplemental file: Informed Consent Form).
2. Aged between 18 and 65 years.
3. American Society of Anesthesiologists (ASA) physical status I-III.
4. Elective laparoscopic colorectal surgery with an expected operative duration ≥2 hours.

Exclusion criteria
1. Pregnant or lactating women.
2. Inability to read, understand or communicate.
3. Previous history of oesophageal or abdominal surgery.
4. Preoperative diagnosis of gastrointestinal obstruction.
5. Long-term use of opioids, non-steroidal anti-inflammatory drugs or steroids.
6. Intraoperative mean BIS out of target range.
7. Stoma formation or conversion to laparotomy.
8. Combined organ resection during the operation.
9. Occurrence of severe perioperative complications.
10. Indwelling intragastric catheter intraoperatively according to decision from the surgeon.

Randomisation and masking
According to a randomisation sequence generated by a statistician, patients will be randomly divided into two groups—deep anaesthesia group (BIS 30–40) and light anaesthesia group (BIS 45–55).[26] The allocation codes will be concealed in opaque, sealed envelopes, and disclosed only when induction of anaesthesia is ready. Both patients and study personnel responsible for postoperative follow-up will be blinded to the grouping.

Procedures
Prior to the induction, BIS sensor (Covidien, USA) will be placed on participant's forehead following manufacturer's instruction and attached to BIS monitor. Intravenous target-controlled infusion (TCI) anaesthesia will be induced with propofol at plasma concentration (Cp) of 2–5 µg/mL (Marsh model) and remifentanil at effect-site concentration (Ce) of 3–6 ng/mL (Minto model). After an initial bolus of cisatracurium (0.2 mg/kg), intraoperative muscle relaxation will be maintained with an additional bolus (0.05 mg/kg) every 30–45 min. All patients will receive flurbiprofen axetil 50 mg intravenously before endotracheal intubation if not contraindicated. In addition, a bolus of sufentanil (0.4 µg/kg) was administered routinely before incision. During the operation, the infusion rate of propofol will be adjusted according to the BIS target range determined by the sealed envelope. No volatile anaesthetic will be given during the whole process. Tropisetron (0.1 mg/kg) and additional sufentanil (0.05 µg/kg) will be administered approximately 30 min prior to skin closure. Intraoperatively, anaesthesiologists will be asked to, as far as possible, maintained patients' mean arterial pressure (MAP) at ±20% baseline and heart rate within 45–110 beats per min. Infusions of propofol and remifentanil will be stopped based on each patient's operation process and guidance of TCI pump. Patient-controlled intravenous analgesia pump will be provided using sufentanil (1 µg · kg^{-1} · d^{-1}) and flurbiprofen axetil (2 mg · kg^{-1} · d^{-1}) mixed with 0.9% saline to a volume of 200 mL, with a background infusion of 4.0 mL/hour, bolus of 4.0 mL and lockout interval of 15 min. After surgical procedure is completed, the grouping information will be placed back into the sealed envelope.

Data collection
Data collection will be performed by trained research staff. Each participant will be distinguished with a unique identifier and initial without full name. To maximise patient's adherence and promote participants retention, assessors will conduct the face-to-face interviews or make phone calls during a 30-day follow-up. The following data required in the protocol will be collected through paper-based case report forms (CRFs) accurately and double-entered into EpiData V.3.1 software:

Baseline characteristics

Demographic data (age, sex, height and weight); ASA physical status; principal diagnosis; medical or surgical history; medication history; laboratory results (blood routine, urine routine, liver function and renal function); the time of admission.

Intraoperative and postoperative measurements

Beginning on the first reach of the BIS target range, intraoperative BIS and MAP will be collected at 10 min intervals, until propofol infusion is discontinued. Means of BIS and MAP will be calculated for each included subject. Infusion doses of propofol and remifentanil, as well as the type of surgery and duration of anaesthesia and surgery, will also be recorded. In post-anaesthesia care unit (PACU), the PACU nurses blinded to the grouping will record the duration of unconsciousness, defined as the time from discontinuation of propofol to eyes opening, and the time to achieve a modified Aldrete score of 9–10.[27]

Primary outcome

The primary outcome is primary postoperative ileus during the hospital stay. We draw on the diagnostic criteria for primary postoperative ileus put forward by Gómez-Izquierdo *et al* in 2017.[4] Patients are diagnosed with primary postoperative ileus when simultaneously meeting the following two conditions starting on 24 hours after surgery: (1) Vomiting or abdominal distension and (2) Absence of flatus/defecation or intolerance to oral diet, in the absence of any precipitating complications. Ileus occurring after discharge will not be included in the main analysis, principally because confounding factors outside the hospital are uncontrollable and thereby affect our ability to draw a strong conclusion.

Secondary outcomes

► Time to gastrointestinal function recovery, interval from surgery until both the following criteria are met: (1) Passage of flatus or stool and (2) Tolerance of an oral diet.[28]
► Another defined postoperative ileus, defined if two or more of the following five criteria are met on or after day 4 postoperatively without gastrointestinal function recovery since surgery (as described above): (1) Nausea or vomiting, (2) Inability to tolerate an oral diet over the last 24 hours, (3) Absence of flatus over the last 24 hours, (4) Abdominal distension and (5) Radiological confirmation.[28]
► A 15-item quality of recovery (QoR-15) score[29] on the 1st, 3rd and 30th day after surgery.
► Length of postoperative stay.
► Postoperative 30-day complications.
► Serum concentrations of intestinal fatty acid-binding protein at 6 hours after surgery.

Safety

Every adverse event related to the study procedures will be observed and documented in detail in the CRFs from the day of surgery to the end of follow-up. The investigator will decide whether to terminate the observation or not according to the condition of subjects. Any serious adverse event will be processed immediately and submitted to the principal researcher and the Medical Ethics Committee within 24 hours.

Data and sample storage

All the clinical trial materials will be reserved for at least 5 years after termination of the study. The investigators and statistician will have access to the final data set. The blood samples will be stored in a $-80°C$ refrigerator at Laboratory of the Department of Anesthesiology, Nanfang Hospital.

Data monitoring

Due to the low-risk nature of the intervention, a Data Monitoring Committee is not deemed necessary. No interim analysis or plan for early termination is planned.

Protocol changes

Any important protocol modifications will be communicated to relevant parties (ie, Medical Ethics Committee of Nanfang Hospital, Chinese Clinical Trials Registry, journals, trial participants and researchers).

Statistical analysis

All randomised subjects who do not violate the exclusion criteria will be considered to be a modified intention-to-treat (ITT) population for analysis of both primary and secondary outcomes. Among them, the patients who complete the follow-up procedure without occurrence of surgical complications during hospitalisation period will be included in per-protocol population for analysis of the incidence of primary postoperative ileus. Unblinded analysis of primary and secondary outcomes will be performed only after the last participant has completed the last follow-up visit.

Based on nearly 50% incidence of postoperative ileus,[30] 388 subjects will be needed in each group to detect a 20% difference in incidence of primary postoperative ileus between two groups, with a power of 0.8 and type I error of 0.05. Allowing for a dropout rate of 10%, a total sample size of 854 (427 in each group) is required.

SPSS V.24.0 software (IBM corporation) will be used for data analysis in this study. Data will be presented as mean (SD) for normally distributed data, median (IQR) for non-normally distributed data and frequencies (percentages) for categorical data. Risk ratio (RR) with 95% CI will also be reported for categorical data. Normally distributed data (passed the Shapiro-Wilk test), non-normally distributed data and categorical data will be compared using the independent two-sample t-test, Mann-Whitney test and Pearson's χ^2 tests (or Fisher's exact test, if appropriate), respectively. Repeated-measures analysis of variance and generalised estimating equations will be used to analyse the effects of anaesthetic depth on postoperative pain score and QoR-15 score. A two-sided p value<0.05 will be considered to be statistically significant.
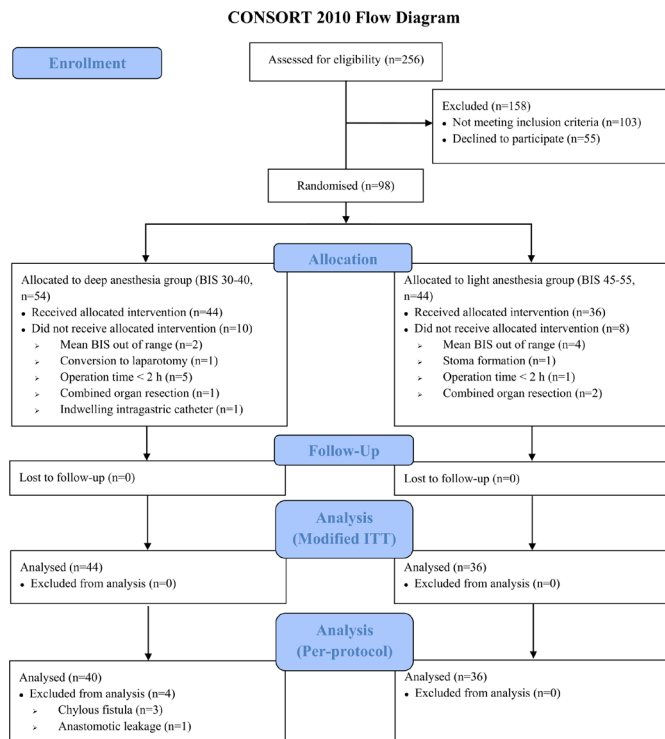
Figure 1 CONSORT flow diagram. BIS, Bispectral Index; CONSORT, Consolidated Standards of Reporting Trials; ITT, intention-to-treat.

Participants and public involvement

No patient involved.

Ethics and dissemination

The study protocol was approved by Medical Ethics Committee of Nanfang Hospital, Southern Medical University (approval number: NFEC-2018–107, approval date: 3 September 2018). All participants will provide written informed consent before randomisation. Results of the study will be disseminated through conference presentations and peer-reviewed journals.

The final report of the findings will be written by the investigators. The coauthors of the publication will be the investigators and clinicians collaborating in this clinical trial. No professional writers will be used.

PRELIMINARY RESULTS

A total of 256 patients were screened from 11 October 2018 to 30 December 2019. Ninety-eight patients were enrolled and subsequently underwent randomisation, 18 of whom were excluded owing to violation of the exclusion criteria before the follow-up visit. No case was lost to follow-up. Consequently, a total of 80 patients were considered for the modified ITT populations: 44 in deep group and 36 in light group (figure 1).

Patients' characteristics and perioperative data

Patients' characteristics and preoperative data were well balanced between two groups (table 1). Intraoperative data (deep group vs light group) are shown in

Table 1 Baseline characteristics

	BIS 30–40 (n=44)	BIS 45–55 (n=36)
Age (years)	54.6 (48.1–63.1)	54.7 (50.9–59.0)
Sex		
Male	24 (54.5)	24 (66.7)
Female	20 (45.5)	12 (33.3)
Weight (kg)	63.5 (53.0–69.0)	61.5 (52.3–72.3)
Height (m)	1.63 (0.08)	1.66 (0.09)
BMI (kg/m^2)	23.2 (2.8)	22.6 (2.9)
Hb (g/L)	122.5 (16.7)	124.9 (17.9)
Preoperative hospital stay (days)	4.0 (3.0–6.0)	4.0 (3.0–5.8)

Data are mean (SD), n (%) or median (IQR).
BIS, Bispectral Index; BMI, body mass index; Hb, haemoglobin.

table 2. It showed a clear separation of intraoperative mean BIS between two groups (36.8 (1.4) vs 48.8 (1.9), p<0.001), accounting well for the difference in propofol consumption (1480 (1185–1883) vs 1105 (954–1393) mg, p<0.001). MAP was statistically lower in deep group (80.4 (75.7–84.6) vs 83.8 (80.9–90.3) mm Hg, p=0.011). Both the duration of unconsciousness and the time to achieve a modified Aldrete score of 9–10 showed a significant increase in deep group (24 (16–31) vs 16 (11–22) min, p=0.005; 49 (38–70) vs 35 (26–48) min, p=0.001). Other variables, including type of surgery, durations of anaesthesia (p=0.677) and surgery (p=0.828), and remifentanil consumption (p=0.101), did not differ statistically.

DISCUSSION

There have been several studies on the role of anaesthetic factors[10–17] on postoperative gastrointestinal function, but none on anaesthetic depth. Inada *et al* found that both propofol and midazolam, the two most commonly used sedatives, inhibited gastric emptying and gastrointestinal transit in a dose-dependent manner, which raises our speculation that anaesthetic depth might influence the recovery of postoperative gastrointestinal function.[31] Under the premise of receiving the same dose, some patients who are sensitive to anaesthetics may achieve deeper anaesthetic depth. BIS could quantify the electrophysiological changes of the brain during anaesthesia, and has been widely used in the clinical practice and research. Thus, we designed this prospective, randomised, controlled trial to explore the relationship between anaesthetic depth based on BIS and primary postoperative ileus, with a view to improving the prognosis of patients undergoing laparoscopic colorectal surgery.

The preliminary results demonstrate the good feasibility of our protocol. The fact that only six subjects were excluded from our analysis due to poor BIS control supports the feasibility of controlling intraoperative mean BIS within the target range (30–40 or 45–55) under the

	BIS 30–40 (n=44)	BIS 45–55 (n=36)	P value
Table 2 Intraoperative data			
BIS	36.8 (1.4)	48.8 (1.9)	<0.001
MAP	80.4 (75.7–84.6)	83.8 (80.9–90.3)	0.011
Perioperative medications			
Propofol (mg)	1480 (1185–1883)	1105 (954–1393)	<0.001
Remifentanil (mg)	1.8 (1.4–2.5)	1.6 (1.3–2.0)	0.101
Duration of anaesthesia (min)	199 (164–242)	208 (174–235)	0.677
Duration of surgery (min)	166 (143–212)	171 (141–209)	0.828
Type of surgery			
Colonic surgery	32 (72.7)	27 (75.0)	0.818
Right haemicolectomy	14 (31.8)	14 (38.9)	0.509
Transverse colectomy	2 (4.5)	1 (2.8)	1
Left haemicolectomy	6 (13.6)	1 (2.8)	0.122
Sigmoidectomy	9 (20.5)	9 (25.0)	0.628
Right haemicolectomy plus sigmoidectomy	1 (2.3)	0 (0)	1
Subtotal colectomy	0 (0)	2 (5.6)	0.199
Rectal surgery	11 (25.0)	9 (25.0)	1
Other			
Rectosigmoid resection	1 (2.3)	0 (0)	1
Postoperative measures in PACU			
Duration of unconsciousness (min)*	24 (16–31)	16 (11–22)	0.005
Time to achieve a modified Aldrete score of 9–10 (min)	49 (38–70)	35 (26–48)	0.001

Data are shown as mean (SD), n (%) or median (IQR).
*Defined as the time from discontinuation of propofol to eyes opening.
BIS, Bispectral Index; MAP, mean arterial pressure; PACU, post-anaesthesia care unit.

current anaesthetic regimen, which establishes a foundation for conducting our following study. Further, the rationality of the study design is also highlighted in the excellent follow-up rate of 100%.

Our preliminary data showed a statistical difference in MAP between two groups. Since the intravenous dose of propofol was increased to maintain deeper anaesthetic depth, incidence and severity of hypotension during anaesthesia would inevitably increase, which were likely to impact gastrointestinal perfusion, thus, affecting patients' outcomes. Given the association between hypotension, defined as a decrease in MAP of >20% from baseline, and the occurrence of adverse outcomes,[32] we set a uniform standard that all included patients' MAP during the intraoperative period was maintained at ±20% baseline to eliminate the difference in blood pressure as much as possible. The MAP difference of 3.4 mm Hg might be of little clinical significance and insufficient to impact final results. Furthermore, previous studies[32 33] indicated that intraoperative hypotension is closely related to adverse outcomes after non-cardiac surgery when MAP below 55–65 mm Hg is satisfied, while the MAP is much higher than this level in both groups in our study.

There are several strengths of this trial. To our knowledge, it is the first clinical trial to focus on the relationship between anaesthetic depth and postoperative gastrointestinal function. Previous animal experiment[31] revealed that anaesthetic depth might influence gastric emptying and gastrointestinal transit, which has not been validated in clinical trial. This prospective, randomised, controlled trial is meaningful as it could potentially improve the outcome of patients with high risks of postoperative gastrointestinal dysfunction. Besides, considering various factors likely to affect primary postoperative ileus, we established the strict inclusion and exclusion criteria of our study, which will increase the validity of the results.

Several limitations have to be acknowledged. First, owing to the strict inclusion and exclusion criteria, the general applicability of the conclusion might be limited. In addition, the results from the single centre needs to be replicated in a multicentre trial. Second, the rationality of selection of anaesthetics is worth further exploring. For volatile anaesthetics, a hysteresis phenomenon exists between changes in vaporiser setting and BIS value, not conducive to adjustment of anaesthetic depth.[34] Therefore, propofol was used for

maintenance of anaesthesia in the present study. The phenomenon that only six subjects were out of BIS target range justifies the current anaesthetic regimen. Nevertheless, a fundamental study[35] suggested that propofol might have protective effect against intestinal disease, while the similar protective effect has also been reported in volatile anaesthetic.[36 37] Additionally, using sufentanil for postoperative analgesia may have an effect on the incidence of PONV,[38] thereby influencing the diagnosis of primary postoperative ileus.

In conclusion, this trial will provide direct evidence as to whether anaesthetic depth has an impact on the incidence of primary postoperative ileus. The trial has the potential to improve anaesthetic management and outcomes for patients undergoing laparoscopic colorectal surgery.

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