CLINICAL STUDY PROTOCOL

A multicenter randomized controlled trial for the effect of dexmedetomidine on postoperative gastrointestinal function in elderly patients undergoing abdominal surgery

[Chinese Clinical Trial Registry (ChiCTR1800017232)]

Study Design Brief Summary

Study Type: Multicenter Randomized controlled trial

Estimated Enrollment: 808 participants

Allocation: Randomized

DEX group: IV dexmedetomidine

CON group: IV NS

Masking: Double (Participant, Investigator)

Primary outcome: time to first flatus

Official Title: Effect of dexmedetomidine on postoperative gastrointestinal function in elderly patients undergoing abdominal surgery: A multicenter randomized, double-blind, controlled trial

Study Start Date: August, 2018

Lead site: The First Affiliated Hospital of Anhui Medical University

PI： Xue-Sheng Liu

Participating centers:

1. The First Affiliated Hospital of Wannan Medical College
2. The Second Affiliated Hospital of Anhui Medical University
3. The Fourth Affiliated Hospital of Anhui Medical University
4. The First Affiliated Hospital of USTC
5. Affiliated Fuyang Hospital of Anhui Medical University
6. Affiliated Chaohu Hospital of Anhui Medical University
7. Affiliated Anqing Hospital of Anhui Medical University
8. Wuhu No.2 Peoples' Hospital

9. Tongling Peoples' Hospital
10. Xuancheng Peoples' Hospital
11. Bengbu No.3 Peoples' Hospital
12. Affiliated Hefei Hospital of Anhui Medical University

Inclusion /Exclusion/Drop criteria

Inclusion criteria

1. Sign the informed consent；
2. Patients who plan to undergo abdominal surgery(site of surgery including: stomach, intestines, liver, cholecyst, bile duct, appendix) under general anesthesia；
3. Older than 60 years old；
4. ASA grades I~III ；
5. with an expected time of duration between 1h to 6h ；

Exclusion criteria

1. Patients with known gastrointestinal motility disorders ；
2. history of abdominal surgery ；
3. severe hepatic and renal dysfunction ；
4. second-degree or third-degree heart block ；
5. bradyarrhythmia with baseline rate below 50 beats per minute ；
6. patients with mental illness ；
7. history of difficult airway or delayed extubation ；
8. abusing narcotic sedative analgesics ；
9. allergy to dexmedetomidine or other anesthetic drugs ；
10. preoperative gastrointestinal hemorrhage (bleeding volume > 800 ml);
11. emergency re-operations;
12. American Society of Anesthesiologists (ASA) classification IV or V

Drop criteria

1. Drugs used not in accordance with this plan；
2. Those who do not have any monitoring records or whose CRF records are incomplete；
3. Surgeons changed the operation plan
4. Patients who quit the research;

1、Research Groups:

DEX group: There is an anesthetic nurse who don't know the patients' assignment taking 2ml of DEX(2ml/0.2mg) and adding it into 48mL 0.9% sodium chloride injection to form a 50ml solution. And then shake it gently and mix it into a concentration of 4ug/mL, a total of 50ml.

Normal saline group (CON group): 0.9% sodium chloride injection was pumped into a 50ml syringe, a total of 50ml

2、Randomization Procedure:

Eligible participants were randomly allocated in a 1:1 ratio to DEX and Control groups that received the drug or normal saline during surgery. Central randomization was performed using a secure, web-based, randomization system. The allocation sequence was generated by computer-generated random numbers. The study statistician did not participate in the inclusion of patients or in the delivery of medication.

3、Blinding:

The corresponding random number of each patient was put into an opaque

envelope and distributed to each center. Each center prepares dexmedetomidine or saline according to the random number. Neither the patient nor the anesthesiologist responsible for the data collection knows about the patient's group. Surgeons and anesthesiologist caring for patients also don’t know intervention methods.

4、Anesthesia protocol

4.1 Preoperative management: After patients entered the room, indwelling needle was used to establish intravenous channels. Then lactate Ringer's solution was injected, and vital signs were monitored, including (1) EEG; (2) non-invasive blood pressure; (3) Pulse oxygen saturation (SpO2); (4) nasopharyngeal temperature; (5) Bispectral index (BIS). The baseline values of all monitoring indicators of the patient are recorded after the patient is stabilized (BP and HR are the basic values at this time).

4.2 Experimental drug administration: The experimental drug (dexmedetomidine or normal saline) was given a load of 0.125ml/kg(0.5mg/kg) for 15min before anesthesia induction. After that, intravenous infusion was maintained at the rate of 0.05ml/kg/h(0.2mg/kg/h), and the infusion was stopped 30min before the end of operation [1].

4.3 Induction of anesthesia: Midazolam 0.02-0.04 mg/kg, sufentanil 0.2-0.3 ug/kg were injected slowly by intravenous induction. Propofol was injected 1.0-2.5 mg/kg after 2min. When BIS<60, cisatracurium 0.2 mg/kg was administrated. The dosage of each anesthesia induction drug was recorded.

4.4 Endotracheal intubation: After patient's eyelash reflex disappeared, muscle relaxation was complete and BIS was stable at 40, endotracheal intubation was completed. Tidal volume was 6-8 ml/kg, respiratory frequency was 10-12 times/min, and PETCO2 was maintained at 35~40 mmHg.

4.5 Anesthesia maintenance: Propofol 50~100 ug/kg/min, remifentanil 0.1~1ug/kg/min and cisatracurium 1~2 ug/kg/min were continuous infused for

anesthesia maintenance. BIS was used to monitor the depth of anesthesia, and maintained at 45-60. Propofol and remifentanil infusion were stopped at the end of the operation, and cisatracurium infusion was stopped 15 min before the end of the operation. Record the amount of each maintenance drug used.

4.6 Liquid management: 1-2 ml/kg/h of Ringer's lactate solution was injected after obtained intravenous access, and 6-8 ml/kg hydroxyethylamyle was used within 10 min after induction. After that, if there was no special condition, it was maintained with 2-3 ml/kg/h of Ringer's lactate solution. Hemoglobin (Hb) < 7g/mL was the absolute indication of blood transfusion, which was carried out in accordance with the guidelines for blood transfusion. Record the amount of the bleeding volume, crystalloid, colloidal solution and urine output.

4.7 Temperature management: Thermal insulation measures are routinely used during the operation to maintain body temperature (nasal temperature >36℃), and inflatable air blower is routinely used to protect body temperature after the operation is completed by PACU.

4.8 Analgesia management: Postoperative analgesia was treated with an intravenous infusion of analgesic cocktail consisting of sufentanil 3 ug/kg and flurbiprofen axetil 100 mg in 100 ml of normal saline. The background infusion rate is 2ml/h.

4.9 Management of nausea and vomiting: Routine use of prophylactics, intravenous infusion of Azasetron 10 mg after surgery.

4.10 Postoperative treatment: After the operation, the patient was given 100% oxygen without neostigmine antagonism. After recovery of spontaneous breath, the patient was transferred into PACU. The patient was extubated when reached the following criteria: 8 breaths/min, PETCO2<45mmHg, could respond to the instruction. The types and doses of remedies for postoperative pain were recorded.

5、Outcome measures:

5.1 The primary outcome:

The time to first flatus according to patients' self-report.

5.2 Secondary outcomes:

(1) postoperative gastrointestinal function score,

(2) time to first faeces,

(3) time to first oral feeding,

(4) incidence of delirium,

(5) postoperative pain scores,

(6) sleep quality,

(7) postoperative nausea and vomiting (PONV),

(8) hospital cost and length of stay.

Postoperative gastrointestinal function was assessed by I-FEED (Intake, Feeling nauseated, Emesis, physical Exam, and Duration of symptoms) scoring system (Appendix 1) [2]. The scoring system attributes 0-2 points for each of 5 components based on the clinical presentation, then categorized patients into 3 basic categories: normal (I-FEED Score 0–2), postoperative gastrointestinal intolerance (POGI, I-FEED Score 3–5) and POGD (I-FEED Score ≥6).

The Confusion Assessment Method (CAM) (Appendix 2) [3] was used twice daily to detect for the presence of delirium of for the first 3 postoperative days. We used a 10-point numeric rating scale to measure degree of pain, postoperative nausea and vomiting, sleep quality for first 7 postoperative days with 0 indicating no pain/PONV or deep sleep, 10 means the most severe pain/PONV or maximal sleep disturbances (Appendix 3).

The intraoperative vital signs and BIS value should be recorded at T1(baseline value), T2(the end of the experiment drugs load dosage),T3(before anesthesia induction), T4(after anesthesia induction), T5(skin incision), T6(the end of surgery),

T7(extubation), T8(discharge from PACU).

A telephone follow-up was conducted at approximately postoperative 28 days, enquiring about the incidence of nausea, vomiting, abdominal distension or constipation and their dietary status categorized into normal diet or liquid diet, and the amount of estimate intake.

6、Adverse Events

An adverse event is an unforeseen medical event that occurs to a patient or a clinical study subject. This adverse event is related to the time of use experiment drugs, whether or not it is related to the drug being used. Adverse events can be any undesirable and unexpected symptom or sign that happens during the time of use the drugs, as well as abnormalities in laboratory test indicators, exacerbation of the original disease, drug ineffectiveness, abuse, and misuse. Adverse event duration in this study were recorded from patient inclusion to 28 days postoperatively.

Record cardiovascular events occurring during hospitalization (from patient inclusion to discharge)

（1） bradycardia: heart rate < 40bpm;

（2） tachycardia: heart rate>120 bpm；

（3） hypertension: Blood pressure >20% increase from baseline or >160mmHg;

（4） hypotension: Blood pressure >20% decrease from baseline or < 80mmHg;

（5） Serious arrhythmias: arrhythmias that can cause serious hemodynamic disorders, temporary loss of consciousness or sudden death;

（6） Angina pectoris and myocardial infarction: Daily EEG examination;

（7） Heart failure；

（8） Acute renal failure；

7、Statistical Analysis Methods

7.1 Sample size

According to our pilot data, we estimated the difference in time to first flatus to be 2.5 h between groups with a within-group standard deviation of 10 h. Using an alpha value of 0.05, and 0.9 power, a minimum sample size of 674 subjects for the present study was calculated using the method suggested by Dupont and Plummer [4]. Allowing for 20% non-compliance, 808 patients were enrolled in the current study.

7.2 Statistical methods

Data was tested for normality using Kolmogorov-Smirnov test and normally distribution were presented as mean ± SD, and the comparison between groups was performed by two-tailed t-test. Continuous variables of skewed distribution were presented as median (interquartile range [IQR]), and comparison between groups was performed by Mann-Whitney U test. Qualitative data were described by frequency, and χ^2 test was used for statistical comparison. The repeated measure of ANOVA was used to analyze pain scores, sleep quality and PONV, and Mann-Whitney U test was used for ranked data. The statistical analyses were performed by SPSS 23.0 (SPSS Inc., Chicago, IL, USA), and 2-sided P values <0.05 were considered statistically significant.

Appendix 1. I-FEED score

I-FEED Scoring system [2]

Scoring Item	Intake	Feeling Nauseated	Emesis	Exam	Duration of symptoms
Description of different scores	Tolerating oral diet (0)	None (0)	None (0)	No distension (0)	0-24 hours (0)
	Limited tolerance (1)	Responsive to treatment (1)	⩾1 episode of low volume(<100ml) and non-bilious (1)	Distension without tympany (1)	24-72 hours (1)
	Complete Intolerance (3)	Resistant to treatment (3)	⩾1 episode of high volume(>100ml) and bilious (3)	Significant distension with tympany (3)	>72 hours (2)

Total score	0-2, Normal
	3-5, Postoperative GI Intolerance (POGI)
	⩾6，Postoperative GI Dysfunction (POGD)

The I-FEED scoring system was created out of the need for a consistent objective definition of impaired postoperative GI function. The scoring system attributes 0–2 points for each of the 5 components based on the clinical presentation of the patient and categorizes patients into normal (0–2), postoperative GI intolerance (3–5), and postoperative GI dysfunction (≥6). GI indicates gastrointestinal; I-FEED, Intake, Feeling nauseated, Emesis, physical Exam, and Duration of symptoms; POGD, postoperative gastrointestinal dysfunction; POGI, postoperative gastrointestinal intolerance.

Appendix 2.1. RASS (Level of Consciousness)

Richmond Agitation Sedation Scale (RASS)

Target RASS	RASS Description
+ 4	Combative, violent, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent nonpurposeful movement, fights ventilator
+ 1	Anxious, apprehensive , but not aggressive
0	Alert and calm
- 1	awakens to voice (eye opening/contact) >10 sec
- 2	light sedation, briefly awakens to voice (eye opening/contact) <10 sec
- 3	moderate sedation, movement or eye opening. No eye contact
- 4	deep sedation, no response to voice, but movement or eye opening to physical stimulation
- 5	Unarousable, no response to voice or physical stimulation

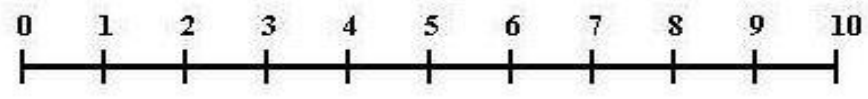
Appendix 2. CAM [3]

Download from www.icudelirium.org

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** or **C A S A B L A N C A** or **A B A D B A D A A Y** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If the patient is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Delirium can be diagnosed if patient characteristics ①②are present, plus either ③ or ④.

Appendix 3. A 10-point numeric rating scale



0 indicating no pain/PONV or deep sleep, 10 means the most severe pain/PONV or maximal sleep disturbances

References

[1] Tufanogullari B, White PF, Peixoto MP, et al. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg. 2008;106(6):1741-1748.

[2] Hedrick TL, McEvoy MD, Mythen MMG, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Gastrointestinal Dysfunction Within an Enhanced Recovery Pathway for Elective Colorectal Surgery. Anesth Analg. 2018;126(6):1896-1907.

[3] Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. Ann Intern Med. 1990;113(12): 941-948.

[4] Dupont WD, Plummer WD Jr. Power and sample size calculations. A review and computer program. Control Clin Trials. 1990;11(2):116-128.