**Supplement 1**

For: Ya-Wei Li, Huai-Jin Li, Hui-Juan Li, et al. Delirium in older patients after combined epidural-general anesthesia or general anesthesia for major surgery: A randomized trial

**This supplement contains the following items:**

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

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# Original study protocol

**Effects of two different anesthesia-analgesia methods on incidence of postoperative delirium in elderly patients undergoing major thoracic and abdominal surgery: A multicenter randomized controlled trial**

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**Date of last revision:** April 19, 2011

**Version of protocol:** V3.0

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**1. Background**

Delirium is an acutely occurred and transient brain dysfunction caused by multiple factors. According to the 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), delirium is defined as an acute transient mental syndrome characterized by (1) disturbance of consciousness with reduced ability to focus, sustain and shift attention, (2) change in cognition (such as memory deficit, disorientation, or language disturbance) or development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia, and (3) disturbance developing over a short period of time (usually hours to days) and tending to fluctuate during the course of the day.1

Delirium is a common postoperative complication, especially in the elderly patients after major surgery. A meta-analysis showed an overall incidence of postoperative delirium of 36.8% (from 0% to 73.5%).2 The incidence can be up to 80% in the critically ill patients in the intensive care unit (ICU).3 In our previous studies, delirium occurred in 51% of patients after cardiac surgery and in 44.5% of patients after non-cardiac surgery.4,5 The occurrence of delirium is associated with worse outcomes, including prolonged length of ICU stay,6 higher risk of postoperative complications,7 prolonged length of hospital stay,8 increased mortality,9,10,11 and elevated medical care costs;12,13 it is also associated with cognitive decline and lowered quality of life in long-term survivors.14,15 A 2-year follow-up study of our group showed that occurrence of delirium was an independent predictor of shortened survival even after correction for confounding factors.16

The pathogenesis of delirium remains unclear.17 Regarding postoperative delirium, it is common in the elderly, indicating that aged brain might be the pathophysiological basis of delirium.2 Another phenomenon is that delirium frequently occurs after major surgery but is rare after minor surgery (such as cataract surgery).18 This indicates that the surgery related stress response is an important precipitating factor. Indeed, previous studies found that severe pain is an independent risk factor,19 whereas effective pain relief may reduce delirium.20,21 Our results showed that high cortisol level predicted the occurrence of delirium after either cardiac and non-cardiac surgeries.4,5 In other studies, serum level of inflammatory cytokines (interleukin [IL]-6 and IL-8) were significantly higher in patients who developed delirium.22,23,24

Opioid is the mainstay of perioperative analgesia. However, high-dose opioids increase not only nausea and vomiting25 but also delirium occurrence.26 On the other hand, epidural block provides better pain relief when compared with intravenous opioids.27,28 Furthermore, epidural anesthesia can effectively blunt surgery-induced stress response and immunosuppression 29,30,31 by blocking afferent noxious stimuli. In previous studies, patients with neuraxial anesthesia had lower incidence of postoperative complications, earlier recovery of gastrointestinal function and shorter duration of hospital stay when compared with general anesthesia;32,33,34 they even had lower postoperative mortality.35

The beneficial effects of neuraxial anesthesia may help to reduce postoperative delirium. However, available studies comparing general anesthesia vs. neuraxial block did not find significant difference,36,37,38 possibly due to insufficient sample size. Major thoracic and abdominal surgeries are usually performed under either general anesthesia or combined epidural-general anesthesia. Moreover, no studies compared the effect of general anesthesia vs. combined epidural-general anesthesia on the incidence of postoperative delirium.

We hypothesize that, in elderly patients undergoing major thoracic and abdominal surgery, combined epidural-general anesthesia plus epidural analgesia may be superior to general anesthesia plus intravenous analgesia in preventing postoperative delirium, possibly by decreasing anesthetic consumption, improving analgesia, and relieving surgical stress response.

**2. Purpose of the study**

To investigate whether combined epidural-general anesthesia plus postoperative epidural analgesia compared with general anesthesia plus postoperative intravenous analgesia can decrease the incidence of delirium in elderly patients after major thoracic and abdominal surgery.

**3. Study design**

***3.1 Type of the study***

This is a multicenter, randomized controlled trial with two parallel arms.

***3.2 Sample size calculation***

In a recent cohort study of our own, the incidence of postoperative delirium in elderly patients after major abdominal surgery (performed under general anesthesia followed by intravenous analgesia) was 13.1%. In our previous study, the incidence of delirium was reduced by roughly one-third when the intervention (haloperidol prophylaxis) was administered in elderly patients after noncardiac surgery.39 Assuming that the general anesthesia group (general anesthesia plus postoperative intravenous analgesia) in the present study will have a similar delirium incidence as in our previous study, a total of 1664 subjects (832 subjects in each group) are required to detect a one-third reduction in the incidence of postoperative delirium at an 80% power with a two-sided significance level of 0.05. Considering a dropout rate of about 7.5 %, we plan to enroll 1800 patients.

***3.3 Participating centers***

3.3.1 This multicenter trial is conducted in six tertiary care hospitals affiliated with Peking University in Beijing, China. The five participating centers include Peking University First Hospital, Peking University People’s Hospital, Peking University Third Hospital, Beijing Hospital, Beijing Cancer Hospital, and China-Japan Friendship Hospital.

3.3.2 The study is coordinated by the Department of Anesthesiology and Critical Care Medicine of Peking University First Hospital; and the Peking University Clinical Research Institute is responsible for the study monitoring, data management and data analysis.

**4. Study participants**

Potential participants will be screened before surgery by the qualified investigators.

***4.1 Inclusion criteria***

4.1.1 Age range 60–90 years.

4.1.2 Planning to undergo noncardiac thoracic or abdominal surgery with an expected duration of 2 hours or longer.

4.1.3 Agree to receive patient-controlled analgesia after surgery.

***4.2 Exclusion criteria***

Patients will be excluded if they meet any of the following criteria:

4.2.1 Previous history of schizophrenia, epilepsy or Parkinson disease, or unable to complete preoperative assessment due to severe dementia, language barrier, or end-stage disease.

4.2.2 History of myocardial infarction or stroke within 3 months before surgery.

4.2.3 Any contraindication to epidural anesthesia and analgesia, including abnormal vertebral anatomy, previous spinal trauma or surgery, severe chronic back pain, coagulation disorder (prothrombin time or activated partial prothrombin time longer than 1.5 times of the upper normal limit, or platelet count of less than 80 × 109/L), local infection near the site of puncture, and severe sepsis.

4.2.4 Severe heart dysfunction (New York Heart Association functional classification 3 or above), hepatic insufficiency (Child-Pugh grades C), or renal insufficiency (serum creatinine of 442 μmol/L or above, with or without serum potassium of 6.5 mmol/L or above, or requirement of renal replacement therapy).

4.2.5 Any other conditions that are considered unsuitable for study participation.

***4.3 Criteria of study interruption***

Study will be interrupted in the following situations:

4.3.1 Severe safety problem occurred during the study.

4.3.2 Serious mistake found in the protocol.

4.3.3 Fund or management problem of the investigators.

4.3.4 Study cancelled by the administrative authority.

Study interruption may be transient or permanent. All recorded case report forms will be preserved for reference in case of study interruption.

# 5. Randomization and masking

***5.1 Randomization***

5.1.1 The randomization will be performed (in a 1:1 ratio) centrally at Peking University Clinical Research Institute through a 24-hour interactive web response system (IWRS, Brightech Clinical Information Management System) before the surgery. The randomization is stratified by study center and type of surgery (thoracic or abdominal surgery) with a block size of four. Allocation is concealed until shortly before anesthesia induction or epidural puncture.

5.1.2 For each recruited patient, a study coordinator will be designated to distribute the randomization result to the anesthesiologists according to the sequence of recruited patients, and to coordinate between investigators.

5.1.3 For each recruited patient, an anesthesiologist will be designated for anesthesia and postoperative pain management (and data collection) according to the result of randomization.

5.1.4 Study intervention (combined epidural-general anesthesia plus postoperative epidural analgesia or general anesthesia plus postoperative intravenous analgesia) will be provided according to the randomization results by anesthesiologists who do not participate in the outcome assessments.

5.1.5 The results of randomization will be concealed and stored at the interactive web response system (IWRS, Brightech Clinical Information Management System) and monitored by Peking University Clinical Research Institute.

***5.2 Masking***

5.2.1 Because of the apparent difference between the two anesthesia-analgesia methods, patients, anesthesiologists and other health-care team members are aware of study group assignment.

5.2.2 Investigators who are responsible for patient recruitment do not participate in the anesthesia and perioperative care of the recruited patients.

5.2.3 Investigators who are responsible for postoperative follow‐up and outcome assessments are not involved in anesthesia and perioperative management and have no knowledge of study group assignment. They have been trained prior to the study to follow the study protocol and to do delirium assessment. They are not allowed to communicate with neither patients nor other health-care team members regarding study group assignment.

5.2.4 Statistical analysis will be performed independently by Peking University Clinical Research Institute.

# 6. Intervention protocol

***6.1 Anesthesia and analgesia***

6.1.1 Intraoperative monitoring includes electrocardiogram, non-invasive blood pressure, pulse oxygen saturation, end-tidal concentrations of inhalational anesthetics and carbon dioxide, nasopharyngeal temperature, and urine output. Intra-arterial pressure and central venous pressure are monitored when necessary.

6.1.2 For patients assigned to receive combined epidural-general anesthesia plus postoperative epidural analgesia (EGA Group), epidural catheterization will be performed first.

6.1.2.1 The intervertebral space for epidural puncture will be selected by the attending anesthesiologists according to the site of planned incision. An epidural catheter will be inserted using a standard technique. After negative aspiration of blood and cerebrospinal fluid, a test dose of 3–4 mL of 2 % lidocaine will be administered to confirm the position of the catheter and the effect of neuraxial block.

6.1.2.2 General anesthesia will be induced with midazolam (0.02-0.03 mg/kg), propofol, sufentanil and rocuronium. For patients with expected difficult airway, endotracheal intubation may be facilitated by succinylcholine or awake intubation may be performed. Anesthesia will be maintained with intravenous (propofol), inhalational (sevoflurane with or without nitrous oxide), or combined intravenous-inhalational anesthetics, together with 0.375%-0.5% ropivacaine administered as bolus and/or continuously through the epidural catheter. Additional opioids (remifentanil, sufentanil, fentanyl, or morphine) and muscle relaxant (rocuronium, atracurium, or cisatracurium) will be administered when deemed necessary. For patients whose epidural local anesthetics has to be decreased or stopped, the reasons, the administered dose and subsequent management should be recorded.

6.1.2.3 Patient-controlled epidural analgesia will be provided after surgery. This is established with 0.12 % ropivacaine and 0.5 μg/mL sufentanil in 250 mL normal saline, programmed to deliver 2-mL boluses with a 20-minute lockout interval and a background infusion of 4 mL/h. For patients with low body weight or poor general condition, doses can be decreased and upper dose limit can be set for the patient-controlled pump.

6.1.2.4 For patients whose epidural analgesia pump has to be decreased or stopped, the reasons, the administered dose and subsequent management should be recorded.

6.1.3 For patients assigned to receive general anesthesia plus postoperative intravenous analgesia (GA Group), epidural catheterization will not be performed.

6.1.3.1 General anesthesia will be induced with midazolam (0.02-0.03 mg/kg), propofol, sufentanil, and rocuronium. For patients with expected difficult airway, endotracheal intubation may be facilitated by succinylcholine or awake intubation may be performed. Anesthesia will be maintained with either intravenous (propofol), inhalational (sevoflurane with or without nitrous oxide), or combined intravenous-inhalational anesthetics. Additional opioids (remifentanil, sufentanil, fentanyl, or morphine) and muscle relaxant (rocuronium, atracurium, or cisatracurium) will be administered when deemed necessary.

6.1.3.2 Patient-controlled intravenous analgesia will be provided after surgery. This is established with 0.5 mg/mL morphine in 100 mL normal saline, programmed to deliver 2-mL boluses with a 6 to 10-minute lockout interval and a 1 mL/h background infusion. For patients with low body weight or poor general condition, doses can be decreased and upper dose limit can be set for the patient-controlled pump.

6.1.3.3 For patients whose intravenous analgesia pump has to be decreased or stopped, the reasons, the administered dose and subsequent management should be recorded.

***6.2 Remedial measures***

6.2.1 Cross-group: For patients in the combined epidural-general anesthesia group but with failed epidural catheterization, general anesthesia and postoperative intravenous analgesia will be performed.

6.2.2 For patients in the combined epidural-general anesthesia group, inadequate anesthesia is managed with additional local anesthetics administered through the epidural catheter, and/or increasing intravenous and/or inhalational anesthetics. For patients in the general anesthesia group, inadequate anesthesia is managed with increasing intravenous and/or inhalational anesthetics.

6.2.3 For patients in the combined epidural-general anesthesia group with unsatisfied postoperative analgesia, pump setting will be adjusted (increased), supplemental analgesics (such as opioids, non-steroidal anti-inflammatory drugs, and others) will be administered, or an intravenous analgesia pump will be provided. For patients in the general anesthesia group with unsatisfied postoperative analgesia, pump setting will be adjusted (increased) and/or supplemental analgesics (such as opioids, non-steroidal anti-inflammatory drugs, and others) will be administered. The above measures will be recorded.

***6.3 Allowed and prohibited medications***

6.3.1 For patients of both groups, no premedication (usually include anticholinergics and sedatives) is administered. Dexmedetomidine is not allowed. Anticholinergics are prohibited unless being used for the treatment of bradycardia, in which case atropine will be administered. Patients enrolled in Peking University First Hospital are prohibited to use etomidate.

6.3.2 During anesthesia, vasopressors (such as ephedrine, phenylephrine, dopamine, adrenaline and norepinephrine), antihypertensives (such as urapidil and nicardipine), atropine and esmolol can be used to maintain hemodynamic stable; glucocorticoids and 5-hydroxytryptamine 3 (5-HT3) receptor antagonists can be used to prevent postoperative nausea and vomiting.

6.3.3 For patients admitted to the ICU with endotracheal intubation, propofol and/or midazolam can be administered for sedation; the target is to maintain the Richmond Agitation-Sedation Scale (RASS, score ranges from –5 [unarousable] to +4 [combative] and 0 indicates alert and calm)40,41 from -2 to +1. For patients admitted to the ICU without endotracheal intubation, sedatives should not be administered unless otherwise needed. Other sedatives are not allowed.

6.3.4 Other perioperative management are provided according to routine practice.

***6.4 Management of delirium***

6.4.1 Precipitating factors should be identified and managed. Usually there are more than one precipitating factors (underlying diseases).

6.4.2 Supportive therapies should be provided. These include reorientation, cognitive stimulation, early mobilization, hearing or vision aids, sleep promotion, and nutritional supply. A safe environment should be guaranteed for both patients and medical staff. Family members of patients should be included in the supportive therapy.

6.4.3 Pharmacological therapy is administered only when the delirium symptoms endanger the safety of patients themselves or others, or affect the normal medical work such as mechanical ventilation and central venous catheterization. Haloperidol (0.5-2 mg) will be administered intravenously, repeated when necessary every 15-20 minutes until control of symptoms. For maintenance treatment, half of the loading dose can be given intravenously every 4 to 6 hours, lasting for several days. Oral antipsychotic drugs will be administered under the guidance of psychiatrists when necessary.

# 7. Data collection

***7.1 Baseline data***

7.1.1 Demographic data, including age, sex, body mass index, and education level.

7.1.2 Diagnosis and medical history, including surgical diagnosis, comorbidities, medical therapy, drinking and smoking history, food and drug allergy, and previous history of surgery and anesthesia.

7.1.3 Results of main laboratory tests and instrumental examinations.

7.1.4 General status, including Charlson Comorbidity Index,42,43 American Society of Anesthesiologists classification, and New York Heart Association classification.

7.1.5 Activities of daily living is assessed with the Barthel Index (score ranges from 0 to 100, with higher score indicating better function). 44,45,46

7.1.6 Cognitive function is assessed with the Mini-Mental State Examination (score ranges from 0 to 30, with higher score indicating better function).47,48

7.1.7 Anxiety and depression are assessed with the Hospital Anxiety and Depression Scale (score ranges from 0 to 21 for either depression or anxiety, with higher score indicating more severe symptoms. A score >7 is adopted as the borderline abnormal).49,50,51

7.1.8 Delirium is assessed with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).52,53

***7.2 Intraoperative data***

7.2.1 Anesthesia method, type and dose of anesthetics and other medications used during anesthesia, duration of anesthesia.

7.2.2 Fluid balance (including fluid infusion, estimated blood loss, and urine output) and transfusion of blood products.

7.2.3 Location, type, name and duration of the surgery.

7.2.4 Data of vital signs and arterial blood gas result (if available).

7.2.5 For patients recruited in Peking University First Hospital, blood samples (4 mL) will be collected before surgery with their agreement. The serum will be separated within 1 hour and stored in the -80°C freezer until measurement of serum cortisol, interleukin (IL)-6 and IL-8 concentration.

***7.3 Postoperative data***

7.3.1 Patients will be visited twice daily during the first seven days after surgery; they will then be followed up weekly until 30 days after surgery. Information from the Electronic Anesthesia Information System and the Electronic Medical Record System will be achieved. Discharged patients will be contacted by telephone.

7.3.2 Occurrence of delirium during the first seven postoperative days will be assessed with the CAM‐ICU twice daily (8-10 AM and 6-8 PM). Immediately before assessing delirium, sedation or agitation will be assessed using the RASS. For deeply sedated or unarousable patients (RASS –4 or –5), delirium is not assessed and the patient is recorded as comatose. For patients with a RASS from -3 to +4, delirium is assessed with the CAM-ICU. Delirium episodes are classified into three motoric subtypes, i.e., hyperactive (RASS is consistently positive, from +1 to +4), hypoactive (RASS is consistently neutral or negative, from –3 to 0), and mixed.54 Investigators for postoperative delirium assessment will be trained by psychiatrists to use the CAM‐ICU before the trial is commenced. For patients who meet the criteria of delirium, the severity of delirium will be assessed with the Chinese version of Delirium rating scale revised-98 (DRS-R-98-C).55

7.3.3 The intensity of postoperative pain both at rest and with coughing during the first three postoperative days will be evaluated twice daily at the same time of delirium assessment (8-10 AM and 6-8 PM) with the numeric rating scale (NRS, a 11-point scale where 0 indicates no pain and 10 indicates the worst pain). For patients who are deeply sedated or unarousable (−4 or −5 on the RASS), pain evaluation will be stopped and repeated later.

7.3.4 The use of analgesics and other medications during the first 7 days after surgery will be recorded.

7.3.5 For patients who are admitted to the ICU after surgery, the worst Acute Physiology and Chronic Health Evaluation II (APACHE II, score ranges from 0 to 71, with higher score indicating more severe disease)56 score during the first 24 hours after surgery, the duration of mechanical ventilation (for those with endotracheal tubes), the use of sedatives, and the length of ICU stay will be recorded.

7.3.6 For patients recruited in Peking University First Hospital, blood samples (4 mL) will be collected on the 1st and 3rd morning (6-8 AM) after surgery with their agreements. The serum will be separated within 1 hour and stored in the -80°C freezer until measurement of serum cortisol, IL-6 and IL-8 concentration. The blood samples will be sent for measurement within 7 days after surgery. All blood samples from delirium patients will be sent for testing. Blood samples from non-delirium patients will be selected in a 1:4 ratio to delirium patients and sent for testing.

7.3.7 Occurrence of non‐delirium complications during the first 30 days after surgery will be recorded. Non-delirium complications are defined as newly occurred medical conditions other than delirium that are harmful to patients’ recovery and required therapeutic intervention, i.e., grade II or higher on the Clavien-Dindo classification.57

7.3.8 Postoperative observation cards will be given to family members/care providers for bedside care. Any potential symptoms will be recorded by the family members/care providers in the observation cards, which are collected by the investigators during each follow-up.

7.3.9 Time to resume fluid and food intake.

7.3.10 Length of hospital stay after surgery.

7.3.11 All‐cause 30‐day mortality after surgery.

**8. Outcomes**

***8.1 Primary outcome***

Incidence of delirium within 7 days after surgery.

***8.2 Secondary outcomes***

8.2.1 The percentage of intensive care unit (ICU) admission after surgery.

8.2.2 The intensity of pain during the first three days after surgery.

8.2.3 The severity of delirium within 7 days after surgery.

8.2.4 The daily prevalence of delirium.

8.2.5 Time to onset of delirium.

8.2.6 Time to resume fluid/food intake.

8.2.7 The length of stay in hospital after surgery.

8.2.8 The incidence of non-delirium major complications within 30 days after surgery.

8.2.9 The 30-day all-cause mortality.

***8.3 Other pre-specified outcomes***

8.3.1 Serum cortisol concentration after surgery (selected patients).

8.3.2 Serum IL-6 concentration after surgery (selected patients).

8.3.3 Serum IL-8 concentration after surgery (selected patients).

**9. Adverse events**

***9.1 Definition***

An adverse event indicates any unpredictable, unfavorable medical event that is associated with any medical intervention and occurs during the study period. It can be related to the study intervention or otherwise. It can manifest as any uncomfortable signs (including abnormal laboratory findings), symptoms or transient morbidity.

***9.2 Predicted adverse events in this study***

9.2.1 Intraoperative adverse events

9.2.1.1 Adverse events related to epidural puncture/catheterization include accidental dural puncture, nerve injury, failed epidural puncture/catheterization, epidural catheter obstruction, blood appear in epidural catheter, epidural catheter dislodgement, local/epidural hematoma, local/nerve injury, etc.

9.2.1.2 Adverse events related to epidural and/or general anesthesia include local anesthetic intoxation, total spinal anesthesia, intraoperative hypotension (systolic blood pressure <80 mmHg), intraoperative hypertension (systolic blood pressure >180 mmHg), intraoperative bradycardia (heart rate <40 bpm), intraoperative tachycardia (heart rate >100 bpm), teeth injury, laryngeal spasm, prophylaxis, arrhythmia, cardiac events, atelectasis, etc.

9.2.2 Postoperative adverse events

9.2.2.1 Adverse events related to epidural analgesia include epidural catheter obstruction, inadequate epidural analgesia, epidural catheter dislodgement, epidural hematoma, epidural abscess, sequelae of nerve injury, post dural puncture headache, pruritus, leg weakness, etc.

9.2.2.2 Other adverse events include nausea, vomiting, postoperative hypotension (systolic blood pressure <90 mmHg), postoperative hypertension (systolic blood pressure >160 mmHg), postoperative bradycardia (heart rate <50 bpm), postoperative tachycardia (heart rate >100 bpm), inadequate analgesia, etc.

9.2.3 In the present study, adverse events will be monitored from the beginning of anesthesia (epidural puncture or induction of general anesthesia) until 72 hours after surgery, i.e., end of patient-controlled analgesia.

***9.3 Management***

9.3.1 Therapies will be provided according to patients’ condition and routine practice. Generally, hypotension is managed with lighting anesthesia, intravenous fluid and vasopressors; hypertension is managed with deepening anesthesia and antihypertensive drugs; bradycardia is managed with lighting anesthesia and atropine; tachycardia is managed with deepening anesthesia, intravenous fluid and esmolol when necessary.

9.3.2 The study intervention (epidural anesthesia or postoperative epidural/intravenous analgesia) can be stopped temporarily or permanently if considered necessarily by the attending anesthesiologist or surgeons. The time and reasons of study intervention interruption will be recorded.

9.3.3 In case that the patient-controlled analgesia (for study intervention) is terminated early, other analgesics will be provided.

***9.4 Record***

9.4.1 Any adverse event should be documented, including occurrence, type/diagnosis, time of diagnosis, management, duration of persistence, and sequelae.

9.4.2 Any adverse event should be followed up until it is completely resolved or therapy terminated.

**10. Severe adverse events**

***10.1 Definition***

A severe adverse event indicates any unpredictable medical events that lead to death, threat of life, prolonged length of hospital stay, persistent disability or dysfunction, or other severe event.

***10.2 Management***

In case of any severe adverse events, the study intervention will be stopped and treatment will be initiated immediately.

***10.3 Record and report***

10.3.1 In case of any severe adverse event, apart from active treatment and record as above, the principal investigator and the Ethics Committee (Peking University Institutional Review Board) will be informed within 24 hours in written report.

10.3.2 In case of study intervention related death, immediately stop the clinical trial, report the event to the Ethics Committee as soon as possible, record in detail and carefully preserve the related documents.

10.3.3 Any severe adverse event must be followed up until it is completely resolved or when therapy is ended.

**11. The rule of unmasking**

11.1 After the follow-up of all cases have been completed, the data of case report forms have been checked as correct, and the data entry have been finished, a database inspection report will be written by the data manager.

11.2 After the database is locked, unmasking will be conducted. And the database will be sent to the statisticians for statistical analysis.

**12. Data management**

12.1 The investigators should record data timely, completely and correctly according to the original observations and assessments.

12.2 The completed case report forms, after signed by the supervisors, will be sent to a clinical data custodian.

12.3 After the data in the case report forms have been input and checked, the case report forms will be stored in sequence order.

12.4 Data management will be inspected by Peking University Clinical Research Institute.

**13 Statistical analysis**

***13.1 General principles***

13.1.1 Numeric variables will be presented as mean ± standard deviation or median (minimum, maximum; or interquartile range). Categorical variables will be presented as number of cases (percentage).

13.1.2 For each hypothesis, two‐tailed tests will be used in all statistical analysis, and p <0.05 will be considered statistically significant.

13.1.3 The primary and secondary outcomes will be analyzed in an intention-to-treat population, i.e., all patients are analyzed in the group to which they are randomized and received at least part of study intervention. If epidural anesthesia and/or analgesia fail, these patients will be converted to general anesthesia and intravenous analgesia but will be analyzed in the group to which they are randomized. Also, we will do per-protocol analysis for the primary endpoint, in this case, drop-out patients will be excluded.

***13.2 Patient recruitment and drop‐out status***

The status of patient recruitment and drop‐out will be summarized and listed. Comparison of the overall elimination/drop‐out rate between the two groups will be performed with Chi‐Square test.

***13.3 Demographics and baseline characteristics***

13.3.1 Demographics and baseline data will be presented.

13.3.2 For between-group differences, continuous variables will be analyzed using independent-samples t test or Mann-Whitney U test; categorical variables will be analyzed using the Chi-Square test, continuity correction Chi-Square test or Fisher exact test.

***13.4 Efficacy analysis***

13.4.1 Evaluation of primary endpoint

The incidence of delirium within 7 days after surgery will be calculated. Comparison between groups will be performed with Chi-Squared test. The difference of risk for postoperative delirium between two groups will be expressed as relative risk (RR) and 95% CI. For patients with missing data due to early hospital discharge or death, the last delirium assessment results will be considered as the missing data when calculating the incidence of delirium within 7 postoperative days; the missing data will not be replaced when calculating the daily prevalence of delirium.

13.4.2 Evaluation of secondary endpoints

13.4.2.1 Time‐to‐event variables (time to onset of delirium, time to resume fluid/food intake, length of stay in hospital after surgery) will be calculated with Kaplan-Meier estimator, with differences between groups assessed by the log-rank test. The estimates hazard ratio (HR) and 95% CI will be provided.

13.4.2.2 Categorical variables (the incidences of major complications other than delirium, the daily prevalence of delirium, and the 30-day all-cause mortality rate) will be analyzed using the Chi-Square test, continuity correction Chi-Square test or Fisher exact test. The estimated relative risk (RR) and 95% CI will be provided.

13.4.2.3 Ranked variables (the severity of delirium, the NRS pain scores after surgery) will be analyzed using the Mann-Whitney U test. The difference between two medians and 95% CI will be calculated with the Hodges-Lehmann estimator.

13.4.2.4 Numeric variables (serum concentrations of cortisol, IL-6 and IL-8) will be analyzed using the independent-samples t test or Mann-Whitney U test. Mean/median differences and 95% CI will be provided.

***13.5 Safety analysis***

13.5.1 Describe the occurrence of adverse events in each group.

13.5.2 Describe the management of adverse events when appropriate.

13.5.3 Describe the occurrence of severe adverse events.

13.5.4 The rates of adverse events and/or managements between the two groups will be compared with Chi-Square test, continuity correction Chi-Square test or Fisher exact test.

***13.6 Missing data***

Missing data or incomplete data will be marked in the case report forms. The principle investigator and the statistician will discuss and determine the management of missing data. Details will be listed in the final statistical analysis plan.

**14. Quality control and quality assurance**

***14.1 Training for investigators***

14.1.1 An investigator training program will be designed by the principle investigator. A study coordinator will be designated to organize and implement the training program, and to record and preserve the related documents.

14.1.2 Investigator training will be performed during the month before starting the study.

14.1.2.1 Delirium assessment will be trained by psychiatrists. Investigators who are in charge of delirium assessment in each study center (at least two investigators in each center) must attend the training program and pass the examination. The training program includes lectures on the clinical manifestations, potential mechanisms, diagnosis and treatment of delirium, a lecture explaining the use of the CAM-ICU, and simulating training courses with patient-actors for delirium assessment with the CAM-ICU. The simulating training will continue until the agreements of delirium diagnoses between psychiatrists and investigators reach >99%.

14.1.2.2 Other training contents that must be finished before starting the study include the Good Clinical Practice principles, the study protocol, the standard operating procedures of the study, the working plan of the study, the instruction for the case report form, and other matters needing attention during the study (collection of blood samples, allowed and prohibited medications, etc.).

14.1.3 The training program will be repeated 2-3 times a year throughout the study period, or will be performed whenever necessary.

***14.2 Monitoring of study conduct***

14.2.1 The study will be monitored by the Peking University Clinical Research Institute.

14.2.2 A project specialist will be designated by the Peking University Clinical Research Institute and will verify that the conduct of the study, the record of data and the analysis are in accord with the study protocol and related regulations. Investigators should cooperate with the project specialist.

14.2.3 Before and during the study period, the project specialist will go to the study centers for initiation inspection, regular inspection, and end of study inspection. The project specialist will schedule the time of inspection but at least one inspection will be performed after recruiting the first three participants, and at least once every 12 weeks for the principle study center and every 24 weeks for the participating centers.

14.2.4 The contents of inspection include the following:

14.2.4.1 To verify that investigators are designated and completed the training program.

14.2.4.2 To verify the authenticity of participants, and the process to obtain written informed consents.

14.2.4.3 To verify the eligibility of participants. For the first three participants recruited in each center, 100% of the original data of will be checked and verified.

14.2.4.4 To verify the correctness of the randomization procedure.

14.2.4.5 To verify that the follow-ups and assessments are performed according to the study protocol.

14.2.4.6 Original data will be inspected in at least 5% of the recruited participants. Original data of the primary outcome will be inspected in 100% of the recruited participants.

14.2.4.7 To verify that all severe adverse events are reported to the Ethics Committee according to the study protocol. The original data of all severe adverse events will be inspected.

14.2.4.8 To verify the transport, dissemination and retrieve of study drugs, and the records of storage and return of study drugs.

14.2.4.9 To verify that the blood samples are collected and stored according to the study protocol and the standard operating procedures.

14.2.4.10 To verify that the revised study protocol, participant-related documents, report of severe adverse events, and annual summary report are submitted to the Ethics Committee timely by the investigators for approval or record.

14.2.4.11 To verify the preservation of study-related documents and original data.

14.2.4.12 To verify the trial management in the study centers, the progress of participant recruitment and the study conduct, the accomplishment of recruited cases, and the situation of case drop-out.

14.2.5 A written report will be provided after each inspection. The report should include date, time, name of inspector, and the problems found during inspection. The project specialist will inform the principal investigator about the identified problems and will discuss the approaches to solve these problems. In case of important problems, such as those regarding participant safety, adherence to the study protocol or Good Clinical Practice principles, or delayed progress, the project specialist should report to the management office of the Peking University Clinical Research Program.

***14.3 Inspection of data quality***

14.3.1 The project specialist will check and verify the completeness and correctness of the data recorded in the case report forms, and will ask investigators to correct or replenish data when necessary.

14.3.2 Data manager from the Peking University Clinical Research Institute will recheck data according to the logical relations and to identify the existence of protocol deviation and out of normal limit. For the drop-out or missing data or data with logical contradictions, query forms will be sent to the investigators. The investigators are responsible to reply queries, and to verify or correct data.

14.3.3 All data queries must be solved before the database can be locked for statistical analysis.

**15. Ethics requirements**

***15.1 Ethics Committee***

The study protocol must be approved by the Peking University Institutional Review Board before the study can be started. The investigators must strictly follow the Helsinki Declaration and China's relevant clinical trial management regulations. The principal investigator is responsible to report the status and the progress of the study to the Institutional Review Board.

***15.2 Written informed consent***

For each potential participant, investigators are responsible to fully explain the purpose, procedures and possible risks of this study in a written form manner. The investigators must let every potential participant know that he/she has the right to withdraw consent from the study at any time. Every potential participant must be given a written informed consent. Every participant or the authorized surrogate of the participant must sign the consent before he/she can be enrolled in the study. The written informed consents will be kept as a part of the clinical trial documents.

***15.3 Privacy and confidentiality***

15.3.1 During the study period, the collected data from participants are labelled with special recruitment numbers and acronyms of names.

15.3.2 All personal information of the participants will be kept confidential. The filing cabinets storing the study documents will be locked. Apart from the study investigators, only authorized inspectors from the Peking University Clinical Research Institute or members from the Peking University Institutional Review Board are allowed to access the information after obtaining consents from the participants.

15.3.3 Results of the study will be published as scientific articles. But all personal data (including name and age, etc.) are strictly confidential.

**16. Study termination**

16.1 In case that severe adverse events or serious quality problem occur during the study period, the study will be stopped. A report will be sent to the Ethics Committee. Restart of the study will need an approval from the Ethics Committee.

16.2 The study will be terminated after accomplishment of required patient recruitment and data collection. Decision will be made by the principal investigator.

**17. Preservation of documents**

Investigators will carefully preserve all documents and data of the clinical trial according to the requirements of Good Clinic Practice for a period of 5 years.

**18. Declaration of interests**

This trial is funded by the Peking University Clinical Research Program (PUCRP201101). The investigators declare no conflict of interests.

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# Final study protocol

**Effects of two different anesthesia-analgesia methods on incidence of postoperative delirium in elderly patients undergoing major thoracic and abdominal surgery: A multicenter randomized controlled trial**

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**Date of last revision:** October 20, 2014

**Version of protocol:** V3.5

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**1. Background**

Delirium is an acutely occurred and transient brain dysfunction caused by multiple factors. According to the 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), delirium is defined as an acute transient mental syndrome characterized by (1) disturbance of consciousness with reduced ability to focus, sustain and shift attention, (2) change in cognition (such as memory deficit, disorientation, or language disturbance) or development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia, and (3) disturbance developing over a short period of time (usually hours to days) and tending to fluctuate during the course of the day.1

Delirium is a common postoperative complication, especially in the elderly patients after major surgery. A meta-analysis showed an overall incidence of postoperative delirium of 36.8% (from 0% to 73.5%).2 The incidence can be up to 80% in the critically ill patients in the intensive care unit (ICU).3 In our previous studies, delirium occurred in 51% of patients after cardiac surgery and in 44.5% of patients after non-cardiac surgery.4,5 The occurrence of delirium is associated with worse outcomes, including prolonged length of ICU stay,6 higher risk of postoperative complications,7 prolonged length of hospital stay,8 increased mortality,9,10,11 and elevated medical care costs;12,13 it is also associated with cognitive decline and lowered quality of life in long-term survivors.14,15 A 2-year follow-up study of our group showed that occurrence of delirium was an independent predictor of shortened survival even after correction for confounding factors.16

The pathogenesis of delirium remains unclear.17 Regarding postoperative delirium, it is common in the elderly, indicating that aged brain might be the pathophysiological basis of delirium.2 Another phenomenon is that delirium frequently occurs after major surgery but is rare after minor surgery (such as cataract surgery).18 This indicates that the surgery related stress response is an important precipitating factor. Indeed, previous studies found that severe pain is an independent risk factor,19 whereas effective pain relief may reduce delirium.20,21 Our results showed that high cortisol level predicted the occurrence of delirium after either cardiac and non-cardiac surgeries.4,5 In other studies, serum level of inflammatory cytokines (interleukin [IL]-6 and IL-8) were significantly higher in patients who developed delirium.22,23,24

Opioid is the mainstay of perioperative analgesia. However, high-dose opioids increase not only nausea and vomiting25 but also delirium occurrence.26 On the other hand, epidural block provides better pain relief when compared with intravenous opioids.27,28 Furthermore, epidural anesthesia can effectively blunt surgery-induced cortisol hypersecretion29,30 and inflammatory response31,32 by blocking afferent noxious stimuli. In previous studies, patients with neuraxial anesthesia had lower incidence of postoperative complications, earlier recovery of gastrointestinal function and shorter duration of hospital stay when compared with general anesthesia;33,34,35 they even had lower postoperative mortality.36

The beneficial effects of neuraxial anesthesia may help to reduce postoperative delirium. However, available studies comparing general anesthesia vs. neuraxial block did not find significant difference,37,38,39 possibly due to insufficient sample size. Major thoracic and abdominal surgeries are usually performed under either general anesthesia or combined epidural-general anesthesia. Moreover, no studies compared the effect of general anesthesia vs. combined epidural-general anesthesia on the incidence of postoperative delirium.

We hypothesize that, in elderly patients undergoing major thoracic and abdominal surgery, combined epidural-general anesthesia plus epidural analgesia may be superior to general anesthesia plus intravenous analgesia in preventing postoperative delirium, possibly by decreasing anesthetic consumption, improving analgesia, and relieving surgical stress response.

**2. Purpose of the study**

To investigate whether combined epidural-general anesthesia plus postoperative epidural analgesia compared with general anesthesia plus postoperative intravenous analgesia can decrease the incidence of delirium in elderly patients after major thoracic and abdominal surgery.

**3. Study design**

***3.1 Type of the study***

This is a multicenter, randomized controlled trial with two parallel arms.

***3.2 Sample size calculation***

In a recent cohort study of our own, the incidence of postoperative delirium in elderly patients after major abdominal surgery (performed under general anesthesia followed by intravenous analgesia) was 13.1%. In our previous study, the incidence of delirium was reduced by roughly one-third when the intervention (haloperidol prophylaxis) was administered in elderly patients after noncardiac surgery.40 Assuming that the general anesthesia group (general anesthesia plus postoperative intravenous analgesia) in the present study will have a similar delirium incidence as in our previous study, a total of 1664 subjects (832 subjects in each group) are required to detect a one-third reduction in the incidence of postoperative delirium at an 80% power with a two-sided significance level of 0.05. Considering a dropout rate of about 7.5 %, we plan to enroll 1800 patients.

***3.3 Participating centers***

3.3.1 This multicenter trial is conducted in five tertiary care hospitals affiliated with Peking University in Beijing, China. The five participating centers include Peking University First Hospital, Peking University People’s Hospital, Peking University Third Hospital, Beijing Hospital, and Beijing Shijitan Hospital.

3.3.2 The study is coordinated by the Department of Anesthesiology and Critical Care Medicine of Peking University First Hospital; and the Peking University Clinical Research Institute is responsible for the study monitoring, data management and data analysis.

**4. Study participants**

Potential participants will be screened before surgery by the qualified investigators.

***4.1 Inclusion criteria***

4.1.1 Age range 60–90 years.

4.1.2 Planning to undergo noncardiac thoracic or abdominal surgery with an expected duration of 2 hours or longer. For those who undergo thoracoscopic or laparoscopic surgery, the expected length of incision must be 5 centimeters or more.

4.1.3 Agree to receive patient-controlled analgesia after surgery.

***4.2 Exclusion criteria***

Patients will be excluded if they meet any of the following criteria:

4.2.1 Previous history of schizophrenia, epilepsy or Parkinson disease, or unable to complete preoperative assessment due to severe dementia, language barrier, or end-stage disease.

4.2.2 History of myocardial infarction or stroke within 3 months before surgery.

4.2.3 Any contraindication to epidural anesthesia and analgesia, including abnormal vertebral anatomy, previous spinal trauma or surgery, severe chronic back pain, coagulation disorder (prothrombin time or activated partial prothrombin time longer than 1.5 times of the upper normal limit, or platelet count of less than 80 × 109/L), local infection near the site of puncture, and severe sepsis.

4.2.4 Severe heart dysfunction (New York Heart Association functional classification 3 or above), hepatic insufficiency (Child-Pugh grades C), or renal insufficiency (serum creatinine of 442 μmol/L or above, with or without serum potassium of 6.5 mmol/L or above, or requirement of renal replacement therapy).

4.2.5 Any other conditions that are considered unsuitable for study participation.

***4.3 Criteria of drop-out***

4.3.1 Study intervention is not administered (due to failed epidural puncture, failed epidural catheterization, epidural catheter obstruction, blood appear in epidural catheter, inadequate epidural analgesia, etc.).

4.3.2 Intervention interrupted by the investigators/anesthesiologists (due to adverse events).

4.3.3 Use of a prohibited drugs.

The causes of protocol deviation should be recorded and corrected when possible. The cases will be followed up according to the study protocol and included in the intention-to-treat analysis.

4.3.4 Withdraw consent after intervention started.

The situation should be recorded. The primary therapeutic effects recorded in the last time will be regarded as the final results. The cases will be included in the intention-to-treat analysis.

***4.4 Criteria of elimination***

Included patients will be excluded if they meet any of the following criteria:

4.4.1 Withdraw consents before intervention.

4.4.2 Surgery cancelled.

4.4.3 No assessment result of the primary outcome.

The causes of elimination should be explained. The case will be excluded from the intention-to-treat analysis. The case report forms will be preserved for reference.

***4.5 Criteria of study interruption***

Study will be interrupted in the following situations:

4.5.1 Severe safety problem occurred during the study.

4.5.2 Serious mistake found in the protocol.

4.5.3 Fund or management problem of the investigators.

4.5.4 Study cancelled by the administrative authority.

Study interruption may be transient or permanent. All recorded case report forms will be preserved for reference in case of study interruption.

# 5. Randomization and masking

***5.1 Randomization***

5.1.1 The randomization will be performed (in a 1:1 ratio) centrally at Peking University Clinical Research Institute through a 24-hour interactive web response system (IWRS, Brightech Clinical Information Management System) before the surgery. The randomization is stratified by study center and type of surgery (thoracic or abdominal surgery) with a block size of four. Allocation is concealed until shortly before anesthesia induction or epidural puncture.

5.1.2 For each recruited patient, a study coordinator will be designated to distribute the randomization result to the anesthesiologists according to the sequence of recruited patients, and to coordinate between investigators.

5.1.3 For each recruited patient, an anesthesiologist will be designated for anesthesia and postoperative pain management (and data collection) according to the result of randomization.

5.1.4 Study intervention (combined epidural-general anesthesia plus postoperative epidural analgesia or general anesthesia plus postoperative intravenous analgesia) will be provided according to the randomization results by anesthesiologists who do not participate in the outcome assessments.

5.1.5 The results of randomization will be concealed and stored at the interactive web response system (IWRS, Brightech Clinical Information Management System) and monitored by Peking University Clinical Research Institute.

***5.2 Masking***

5.2.1 Because of the apparent difference between the two anesthesia-analgesia methods, patients, anesthesiologists and other health-care team members are aware of study group assignment.

5.2.2 Investigators who are responsible for patient recruitment do not participate in the anesthesia and perioperative care of the recruited patients.

5.2.3 Investigators who are responsible for postoperative follow‐up and outcome assessments are not involved in anesthesia and perioperative management and have no knowledge of study group assignment. They have been trained prior to the study to follow the study protocol and to do delirium assessment. They are not allowed to communicate with neither patients nor other health-care team members regarding study group assignment.

5.2.4 Statistical analysis will be performed independently by Peking University Clinical Research Institute.

# 6. Intervention protocol

***6.1 Anesthesia and analgesia***

6.1.1 Intraoperative monitoring includes electrocardiogram, non-invasive blood pressure, pulse oxygen saturation, end-tidal concentrations of inhalational anesthetics and carbon dioxide, nasopharyngeal temperature, and urine output. Intra-arterial pressure and central venous pressure are monitored when necessary.

6.1.2 For patients assigned to receive combined epidural-general anesthesia plus postoperative epidural analgesia (EGA Group), epidural catheterization will be performed first.

6.1.2.1 The intervertebral space for epidural puncture will be selected by the attending anesthesiologists according to the site of planned incision. An epidural catheter will be inserted using a standard technique. After negative aspiration of blood and cerebrospinal fluid, a test dose of 3–4 mL of 2 % lidocaine will be administered to confirm the position of the catheter and the effect of neuraxial block.

6.1.2.2 Failed epidural puncture/catheterization includes the following conditions: (1) failed attempts of more than 5 times by senior anesthesiologists; (2) patients refuse further epidural puncture attempts; (3) no dermatomes with sensory block appear after testing dose of epidural lidocaine (usually 10-20 min are required), and judged as failed epidural catheterization by the attending anesthesiologists.

6.1.2.3 General anesthesia will be induced with midazolam (0.02-0.03 mg/kg), propofol, sufentanil and rocuronium. For patients with expected difficult airway, endotracheal intubation may be facilitated by succinylcholine or awake intubation may be performed. Anesthesia will be maintained with intravenous (propofol), inhalational (sevoflurane with or without nitrous oxide), or combined intravenous-inhalational anesthetics, together with 0.375%-0.5% ropivacaine administered as bolus and/or continuously through the epidural catheter. Additional opioids (remifentanil, sufentanil, fentanyl, or morphine) and muscle relaxant (rocuronium, atracurium, or cisatracurium) will be administered when deemed necessary. For patients whose epidural local anesthetics has to be decreased or stopped, the reasons, the administered dose and subsequent management should be recorded.

6.1.2.4 Patient-controlled epidural analgesia will be provided after surgery. This is established with 0.12 % ropivacaine and 0.5 μg/mL sufentanil in 250 mL normal saline, programmed to deliver 2-mL boluses with a 20-minute lockout interval and a background infusion of 4 mL/h. For patients with low body weight or poor general condition, doses can be decreased and upper dose limit can be set for the patient-controlled pump.

6.1.2.5 For patients whose epidural analgesia pump has to be decreased or stopped, the reasons, the administered dose and subsequent management should be recorded.

6.1.3 For patients assigned to receive general anesthesia plus postoperative intravenous analgesia (GA Group), epidural catheterization will not be performed.

6.1.3.1 General anesthesia will be induced with midazolam (0.02-0.03 mg/kg), propofol, sufentanil, and rocuronium. For patients with expected difficult airway, endotracheal intubation may be facilitated by succinylcholine or awake intubation may be performed. Anesthesia will be maintained with either intravenous (propofol), inhalational (sevoflurane with or without nitrous oxide), or combined intravenous-inhalational anesthetics. Additional opioids (remifentanil, sufentanil, fentanyl, or morphine) and muscle relaxant (rocuronium, atracurium, or cisatracurium) will be administered when deemed necessary.

6.1.3.2 Patient-controlled intravenous analgesia will be provided after surgery. This is established with 0.5 mg/mL morphine in 100 mL normal saline, programmed to deliver 2-mL boluses with a 6 to 10-minute lockout interval and a 1 mL/h background infusion. For patients with low body weight or poor general condition, doses can be decreased and upper dose limit can be set for the patient-controlled pump.

6.1.3.3 For patients whose intravenous analgesia pump has to be decreased or stopped, the reasons, the administered dose and subsequent management should be recorded.

***6.2 Remedial measures***

6.2.1 For patients in the combined epidural-general anesthesia group but with failed epidural catheterization, anesthesia and postoperative analgesia will be performed as those in the general anesthesia plus postoperative intravenous analgesia group.

6.2.2 For patients in the combined epidural-general anesthesia group, inadequate anesthesia is managed with additional local anesthetics administered through the epidural catheter, and/or increasing intravenous and/or inhalational anesthetics. For patients in the general anesthesia group, inadequate anesthesia is managed with increasing intravenous and/or inhalational anesthetics.

6.2.3 For patients in the combined epidural-general anesthesia group with unsatisfied postoperative analgesia, pump setting will be adjusted (increased), supplemental analgesics (such as opioids, non-steroidal anti-inflammatory drugs, and others) will be administered, or an intravenous analgesia pump will be provided. For patients in the general anesthesia group with unsatisfied postoperative analgesia, pump setting will be adjusted (increased) and/or supplemental analgesics (such as opioids, non-steroidal anti-inflammatory drugs, and others) will be administered. The above measures will be recorded.

***6.3 Allowed and prohibited medications***

6.3.1 For patients of both groups, no premedication (usually include anticholinergics and sedatives) is administered. Dexmedetomidine is not allowed. Anticholinergics are prohibited unless being used for the treatment of bradycardia, in which case atropine will be administered. Patients enrolled in Peking University First Hospital are prohibited to use etomidate.

6.3.2 During anesthesia, vasopressors (such as ephedrine, phenylephrine, dopamine, adrenaline and norepinephrine), antihypertensives (such as urapidil and nicardipine), atropine and esmolol can be used to maintain hemodynamic stable; glucocorticoids and 5-hydroxytryptamine 3 (5-HT3) receptor antagonists can be used to prevent postoperative nausea and vomiting.

6.3.3 For patients admitted to the ICU with endotracheal intubation, propofol and/or midazolam can be administered for sedation; the target is to maintain the Richmond Agitation-Sedation Scale (RASS, score ranges from –5 [unarousable] to +4 [combative] and 0 indicates alert and calm)41,42 from -2 to +1. For patients admitted to the ICU without endotracheal intubation, sedatives should not be administered unless otherwise needed. Other sedatives are not allowed.

6.3.4 Other perioperative management are provided according to routine practice.

***6.4 Management of delirium***

6.4.1 Precipitating factors should be identified and managed. Usually there are more than one precipitating factors (underlying diseases).

6.4.2 Supportive therapies should be provided. These include reorientation, cognitive stimulation, early mobilization, hearing or vision aids, sleep promotion, and nutritional supply. A safe environment should be guaranteed for both patients and medical staff. Family members of patients should be included in the supportive therapy.

6.4.3 Pharmacological therapy is administered only when the delirium symptoms endanger the safety of patients themselves or others, or affect the normal medical work such as mechanical ventilation and central venous catheterization. Haloperidol (0.5-2 mg) will be administered intravenously, repeated when necessary every 15-20 minutes until control of symptoms. For maintenance treatment, half of the loading dose can be given intravenously every 4 to 6 hours, lasting for several days. Oral antipsychotic drugs will be administered under the guidance of psychiatrists when necessary.

# 7. Data collection

***7.1 Baseline data***

7.1.1 Demographic data, including age, sex, body mass index, and education level.

7.1.2 Diagnosis and medical history, including surgical diagnosis, comorbidities, medical therapy, drinking and smoking history, food and drug allergy, and previous history of surgery and anesthesia.

7.1.3 Results of main laboratory tests and instrumental examinations.

7.1.4 General status, including Charlson Comorbidity Index,43,44 American Society of Anesthesiologists classification, and New York Heart Association classification.

7.1.5 Activities of daily living is assessed with the Barthel Index (score ranges from 0 to 100, with higher score indicating better function). 45,46,47

7.1.6 Cognitive function is assessed with the Mini-Mental State Examination (score ranges from 0 to 30, with higher score indicating better function).48,49

7.1.7 Anxiety and depression are assessed with the Hospital Anxiety and Depression Scale (score ranges from 0 to 21 for either depression or anxiety, with higher score indicating more severe symptoms. A score >7 is adopted as the borderline abnormal).50,51,52

7.1.8 Delirium is assessed with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).53,54,55

***7.2 Intraoperative data***

7.2.1 Anesthesia method, type and dose of anesthetics and other medications used during anesthesia, duration of anesthesia.

7.2.2 Fluid balance (including fluid infusion, estimated blood loss, and urine output) and transfusion of blood products.

7.2.3 Location, type, name and duration of the surgery.

7.2.4 Data of vital signs and arterial blood gas result (if available).

7.2.5 For patients recruited in Peking University First Hospital, blood samples (4 mL) will be collected before surgery with their agreement. The serum will be separated within 1 hour and stored in the -80°C freezer until measurement of serum cortisol, interleukin (IL)-6 and IL-8 concentration.

***7.3 Postoperative data***

7.3.1 Patients will be visited twice daily during the first seven days after surgery; they will then be followed up weekly until 30 days after surgery. Information from the Electronic Anesthesia Information System and the Electronic Medical Record System will be achieved. Discharged patients will be contacted by telephone.

7.3.2 Occurrence of delirium during the first seven postoperative days will be assessed with the CAM‐ICU twice daily (8-10 AM and 6-8 PM). Immediately before assessing delirium, sedation or agitation will be assessed using the RASS. For deeply sedated or unarousable patients (RASS –4 or –5), delirium is not assessed and the patient is recorded as comatose. For patients with a RASS from -3 to +4, delirium is assessed with the CAM-ICU. Delirium episodes are classified into three motoric subtypes, i.e., hyperactive (RASS is consistently positive, from +1 to +4), hypoactive (RASS is consistently neutral or negative, from –3 to 0), and mixed.56 Investigators for postoperative delirium assessment will be trained by psychiatrists to use the CAM‐ICU before the trial is commenced.

7.3.3 The intensity of postoperative pain both at rest and with coughing during the first three postoperative days will be evaluated twice daily at the same time of delirium assessment (8-10 AM and 6-8 PM) with the numeric rating scale (NRS, a 11-point scale where 0 indicates no pain and 10 indicates the worst pain). For patients who are deeply sedated or unarousable (−4 or −5 on the RASS), pain evaluation will be stopped and repeated later.

7.3.4 The use of analgesics and other medications during the first 7 days after surgery will be recorded.

7.3.5 For patients who are admitted to the ICU after surgery, the worst Acute Physiology and Chronic Health Evaluation II (APACHE II, score ranges from 0 to 71, with higher score indicating more severe disease)57 score during the first 24 hours after surgery, the duration of mechanical ventilation (for those with endotracheal tubes), the use of sedatives, and the length of ICU stay will be recorded.

7.3.6 For patients recruited in Peking University First Hospital, blood samples (4 mL) will be collected on the 1st and 3rd morning (6-8 AM) after surgery with their agreements. The serum will be separated within 1 hour and stored in the -80°C freezer until measurement of serum cortisol, IL-6 and IL-8 concentration. According to the study budget, blood samples from about 300 patients will be tested. Convenient sampling will be used in selecting patients from the two groups in a 1:1 ratio.

7.3.7 Occurrence of non‐delirium complications during the first 30 days after surgery will be recorded. Non-delirium complications are defined as newly occurred medical conditions other than delirium that are harmful to patients’ recovery and required therapeutic intervention, i.e., grade II or higher on the Clavien-Dindo classification.58

7.3.8 Time to resume fluid and food intake.

7.3.9 Length of hospital stay after surgery.

7.3.10 All‐cause 30‐day mortality after surgery.

**8. Outcomes**

***8.1 Primary outcome***

Incidence of delirium within 7 days after surgery.

***8.2 Secondary outcomes***

8.2.1 The percentage of intensive care unit (ICU) admission after surgery.

8.2.1.1 The worst APACHE II score within 24 hours of ICU admission.

8.2.1.2 The percentage of ICU admission with endotracheal intubation.

8.2.1.3 The duration of mechanical ventilation in ICU.

8.2.1.4 The length of stay in ICU after surgery.

8.2.2 The intensity of pain during the first three days after surgery.

8.2.3 Time to onset of delirium.

8.2.4 Time to resume fluid/food intake.

8.2.5 The length of stay in hospital after surgery.

8.2.6 The incidence of non-delirium major complications within 30 days after surgery.

8.2.7 The 30-day all-cause mortality.

***8.3 Other pre-specified outcomes***

8.3.1 Serum cortisol concentration after surgery (selected patients).

8.3.2 Serum IL-6 concentration after surgery (selected patients).

8.3.3 Serum IL-8 concentration after surgery (selected patients).

**9. Adverse events**

***9.1 Definition***

An adverse event indicates any unpredictable, unfavorable medical event that is associated with any medical intervention and occurs during the study period. It can be related to the study intervention or otherwise. It can manifest as any uncomfortable signs (including abnormal laboratory findings), symptoms or transient morbidity.

***9.2 Predicted adverse events in this study***

9.2.1 Intraoperative adverse events

9.2.1.1 Adverse events related to epidural puncture/catheterization include accidental dural puncture, nerve injury, failed epidural puncture/catheterization, epidural catheter obstruction, blood appear in epidural catheter, epidural catheter dislodgement, local/epidural hematoma, local/nerve injury, etc.

9.2.1.2 Adverse events related to epidural and/or general anesthesia include local anesthetic intoxation, total spinal anesthesia, intraoperative hypotension (systolic blood pressure <80 mmHg), intraoperative hypertension (systolic blood pressure >180 mmHg), intraoperative bradycardia (heart rate <40 bpm), intraoperative tachycardia (heart rate >100 bpm), teeth injury, laryngeal spasm, prophylaxis, arrhythmia, cardiac events, atelectasis, etc.

9.2.2 Postoperative adverse events

9.2.2.1 Adverse events related to epidural analgesia include epidural catheter obstruction, inadequate epidural analgesia, epidural catheter dislodgement, epidural hematoma, epidural abscess, sequelae of nerve injury, post dural puncture headache, pruritus, leg weakness, etc.

9.2.2.2 Other adverse events include nausea, vomiting, postoperative hypotension (systolic blood pressure <90 mmHg), postoperative hypertension (systolic blood pressure >160 mmHg), postoperative bradycardia (heart rate <50 bpm), postoperative tachycardia (heart rate >100 bpm), inadequate analgesia, etc.

9.2.3 In the present study, adverse events will be monitored from the beginning of anesthesia (epidural puncture or induction of general anesthesia) until 72 hours after surgery, i.e., end of patient-controlled analgesia.

***9.3 Management***

9.3.1 Therapies will be provided according to patients’ condition and routine practice. Generally, hypotension is managed with lighting anesthesia, intravenous fluid and vasopressors; hypertension is managed with deepening anesthesia and antihypertensive drugs; bradycardia is managed with lighting anesthesia and atropine; tachycardia is managed with deepening anesthesia, intravenous fluid and esmolol when necessary.

9.3.2 The study intervention (epidural anesthesia or postoperative epidural/intravenous analgesia) can be stopped temporarily or permanently if considered necessarily by the attending anesthesiologist or surgeons. The time and reasons of study intervention interruption will be recorded.

9.3.3 In case that the patient-controlled analgesia (for study intervention) is terminated early, other analgesics will be provided.

***9.4 Record***

9.4.1 Any adverse event should be documented, including occurrence, type/diagnosis, time of diagnosis, management, duration of persistence, and sequelae.

9.4.2 Any adverse event should be followed up until it is completely resolved or therapy terminated.

**10. Severe adverse events**

***10.1 Definition***

A severe adverse event indicates any unpredictable medical events that lead to death, threat of life, prolonged length of hospital stay, persistent disability or dysfunction, or other severe event.

***10.2 Management***

In case of any severe adverse events, the study intervention will be stopped and treatment will be initiated immediately.

***10.3 Record and report***

10.3.1 In case of any severe adverse event, apart from active treatment and record as above, the principal investigator and the Ethics Committee (Peking University Institutional Review Board) will be informed within 24 hours in written report.

10.3.2 In case of study intervention related death, immediately stop the clinical trial, report the event to the Ethics Committee as soon as possible, record in detail and carefully preserve the related documents.

10.3.3 Any severe adverse event must be followed up until it is completely resolved or when therapy is ended.

**11. The rule of unmasking**

11.1 After the follow-up of all cases have been completed, the data of case report forms have been checked as correct, and the data entry have been finished, a database inspection report will be written by the data manager.

11.2 After the database is locked, unmasking will be conducted. And the database will be sent to the statisticians for statistical analysis.

**12. Data management**

12.1 The investigators should record data timely, completely and correctly according to the original observations and assessments.

12.2 The completed case report forms, after signed by the supervisors, will be sent to a clinical data custodian.

12.3 After the data in the case report forms have been input and checked, the case report forms will be stored in sequence order.

12.4 Data management will be inspected by Peking University Clinical Research Institute.

**13. Statistical analysis**

***13.1 General principles***

13.1.1 Numeric variables will be presented as mean ± standard deviation or median (minimum, maximum; or interquartile range). Categorical variables will be presented as number of cases (percentage).

13.1.2 For each hypothesis, two‐tailed tests will be used in all statistical analysis, and p <0.05 will be considered statistically significant. For the treatment-by-covariate interaction in predefined subgroup analyses, a p<0.10 will be defined as statistically significant.

13.1.3 The primary and secondary outcomes will be analyzed in an intention-to-treat population, i.e., all patients are analyzed in the group to which they are randomized and received at least part of study intervention. If epidural anesthesia and/or analgesia fail, these patients will be converted to general anesthesia and intravenous analgesia but will be analyzed in the group to which they are randomized. Also, we will do per-protocol analysis for the primary endpoint, in this case, drop-out patients will be excluded.

***13.2 Patient recruitment and drop‐out status***

The status of patient recruitment and drop‐out will be summarized and listed. Comparison of the overall elimination/drop‐out rate between the two groups will be performed with Chi‐Square test.

***13.3 Demographics and baseline characteristics***

13.3.1 Demographics and baseline data will be presented.

13.3.2 Between-group differences are compared using the absolute standardized differences (ASDs), which are defined as the absolute difference in means, mean ranks or proportions divided by the pooled standard deviation and calculated with the formula published by Austin.59 Baseline variables with an absolute standardized difference ≥ will be considered imbalanced between the two groups and adjusted for in all analyses if considered necessary.



***13.4 Intra- and postoperative variables***

Numeric variables will be analyzed using the independent-samples t test or Mann-Whitney U test; categorical variables will be analyzed using the chi square test, continuity correction chi square test or Fisher exact test. Missing data will not be replaced.

***13.5 Efficacy analysis***

13.5.1 Evaluation of primary endpoint

13.5.1.1 The incidence of delirium within 7 days after surgery will be calculated. Comparison between groups will be performed with Chi-Squared test. The difference of risk for postoperative delirium between two groups will be expressed as relative risk (RR) and 95% CI. For patients with missing data due to early hospital discharge or death, the last delirium assessment results will be considered as the missing data when calculating the incidence of delirium within 7 postoperative days.

13.5.1.2 Unadjusted relative risks and corresponding 95% CI are calculated to assess the treatment effect in predefined subgroups. The interactions between the treatment effect and each predefined factor will be assessed separately using logistic regression. The predefined factors include study center (center 1 vs. others), age (<70 years vs. ≥70 years), sex (female vs. male), education (≤9 years vs. >9 years), body mass index (≤24 kg/m2 vs. >24 kg/m2), duration of surgery (<240 min vs. ≥240 min), location of surgery (thoracic vs. abdominal), type of surgery (mini-invasive vs. open), and ICU admission (no vs. yes). The relative risk (95% CI) for each subgroup and the p values of treat-by-covariate interactions will be displayed in a forest plot.

13.5.2 Evaluation of secondary endpoints

13.5.2.1 Time‐to‐event variables (time to onset of delirium, time to extubation, length of stay in ICU, time to resume fluid/food intake, length of stay in hospital after surgery) will be calculated with the Kaplan-Meier estimator, with differences between groups assessed by the log-rank test. The estimates hazard ratio (HR) and 95% CI will be provided. Patients who die within 30 days after surgery will be censored at the time of death.

13.5.2.2 Categorical variables (percentage with endotracheal intubation at ICU admission, incidence of non-delirium complications within 30 days, 30-day all-cause mortality rate, percentage with moderate to severe pain, and percentage of motoric delirium subtypes) will be analyzed using the Chi-Square test, continuity correction Chi-Square test or Fisher exact test. The estimated relative risk (RR) and 95% CI will be provided when possible. Missing data will not be replaced.

13.5.2.3 Numeric variable (NRS pain score, APACHE II score at ICU admission, serum concentrations of cortisol, IL-6 and IL-8 [sub-study]) will be analyzed using the independent-samples t test or Mann-Whitney U test. The mean/median difference and 95% CI will be provided. The difference between two medians (and 95% CI) will be calculated with the Hodges-Lehmann estimator. Missing data will not be replaced.

***13.6 Safety analysis***

13.6.1 Describe the occurrence of adverse events in each group.

13.6.2 Describe the management of adverse events when appropriate.

13.6.3 Describe the occurrence of severe adverse events.

13.6.4 The rates of adverse events and/or managements between the two groups will be compared with Chi-Square test, continuity correction Chi-Square test or Fisher exact test.

13.6.5 Missing data will not be replaced.

**14. Quality control and quality assurance**

***14.1 Training for investigators***

14.1.1 An investigator training program will be designed by the principle investigator. A study coordinator will be designated to organize and implement the training program, and to record and preserve the related documents.

14.1.2 Investigator training will be performed during the month before starting the study.

14.1.2.1 Delirium assessment will be trained by psychiatrists. Investigators who are in charge of delirium assessment in each study center (at least two investigators in each center) must attend the training program and pass the examination. The training program includes lectures on the clinical manifestations, potential mechanisms, diagnosis and treatment of delirium, a lecture explaining the use of the CAM-ICU, and simulating training courses with patient-actors for delirium assessment with the CAM-ICU. The simulating training will continue until the agreements of delirium diagnoses between psychiatrists and investigators reach >99%.

14.1.2.2 Other training contents that must be finished before starting the study include the Good Clinical Practice principles, the study protocol, the standard operating procedures of the study, the working plan of the study, the instruction for the case report form, and other matters needing attention during the study (collection of blood samples, allowed and prohibited medications, etc.).

14.1.3 The training program will be repeated 2-3 times a year throughout the study period, or will be performed whenever necessary.

***14.2 Monitoring of study conduct***

14.2.1 The study will be monitored by the Peking University Clinical Research Institute.

14.2.2 A project specialist will be designated by the Peking University Clinical Research Institute and will verify that the conduct of the study, the record of data and the analysis are in accord with the study protocol and related regulations. Investigators should cooperate with the project specialist.

14.2.3 Before and during the study period, the project specialist will go to the study centers for initiation inspection, regular inspection, and end of study inspection. The project specialist will schedule the time of inspection but at least one inspection will be performed after recruiting the first three participants, and at least once every 12 weeks for the principle study center and every 24 weeks for the participating centers.

14.2.4 The contents of inspection include the following:

14.2.4.1 To verify that investigators are designated and completed the training program.

14.2.4.2 To verify the authenticity of participants, and the process to obtain written informed consents.

14.2.4.3 To verify the eligibility of participants. For the first three participants recruited in each center, 100% of the original data of will be checked and verified.

14.2.4.4 To verify the correctness of the randomization procedure.

14.2.4.5 To verify that the follow-ups and assessments are performed according to the study protocol.

14.2.4.6 Original data will be inspected in at least 5% of the recruited participants. Original data of the primary outcome will be inspected in 100% of the recruited participants.

14.2.4.7 To verify that all severe adverse events are reported to the Ethics Committee according to the study protocol. The original data of all severe adverse events will be inspected.

14.2.4.8 To verify the transport, dissemination and retrieve of study drugs, and the records of storage and return of study drugs.

14.2.4.9 To verify that the blood samples are collected and stored according to the study protocol and the standard operating procedures.

14.2.4.10 To verify that the revised study protocol, participant-related documents, report of severe adverse events, and annual summary report are submitted to the Ethics Committee timely by the investigators for approval or record.

14.2.4.11 To verify the preservation of study-related documents and original data.

14.2.4.12 To verify the trial management in the study centers, the progress of participant recruitment and the study conduct, the accomplishment of recruited cases, and the situation of case drop-out.

14.2.5 A written report will be provided after each inspection. The report should include date, time, name of inspector, and the problems found during inspection. The project specialist will inform the principal investigator about the identified problems and will discuss the approaches to solve these problems. In case of important problems, such as those regarding participant safety, adherence to the study protocol or Good Clinical Practice principles, or delayed progress, the project specialist should report to the management office of the Peking University Clinical Research Program.

***14.3 Inspection of data quality***

14.3.1 The project specialist will check and verify the completeness and correctness of the data recorded in the case report forms, and will ask investigators to correct or replenish data when necessary.

14.3.2 Data manager from the Peking University Clinical Research Institute will recheck data according to the logical relations and to identify the existence of protocol deviation and out of normal limit. For the drop-out or missing data or data with logical contradictions, query forms will be sent to the investigators. The investigators are responsible to reply queries, and to verify or correct data.

14.3.3 All data queries must be solved before the database can be locked for statistical analysis.

**15. Ethics requirements**

***15.1 Ethics Committee***

The study protocol must be approved by the Peking University Institutional Review Board before the study can be started. The investigators must strictly follow the Helsinki Declaration and China's relevant clinical trial management regulations. The principal investigator is responsible to report the status and the progress of the study to the Institutional Review Board.

***15.2 Written informed consent***

Investigators responsible for recruiting participants must have been trained and qualified by the principle investigator. For each potential participant, investigators are responsible to fully explain the purpose, procedures and possible risks of this study in a written form manner. The investigators must let every potential participant know that he/she has the right to withdraw consent from the study at any time. Every potential participant must be given a written informed consent. Every participant or the authorized surrogate of the participant must sign the consent before he/she can be enrolled in the study. The written informed consents will be kept as a part of the clinical trial documents. For participants with mild dementia (MMSE ≤17 for illiterate, ≤20 for those with primary school education, ≤24 for those with junior high school education or higher) or incompetence, written informed consents must be signed by legal representatives.

***15.3 Privacy and confidentiality***

15.3.1 During the study period, the collected data from participants are labelled with special recruitment numbers and acronyms of names.

15.3.2 All personal information of the participants will be kept confidential. The filing cabinets storing the study documents will be locked. Apart from the study investigators, only authorized inspectors from the Peking University Clinical Research Institute or members from the Peking University Institutional Review Board are allowed to access the information after obtaining consents from the participants.

15.3.3 Results of the study will be published as scientific articles. But all personal data (including name and age, etc.) are strictly confidential.

**16. Study termination**

16.1 In case that severe adverse events or serious quality problem occur during the study period, the study will be stopped. A report will be sent to the Ethics Committee. Restart of the study will need an approval from the Ethics Committee.

16.2 The study will be terminated after accomplishment of required patient recruitment and data collection. Decision will be made by the principal investigator.

**17. Preservation of documents**

Investigators will carefully preserve all documents and data of the clinical trial according to the requirements of Good Clinic Practice for a period of 5 years.

**18. Declaration of interests**

This trial is funded by the Peking University Clinical Research Program (PUCRP201101). The investigators declare no conflict of interests.

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**Summary of changes from the original study protocol approved by the ethics committee**

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| --- | --- | --- | --- | --- |
|  | **Version** | **Date of version** | **Drafter/**  **reviser** | **Contents of revision** |
| 1 | 3.0 | Apr. 19, 2011 | Y.-W.L., D.-X.W. | (This was the first version approved by the ethics committee before recruiting patients). |
| 2 | 3.1 | Nov. 17, 2011 | Y.-W.L., D.-X.W. | Deleted the assessment of delirium severity (clause 7.3.2). |
| 3 | 3.2 | Sept. 3, 2012 | Y.-W.L., D.-X.W. | Revised the method of serum collection (clause 7.3.6). |
| 4 | 3.3 | Mar. 11, 2013 | Y.-W.L., D.-X.W. | 1) Opened a new study center (clause 3.3.1).  2) Added the criteria of drop-out and elimination (clause 4.3 and clause 4.4).  3) Added the definition of patients with failed epidural puncture or catheterization (clause 6.1.2.2).  4) Deleted the collection of postoperative observations cards (original clause 7.3.8).  5) Added the supplementary provisions for the required qualification of the investigators recruiting participants (clause 15.2). Added supplementary provisions when recruiting patients with mild dementia or incompetence (clause 15.2). |
| 5 | 3.4 | May 20, 2013 | Y.-W.L., D.-X.W. | Deleted the “cross-group” statement. Clarified the management of patients with failed epidural puncture (clause 6.2.1). |
| 6 | 3.5 | Oct. 20, 2014 | Y.-W.L., D.-X.W. | 1) Closed two study centers (clause 3.3.1).  2) Added “For those who undergo thoracoscopic or laparoscopic surgery, the expected length of incision must be five centimeters or more” (clause 4.1.2). |

**Original statistical analysis plan**

Original statistical analysis plan as reported in the original trial protocol.

**1. Sample size calculation**

In a recent cohort study of our own, the incidence of postoperative delirium in elderly patients after major abdominal surgery (performed under general anesthesia followed by intravenous analgesia) was 13.1%. In our previous study, the incidence of delirium was reduced by roughly one-third when the intervention (haloperidol prophylaxis) was administered in elderly patients after noncardiac surgery.1 Assuming that the general anesthesia group (general anesthesia plus postoperative intravenous analgesia) in the present study will have a similar delirium incidence as in our previous study, a total of 1664 subjects (832 subjects in each group) are required to detect a one-third reduction in the incidence of postoperative delirium at an 80% power with a two-sided significance level of 0.05. Considering a dropout rate of about 7.5 %, we plan to enroll 1800 patients.

**2. Outcomes**

***2.1 Primary outcome***

Incidence of delirium within 7 days after surgery.

***2.2 Secondary outcomes***

2.2.1 The percentage of intensive care unit (ICU) admission after surgery.

2.2.2 The intensity of pain during the first three days after surgery.

2.2.3 The severity of delirium within 7 days after surgery.

2.2.4 The daily prevalence of delirium.

2.2.5 Time to onset of delirium.

2.2.6 Time to resume fluid/food intake.

2.2.7 The length of stay in hospital after surgery.

2.2.8 The incidence of non-delirium major complications within 30 days after surgery.

2.2.9 The 30-day all-cause mortality.

***2.3 Other pre-specified outcomes***

2.3.1 Serum cortisol concentration after surgery (selected patients).

2.3.2 Serum IL-6 concentration after surgery (selected patients).

2.3.3 Serum IL-8 concentration after surgery (selected patients).

**3. Statistical analysis**

***3.1 General principles***

3.1.1 Numeric variables will be presented as mean ± standard deviation or median (minimum, maximum; or interquartile range). Categorical variables will be presented as number of cases (percentage).

3.1.2 For each hypothesis, two‐tailed tests will be used in all statistical analysis, and p <0.05 will be considered statistically significant.

3.1.3 The primary and secondary outcomes will be analyzed in an intention-to-treat population, i.e., all patients are analyzed in the group to which they are randomized and received at least part of study intervention. If epidural anesthesia and/or analgesia fail, these patients will be converted to general anesthesia and intravenous analgesia but will be analyzed in the group to which they are randomized. Also, we will do per-protocol analysis for the primary endpoint, in this case, drop-out patients will be excluded.

***3.2 Patient recruitment and drop‐out status***

The status of patient recruitment and drop‐out will be summarized and listed. Comparison of the overall elimination/drop‐out rate between the two groups will be performed with Chi‐Square test.

***3.3 Demographics and baseline characteristics***

3.3.1 Demographics and baseline data will be presented.

3.3.2 For between-group differences, continuous variables will be analyzed using independent-samples t test or Mann-Whitney U test; categorical variables will be analyzed using the Chi-Square test, continuity correction Chi-Square test or Fisher exact test.

***3.4 Efficacy analysis***

3.4.1 Evaluation of primary endpoint

The incidence of delirium within 7 days after surgery will be calculated. Comparison between groups will be performed with Chi-Squared test. The difference of risk for postoperative delirium between two groups will be expressed as relative risk (RR) and 95% CI. For patients with missing data due to early hospital discharge or death, the last delirium assessment results will be considered as the missing data when calculating the incidence of delirium within 7 postoperative days; the missing data will not be replaced when calculating the daily prevalence of delirium.

3.4.2 Evaluation of secondary endpoints

3.4.2.1 Time‐to‐event variables (time to the first onset of delirium, time to resume fluid/food intake, length of stay in hospital after surgery) will be calculated with Kaplan-Meier estimator, with differences between groups assessed by the log-rank test. The estimates hazard ratio (HR) and 95% CI will be provided.

3.4.2.2 Categorical variables (the incidences of major complications other than delirium, the daily prevalence of delirium, and the 30-day all-cause mortality rate) will be analyzed using the Chi-Square test, continuity correction Chi-Square test or Fisher exact test. The estimated relative risk (RR) and 95% CI will be provided.

3.4.2.3 Ranked variables (the severity of delirium, the NRS pain scores after surgery) will be analyzed using the Mann-Whitney U test. The difference between two medians and 95% CI will be calculated with the Hodges-Lehmann estimator.

3.4.2.4 Numeric variables (serum concentrations of cortisol, IL-6 and IL-8) will be analyzed using the independent-samples t test or Mann-Whitney U test. Mean/median differences and 95% CI will be provided.

***3.5 Safety analysis***

3.5.1 Describe the occurrence of adverse events in each group.

3.5.2 Describe the management of adverse events when appropriate.

3.5.3 Describe the occurrence of severe adverse events.

3.5.4 The rates of adverse events and/or managements between the two groups will be compared with Chi-Square test, continuity correction Chi-Square test or Fisher exact test.

***3.6 Missing data***

Missing data or incomplete data will be marked in the case report forms. The principle investigator and the statistician will discuss and determine the management of missing data. Details will be listed in the final statistical analysis plan.

**4. References**

1. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE, Zhu SN: Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: A randomized controlled trial\*(to be published)

**Final statistical analysis plan**

Final statistical analysis plan as reported in the final trial protocol.

**1. Sample size calculation**

In a recent cohort study of our own, the incidence of postoperative delirium in elderly patients after major abdominal surgery (performed under general anesthesia followed by intravenous analgesia) was 13.1%. In our previous study, the incidence of delirium was reduced by roughly one-third when the intervention (haloperidol prophylaxis) was administered in elderly patients after noncardiac surgery.1 Assuming that the general anesthesia group (general anesthesia plus postoperative intravenous analgesia) in the present study will have a similar delirium incidence as in our previous study, a total of 1664 subjects (832 subjects in each group) are required to detect a one-third reduction in the incidence of postoperative delirium at an 80% power with a two-sided significance level of 0.05. Considering a dropout rate of about 7.5 %, we plan to enroll 1800 patients.

**2. Outcomes**

***2.1 Primary outcome***

Incidence of delirium within 7 days after surgery.

***2.2 Secondary outcomes***

2.2.1 The percentage of intensive care unit (ICU) admission after surgery.

2.2.1.1 The worst APACHE II score within 24 hours of ICU admission.

2.2.1.2 The percentage of ICU admission with endotracheal intubation.

2.2.1.3 The duration of mechanical ventilation in ICU.

2.2.1.4 The length of stay in ICU after surgery.

2.2.2 The intensity of pain during the first three days after surgery.

2.2.3 Time to onset of delirium.

2.2.4 Time to resume fluid/food intake.

2.2.5 The length of stay in hospital after surgery.

2.2.6 The incidence of non-delirium major complications within 30 days after surgery.

2.2.7 The 30-day all-cause mortality.

***3.3 Other pre-specified outcomes***

3.3.1 Serum cortisol concentration after surgery (selected patients).

3.3.2 Serum IL-6 concentration after surgery (selected patients).

3.3.3 Serum IL-8 concentration after surgery (selected patients).

**3. Statistical analysis**

***3.1 General principles***

3.1.1 Numeric variables will be presented as mean ± standard deviation or median (minimum, maximum; or interquartile range). Categorical variables will be presented as number of cases (percentage).

3.1.2 For each hypothesis, two‐tailed tests will be used in all statistical analysis, and p <0.05 will be considered statistically significant. For the treatment-by-covariate interaction in predefined subgroup analyses, a p<0.10 will be defined as statistically significant.

3.1.3 The primary and secondary outcomes will be analyzed in an intention-to-treat population, i.e., all patients are analyzed in the group to which they are randomized and received at least part of study intervention. If epidural anesthesia and/or analgesia fail, these patients will be converted to general anesthesia and intravenous analgesia but will be analyzed in the group to which they are randomized. Also, we will do per-protocol analysis for the primary endpoint, in this case, drop-out patients will be excluded.

***3.2 Patient recruitment and drop‐out status***

The status of patient recruitment and drop‐out will be summarized and listed. Comparison of the overall elimination/drop‐out rate between the two groups will be performed with Chi‐Square test.

***3.3*** ***Demographics and baseline characteristics***

3.3.1 Demographics and baseline data will be presented.

3.3.2 Between-group differences are compared using the absolute standardized differences (ASDs), which are defined as the absolute difference in means, mean ranks or proportions divided by the pooled standard deviation and calculated with the formula published by Austin.2 Baseline variables with an absolute standardized difference ≥ will be considered imbalanced between the two groups and adjusted for in all analyses if considered necessary.



***3.4 Intra- and postoperative variables***

Numeric variables will be analyzed using the independent-samples t test or Mann-Whitney U test; categorical variables will be analyzed using the chi square test, continuity correction chi square test or Fisher exact test. Missing data will not be replaced.

***3.5 Efficacy analysis***

3.5.1 Evaluation of primary endpoint

3.5.1.1 The incidence of delirium within 7 days after surgery will be calculated. Comparison between groups will be performed with Chi-Squared test. The difference of risk for postoperative delirium between two groups will be expressed as relative risk (RR) and 95% CI. For patients with missing data due to early hospital discharge or death, the last delirium assessment results will be considered as the missing data when calculating the incidence of delirium within 7 postoperative days.

3.5.1.2 Unadjusted relative risks and corresponding 95% CI are calculated to assess the treatment effect in predefined subgroups. The interactions between the treatment effect and each predefined factor will be assessed separately using logistic regression. The predefined factors include study center (center 1 vs. others), age (<70 years vs. ≥70 years), sex (female vs. male), education (≤9 years vs. >9 years), body mass index (≤24 kg/m2 vs. >24 kg/m2), duration of surgery (<240 min vs. ≥240 min), location of surgery (thoracic vs. abdominal), type of surgery (mini-invasive vs. open), and ICU admission (no vs. yes). The relative risk (95% CI) for each subgroup and the p values of treat-by-covariate interactions will be displayed in a forest plot.

3.5.2 Evaluation of secondary endpoints

3.5.2.1 Time‐to‐event variables (time to onset of delirium, time to extubation, length of stay in ICU, time to resume fluid/food intake, length of stay in hospital after surgery) will be calculated with the Kaplan-Meier estimator, with differences between groups assessed by the log-rank test. The estimates hazard ratio (HR) and 95% CI will be provided. Patients who die within 30 days after surgery will be censored at the time of death.

3.5.2.2 Categorical variables (percentage with endotracheal intubation at ICU admission, incidence of non-delirium complications within 30 days, 30-day all-cause mortality rate, percentage with moderate to severe pain, and percentage of motoric delirium subtypes) will be analyzed using the Chi-Square test, continuity correction Chi-Square test or Fisher exact test. The estimated relative risk (RR) and 95% CI will be provided when possible. Missing data will not be replaced.

3.5.2.3 Numeric variable (APACHE II score at ICU admission, serum concentrations of cortisol, IL-6 and IL-8) will be analyzed using the independent-samples t test or Mann-Whitney U test. The mean/median difference and 95% CI will be provided. The difference between two medians (and 95% CI) will be calculated with the Hodges-Lehmann estimator. Missing data will not be replaced.

***3.6 Safety analysis***

3.6.1 Describe the occurrence of adverse events in each group.

3.6.2 Describe the management of adverse events when appropriate.

3.6.3 Describe the occurrence of severe adverse events.

3.6.4 The rates of adverse events and/or managements between the two groups will be compared with Chi-Square test, continuity correction Chi-Square test or Fisher exact test.

3.6.5 Missing data will not be replaced.

**4. References**

1. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE, Zhu SN: Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: A randomized controlled trial\*. Crit Care Med 2012; 40:731–9
2. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28:3083–107

**Summary of changes from the original statistical analysis plan**

In “General principles” section, we added the significant level for treat-by-covariate interaction: “For the treatment-by-covariate interaction in predefined subgroup analyses, a p<0.10 will be defined as statistically significant” (clause 3.1.2).

In “Demographics and baseline characteristics” section, we changed the method to compare between-group differences: “Between-group differences are compared using the absolute standardized differences (ASDs), which are defined as the absolute difference in means, mean ranks or proportions divided by the pooled standard deviation and calculated with the formula published by Austin.1 Baseline variables with an absolute standardized difference ≥ will be considered imbalanced between the two groups and adjusted for in all analyses if considered necessary (clause 3.3.2).”



We added a “Intra- and postoperative variables” section to describe methods to compare between-group differences regarding intra- and postoperative variables: “Numeric variables will be analyzed using the independent-samples t test or Mann-Whitney U test; categorical variables will be analyzed using the chi square test, continuity correction chi square test or Fisher exact test. Missing data will not be replaced” (clause 3.4).

In the “Evaluation of primary endpoint” section, we added methods to assess treatment effect in predefined subgroups and treat-by-covariate interactions: “Unadjusted relative risks and corresponding 95% CI are calculated to assess the treatment effect in predefined subgroups. The interactions between the treatment effect and each predefined factor will be assessed separately using logistic regression. The predefined factors include study center (center 1 vs. others), age (<70 years vs. ≥70 years), sex (female vs. male), education (≤9 years vs. >9 years), body mass index (≤24 kg/m2 vs. >24 kg/m2), duration of surgery (<240 min vs. ≥240 min), location of surgery (thoracic vs. abdominal), type of surgery (mini-invasive vs. open), and ICU admission (no vs. yes). The relative risk (95% CI) for each subgroup and the p values of treat-by-covariate interactions will be displayed in a forest plot (3.5.1.2).”

In the “Evaluation of secondary endpoints”, we added “time to extubation, length of stay in ICU, percentage with endotracheal intubation at ICU admission, and APACHE II score at ICU admission” for patients admitted to the ICU after surgery; we deleted “the daily prevalence of delirium” because we provided “time to the first onset of delirium”; we deleted “the severity of delirium” because this variable was deleted in the protocol (clause 3.5.2).

We provided management of missing data in each paragraph.

**References**

1.Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28:3083–107