BMJ Open

Impact of dexmedetomidine infusion during general anesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019549
Article Type:	Protocol
Date Submitted by the Author:	12-Sep-2017
Complete List of Authors:	Wang, Bojie; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Chunjing; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Hu, Jian; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Huaijin; Peking University First Hospital, Department of Anesthesiology and Critical Care Guo, Chao; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Wang, Zhenhan; Dongping People's Hospital, Department of anesthesiology Zhang, Qiaochu; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Mu, Dongliang; Department of Anesthesiology and Critical Care Medicine Wang, Dong-Xin; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Adult anaesthesia < ANAESTHETICS, Delirium & cognitive disorders < PSYCHIATRY, Pain management < RADIOTHERAPY

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scores as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

Impact of dexmedetomidine infusion during general anesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

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Word Count：2547

Abstract for protocol

Introduction: Delirium is a common complication in the elderly after surgery and is associated with worse outcomes. Multiple risk factors are related with postoperative delirium, such as exposure to general anesthetics, pain and inflammatory response. Preclinical and clinical studies reported that dexmedetomidine could attenuate neurotoxicity induced by general anesthetics, improve pain management and inhibit inflammatory response. Several studies observed the relationship between intraoperative use of dexmedetomidine and postoperative delirium, but the results were inconsistent. This study is designed to investigate the impact of dexmedetomidine administered during general anesthesia in preventing delirium in elderly patients after major non-cardiac surgery.

Method and analysis: This is a randomized, double-blinded, and placebo-controlled trial. 620 elderly patients (age ≥ 60 years) who are scheduled to undertake elective major non-cardiac surgery (with an expected duration ≥ 2 hours) are randomly divided into two groups. For patients in dexmedetomidine group, a loading dose dexmedetomidine (0.6 μg/kg) will be administered in 10 minutes before anesthesia induction, followed by a continuous infusion at a rate of 0.5 μg/kg/h till 1 hour before the end of surgery. For patients in control group, normal saline will be administered in the same rate and volume as in the dexmedetomidine group. The primary endpoint is the incidence of delirium during the first five postoperative days. Secondary endpoints include pain intensity, cumulative opioid consumption and subjective sleep quality during the first 3 postoperative days, and the incidence of non-delirium complications and all-cause mortality within 30 days after surgery.

Ethics and dissemination: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987) and registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) with identifier ChiCTR-IPR-15007654. Results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Key words: intraoperative dexmedetomidine; postoperative delirium; old patient; major non-cardiac surgery

Strengths and limitations

1. This study is designed as a randomized, double-blinded and placebo-controlled trial with a large sample size.
2. Results of our study will provide evidence on the impact of dexmedetomidine infusion during general anesthesia on the incidence of delirium in elderly patients after non-cardiac surgery.
3. Bispectral index is monitored to guide anesthesia maintenance which will overcome an important limitation in a recent trial.
4. Safety outcome data will be recorded in detail.
5. As a single site trial, the generalizability of our results will be limited.

Introduction

Delirium is considered as an organic brain syndrome which is characterized by altered consciousness, inattention, and changes in cognition or perception; it develops acutely with clinical manifestations fluctuate during the course of the day.[1] Prevalence of delirium varies from 14.8% to 23.0% in patients after major non-cardiac surgery.[2-3] The occurrence of postoperative delirium (POD) is associated with worsen outcomes including prolonged mechanical ventilation and intensive care unit stay, increased postoperative complications, high mortality rate and long-term cognitive decline.[2-5]

The etiology of POD is multifactorial and includes several intraoperative factors.[6] For example, exposure to general anesthetics (e.g., propofol or sevoflurane) might produce neurotoxicity;[7-8] whereas reduced anesthetic exposure by avoiding deep anesthesia reduced the occurrence of delirium in elderly patients undergoing major non-cardiac surgery.[9] Poor pain management is another risk factor of POD.[6, 10] It was reported that the risk of postoperative delirium was 1.2 times higher for every unit increment in visual analogue pain score (an 11-point pain scale where 0 indicates no pain and 10 the most severe pain).[11] Inflammation is also proposed to play an important role in the pathogenesis of POD.[2] Inflammatory responses induced by surgery and anesthesia are manifested by elevated levels of interleukins (IL), C-reactive protein (CRP) and tumor necrosis factor (TNF).[2, 12] Studies by our group and other found that higher levels of inflammatory mediators are associated with increased risk of POD.[2, 13-16.]

Dexmedetomidine is a highly selective α2-receptor agonist with sedative, analgesic and anxiolytic effects.[17-21] When used as a supplement during intraoperative anesthesia, it reduces the consumption of general anesthetics.[17] Preclinical evidences

suggest that use of dexmedetomidine might attenuate neurotoxicity induced by general anesthetics.[18-19] In a meta-analysis, intraoperative administration of dexmedetomidine lowers postoperative pain intensity and reduces opioid consumption.[20] Clinical evidence also showed that intraoperative dexmedetomidine significantly inhibits hyper-secretion of inflammatory cytokines during and after surgery.[21-22]

Use of dexmedetomidine during general anesthesia may reduce POD. In pediatric patients undergoing tonsillectomy and cardiac surgery, intraoperative infusion of dexmedetomidine lowered the incidence of emergence delirium.[23,24] In adult patients undergoing cardiac surgery and microvascular free flap surgery, intraoperative dexmedetomidine (comparison with normal saline) slightly decreased the incidence of delirium, although the differences were not statistically significant between two groups possibly due to underpowered sample size.[25,26] In a recent study of Deiner et al.,[27] use of dexmedetomidine during general anesthesia did not reduce delirium after major non-cardiac surgery in the elderly. However, in that study, anesthesia depth was not monitored and the consumption of anesthetics (such as propofol and fentanyl) was similar between the two groups. It was possible that patients in the dexmedetomidine group received deeper anesthesia which might have increased the risk of delirium.[27] Therefore, the effects of dexmedetomidine administered during general anesthesia on the occurrence of POD need to be evaluated further.

This study is designed to investigate whether dexmedetomidine use during general anesthesia can decrease the incidence of POD in elderly patients after major non-cardiac surgery.

Method and analysis

Study design

This randomized, double-blinded, and placebo-controlled trial with two parallel arms is designed to test the superiority of dexmedetomidine administered during general anesthesia on the incidence of delirium after surgery. Patients will be randomized into either the dexmedetomidine group or the control group (Figure 1). The study is conducted in the Department of Anesthesiology and Critical Care Medicine of Peking University First Hospital.

Ethics approval

The study protocol (version 1.1, issue date Nov, 2015) was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). Any protocol modifications will be submitted for review and approval by the Ethics Committee. The trial was registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) on December 1, 2015, with identifier ChiCTR-IPR-15007654. Written informed consents are obtained from patients or their surrogate in law.

Participants

Elderly (age $\geqslant$ 60 years) patients who are scheduled to undergo elective non-cardiac surgery with expected duration $\geqslant$ 2 hours under general anesthesia are screened for inclusion. Those who meet any of the following criteria will be excluded: (1) do not provide written informed consents; (2) previous history of schizophrenia, epilepsy or Parkinson disease; (3) visual, hearing, language or other barrier which impede communication and preoperative delirium assessment; (4) neurosurgery or traumatic brain injury; (5) severe bradycardia (heart rate less than 40 beats per minute), sick

sinus syndrome or atrioventricular block of degree 2 or above; (6) severe hepatic dysfunction (Child-Pugh grade C); or (7) renal failure (requirement of renal replacement therapy).

Patient recruitment and baseline data collection

Potential participants are screened by qualified investigators the day before surgery (or on Friday for those who will undergo surgery next Monday). The study protocol including potential risks and benefits is explained in detail. Those who meet the inclusion and exclusion are invited to participate in the study.

After obtaining written informed consents, the following baseline data are collected: demographic data, preoperative diagnosis, comorbidity, current medical therapy, previous surgery, and main results of physical and laboratory examinations. Barthel index is used for evaluation of activities of daily living.[28] Cognitive function is assessed with Mini-Mental State Examination (MMSE).[29] Preoperative delirium is assessed with confusion assessment method (CAM).[30]

Randomization, grouping and blinding

Random numbers were created by an independent statistician using SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA) in a 1:1 ratio and were sealed in sequentially numbered envelopes. A study coordinator, who does not participate in anesthesia and postoperative follow-up of enrolled patients, will open envelop for random numbers and prepare study drugs before induction of anesthesia. In this way, patients are randomly divided into either dexmedetomidine or control group.

Information regarding randomization, study drug preparation and group allocation will be masked from investigators who perform data collection and postoperative follow-up, anesthesiologists, patients and other healthcare team members. Blinding will be maintained throughout the entire study period.

To ensure patients' safety, study group allocation can be unmasked in the following conditions, i.e., occurrence of severe adverse events or any unexpected deterioration in the patient's clinical status. These situations will be documented in the Case Report Forms (CRFs). The unmasked patients will be included in the intention-to-treat population but excluded from per-protocol analysis.

Interventions, anesthesia and analgesia

Intraoperative monitoring includes electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, end-tidal carbon dioxide, nasopharyngeal temperature, urine output, and bispectral index (BIS). Intraarterial pressure (including derivative dynamic parameters such as stroke volume variation by FlowTrac system) and central venous pressure are monitored according to patients' conditions.

Study drugs, either 200 μg (2 ml) dexmedetomidine (Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China) or 2 ml normal saline, are diluted in 50 ml normal saline. All study drugs are colorless solution provided in syringes of the same size and brand. The regimen of study drug administration includes a loading dose of 0.15 ml/kg (i.e., 0.6 μg/kg dexmedetomidine for patients in the dexmedetomidine group) administered during a 10-minute period before anesthesia induction. This is followed by a continuous infusion at a rate of 0.125 ml/kg/h (i.e., a rate of 0.5 μg/kg/h dexmedetomidine for patients in the dexmedetomidine group) till 1 hour before the end of surgery. Study drug infusion is performed by an infusion pump specially designed for dexmedetomidine administration (Slgo® CP1000, Beijing Slgo medical technology Co., Ltd.).

Attending anesthesiologists can decrease or stop study drug infusion in the following conditions: (1) severe bradycardia or hypotension which does not improve after routine treatment; (2) new onset atrioventricular block which does not improve

after routine treatment; or (3) other conditions that anesthesiologists consider it necessary. In these conditions the reasons that lead to any protocol deviations will be recorded in the Case Report Forms. These patients will be included in the intention-to-treat analysis but excluded from the per-protocol analysis.

Total intravenous anesthesia is performed for all patients. Anesthesia is induced with intravenous sufentanil (target controlled infusion with effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (2-3 mg/kg) and maintained with sufentanil (effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (4-12 mg/kg/h). Rocuronium and/or cisatracurium are administered for muscle relaxation. The mean arterial pressure is maintained above 60 mmHg or within 20% from baseline. BIS is maintained between 40 and 60. Mechanical ventilated is performed with a 1:1 nitrous oxide-oxygen mixture.

All patients are transferred to post-anesthesia care unit (PACU) or intensive care unit (ICU) before they are sent back to general wards. Patient-controlled intravenous analgesia (PCIA) is provided for all patients, which is established with 0.5 mg/ml morphine in 100 ml normal saline and programmed to deliver a 1 mg bolus with a lock-out interval of 8 minutes and a background infusion at 0.5 mg/h. Supplemental morphine at dose of 2 to 4 mg will be administered at 10-minute intervals if the numeric rating scale (NRS) pain score (a 11-point scale where 0 indicates no pain and 10 indicates the worst pain) remains above 4 after 3 consecutive PCIA boluses.[31]

Outcome assessment

Patients are followed up twice daily during the first 5 postoperative days and then weekly until 30 days after surgery.

Primary endpoint

The primary endpoint is the incidence of delirium during the first 5 days after surgery. Delirium is assessed twice daily (at 08:00-09:00 and 19:00-20:00, respectively) with CAM for non-intubated patients[30] or CAM for the Intensive Care Unit (CAM-ICU) for intubated patients.[32] These delirium assessment methods had been used in our previous studies.[2-3, 31] For patients who are discharged or died within 5 days after surgery, the results of last delirium assessment will be considered the results of the missing data. These patients will be excluded when calculating daily prevalence of delirium in a post-hoc analysis.

Investigators who are responsible for delirium assessment and postoperative follow-up are not involved in anesthesia and perioperative care. Before the beginning of the study, they are trained by a psychiatrist to perform delirium assessment and the training process is repeated at 4-month intervals during the study period.[2-3, 31]

Secondary endpoints

Postoperative pain intensities at rest and with movement are assessed with NRS pain score at 24, 48 and 72 hours after surgery, respectively.[31] Cumulative morphine consumptions at these time points are recorded. Subjective sleep quality is assessed with NRS (an 11-point scale where 0 indicates the worst possible sleep and 10 the best possible sleep) at 08:00 on the first, second and third morning after surgery.[3, 31] Other secondary endpoints include non-delirium complications within 30 days after surgery, length of stay in hospital after surgery and all-cause 30-day mortality. Non-delirium complications are generally defined as new-onset non-delirium conditions after surgery that are harmful to patients' recovery and require therapeutic intervention.

Safety outcomes

In the present study, adverse events are monitored from the start of study drug administration until PACU discharge or 2 hours after ICU admission. Hypotension is defined as systolic blood pressure of less than 90 mmHg or a decrement of more than 30% from baseline. Hypertension is defined as systolic blood pressure of more than 180 mmHg or an increment of more than 30% from baseline. Bradycardia is defined as heart rate of less than 40 beats per minute. Tachycardia is defined as heart rate of more than 100 beats per minute. Desaturation is defined as SpO_2 of less than 90%. Emergence agitation is defined as a Richmond Agitation-Sedation Scale (RASS) score of more than +2 within 30 minutes after extubation. Delayed extubation is defined when time to extubation is more than 2 hours (from the end of surgery) in PACU patients or more than 4 hours in ICU patients.[2, 22-25]

Severe adverse events that impede patient's safety or prolong in-hospital stay will be reported to Clinical Research Ethics Committee of Peking University First Hospital within 24 hours. For patients who suffered harm from present trial, medical treatment will be initiated as soon as possible and compensation will be completed according to local laws and regulations.

Data monitoring and management

Original data will be recorded in the CRFs accordingly. ALL data will be kept confidentially. The completed CRFs will be checked by a study coordinator who is qualified by the principal investigator. Supplementations and corrections will be made when necessary. Data entry will be performed in a double-input and double-check way with the Data Management System (Fantastic Eight Tech. Co., Ltd, Beijing, China) of the Peking University First Hospital.

The conduct of the study and the quality of data will be monitored by the Clinical Research Ethics Committee of Peking University First Hospital. Data

management and statistical analysis will be performed by the Department of Biostatistics of Peking University First Hospital. Considering that dexmedetomidine has been widely used during general anesthesia and its safety has been confirmed, no interim analysis will be performed and the trial will continue until the target sample size is achieved.

Statistical analysis

Sample size calculation

In our previous study, the incidence of delirium was 14.8% in elderly patients after non-cardiac surgery.[2] Previous studies reported that intraoperative dexmedetomidine decreased the incidence of POD by 60-77% in comparison with placebo.[22, 25] We assumed that the incidence of POD will be reduced from 14.8% to 7.4% (i.e., a 50% reduction) in the present study. With the power set at 80% and significant level at 0.05, 564 patients are required to detect the difference. Considering a loss to follow-up rate of about 9%, we plan to enroll 620 patients in this study.

Outcome analysis

Continuous data with normal distribution will be compared using independent sample T-test. Continuous data with asymmetric distribution will be compared using independent sample Mann-Whitney U test. Categorical data will be compared using Chi-squared test or continuity correction Chi-squared test. The difference (and 95% confidence interval of the difference) between two means or medians will be estimated using the methodology of Levene's test or Hodges-Lehmann estimator. Time-to-event data will be analyzed by survival analysis with differences between groups compared with log-rank test.

Statistical analyses will be performed with the SPSS 14.0 (SPSS, Inc., Chicago, IL) and SAS 9.3 (SAS Institute, Cary, NC, USA). All tests are two tailed, and P

values of less than 0.05 are considered to be statistically significant. The Bonferroni adjustment is made to control type I error for multiple testing.

Discussion

This randomized, double-blinded, placebo-controlled single center trial is designed to investigate if dexmedetomidine administration during general anesthesia can decrease the incidence of POD in elderly patients after major non-cardiac surgery.

In the present study, the dosing regimen of dexmedetomidine is similar to our previous study because it does not increase drug-related adverse events (such as severe bradycardia and hypotension).[24] Furthermore, the CAM and CAM-ICU are used to assess delirium in patients with or without intubation, respectively.[30, 32] Both CAM and CAM-ICU have been translated and validated in Chinese population.[33-34] Feasibility of these two assessment tools have been confirmed in our previous studies.[2-3, 31] To maintain the quality of delirium assessment, investigators in charge of postoperative follow-up are trained by a psychiatrist before the study and will be retrained at 4-month intervals.

The strengths of the present study include the following when compared with previous studies.[22-24] Firstly, a randomized, double-blind, and placebo-controlled study design with a relative large sample size (620 patients) is adopted. Results of the study will provide high quality evidences. Secondly, BIS level is monitored in all enrolled patients, which will help us to avoid unnecessary and potentially harmful deep anesthesia. Thirdly, safety data will be recorded in detail.

Trail status:

This study is currently at stage of patient enrollment and data collection. The current version of study protocol is V1.1 and is approved on November 27, 2015. Patient

recruitment started from December 2, 2015 and is expected to be finished by March 31, 2018.

List of abbreviations

POD=postoperative delirium; IL=interleukins; CRP=C-reactive protein; TNF=tumor necrosis factor; IRB=Institutional Review Board; MMSE=Mini-Mental State Examination; CAM=confusion assessment method (CAM); BIS=Bispectral index; NRS=numeric rating scale; CAM-ICU=confusion assessment method-intensive care unit

Declarations

Ethics approval and consent to participate: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). The trial was registered at Chinese Clinical Trial Registry (www.chictr.org.cn) with identifier ChiCTR-IPR-15007654 on December 1, 2015). Written informed consent will be obtained from all patients or their surrogate in law.

Dissemination: Results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Competing interests: DXW reports lecture fees and travel expenses for lectures given at academic meetings from Jiangsu Hengrui Medicine Co Ltd, China, and Yichang Humanwell Pharmaceutical Co Ltd, China. DLM is primary investigator of present study which was supported by Beijing Excellent Talent Support Program. Other authors reported no conflict of interests.

Funding: This trial was supported by Beijing Excellent Talent Support Program (No. 2014000020124G025). The program committee had no role in study design, data collection, management, analysis, interpretation of data, writing of the report and any other ultimate authority over any of these activities.

Authors' contributions: DXW and DLM designed this study. DLM draft the manuscript of protocol. DXW critically revised the manuscript. DLM, BJW, CJL, JH,

HJL, CG, ZHW and QCZ participate in the conduct of the study. All authors read and approved the final manuscript.

Acknowledgements: We thank professor Xin-Yu Sun (Department of Psychiatrics, Peking University Sixth Hospital, Beijing, China) for her help in psychiatric consultation and personnel training. We also thank Dr. Xue-Ying Li (Department of Medical Statistic, Peking University First Hospital, Beijing, China) for her help in statistical analysis of this research.

Data sharing: No plan

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Washington, DC: American Psychiatric Association; 1994.
2. Liu P, Li YW, Wang XS, et al. High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a prospective cohort study. Chin Med J (Engl). 2013; 126(19): 3621-7.
3. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016 Oct 15; 388(10054): 1893-1902.
4. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr 14; 291(14): 1753-62.
5. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012 Jul 5; 367(1): 30-9.
6. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium. Eur J Anaesthesiol. 2017 Apr; 34(4):192-214.
7. Creeley C, Dikranian K, Dissen G, et al. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth. 2013 Jun; 110 Suppl 1: i29-38.
8. Xiong WX, Zhou GX, Wang B, et al. Impaired spatial learning and memory after sevoflurane-nitrous oxide anesthesia in aged rats is associated with down-regulated cAMP/CREB signaling. PLoS One. 2013 Nov 15;8(11): e79408.

9. Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013 Jan; 25(1): 33-42.

10. Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006 Apr; 102(4): 1267-73.

11. Lynch EP, Lazor MA, Gellis JE, et al. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998; 86:781-5

12. Hirsch J, Vacas S, Terrando N, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation. 2016 Aug 30; 13(1): 211.

13. Cape E, Hall RJ, van Munster BC,et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. J Psychosom Res. 2014 Sep; 77(3): 219-25.

14. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. Crit Care. 2011; 15(6): R297.

15. McGrane S, Girard TD, Thompson JL,et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care. 2011; 15(2): R78.

16. Kazmierski J, Banys A, Latek J, et al. Raised IL-2 and TNF-α concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. Int Psychogeriatr. 2014 May; 26(5): 845-55.

17. Shin HW, Yoo HN, Kim DH, et al. Preanesthetic dexmedetomidine 1μg/kg single infusion is a simple, easy, and economic adjuvant for general anesthesia.

Korean J Anesthesiol. 2013 Aug; 65(2): 114-20.

18. Li J, Xiong M, Nadavaluru PR, et al. Dexmedetomidine attenuates neurotoxicity induced by prenatal propofol exposure. J Neurosurg Anesthesiol. 2016 Jan; 28(1): 51-64.
19. Sanders RD, Xu J, Shu Y, et al. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology. 2009 May; 110(5): 1077-85.
20. Le Bot A, Michelet D, Hilly J, et al. Efficacy of intraoperative dexmedetomidine compared with placebo for surgery in adults: a meta-analysis of published studies. Minerva Anestesiol. 2015 Oct; 81(10): 1105-17.
21. Kang SH, Kim YS, Hong TH, et al. Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2013 Apr; 57(4): 480-7.
22. Li Y, Wang B, Zhang LL,et al. Dexmedetomidine Combined with General Anesthesia Provides Similar Intraoperative Stress Response Reduction When Compared with a Combined General and Epidural Anesthetic Technique. Anesth Analg. 2016 Apr;122(4):1202-10
23. Cao JL, Pei YP, Wei JQ, et al. Effects of intraoperative dexmedetomidine with intravenous anesthesia on postoperative emergence agitation/delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy: A CONSORT-prospective, randomized, controlled clinical trial. Medicine (Baltimore). 2016 Dec; 95(49): e5566.
24. Sun Y, Liu J, Yuan X, et al. Effects of dexmedetomidine on emergence delirium in pediatric cardiac surgery. Minerva Pediatr. 2017 Jun; 69(3): 165-173.
25. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of

delirium in elderly patients after cardiac surgery: A randomized controlled trial. PLoS One. 2017 Feb 9; 12(2): e0170757.

26. Yang X, Li Z, Gao C, et al. Effect of dexmedetomidine on preventing agitation and delirium after microvascular free flap surgery: a randomized, double-blind, control study. J Oral Maxillofac Surg. 2015 Jun; 73(6): 1065-72.
27. Deiner S, Luo X, Lin HM, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. JAMA Surg. 2017 Aug 16; 152(8): e171505.
28. Collin C, Wade DT, Davies S, et al. The Barthel ADL Index: a reliability study. Int Disabil Stud. 1988; 10: 61-3.
29. Katzman R, Zhang MY, Ouang-Ya-Qu, et al. A Chinese version of the Mini-Mental State Examination; impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol. 1988; 41: 971-8.
30. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The Confusion Assessment Method. A new method for detecting delirium. Ann Intern Med 1990; 113:941-8
31. Mu DL, Zhang DZ, Wang DX, et al. Parecoxib Supplementation to Morphine Analgesia Decreases Incidence of Delirium in Elderly Patients After Hip or Knee Replacement Surgery: A Randomized Controlled Trial. Anesth Analg. 2017 Jun; 124(6):1992-2000.
32. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001 Jul; 29(7): 1370-9.
33. Jl L, Vc L, Leung CM, et al. Clinical utility and validation of two instruments

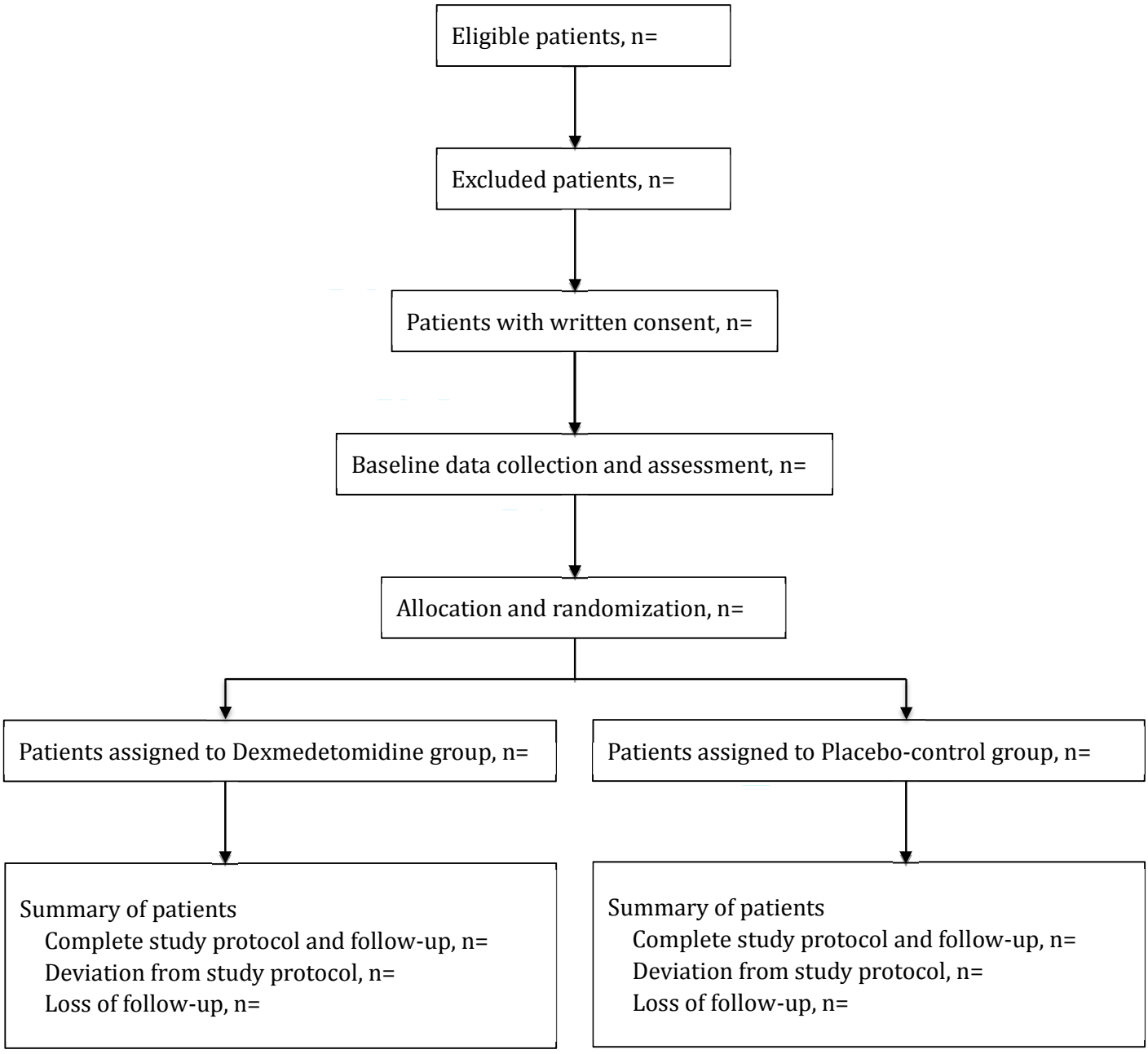
(the Confusion Assessment Method Algorithm and the Chinese version of Nursing Delirium Screening Scale) to detect delirium in geriatric inpatients. Gen Hosp Psychiatry. 2008; 30: 171-6.

34. Wang C, Wu Y, Yue P, et al. Delirium assessment using Confusion Assessment Method for the Intensive Care Unit in Chinese critically ill patients. J Crit Care. 2013; 28: 223-9.

Figure legend

Figure 1. Flowchart of this study.

Figure 1 Flow chart of this study



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4 , 8, 19
	2b	All items from the World Health Organization Trial Registration Data Set	8
Protocol version	3	Date and version identifier	8
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7, 10-11
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13-14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13-14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4, 8, 19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19-20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Impact of dexmedetomidine infusion during general anesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019549.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2017
Complete List of Authors:	Wang, Bojie; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Chunjing; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Hu, Jian; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Huaijin; Peking University First Hospital, Department of Anesthesiology and Critical Care Guo, Chao; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Wang, Zhenhan; Dongping People's Hospital, Department of anesthesiology Zhang, Qiaochu; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Mu, Dongliang; Department of Anesthesiology and Critical Care Medicine Wang, Dong-Xin; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Adult anaesthesia < ANAESTHETICS, Delirium & cognitive disorders < PSYCHIATRY, Pain management < RADIOTHERAPY

Impact of dexmedetomidine infusion during general anesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

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2

3 Word Count：2843

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5

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Abstract for protocol

Introduction: Delirium is a common complication in the elderly after surgery and is associated with worse outcomes. Multiple risk factors are related with postoperative delirium, such as exposure to general anesthetics, pain and inflammatory response. Preclinical and clinical studies reported that dexmedetomidine could attenuate neurotoxicity induced by general anesthetics, improve pain management and inhibit inflammatory response. Several studies observed the relationship between intraoperative use of dexmedetomidine and postoperative delirium, but the results were inconsistent. This study is designed to investigate the impact of dexmedetomidine administered during general anesthesia in preventing delirium in elderly patients after major non-cardiac surgery.

Method and analysis: This is a randomized, double-blinded, and placebo-controlled trial. 620 elderly patients (age ≥ 60 years) who are scheduled to undertake elective major non-cardiac surgery (with an expected duration ≥ 2 hours) are randomly divided into two groups. For patients in dexmedetomidine group, a loading dose dexmedetomidine (0.6 μg/kg) will be administered in 10 minutes before anesthesia induction, followed by a continuous infusion at a rate of 0.5 μg/kg/h till 1 hour before the end of surgery. For patients in control group, normal saline will be administered in the same rate and volume as in the dexmedetomidine group. The primary endpoint is the incidence of delirium during the first five postoperative days. Secondary endpoints include pain intensity, cumulative opioid consumption and subjective sleep quality during the first 3 postoperative days, and the incidence of non-delirium complications and all-cause mortality within 30 days after surgery.

Ethics and dissemination: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987) and registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) with identifier ChiCTR-IPR-15007654. Results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Key words: intraoperative dexmedetomidine; postoperative delirium; old patient; major non-cardiac surgery

Strengths and limitations

1. The study will investigate the impact of dexmedetomidine infusion during general anesthesia on the incidence of delirium in elderly patients after non-cardiac surgery.
2. The study designed will be a randomized, double-blinded and placebo-controlled, with a relative large sample size.
3. Anesthesia depth (Bispectral index) will be monitored to guide anesthesia maintenance. This will overcome an important limitation in a recent trial.
4. One limitation is that this is a single center trial, which will limit the generalizability of our results. Another limitation is that only early outcomes (up to 30 days after surgery) will be explored.

Introduction

Delirium is a transient brain dysfunction which is characterized by altered consciousness, inattention, and changes in cognition or perception; it develops acutely with clinical manifestations fluctuate during the course of the day.[1] Prevalence of delirium varies from 12% to 51% in patients after non-cardiac surgery, and its prevalence increases with age.[2-3] The occurrence of postoperative delirium (POD) is associated with worsen outcomes including prolonged mechanical ventilation and intensive care unit stay, increased postoperative complications, high mortality rate and long-term cognitive decline.[2-5]

The etiology of POD is multifactorial and includes several intraoperative factors.[6] For example, exposure to general anesthetics (e.g., propofol or sevoflurane) might produce neurotoxicity;[7-8] whereas reduced anesthetic exposure by avoiding deep anesthesia reduced the occurrence of delirium in elderly patients undergoing major non-cardiac surgery.[9] Poor pain management is another risk factor of POD.[6, 10] It was reported that the risk of postoperative delirium was 1.2 times higher for every unit increment in visual analogue pain score (an 11-point pain scale where 0 indicates no pain and 10 the most severe pain).[11] Inflammation is also proposed to play an important role in the pathogenesis of POD.[2] Inflammatory responses induced by surgery and anesthesia are manifested by elevated levels of interleukins (IL), C-reactive protein (CRP) and tumor necrosis factor (TNF).[2, 12] Studies by our group and other found that higher levels of inflammatory mediators are associated with increased risk of POD.[2, 13-16.]

Dexmedetomidine is a highly selective α2-receptor agonist with sedative, analgesic and anxiolytic effects.[17-21] When used as a supplement during intraoperative

anesthesia, it reduces the consumption of general anesthetics.[17] Preclinical evidences suggest that use of dexmedetomidine might attenuate neurotoxicity induced by general anesthetics.[18-19] In a meta-analysis, intraoperative administration of dexmedetomidine lowers postoperative pain intensity and reduces opioid consumption.[20] Clinical evidence also showed that intraoperative dexmedetomidine significantly inhibits hyper-secretion of inflammatory cytokines during and after surgery.[21-22]

Use of dexmedetomidine during general anesthesia may reduce POD. In pediatric patients undergoing tonsillectomy and cardiac surgery, intraoperative infusion of dexmedetomidine lowered the incidence of emergence delirium.[23,24] In adult patients undergoing cardiac surgery and microvascular free flap surgery, intraoperative dexmedetomidine (comparison with normal saline) slightly decreased the incidence of delirium, although the differences were not statistically significant between two groups possibly due to underpowered sample size.[25,26] In a recent study of Deiner et al.,[27] use of dexmedetomidine during general anesthesia did not reduce delirium after major non-cardiac surgery in the elderly. However, in that study, anesthesia depth was not monitored and the consumption of anesthetics (such as propofol and fentanyl) was similar between the two groups. It was possible that patients in the dexmedetomidine group received deeper anesthesia which might have increased the risk of delirium.[27] Therefore, the effects of dexmedetomidine administered during general anesthesia on the occurrence of POD need to be evaluated further.

This study is designed to investigate whether dexmedetomidine use during general anesthesia can decrease the incidence of POD in elderly patients after major non-cardiac surgery.

Method and analysis

Study design

This randomized, double-blinded, and placebo-controlled trial with two parallel arms is designed to test the superiority of dexmedetomidine administered during general anesthesia on the incidence of delirium after surgery. Patients will be randomized into either the dexmedetomidine group or the control group (Figure 1). The study is conducted in the Department of Anesthesiology and Critical Care Medicine of Peking University First Hospital.

Ethics approval

The study protocol (version 1.1, issue date Nov, 2015) was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). Any protocol modifications will be submitted for review and approval by the Ethics Committee. The trial was registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) on December 1, 2015, with identifier ChiCTR-IPR-15007654. Written informed consents are obtained from patients or their surrogate in law.

Participants

Elderly (age ≥ 60 years) patients who are scheduled to undergo elective non-cardiac surgery with expected duration ≥ 2 hours under general anesthesia are screened for inclusion. Those who meet any of the following criteria will be excluded: (1) do not provide written informed consents; (2) previous history of schizophrenia, epilepsy or Parkinson disease; (3) visual, hearing, language or other barrier which impede communication and preoperative delirium assessment; (4) neurosurgery or traumatic brain injury; (5) severe bradycardia (heart rate less than 40 beats per minute), sick

sinus syndrome or atrioventricular block of degree 2 or above; (6) severe hepatic dysfunction (Child-Pugh grade C); or (7) renal failure (requirement of renal replacement therapy).

Patient recruitment and baseline data collection

Potential participants are screened by qualified investigators the day before surgery (or on Friday for those who will undergo surgery next Monday). The study protocol including potential risks and benefits is explained in detail. Those who meet the inclusion and exclusion criteria are invited to participate in the study.

After obtaining written informed consents, the following baseline data are collected: demographic data, preoperative diagnosis, comorbidity, current medical therapy, previous surgery, and main results of physical and laboratory examinations. Barthel index is used for evaluation of activities of daily living.[28] Cognitive function is assessed with Mini-Mental State Examination (MMSE).[29] Preoperative delirium is assessed with confusion assessment method (CAM).[30]

Randomization, grouping and blinding

Random numbers were created by an independent statistician using SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA) in a 1:1 ratio and were sealed in sequentially numbered envelopes. A study coordinator, who has no knowledge of patients before randomization and does not participate in anesthesia and postoperative follow-up of enrolled patients, will open envelop for random numbers and prepare study drugs before induction of anesthesia. In this way, patients are randomly divided into either dexmedetomidine or control group.

Information regarding randomization, study drug preparation and group allocation will be masked from investigators who perform data collection and

postoperative follow-up, anesthesiologists, patients and other healthcare team members. Blinding will be maintained throughout the entire study period.

To ensure patients' safety, study group allocation can be unmasked in the following conditions, i.e., occurrence of severe adverse events or any unexpected deterioration in the patient's clinical status. These situations will be documented in the Case Report Forms (CRFs). The unmasked patients will be included in the intention-to-treat population but excluded from per-protocol analysis.

Interventions, anesthesia and analgesia

Intraoperative monitoring includes electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, end-tidal carbon dioxide, nasopharyngeal temperature, urine output, and bispectral index (BIS). Intraarterial pressure (including derivative dynamic parameters such as stroke volume variation by FlowTrac system) and central venous pressure are monitored according to patients' conditions.

Study drugs, either 200 μg (2 ml) dexmedetomidine (Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China) or 2 ml normal saline, are diluted in 50 ml normal saline. All study drugs are colorless solution provided in syringes of the same size and brand. The regimen of study drug administration includes a loading dose of 0.15 ml/kg (i.e., 0.6 μg/kg dexmedetomidine for patients in the dexmedetomidine group) administered during a 10-minute period before anesthesia induction. This is followed by a continuous infusion at a rate of 0.125 ml/kg/h (i.e., a rate of 0.5 μg/kg/h dexmedetomidine for patients in the dexmedetomidine group) till 1 hour before the end of surgery. Study drug infusion is performed by an infusion pump specially designed for dexmedetomidine administration (Slgo® CP1000, Beijing Slgo medical technology Co., Ltd.).

Attending anesthesiologists can decrease or stop study drug infusion in the following conditions: (1) severe bradycardia or hypotension which does not improve after routine treatment; (2) new onset atrioventricular block which does not improve after routine treatment; or (3) other conditions that anesthesiologists consider it necessary. In these conditions the reasons that lead to any protocol deviations will be recorded in the Case Report Forms. These patients will be included in the intention-to-treat analysis but excluded from the per-protocol analysis.

Total intravenous anesthesia is performed for all patients. Anesthesia is induced with intravenous sufentanil (target controlled infusion with effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (2-3 mg/kg) and maintained with sufentanil (effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (4-12 mg/kg/h). Rocuronium and/or cisatracurium are administered for muscle relaxation. The mean arterial pressure is maintained above 60 mmHg or within 20% from baseline. BIS is maintained between 40 and 60. Body temperature is maintained with air-warming and fluid heating systems. The target of nasopharyngeal temperature maintenance during surgery is from 36.0 to 37°C. Mechanical ventilated is performed with a 1:1 nitrous oxide-oxygen mixture.

All patients are transferred to post-anesthesia care unit (PACU) or intensive care unit (ICU) before they are sent back to general wards. Patient-controlled intravenous analgesia (PCIA) is provided for all patients, which is established with 0.5 mg/ml morphine in 100 ml normal saline and programmed to deliver a 1 mg bolus with a lock-out interval of 8 minutes and a background infusion at 0.5 mg/h. Supplemental morphine at dose of 2 to 4 mg will be administered at 10-minute intervals if the numeric rating scale (NRS) pain score (a 11-point scale where 0 indicates no pain and

10 indicates the worst pain) remains above 4 after 3 consecutive PCIA boluses.[31] Other postoperative managements were performed according to routine practice.

Outcome assessment

Patients are followed up twice daily during the first 5 postoperative days and then weekly until 30 days after surgery. Investigators who are responsible for postoperative follow-up are not involved in anesthesia and perioperative care, and are not allowed to exchange patients' information with anesthesiologists who take care of patients in the operating room. Before the beginning of the study, investigators are trained to follow the study protocol and to perform delirium assessment and the training process is repeated at 4 to 6 months intervals during the study period.[2-3, 31] The 4-hour training courses of delirium assessment include the following contents: (1) lectures regarding signs/symptoms, diagnosis and treatment of delirium by psychiatrists; (2) training courses of the use of CAM and CAM-ICU on patient-actors (trained ICU physicians or nurses who act as patients with or without delirium) conducted by psychiatrists. The process continued until 100% agreement is achieved in diagnosing delirium.

Primary endpoint

The primary endpoint is the incidence of delirium during the first 5 days after surgery. Delirium is assessed twice daily (at 08:00-09:00 and 19:00-20:00, respectively) with CAM for non-intubated patients[30] or CAM for the Intensive Care Unit (CAM-ICU) for intubated patients.[32] These delirium assessment methods had been used in our previous studies.[2-3, 31] For patients who are discharged or died within 5 days after surgery, the results of last delirium assessment will be considered the results of the missing data. These patients will be excluded when calculating daily prevalence of delirium in a post-hoc analysis.

Secondary endpoints

Postoperative pain intensities at rest and with movement are assessed with NRS pain score at 24, 48 and 72 hours after surgery, respectively.[31] Cumulative morphine consumptions at these time points are recorded. Subjective sleep quality is assessed with NRS (an 11-point scale where 0 indicates the worst possible sleep and 10 the best possible sleep) at 08:00 on the first, second and third morning after surgery.[3, 31] Other secondary endpoints include non-delirium complications within 30 days after surgery, length of stay in hospital after surgery and all-cause 30-day mortality. Non-delirium complications are generally defined as new-onset non-delirium conditions after surgery that are harmful to patients' recovery and require therapeutic intervention.

Safety outcomes

In the present study, adverse events are monitored from the start of study drug administration until PACU discharge or 2 hours after ICU admission. Hypotension is defined as systolic blood pressure of less than 90 mmHg or a decrement of more than 30% from baseline. Hypertension is defined as systolic blood pressure of more than 180 mmHg or an increment of more than 30% from baseline. Bradycardia is defined as heart rate of less than 40 beats per minute. Tachycardia is defined as heart rate of more than 100 beats per minute. Desaturation is defined as SpO_2 of less than 90%. Emergence agitation is defined as a Richmond Agitation-Sedation Scale (RASS) score of more than +2 within 30 minutes after extubation. Delayed extubation is defined when time to extubation is more than 2 hours (from the end of surgery) in PACU patients or more than 4 hours in ICU patients.[2, 22-25]

Severe adverse events, i.e., those that might result in patient's disability/deformity, prolong in-hospital stay, or life threatening events, will be

reported to Clinical Research Ethics Committee of Peking University First Hospital within 24 hours. For patients who suffered harm from present trial, medical treatment will be initiated as soon as possible and compensation will be completed according to local laws and regulations.

Data monitoring and management

Original data will be recorded in the CRFs accordingly. ALL data will be kept confidentially. The completed CRFs will be checked by a study coordinator who is qualified by the principal investigator. Supplementations and corrections will be made when necessary. Data entry will be performed in a double-input and double-check way with the Data Management System (Fantastic Eight Tech. Co., Ltd, Beijing, China) of the Peking University First Hospital.

The conduct of the study and the quality of data will be monitored by the Clinical Research Ethics Committee of Peking University First Hospital. Data management and statistical analysis will be performed by the Department of Biostatistics of Peking University First Hospital. Considering that dexmedetomidine has been widely used during general anesthesia and its safety has been confirmed, no interim analysis will be performed and the trial will continue until the target sample size is achieved.

Statistical analysis

Sample size calculation

In our previous study, the incidence of delirium was 14.8% in elderly patients after non-cardiac surgery.[2] Previous studies reported that intraoperative dexmedetomidine decreased the incidence of POD by 60-77% in comparison with placebo.[22, 25] We assumed that the incidence of POD will be reduced from 14.8% to 7.4% (i.e., a 50% reduction) in the present study. With the power set at 80% and significant level at

0.05, 564 patients are required to detect the difference. Considering a loss to follow-up rate of about 9%, we plan to enroll 620 patients in this study.

Outcome analysis

Continuous data with normal distribution will be compared using independent sample T-test. Continuous data with asymmetric distribution will be compared using independent sample Mann-Whitney U test. Categorical data will be compared using Chi-squared test or continuity correction Chi-squared test. The difference (and 95% confidence interval of the difference) between two means or medians will be estimated using the methodology of Levene's test or Hodges-Lehmann estimator. Time-to-event data will be analyzed by survival analysis with differences between groups compared with log-rank test.

Statistical analyses will be performed with the SPSS 14.0 (SPSS, Inc., Chicago, IL) and SAS 9.3 (SAS Institute, Cary, NC, USA). All tests are two tailed, and P values of less than 0.05 are considered to be statistically significant. The Bonferroni adjustment is made to control type I error for multiple testing.

Discussion

This randomized, double-blinded, placebo-controlled single center trial is designed to investigate if dexmedetomidine administration during general anesthesia can decrease the incidence of POD in elderly patients after major non-cardiac surgery.

In the present study, the dosing regimen of dexmedetomidine is similar to our previous study because it does not increase drug-related adverse events (such as severe bradycardia and hypotension).[24] Furthermore, the CAM and CAM-ICU are used to assess delirium in patients with or without intubation, respectively.[30, 32] Both CAM and CAM-ICU have been translated and validated in Chinese population.[33-34] Feasibility of these two assessment tools have been confirmed in our previous studies.[2-3, 31] To maintain the quality of delirium assessment, investigators in charge of postoperative follow-up are trained by a psychiatrist before the study and will be retrained at 4 to 6-month intervals.

Because of the hemodynamic and anesthetic-sparing effect of dexmedetomidine, it is not very difficult for the experienced anesthesiologists to guess which study drug is administrated. This might weak the blinding to anesthesiologists. However, in the present study, investigators who are responsible for postoperative follow-up and delirium assessment are not involved in anesthesia and perioperative care; and they are not allowed to exchange patients' information with anesthesiologists who take care of patients in the operating room. In this way the blinding of investigators to study group assignment can be guaranteed.

The strengths of the present study include the following when compared with previous studies.[22-24] Firstly, a randomized, double-blind, and placebo-controlled study design with a relative large sample size (620 patients) is adopted. Results of the

study will provide high quality evidences. Secondly, BIS level is monitored in all enrolled patients, which will help us to avoid unnecessary and potentially harmful deep anesthesia. Thirdly, safety data will be recorded in detail. Our study also has some limitations. One is that this is a single center trial, which will limit the external validity of our results. Another one is that only early outcomes (up to 30 days after surgery) will be explored.

Trail status:

This study is currently at stage of patient enrollment and data collection. The current version of study protocol is V1.1 and is approved on November 27, 2015. Patient recruitment started from December 2, 2015 and is expected to be finished by March 31, 2018.

List of abbreviations

POD=postoperative delirium; IL=interleukins; CRP=C-reactive protein; TNF=tumor necrosis factor; IRB=Institutional Review Board; MMSE=Mini-Mental State Examination; CAM=confusion assessment method (CAM); BIS=Bispectral index; NRS=numeric rating scale; CAM-ICU=confusion assessment method-intensive care unit

Declarations

Ethics approval and consent to participate: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). The trial was registered at Chinese Clinical Trial Registry (www.chictr.org.cn) with identifier ChiCTR-IPR-15007654 on December 1, 2015). Written informed consent will be obtained from all patients or their surrogate in law.

Dissemination: Results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Competing interests: DXW reports lecture fees and travel expenses for lectures given at academic meetings from Jiangsu Hengrui Medicine Co Ltd, China, and Yichang Humanwell Pharmaceutical Co Ltd, China. DLM is primary investigator of present study which was supported by Beijing Excellent Talent Support Program. Other authors reported no conflict of interests.

Funding: This trial was supported by Beijing Excellent Talent Support Program (No. 2014000020124G025). The program committee had no role in study design, data collection, management, analysis, interpretation of data, writing of the report and any other ultimate authority over any of these activities.

Authors' contributions: DXW and DLM designed this study. DLM draft the manuscript of protocol. DXW critically revised the manuscript. DLM, BJW, CJL, JH,

HJL, CG, ZHW and QCZ participate in the conduct of the study. All authors read and approved the final manuscript.

Acknowledgements: We thank professor Xin-Yu Sun (Department of Psychiatrics, Peking University Sixth Hospital, Beijing, China) for her help in psychiatric consultation and personnel training. We also thank Dr. Xue-Ying Li (Department of Medical Statistic, Peking University First Hospital, Beijing, China) for her help in statistical analysis of this research.

Data sharing: No plan

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Washington, DC: American Psychiatric Association; 1994.
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014 Mar 8;383(9920):911-22.
3. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016 Oct 15; 388(10054): 1893-1902.
4. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr 14; 291(14): 1753-62.
5. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012 Jul 5; 367(1): 30-9.
6. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium. Eur J Anaesthesiol. 2017 Apr; 34(4):192-214.
7. Creeley C, Dikranian K, Dissen G, et al. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth. 2013 Jun; 110 Suppl 1: i29-38.
8. Xiong WX, Zhou GX, Wang B, et al. Impaired spatial learning and memory after sevoflurane-nitrous oxide anesthesia in aged rats is associated with down-regulated cAMP/CREB signaling. PLoS One. 2013 Nov 15;8(11): e79408.
9. Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases

postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013 Jan; 25(1): 33-42.

10. Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006 Apr; 102(4): 1267-73.
11. Lynch EP, Lazor MA, Gellis JE, et al. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998; 86:781-5
12. Hirsch J, Vacas S, Terrando N, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation. 2016 Aug 30; 13(1): 211.
13. Cape E, Hall RJ, van Munster BC,et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. J Psychosom Res. 2014 Sep; 77(3): 219-25.
14. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. Crit Care. 2011; 15(6): R297.
15. McGrane S, Girard TD, Thompson JL,et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care. 2011; 15(2): R78.
16. Kazmierski J, Banys A, Latek J, et al. Raised IL-2 and TNF-α concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. Int Psychogeriatr. 2014 May; 26(5): 845-55.
17. Shin HW, Yoo HN, Kim DH, et al. Preanesthetic dexmedetomidine 1μg/kg single infusion is a simple, easy, and economic adjuvant for general anesthesia. Korean J Anesthesiol. 2013 Aug; 65(2): 114-20.

18. Li J, Xiong M, Nadavaluru PR, et al. Dexmedetomidine attenuates neurotoxicity induced by prenatal propofol exposure. J Neurosurg Anesthesiol. 2016 Jan; 28(1): 51-64.

19. Sanders RD, Xu J, Shu Y, et al. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology. 2009 May; 110(5): 1077-85.

20. Le Bot A, Michelet D, Hilly J, et al. Efficacy of intraoperative dexmedetomidine compared with placebo for surgery in adults: a meta-analysis of published studies. Minerva Anestesiol. 2015 Oct; 81(10): 1105-17.

21. Kang SH, Kim YS, Hong TH, et al. Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2013 Apr; 57(4): 480-7.

22. Li Y, Wang B, Zhang LL,et al. Dexmedetomidine Combined with General Anesthesia Provides Similar Intraoperative Stress Response Reduction When Compared with a Combined General and Epidural Anesthetic Technique. Anesth Analg. 2016 Apr;122(4):1202-10

23. Cao JL, Pei YP, Wei JQ, et al. Effects of intraoperative dexmedetomidine with intravenous anesthesia on postoperative emergence agitation/delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy: A CONSORT-prospective, randomized, controlled clinical trial. Medicine (Baltimore). 2016 Dec; 95(49): e5566.

24. Sun Y, Liu J, Yuan X, et al. Effects of dexmedetomidine on emergence delirium in pediatric cardiac surgery. Minerva Pediatr. 2017 Jun; 69(3): 165-173.

25. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial.

PLoS One. 2017 Feb 9; 12(2): e0170757.

26. Yang X, Li Z, Gao C, et al. Effect of dexmedetomidine on preventing agitation and delirium after microvascular free flap surgery: a randomized, double-blind, control study. J Oral Maxillofac Surg. 2015 Jun; 73(6): 1065-72.

27. Deiner S, Luo X, Lin HM, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. JAMA Surg. 2017 Aug 16; 152(8): e171505.

28. Collin C, Wade DT, Davies S, et al. The Barthel ADL Index: a reliability study. Int Disabil Stud. 1988; 10: 61-3.

29. Katzman R, Zhang MY, Ouang-Ya-Qu, et al. A Chinese version of the Mini-Mental State Examination; impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol. 1988; 41: 971-8.

30. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The Confusion Assessment Method. A new method for detecting delirium. Ann Intern Med 1990; 113:941-8

31. Mu DL, Zhang DZ, Wang DX, et al. Parecoxib Supplementation to Morphine Analgesia Decreases Incidence of Delirium in Elderly Patients After Hip or Knee Replacement Surgery: A Randomized Controlled Trial. Anesth Analg. 2017 Jun; 124(6):1992-2000.

32. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001 Jul; 29(7): 1370-9.

33. Jl L, Vc L, Leung CM, et al. Clinical utility and validation of two instruments (the Confusion Assessment Method Algorithm and the Chinese version of

Nursing Delirium Screening Scale) to detect delirium in geriatric inpatients. Gen Hosp Psychiatry. 2008; 30: 171-6.

34. Wang C, Wu Y, Yue P, et al. Delirium assessment using Confusion Assessment Method for the Intensive Care Unit in Chinese critically ill patients. J Crit Care. 2013; 28: 223-9.

Figure legend

Figure 1. Flowchart of this study.

Figure 1 Flow chart of this study

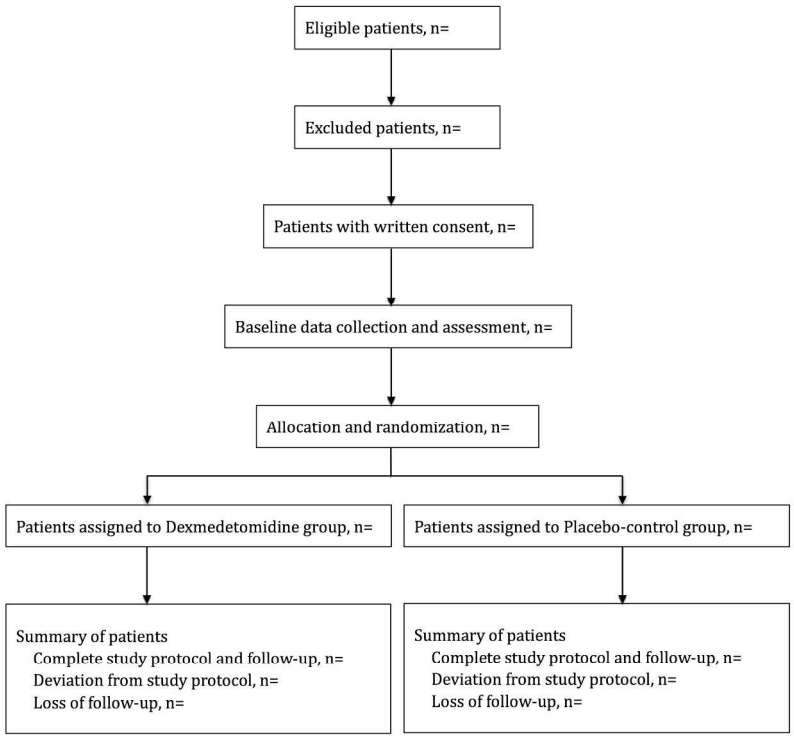

Figure1 Flow chart of this study

209x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4 , 8, 19
	2b	All items from the World Health Organization Trial Registration Data Set	8
Protocol version	3	Date and version identifier	8
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7, 10
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10, 12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-15

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13-14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13-14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4, 8, 19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Impact of dexmedetomidine infusion during general anesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019549.R2
Article Type:	Protocol
Date Submitted by the Author:	05-Feb-2018
Complete List of Authors:	Wang, Bojie; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Chunjing; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Hu, Jian; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Huaijin; Peking University First Hospital, Department of Anesthesiology and Critical Care Guo, Chao; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Wang, Zhenhan; Dongping People's Hospital, Department of anesthesiology Zhang, Qiaochu; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Mu, Dongliang; Department of Anesthesiology and Critical Care Medicine Wang, Dong-Xin; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Elderly, Major non-cardiac surgery, Intraoperative dexmedetomidine, Postoperative delirium

Impact of dexmedetomidine infusion during general anaesthesia on incidence of postoperative delirium in elderly after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

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3 Word Count：2845

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Abstract for protocol

Introduction: Delirium is a common complication in elderly after surgery and is associated with worse outcomes. Multiple risk factors are related with postoperative delirium, such as exposure to general anaesthetics, pain and postoperative inflammatory response. Preclinical and clinical studies have shown that dexmedetomidine attenuated neurotoxicity induced by general anaesthetics, improved postoperative analgesia and inhibited inflammatory response after surgery. Several studies found that intraoperative use of dexmedetomidine can prevent postoperative delirium, but data were inconsistent. This study was designed to investigate the impact of dexmedetomidine administered during general anaesthesia in preventing delirium in elderly after major non-cardiac surgery.

Method and analysis: This is a randomized, double-blinded, and placebo-controlled trial. 620 elderly patients (age ≥ 60 years) who are scheduled to undertake elective major non-cardiac surgery (with an expected duration ≥ 2 hours) are randomly divided into two groups. For patients in the dexmedetomidine group, a loading dose dexmedetomidine (0.6 μg/kg) will be administered in 10 minutes before anaesthesia induction, followed by a continuous infusion at a rate of 0.5 μg/kg/h till 1 hour before the end of surgery. For patients in the control group, normal saline will be administered with an identical rate as in the dexmedetomidine group. The primary endpoint is the incidence of delirium during the first five postoperative days. Secondary endpoints include pain intensity, cumulative opioid consumption and subjective sleep quality during the first 3 postoperative days as well as the incidence of non-delirium complications and all-cause mortality within 30 days after surgery.

Ethics and dissemination: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987) and registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) with identifier ChiCTR-IPR-15007654. The results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Key words: Elderly; Major non-cardiac surgery; Intraoperative dexmedetomidine; Postoperative delirium

Strengths and limitations

Strengths

1. The study design will be a randomized, double-blinded and placebo-controlled, with a relative large sample size.
2. Anaesthesia depth (Bispectral Index) will be monitored to guide anaesthesia maintenance to ensure patients in both groups received equal depth anaesthesia.

Limitations

1. This is a single center trial, which will limit the generalizability of our results.
2. Only early outcomes (up to 30 days after surgery) are assessed in this trial.

Introduction

Delirium is a transient brain dysfunction which is characterized by altered consciousness, inattention, and changes in cognition or perception; it develops acutely with clinical manifestations to be fluctuated with aggressive and depressive manner during developing course.[1] Prevalence of delirium varies from 12% to 51% in patients after non-cardiac surgery, and it is increased with age.[2-3] The occurrence of postoperative delirium (POD) is associated with worsen outcomes including prolonged mechanical ventilation and intensive care unit stay, increased postoperative complications, high mortality rate and long-term cognitive decline.[2-5]

The aetiology of POD is multifactorial and includes several intraoperative factors.[6] For example, exposure to general anaesthetics (e.g., propofol or sevoflurane) might produce neurotoxicity;[7-8] whereas reduced anaesthetic consumption by avoiding deep anaesthesia reduced the occurrence of delirium in elderly patients undergoing major non-cardiac surgery.[9] Poor pain management is another risk factor of POD.[6, 10] It was reported that the risk of postoperative delirium was 1.2 times higher for every unit increment in visual analogue pain score (an 11-point pain scale where 0 indicates no pain and 10 the most severe pain).[11] Inflammation is also proposed to play an important role in the pathogenesis of POD.[2] Inflammatory responses induced by surgery and anaesthesia are manifested by elevated levels of interleukins (IL), C-reactive protein (CRP) and tumor necrosis factor (TNF).[2, 12] Studies by our group and others found that higher levels of inflammatory mediators are associated with increased risk of POD.[2, 13-16.]

Dexmedetomidine is a highly selective α2-receptor agonist with sedative, analgesic and anxiolytic effects.[17-21] When used as a supplement during intraoperative

anaesthesia, it reduces the consumption of general anaesthetics.[17] Preclinical evidence suggested that use of dexmedetomidine might attenuate neurotoxicity induced by general anaesthetics.[18-19] In a meta-analysis, intraoperative administration of dexmedetomidine lowers postoperative pain intensity and reduces opioid consumption.[20] Clinical evidence also showed that intraoperative dexmedetomidine significantly inhibits hyper-secretion of inflammatory cytokines during and after surgery.[21-22]

Use of dexmedetomidine during general anaesthesia may reduce POD. In pediatric patients undergoing tonsillectomy and cardiac surgery, intraoperative infusion of dexmedetomidine lowered the incidence of emergence delirium.[23,24] In adult patients undergoing cardiac surgery and microvascular free flap surgery, intraoperative dexmedetomidine (comparison with normal saline) slightly decreased the incidence of delirium, although the differences were not statistically significant between two groups possibly due to underpowered sample size.[25,26] In a recent study of Deiner et al.,[27] use of dexmedetomidine during general anaesthesia did not reduce delirium after major non-cardiac surgery in the elderly. However, in that study, anaesthesia depth was not monitored and the consumption of anaesthetics (such as propofol and fentanyl) was similar between the two groups. It was possible that patients in the dexmedetomidine group had deeper anaesthesia which might have increased the risk of delirium.[27] Therefore, the effects of dexmedetomidine administered during general anaesthesia on the occurrence of POD need to be evaluated further.

This study is designed to investigate whether dexmedetomidine use during general anaesthesia can decrease the incidence of POD in elderly after major non-cardiac surgery.

Method and analysis

Study design

This randomized, double-blinded, and placebo-controlled trial with two parallel arms was designed to test the superiority of dexmedetomidine administered during general anaesthesia on the incidence of delirium after surgery. Patients will be randomized into either the dexmedetomidine group or the control group (Figure 1). The study is conducted in the Department of Anesthesiology and Critical Care Medicine of Peking University First Hospital.

Ethics approval

The study protocol (version 1.1, issue date Nov, 2015) was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). Any protocol modifications will be submitted for review and approval by the Ethics Committee. The trial was registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) on December 1, 2015, with identifier ChiCTR-IPR-15007654. Written informed consents are obtained from every patients or their surrogate in law.

Participants

Elderly patients (age ≥ 60 years) who are scheduled to undergo elective non-cardiac surgery with expected duration ≥ 2 hours under general anaesthesia are screened for inclusion. Those who meet any of the following criteria will be excluded: (1) do not provide written informed consents; (2) previous history of schizophrenia, epilepsy or Parkinson disease; (3) visual, hearing, language or other barrier which impede communication and preoperative delirium assessment; (4) neurosurgery or traumatic brain injury; (5) severe bradycardia (heart rate less than 40 beats per minute), sick

sinus syndrome or atrioventricular block of degree 2 or above; (6) severe hepatic dysfunction (Child-Pugh grade C); or (7) renal failure (requirement of renal replacement therapy).

Patient recruitment and baseline data collection

Potential participants are screened by investigators the day before surgery (or on Friday for those who will undergo surgery next Monday). The study protocol including potential risks and benefits will be explained to patients in person. Those who do not meet the exclusion criteria are invited to participate in the study.

After obtaining written informed consents, the following baseline data are collected: demographic data, preoperative diagnosis, comorbidity, current medical therapy, previous surgery, and main results of physical and laboratory examinations. Barthel index is used for evaluation of activities of daily living.[28] Cognitive function is assessed with Mini-Mental State Examination (MMSE).[29] Preoperative delirium is assessed with confusion assessment method (CAM).[30]

Randomization, grouping and blinding

Random numbers were created by an independent statistician using SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA) in a 1:1 ratio and were sealed in envelopes. A study coordinator, who has no knowledge of patients before randomization and does not participate in anaesthesia and postoperative follow-up of enrolled patients, will open envelop for random numbers and prepare study drugs before induction of anaesthesia.

Information regarding randomization, study drug preparation and group allocation will be masked from investigators who perform data collection and postoperative follow-up, anaesthesiologists, patients and other healthcare team members. Blinding will be maintained throughout the entire study period.

To ensure patients' safety, study group allocation can be unmasked in the following conditions, i.e., occurrence of severe adverse events or any unexpected deterioration of patient's clinical status. These situations will be documented in the Case Report Forms (CRFs). The unmasked patients will be included in the intention-to-treat population but excluded from per-protocol analysis.

Interventions, anaesthesia and analgesia

Intraoperative monitoring includes electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, end-tidal carbon dioxide, nasopharyngeal temperature, urine output, and bispectral index (BIS). Intraarterial pressure (including derivative dynamic parameters such as stroke volume variation by FlowTrac system) and central venous pressure are monitored according to patients' conditions.

Study drugs, either 200 μg (2 ml) dexmedetomidine (Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China) or 2 ml normal saline, are diluted into 50 ml normal saline. All study drugs are colorless solution provided in syringes of the same size and brand. The regimen of study drug administration includes a loading dose of 0.15 ml/kg (i.e., 0.6 μg/kg dexmedetomidine for patients in the dexmedetomidine group) administered during a 10-minute period before anaesthesia induction. This is followed by a continuous infusion at a rate of 0.125 ml/kg/h (i.e., a rate of 0.5 μg/kg/h dexmedetomidine for patients in the dexmedetomidine group) till 1 hour before the end of surgery. Study drug infusion is performed by an infusion pump specially designed for dexmedetomidine administration (Slgo® CP1000, Beijing Slgo medical technology Co., Ltd.).

Attending anaesthesiologists can decrease or stop study drug infusion in the following conditions: (1) severe bradycardia or hypotension which does not improve after routine treatment; (2) new onset atrioventricular block which does not improve

after routine treatment; or (3) other conditions that anaesthesiologists consider it necessary. In these conditions, the reasons that lead to any protocol deviations will be recorded in the case report forms (CRF). These patients will be included in the intention-to-treat analysis but excluded from the per-protocol analysis.

Anaesthesia is induced with intravenous sufentanil (target controlled infusion with effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (2-3 mg/kg) and maintained with intravenous sufentanil (effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (4-12 mg/kg/h) and inhalation of a 1:1 nitrous oxide-oxygen mixture. Rocuronium and/or cisatracurium are administered for muscle relaxation. Patients will be mechanically ventilated with a tidal volume of 6-8 ml/kg and a positive end-expiratory pressure of 5 cm H_2O. The mean arterial pressure is maintained above 60 mmHg or within 20% from baseline. BIS is maintained between 40 and 60. Body temperature is maintained with air-warming and fluid heating systems. The target of nasopharyngeal temperature maintenance during surgery is from 36.0 to 37°C.

All patients are transferred to post-anaesthesia care unit (PACU) or intensive care unit (ICU) before they are sent back to general wards. Patient-controlled intravenous analgesia (PCIA) is provided for all patients, which is established with 0.5 mg/ml morphine in 100 ml normal saline and programmed to deliver a 1 mg bolus with a lock-out interval of 8 minutes and a background infusion at 0.5 mg/h. Supplemental morphine at dose of 2 to 4 mg will be administered at 10-minute intervals if the numeric rating scale (NRS) pain score (a 11-point scale where 0 indicates no pain and 10 indicates the worst pain) remains above 4 after 3 consecutive PCIA boluses.[31] Other postoperative managements were performed according to routine practice.

Outcome assessment

Patients are followed up twice daily during the first 5 postoperative days and then weekly until 30 days after surgery. Investigators who are responsible for postoperative follow-up are not involved in anaesthesia and perioperative care, and are not allowed to exchange patients' information with anaesthesiologists who take care of patients in the operating room. Before the beginning of the study, investigators are trained to follow the study protocol and to perform delirium assessment and the training process is repeated at 4 to 6 months intervals during the study period.[2-3, 31] The 4-hour training courses of delirium assessment include the following contents: (1) lectures regarding signs/symptoms, diagnosis and treatment of delirium by psychiatrists; (2) training courses of the use of CAM and CAM-ICU on patient-actors (trained ICU physicians or nurses who act as patients with or without delirium) conducted by psychiatrists. The process continued until 100% agreement is achieved in diagnosing delirium.

Primary endpoint

The primary endpoint is the incidence of delirium during the first 5 days after surgery. Delirium is assessed twice daily (at 08:00-09:00 and 19:00-20:00, respectively) with CAM for non-intubated patients[30] or CAM for the Intensive Care Unit (CAM-ICU) for intubated patients.[32] These delirium assessment methods had been used in our previous studies.[2-3, 31] For patients who are discharged or died within 5 days after surgery, the results of last delirium assessment will be considered the results of the missing data. These patients will be excluded when calculating daily prevalence of delirium in a post-hoc analysis.

Secondary endpoints

Postoperative pain intensities at rest and with movement are assessed with NRS pain score at 24, 48 and 72 hours after surgery, respectively.[31] Cumulative morphine consumptions at these time points are recorded. Subjective sleep quality is assessed with NRS (an 11-point scale where 0 indicates the worst possible sleep and 10 the best possible sleep) at 08:00 on the first, second and third morning after surgery.[3, 31] Other secondary endpoints include non-delirium complications within 30 days after surgery, length of stay in hospital after surgery and all-cause 30-day mortality. Non-delirium complications are generally defined as new-onset non-delirium conditions after surgery that are harmful to patients' recovery and require therapeutic intervention.

Safety outcomes

In the present study, adverse events are monitored from the start of study drug administration until PACU discharge or 2 hours after ICU admission. Hypotension is defined as systolic blood pressure of less than 90 mmHg or a decrement of more than 30% from baseline. Hypertension is defined as systolic blood pressure of more than 180 mmHg or an increment of more than 30% from baseline. Bradycardia is defined as heart rate of less than 40 beats per minute. Tachycardia is defined as heart rate of more than 100 beats per minute. Desaturation is defined as SpO_2 of less than 90%. Emergence agitation is defined as a Richmond Agitation-Sedation Scale (RASS) score of more than +2 within 30 minutes after extubation. Delayed extubation is defined when time to extubation is more than 2 hours (from the end of surgery) in PACU patients or more than 4 hours in ICU patients.[2, 22-25]

Severe adverse events, i.e., those that might result in patient's disability/deformity, prolong in-hospital stay, or life threatening events, will be reported to Clinical Research Ethics Committee of Peking University First Hospital

within 24 hours. For patients who suffered harm from present trial, medical treatment will be initiated as soon as possible and compensation will be completed according to local laws and regulations.

Data monitoring and management

Original data will be recorded in the CRFs accordingly. All data will be kept confidentially. The completed CRFs will be checked by a study coordinator who is qualified by the principal investigator. Supplementations and corrections will be made when necessary. Data entry will be performed in a double-input and double-check way with the Data Management System (Fantastic Eight Tech. Co., Ltd, Beijing, China) of the Peking University First Hospital.

The conduct of the study and the quality of data will be monitored by the Clinical Research Ethics Committee of Peking University First Hospital. Data management and statistical analysis will be performed by the Department of Biostatistics of Peking University First Hospital. Considering that dexmedetomidine has been widely used during general anaesthesia and its safety has been confirmed, no interim analysis will be performed and the trial will continue until the target sample size is achieved.

Statistical analysis

Sample size calculation

In our previous study, the incidence of delirium was 14.8% in elderly patients after non-cardiac surgery.[33] Previous studies reported that intraoperative dexmedetomidine decreased the incidence of POD by 60-77% in comparison with placebo.[22, 25] We assumed that the incidence of POD will be reduced from 14.8% to 7.4% (i.e., a 50% reduction) in the present study. With the power set at 80% and significant level at

0.05, 564 patients are required to detect the difference. Considering a loss to follow-up rate of about 9%, we plan to enroll 620 patients in this study.

Outcome analysis

Continuous data with normal distribution will be compared using independent sample T-test. Continuous data with asymmetric distribution will be compared using independent sample Mann-Whitney U test. Categorical data will be compared using Chi-squared test or continuity correction Chi-squared test. The difference (and 95% confidence interval of the difference) between two means or medians will be estimated using the methodology of Levene's test or Hodges-Lehmann estimator. Time-to-event data will be analyzed by survival analysis with differences between groups compared with log-rank test.

Statistical analyses will be performed with the SPSS 14.0 (SPSS, Inc., Chicago, IL) and SAS 9.3 (SAS Institute, Cary, NC, USA). All tests are two tailed, and P values of less than 0.05 are considered to be statistically significant. The Bonferroni adjustment is made to control type I error for multiple testing.

Discussion

This randomized, double-blinded, and placebo-controlled single center trial was designed to investigate if dexmedetomidine administration during general anaesthesia can decrease the incidence of POD in elderly patients after major non-cardiac surgery.

In the present study, the dosing regimen of dexmedetomidine is similar to our previous study because it does not increase drug-related adverse events (such as severe bradycardia and hypotension).[25] Furthermore, the CAM and CAM-ICU are used to assess delirium in patients with or without intubation, respectively.[30, 32] Both CAM and CAM-ICU have been validated in Chinese population.[34, 35] Feasibility of these two assessment tools have been confirmed in our previous studies.[2-3, 31] To maintain the quality of delirium assessment, investigators in charge of postoperative follow-up are trained by a psychiatrist before the study and will be retrained at 4 to 6-month intervals.

Because of the hemodynamic and anaesthetic-sparing effect of dexmedetomidine, it is not very difficult for the experienced anaesthesiologists to guess which study drug is administrated. This might weak the blinding to anaesthesiologists. However, in the present study, investigators who are responsible for postoperative follow-up and delirium assessment are not involved in anaesthesia and perioperative care; and they are not allowed to exchange patients' information with anaesthesiologists who take care of patients in the operating room. In this way the blinding of investigators to study group assignment can be guaranteed.

The strengths of the present study include the following when compared with previous studies.[22-24] Firstly, a randomized, double-blind, and placebo-controlled study design with a relative large sample size (620 patients) is adopted. Results of the

study will provide high quality evidences. Secondly, BIS level is monitored in all enrolled patients, which will help us to avoid unnecessary and potentially harmful deep anaesthesia. Thirdly, safety data will be recorded in detail. Our study also has some limitations. One is that this is a single center trial, which will limit the external validity of our results. Another one is that only early outcomes (up to 30 days after surgery) will be explored.

Trail status:

This study is currently at stage of patient enrollment and data collection. The current version of study protocol is V1.1 and is approved on November 27, 2015. Patient recruitment started from December 2, 2015 and is expected to be finished by March 31, 2018.

List of abbreviations

POD=postoperative delirium; IL=interleukins; CRP=C-reactive protein; TNF=tumor necrosis factor; IRB=Institutional Review Board; MMSE=Mini-Mental State Examination; CAM=confusion assessment method (CAM); BIS=Bispectral index; NRS=numeric rating scale; CAM-ICU=confusion assessment method-intensive care unit

Declarations

Ethics approval and consent to participate: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). The trial was registered at Chinese Clinical Trial Registry (www.chictr.org.cn) with identifier ChiCTR-IPR-15007654 on December 1, 2015). Written informed consent will be obtained from all patients or their surrogate in law.

Dissemination: Results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Competing interests: DXW reports lecture fees and travel expenses for lectures given at academic meetings from Jiangsu Hengrui Medicine Co Ltd, China, and Yichang Humanwell Pharmaceutical Co Ltd, China. DLM is primary investigator of present study which was supported by Beijing Excellent Talent Support Program. Other authors reported no conflict of interests.

Funding: This trial was supported by Beijing Excellent Talent Support Program (No. 2014000020124G025). The sponsors have no role in the study design and conduct; the collection, management, analysis, and interpretation of the data; or the preparation and approval of the manuscript.

Authors' contributions: DXW and DLM designed this study. DLM draft the manuscript of protocol. DXW critically revised the manuscript. DLM, BJW, CJL, JH,

HJL, CG, ZHW and QCZ participate in the conduct of the study. All authors read and approved the final manuscript.

Acknowledgements: We thank professor Xin-Yu Sun (Department of Psychiatrics, Peking University Sixth Hospital, Beijing, China) for her help in psychiatric consultation and personnel training and Dr. Xue-Ying Li (Department of Biostatistics, Peking University First Hospital, Beijing, China) for her help in statistical consultation. We also thank |Professor Daqing Ma (Section of Anesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College London, London, UK) for his help in revising the manuscript.

Data sharing: Will be provided on request.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Washington, DC: American Psychiatric Association; 1994.
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014 Mar 8;383(9920):911-22.
3. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016 Oct 15; 388(10054): 1893-1902.
4. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr 14; 291(14): 1753-62.
5. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012 Jul 5; 367(1): 30-9.
6. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium. Eur J Anaesthesiol. 2017 Apr; 34(4):192-214.
7. Creeley C, Dikranian K, Dissen G, et al. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth. 2013 Jun; 110 Suppl 1: i29-38.
8. Xiong WX, Zhou GX, Wang B, et al. Impaired spatial learning and memory after sevoflurane-nitrous oxide anesthesia in aged rats is associated with down-regulated cAMP/CREB signaling. PLoS One. 2013 Nov 15;8(11): e79408.
9. Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases

postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013 Jan; 25(1): 33-42.

10. Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006 Apr; 102(4): 1267-73.
11. Lynch EP, Lazor MA, Gellis JE, et al. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998; 86:781-5
12. Hirsch J, Vacas S, Terrando N, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation. 2016 Aug 30; 13(1): 211.
13. Cape E, Hall RJ, van Munster BC,et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. J Psychosom Res. 2014 Sep; 77(3): 219-25.
14. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. Crit Care. 2011; 15(6): R297.
15. McGrane S, Girard TD, Thompson JL,et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care. 2011; 15(2): R78.
16. Kazmierski J, Banys A, Latek J, et al. Raised IL-2 and TNF-α concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. Int Psychogeriatr. 2014 May; 26(5): 845-55.
17. Shin HW, Yoo HN, Kim DH, et al. Preanesthetic dexmedetomidine 1μg/kg single infusion is a simple, easy, and economic adjuvant for general anesthesia. Korean J Anaesthesiol. 2013 Aug; 65(2): 114-20.

18. Li J, Xiong M, Nadavaluru PR, et al. Dexmedetomidine attenuates neurotoxicity induced by prenatal propofol exposure. J Neurosurg Anesthesiol. 2016 Jan; 28(1): 51-64.

19. Sanders RD, Xu J, Shu Y, et al. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology. 2009 May; 110(5): 1077-85.

20. Le Bot A, Michelet D, Hilly J, et al. Efficacy of intraoperative dexmedetomidine compared with placebo for surgery in adults: a meta-analysis of published studies. Minerva Anestesiol. 2015 Oct; 81(10): 1105-17.

21. Kang SH, Kim YS, Hong TH, et al. Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. Acta Anesthesiol Scand. 2013 Apr; 57(4): 480-7.

22. Li Y, Wang B, Zhang LL,et al. Dexmedetomidine Combined with General Anesthesia Provides Similar Intraoperative Stress Response Reduction When Compared with a Combined General and Epidural Anesthetic Technique. Anaesth Analg. 2016 Apr;122(4):1202-10

23. Cao JL, Pei YP, Wei JQ, et al. Effects of intraoperative dexmedetomidine with intravenous anesthesia on postoperative emergence agitation/delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy: A CONSORT-prospective, randomized, controlled clinical trial. Medicine (Baltimore). 2016 Dec; 95(49): e5566.

24. Sun Y, Liu J, Yuan X, et al. Effects of dexmedetomidine on emergence delirium in pediatric cardiac surgery. Minerva Pediatr. 2017 Jun; 69(3): 165-173.

25. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial.

PLoS One. 2017 Feb 9; 12(2): e0170757.

26. Yang X, Li Z, Gao C, et al. Effect of dexmedetomidine on preventing agitation and delirium after microvascular free flap surgery: a randomized, double-blind, control study. J Oral Maxillofac Surg. 2015 Jun; 73(6): 1065-72.

27. Deiner S, Luo X, Lin HM, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. JAMA Surg. 2017 Aug 16; 152(8): e171505.

28. Collin C, Wade DT, Davies S, et al. The Barthel ADL Index: a reliability study. Int Disabil Stud. 1988; 10: 61-3.

29. Katzman R, Zhang MY, Ouang-Ya-Qu, et al. A Chinese version of the Mini-Mental State Examination; impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol. 1988; 41: 971-8.

30. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The Confusion Assessment Method. A new method for detecting delirium. Ann Intern Med 1990; 113:941-8

31. Mu DL, Zhang DZ, Wang DX, et al. Parecoxib Supplementation to Morphine Analgesia Decreases Incidence of Delirium in Elderly Patients After Hip or Knee Replacement Surgery: A Randomized Controlled Trial. Anaesth Analg. 2017 Jun; 124(6):1992-2000.

32. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001 Jul; 29(7): 1370-9.

33. Liu P, Li YW, Wang XS, et al. High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a

prospective cohort study. Chin Med J (Engl). 2013;126(19):3621-7.

34. Jl L, Vc L, Leung CM, et al. Clinical utility and validation of two instruments (the Confusion Assessment Method Algorithm and the Chinese version of Nursing Delirium Screening Scale) to detect delirium in geriatric inpatients. Gen Hosp Psychiatry. 2008; 30: 171-6.

35. Wang C, Wu Y, Yue P, et al. Delirium assessment using Confusion Assessment Method for the Intensive Care Unit in Chinese critically ill patients. J Crit Care. 2013; 28: 223-9.

Figure legend

Figure 1. Flowchart of this study.

Figure 1 Flow chart of this study

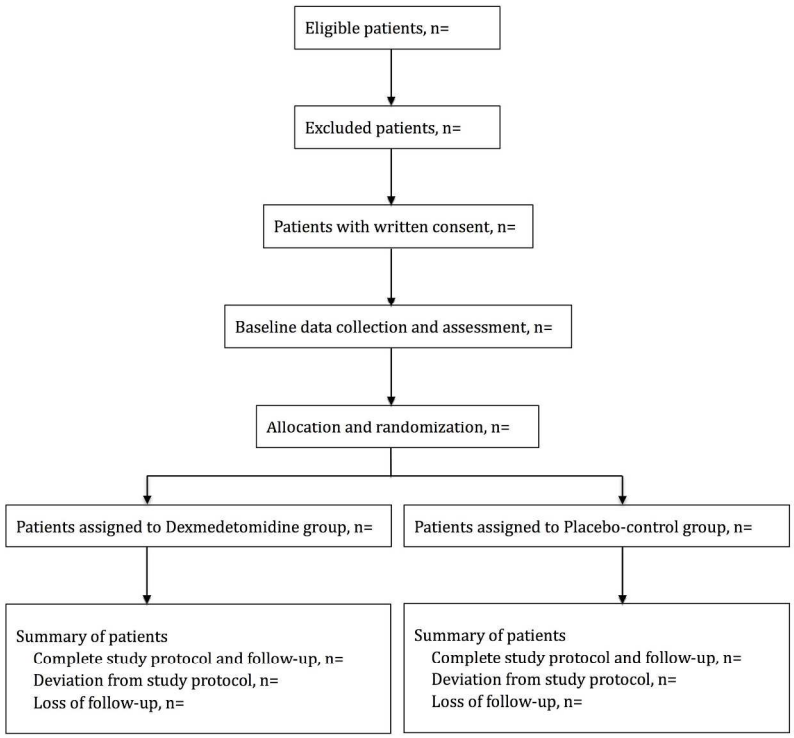

Figure1 Flow chart of this study

209x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/L1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P4/L7-8; P8/L14-16; P19/L4-7
	2b	All items from the World Health Organization Trial Registration Data Set	P8/L3-L17
Protocol version	3	Date and version identifier	P8/L11
Funding	4	Sources and types of financial, material, and other support	P19/L18-21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1/L5-125; P2/L1
	5b	Name and contact information for the trial sponsor	P19/L18-21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P19/L18-21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P6-7
	6b	Explanation for choice of comparators	P7/L8-22; P10/L12-22
Objectives	7	Specific objectives or hypotheses	P7/L23-25
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P8/L3-9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P8/L7-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P8/L18-P9/L3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10/L12-22
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P10/L23-P11/L4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P12/L15-P14/L3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P14/L19-P15/L2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P9/L5-14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P9/L16-21
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P9/L22-P10/L5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9-/L18-21
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P9/L22-25
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P10/L1-5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P12/L1-P15/L15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P12/L20-23

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P14/L5-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P14/L20-P15/L15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P15/L4-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P11/L3-4; P12/L20-23
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/L11-14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P14/L14-17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P13/L23-P14/L3
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14/L11-14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P8/L11-14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P8/L11-14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8/L16-17 P19/L3-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P14/L5-7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P19/L12-16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P14/L11-14; P20/L12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	P14/L1-3
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P4/L4-5; P19/L9-10
	31b	Authorship eligibility guidelines and any intended use of professional writers	P19/L23-P20/L2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P20/L12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Impact of dexmedetomidine infusion during general anaesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019549.R3
Article Type:	Protocol
Date Submitted by the Author:	26-Mar-2018
Complete List of Authors:	Wang, Bojie; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Chunjing; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Hu, Jian; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Li, Huaijin; Peking University First Hospital, Department of Anesthesiology and Critical Care Guo, Chao; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Wang, Zhenhan; Dongping People's Hospital, Department of anesthesiology Zhang, Qiaochu; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine Mu, Dongliang; Department of Anesthesiology and Critical Care Medicine Wang, Dong-Xin; Peking University First Hospital, Department of Anesthesiology and Critical Care Medicine
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Elderly, Major non-cardiac surgery, Intraoperative dexmedetomidine, Postoperative delirium

Impact of dexmedetomidine infusion during general anaesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial

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Abstract for protocol

Introduction: Delirium is a common complication in elderly after surgery and is associated with worse outcomes. Multiple risk factors are related with postoperative delirium, such as exposure to general anaesthetics, pain and postoperative inflammatory response. Preclinical and clinical studies have shown that dexmedetomidine attenuated neurotoxicity induced by general anaesthetics, improved postoperative analgesia and inhibited inflammatory response after surgery. Several studies found that intraoperative use of dexmedetomidine can prevent postoperative delirium, but data were inconsistent. This study was designed to investigate the impact of dexmedetomidine administered during general anaesthesia in preventing delirium in elderly after major non-cardiac surgery.

Method and analysis: This is a randomized, double-blinded, and placebo-controlled trial. 620 elderly patients (age ≥ 60 years) who are scheduled to undertake elective major non-cardiac surgery (with an expected duration ≥ 2 hours) are randomly divided into two groups. For patients in the dexmedetomidine group, a loading dose dexmedetomidine (0.6 μg/kg) will be administered in 10 minutes before anaesthesia induction, followed by a continuous infusion at a rate of 0.5 μg/kg/h till 1 hour before the end of surgery. For patients in the control group, normal saline will be administered with an identical rate as in the dexmedetomidine group. The primary endpoint is the incidence of delirium during the first five postoperative days. Secondary endpoints include pain intensity, cumulative opioid consumption and subjective sleep quality during the first 3 postoperative days as well as the incidence of non-delirium complications and all-cause mortality within 30 days after surgery.

Ethics and dissemination: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987) and registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) with identifier ChiCTR-IPR-15007654. The results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Key words: Elderly; Major non-cardiac surgery; Intraoperative dexmedetomidine; Postoperative delirium

Strengths and limitations

Strengths

1. The study design will be a randomized, double-blinded and placebo-controlled, with a relative large sample size.
2. Anaesthesia depth (Bispectral Index) will be monitored to guide anaesthesia maintenance to ensure patients in both groups received equal depth anaesthesia.

Limitations

1. This is a single center trial, which will limit the generalizability of our results.
2. Only early outcomes (up to 30 days after surgery) are assessed in this trial.
3. The hemodynamic and anaesthetic-sparing effects of dexmedetomidine might weaken the efficiency of blindness to the treating anaesthesiologist.

Introduction

Delirium is a transient brain dysfunction which is characterized by altered consciousness, inattention, and changes in cognition or perception; it develops acutely with clinical manifestations to be fluctuated with aggressive and depressive manner during developing course.[1] Prevalence of delirium varies from 12% to 51% in patients after non-cardiac surgery, and it is increased with age.[2-3] The occurrence of postoperative delirium (POD) is associated with worsen outcomes including prolonged mechanical ventilation and intensive care unit stay, increased postoperative complications, high mortality rate and long-term cognitive decline.[2-5]

The aetiology of POD is multifactorial and includes several intraoperative factors.[6] For example, exposure to general anaesthetics (e.g., propofol or sevoflurane) might produce neurotoxicity;[7-8] whereas reduced anaesthetic consumption by avoiding deep anaesthesia reduced the occurrence of delirium in elderly patients undergoing major non-cardiac surgery.[9] Poor pain management is another risk factor of POD.[6, 10] It was reported that the risk of postoperative delirium was 1.2 times higher for every unit increment in visual analogue pain score (an 11-point pain scale where 0 indicates no pain and 10 the most severe pain).[11] Inflammation is also proposed to play an important role in the pathogenesis of POD.[2] Inflammatory responses induced by surgery and anaesthesia are manifested by elevated levels of interleukins (IL), C-reactive protein (CRP) and tumor necrosis factor (TNF).[2, 12] Studies by our group and others found that higher levels of inflammatory mediators are associated with increased risk of POD.[2, 13-16.]

Dexmedetomidine is a highly selective α2-receptor agonist with sedative, analgesic and anxiolytic effects.[17-21] When used as a supplement during intraoperative

anaesthesia, it reduces the consumption of general anaesthetics.[17] Preclinical evidence suggested that use of dexmedetomidine might attenuate neurotoxicity induced by general anaesthetics.[18-19] In a meta-analysis, intraoperative administration of dexmedetomidine lowers postoperative pain intensity and reduces opioid consumption.[20] Clinical evidence also showed that intraoperative dexmedetomidine significantly inhibits hyper-secretion of inflammatory cytokines during and after surgery.[21-22]

Use of dexmedetomidine during general anaesthesia may reduce POD. In pediatric patients undergoing tonsillectomy and cardiac surgery, intraoperative infusion of dexmedetomidine lowered the incidence of emergence delirium.[23,24] In adult patients undergoing cardiac surgery and microvascular free flap surgery, intraoperative dexmedetomidine (comparison with normal saline) slightly decreased the incidence of delirium, although the differences were not statistically significant between two groups possibly due to underpowered sample size.[25,26] In a recent study of Deiner et al.,[27] use of dexmedetomidine during general anaesthesia did not reduce delirium after major non-cardiac surgery in the elderly. However, in that study, anaesthesia depth was not monitored and the consumption of anaesthetics (such as propofol and fentanyl) was similar between the two groups. It was possible that patients in the dexmedetomidine group had deeper anaesthesia which might have increased the risk of delirium.[27] Therefore, the effect of dexmedetomidine administered during general anaesthesia on the occurrence of POD needs to be evaluated further.

This study is designed to investigate whether dexmedetomidine use during general anaesthesia can decrease the incidence of POD in elderly after major non-cardiac surgery.

Method and analysis

Study design

This randomized, double-blinded, and placebo-controlled trial with two parallel arms was designed to test the superiority of dexmedetomidine administered during general anaesthesia on the incidence of delirium after surgery. Patients will be randomized into either the dexmedetomidine group or the control group (Figure 1). The study is conducted in the Department of Anesthesiology and Critical Care Medicine of Peking University First Hospital.

Ethics approval

The study protocol (version 1.1, issue date Nov, 2015) was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). Any protocol modification will be submitted for review and approval by the Ethics Committee. The trial was registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn) on December 1, 2015, with identifier ChiCTR-IPR-15007654. Written informed consents are obtained from every patient or his/her surrogate in law.

Patient and public involvement

Patients and public were not involved in study design or conduct of study. There is no plan to disseminate the results to study participants.

Participants

Elderly patients (age ≥ 60 years) who are scheduled to undergo elective non-cardiac surgery with expected duration ≥ 2 hours under general anaesthesia are screened for inclusion. Those who meet any of the following criteria will be excluded: (1) do not provide written informed consents; (2) previous history of schizophrenia, epilepsy or

Parkinson disease; (3) visual, hearing, language or other barrier which impede communication and preoperative delirium assessment; (4) neurosurgery or traumatic brain injury; (5) severe bradycardia (heart rate less than 40 beats per minute), sick sinus syndrome or atrioventricular block of degree 2 or above; (6) severe hepatic dysfunction (Child-Pugh grade C); or (7) renal failure (requirement of renal replacement therapy).

Patient recruitment and baseline data collection

Potential participants are screened by investigators the day before surgery (or on Friday for those who will undergo surgery next Monday). The study protocol including potential risks and benefits will be explained to patients in person. Those who do not meet the exclusion criteria are invited to participate in the study.

After obtaining written informed consents, the following baseline data are collected: demographic data, preoperative diagnosis, comorbidity, current medical therapy, previous surgery, and main results of physical and laboratory examinations. Barthel index is used for evaluation of activities of daily living.[28] Cognitive function is assessed with Mini-Mental State Examination (MMSE).[29] Preoperative delirium is assessed with confusion assessment method (CAM).[30]

Randomization, grouping and blinding

Random numbers were created by an independent statistician using SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA) in a 1:1 ratio and were sealed in envelopes. A study coordinator, who has no knowledge of patients before randomization and does not participate in anaesthesia and postoperative follow-up of enrolled patients, will open envelop for random numbers and prepare study drugs before induction of anaesthesia.

Information regarding randomization, study drug preparation and group allocation will be masked from investigators who perform data collection and postoperative follow-up, anaesthesiologists, patients and other healthcare team members. Blinding will be maintained throughout the entire study period.

To ensure patients' safety, study group allocation can be unmasked in the following conditions, i.e., occurrence of severe adverse events or any unexpected deterioration of patient's clinical status. These situations will be documented in the Case Report Forms (CRFs). The unmasked patients will be included in the intention-to-treat population but excluded from per-protocol analysis.

Interventions, anaesthesia and analgesia

Intraoperative monitoring includes electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, end-tidal carbon dioxide, nasopharyngeal temperature, urine output, and bispectral index (BIS). Intra-arterial pressure (including derivative dynamic parameters such as stroke volume variation by FlowTrac system) and central venous pressure are monitored according to patients' conditions.

Study drugs, either 200 μg (2 ml) dexmedetomidine (Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China) or 2 ml normal saline, are diluted into 50 ml normal saline. All study drugs are colorless solution provided in syringes of the same size and brand. The regimen of study drug administration includes a loading dose of 0.15 ml/kg (i.e., 0.6 μg/kg dexmedetomidine for patients in the dexmedetomidine group) administered during a 10-minute period before anaesthesia induction. This is followed by a continuous infusion at a rate of 0.125 ml/kg/h (i.e., a rate of 0.5 μg/kg/h dexmedetomidine for patients in the dexmedetomidine group) till 1 hour before the end of surgery. Study drug infusion is performed by an infusion pump specially

designed for dexmedetomidine administration (Slgo® CP1000, Beijing Slgo medical technology Co., Ltd.).

Attending anaesthesiologists can decrease or stop study drug infusion in the following conditions: (1) severe bradycardia or hypotension which does not improve after routine treatment; (2) new onset atrioventricular block which does not improve after routine treatment; or (3) other conditions that anaesthesiologists consider it necessary. In these conditions, the reasons that lead to any protocol deviations will be recorded in the case report forms (CRF). These patients will be included in the intention-to-treat analysis but excluded from the per-protocol analysis.

Anaesthesia is induced with intravenous sufentanil (target controlled infusion with effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (2-3 mg/kg) and maintained with intravenous sufentanil (effect-site concentration from 0.2 to 0.5 ng/ml) and propofol (4-12 mg/kg/h) and inhalation of a 1:1 nitrous oxide-oxygen mixture. Rocuronium and/or cisatracurium are administered for muscle relaxation. Patients will be mechanically ventilated with a tidal volume of 6-8 ml/kg and a positive end-expiratory pressure of 5 cm H_2O. The mean arterial pressure is maintained above 60 mmHg or within 20% from baseline. BIS is maintained between 40 and 60. Body temperature is maintained with air-warming and fluid heating systems. The target of nasopharyngeal temperature maintenance during surgery is from 36.0 to 37°C.

All patients are transferred to post-anaesthesia care unit (PACU) or intensive care unit (ICU) before they are sent back to general wards. Patient-controlled intravenous analgesia (PCIA) is provided for all patients, which is established with 0.5 mg/ml morphine in 100 ml normal saline and programmed to deliver a 1 mg bolus with a lock-out interval of 8 minutes and a background infusion at 0.5 mg/h.

Supplemental morphine at dose of 2 to 4 mg will be administered at 10-minute intervals if the numeric rating scale (NRS) pain score (a 11-point scale where 0 indicates no pain and 10 indicates the worst pain) remains above 4 after 3 consecutive PCIA boluses.[31] Other postoperative managements were performed according to routine practice.

Outcome assessment

Patients are followed up twice daily during the first 5 postoperative days and then weekly until 30 days after surgery. Investigators who are responsible for postoperative follow-up are not involved in anaesthesia and perioperative care, and are not allowed to exchange patients' information with anaesthesiologists who take care of patients in the operating room. Before the beginning of the study, investigators are trained to follow the study protocol and to perform delirium assessment and the training process is repeated at 4 to 6 months intervals during the study period.[2-3, 31] The 4-hour training courses of delirium assessment include the following contents: (1) lectures regarding signs/symptoms, diagnosis and treatment of delirium by psychiatrists; (2) training courses of the use of CAM and CAM-ICU on patient-actors (trained ICU physicians or nurses who act as patients with or without delirium) conducted by psychiatrists. The process continued until 100% agreement is achieved in diagnosing delirium.

Primary endpoint

The primary endpoint is the incidence of delirium during the first 5 days after surgery. Delirium is assessed twice daily (at 08:00-09:00 and 19:00-20:00, respectively) with CAM for non-intubated patients[30] or CAM for the Intensive Care Unit (CAM-ICU) for intubated patients.[32] These delirium assessment methods had been used in our previous studies.[2-3, 31] For patients who are discharged or died within 5 days after

surgery, the results of last delirium assessment will be considered the results of the missing data. These patients will be excluded when calculating daily prevalence of delirium in a post-hoc analysis.

Secondary endpoints

Postoperative pain intensities at rest and with movement are assessed with NRS pain score at 24, 48 and 72 hours after surgery, respectively.[31] Cumulative morphine consumptions at these time points are recorded. Subjective sleep quality is assessed with NRS (an 11-point scale where 0 indicates the worst possible sleep and 10 the best possible sleep) at 08:00 on the first, second and third morning after surgery.[3, 31] Other secondary endpoints include non-delirium complications within 30 days after surgery, length of stay in hospital after surgery and all-cause 30-day mortality. Non-delirium complications are generally defined as new-onset non-delirium conditions after surgery that are harmful to patients' recovery and require therapeutic intervention.

Safety outcomes

In the present study, adverse events are monitored from the start of study drug administration until PACU discharge or 2 hours after ICU admission. Hypotension is defined as systolic blood pressure of less than 90 mmHg or a decrement of more than 30% from baseline. Hypertension is defined as systolic blood pressure of more than 180 mmHg or an increment of more than 30% from baseline. Bradycardia is defined as heart rate of less than 40 beats per minute. Tachycardia is defined as heart rate of more than 100 beats per minute. Desaturation is defined as SpO_2 of less than 90%. Emergence agitation is defined as a Richmond Agitation-Sedation Scale (RASS) score of more than +2 within 30 minutes after extubation. Delayed extubation is

defined when time to extubation is more than 2 hours (from the end of surgery) in PACU patients or more than 4 hours in ICU patients.[2, 22-25]

Severe adverse events, i.e., those that might result in patient's disability/deformity, prolong in-hospital stay, or life threatening events, will be reported to Clinical Research Ethics Committee of Peking University First Hospital within 24 hours. For patients who suffered harm from present trial, medical treatment will be initiated as soon as possible and compensation will be completed according to local laws and regulations.

Data monitoring and management

Original data will be recorded in the CRFs accordingly. All data will be kept confidentially. The completed CRFs will be checked by a study coordinator who is qualified by the principal investigator. Supplementations and corrections will be made when necessary. Data entry will be performed in a double-input and double-check way with the Data Management System (Fantastic Eight Tech. Co., Ltd, Beijing, China) of the Peking University First Hospital.

The conduct of the study and the quality of data will be monitored by the Clinical Research Ethics Committee of Peking University First Hospital. Data management and statistical analysis will be performed by the Department of Biostatistics of Peking University First Hospital. Considering that dexmedetomidine has been widely used during general anaesthesia and its safety has been confirmed, no interim analysis will be performed and the trial will continue until the target sample size is achieved.

Statistical analysis

Sample size calculation

In our previous study, the incidence of delirium was 14.8% in elderly patients after non-cardiac surgery.[33] Previous studies reported that intraoperative dexmedetomidine decreased the incidence of POD by 60-77% in comparison with placebo.[22, 25] We assumed that the incidence of POD will be reduced from 14.8% to 7.4% (i.e., a 50% reduction) in the present study. With the power set at 80% and significant level at 0.05, 564 patients are required to detect the difference. Considering a loss to follow-up rate of about 9%, we plan to enroll 620 patients in this study.

Outcome analysis

Continuous data with normal distribution will be compared using independent sample T-test. Continuous data with asymmetric distribution will be compared using independent sample Mann-Whitney U test. Categorical data will be compared using Chi-squared test or continuity correction Chi-squared test. The difference (and 95% confidence interval of the difference) between two means or medians will be estimated using the methodology of Levene's test or Hodges-Lehmann estimator. Time-to-event data will be analyzed by survival analysis with differences between groups compared with log-rank test.

Statistical analyses will be performed with the SPSS 14.0 (SPSS, Inc., Chicago, IL) and SAS 9.3 (SAS Institute, Cary, NC, USA). All tests are two tailed, and P values of less than 0.05 are considered to be statistically significant. The Bonferroni adjustment is made to control type I error for multiple testing.

Discussion

This randomized, double-blinded, and placebo-controlled single center trial was designed to investigate if dexmedetomidine administration during general anaesthesia can decrease the incidence of POD in elderly patients after major non-cardiac surgery.

In the present study, the dosing regimen of dexmedetomidine is similar to our previous study because it does not increase drug-related adverse events (such as severe bradycardia and hypotension).[25] Furthermore, the CAM and CAM-ICU are used to assess delirium in patients with or without intubation, respectively.[30, 32] Both CAM and CAM-ICU have been validated in Chinese population.[34, 35] Feasibility of these two assessment tools has been confirmed in our previous studies.[2-3, 31] To maintain the quality of delirium assessment, investigators in charge of postoperative follow-up are trained by a psychiatrist before the study and will be retrained at 4 to 6-month intervals.

Because of the hemodynamic and anaesthetic-sparing effects of dexmedetomidine, it is not very difficult for the experienced anaesthesiologists to guess which study drug is administrated. This might weaken the blinding to anaesthesiologists. However, in the present study, investigators who are responsible for postoperative follow-up and delirium assessment are not involved in anaesthesia and perioperative care; and they are not allowed to exchange patients' information with anaesthesiologists who take care of patients in the operating room. In this way, the blinding of investigators to study group assignment can be guaranteed.

The strengths of the present study include the following when compared with previous studies.[22-24] Firstly, a randomized, double-blind, and placebo-controlled study design with a relative large sample size (620 patients) is adopted. Results of the

study will provide high quality evidences. Secondly, BIS level is monitored in all enrolled patients, which will help us to avoid unnecessary and potentially harmful deep anaesthesia. Thirdly, safety data will be recorded in detail. Our study also has some limitations. One is that this is a single center trial, which will limit the external validity of our results. Second, only early outcomes (up to 30 days after surgery) will be explored. Third, the hemodynamic and anaesthetic-sparing effects of dexmedetomidine might weaken the efficiency of blindness to the treating anaesthesiologist.

Trail status:

This study is currently at stage of patient enrollment and data collection. The current version of study protocol is V1.1 and is approved on November 27, 2015. Patient recruitment started from December 2, 2015 and is expected to be finished by March 31, 2018.

List of abbreviations

POD=postoperative delirium; IL=interleukins; CRP=C-reactive protein; TNF=tumor necrosis factor; IRB=Institutional Review Board; MMSE=Mini-Mental State Examination; CAM=confusion assessment method (CAM); BIS=Bispectral index; NRS=numeric rating scale; CAM-ICU=confusion assessment method-intensive care unit

Declarations

Ethics approval and consent to participate: The study protocol was approved by Clinical Research Ethics Committee of Peking University First Hospital (2015-987). The trial was registered at Chinese Clinical Trial Registry (www.chictr.org.cn) with identifier ChiCTR-IPR-15007654 on December 1, 2015). Written informed consent will be obtained from all patients or their surrogate in law.

Dissemination: Results of the study will be presented at academic conferences and submitted to peer-reviewed journals.

Competing interests: DXW reports lecture fees and travel expenses for lectures given at academic meetings from Jiangsu Hengrui Medicine Co Ltd, China, and Yichang Humanwell Pharmaceutical Co Ltd, China. DLM is primary investigator of present study which was supported by Beijing Excellent Talent Support Program. Other authors reported no conflict of interests.

Funding: This trial was supported by Beijing Excellent Talent Support Program (No. 2014000020124G025). The sponsors have no role in the study design and conduct; the collection, management, analysis, and interpretation of the data; or the preparation and approval of the manuscript.

Authors' contributions: DXW and DLM designed this study. DLM draft the manuscript of protocol. DXW critically revised the manuscript. DLM, BJW, CJL, JH,

HJL, CG, ZHW and QCZ participate in the conduct of the study. All authors read and approved the final manuscript.

Acknowledgements: We thank professor Xin-Yu Sun (Department of Psychiatrics, Peking University Sixth Hospital, Beijing, China) for her help in psychiatric consultation and personnel training and Dr. Xue-Ying Li (Department of Biostatistics, Peking University First Hospital, Beijing, China) for her help in statistical consultation. We also thank |Professor Daqing Ma (Section of Anesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College London, London, UK) for his help in revising the manuscript.

Data sharing: Will be provided on request.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Washington, DC: American Psychiatric Association; 1994.
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014 Mar 8;383(9920):911-22.
3. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016 Oct 15; 388(10054): 1893-1902.
4. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr 14; 291(14): 1753-62.
5. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012 Jul 5; 367(1): 30-9.
6. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium. Eur J Anaesthesiol. 2017 Apr; 34(4):192-214.
7. Creeley C, Dikranian K, Dissen G, et al. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth. 2013 Jun; 110 Suppl 1: i29-38.
8. Xiong WX, Zhou GX, Wang B, et al. Impaired spatial learning and memory after sevoflurane-nitrous oxide anesthesia in aged rats is associated with down-regulated cAMP/CREB signaling. PLoS One. 2013 Nov 15;8(11): e79408.
9. Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases

postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013 Jan; 25(1): 33-42.

10. Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006 Apr; 102(4): 1267-73.
11. Lynch EP, Lazor MA, Gellis JE, et al. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998; 86:781-5
12. Hirsch J, Vacas S, Terrando N, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation. 2016 Aug 30; 13(1): 211.
13. Cape E, Hall RJ, van Munster BC,et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. J Psychosom Res. 2014 Sep; 77(3): 219-25.
14. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. Crit Care. 2011; 15(6): R297.
15. McGrane S, Girard TD, Thompson JL,et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care. 2011; 15(2): R78.
16. Kazmierski J, Banys A, Latek J, et al. Raised IL-2 and TNF-α concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. Int Psychogeriatr. 2014 May; 26(5): 845-55.
17. Shin HW, Yoo HN, Kim DH, et al. Preanesthetic dexmedetomidine 1μg/kg single infusion is a simple, easy, and economic adjuvant for general anesthesia. Korean J Anaesthesiol. 2013 Aug; 65(2): 114-20.

18. Li J, Xiong M, Nadavaluru PR, et al. Dexmedetomidine attenuates neurotoxicity induced by prenatal propofol exposure. J Neurosurg Anesthesiol. 2016 Jan; 28(1): 51-64.

19. Sanders RD, Xu J, Shu Y, et al. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology. 2009 May; 110(5): 1077-85.

20. Le Bot A, Michelet D, Hilly J, et al. Efficacy of intraoperative dexmedetomidine compared with placebo for surgery in adults: a meta-analysis of published studies. Minerva Anestesiol. 2015 Oct; 81(10): 1105-17.

21. Kang SH, Kim YS, Hong TH, et al. Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. Acta Anesthesiol Scand. 2013 Apr; 57(4): 480-7.

22. Li Y, Wang B, Zhang LL,et al. Dexmedetomidine Combined with General Anesthesia Provides Similar Intraoperative Stress Response Reduction When Compared with a Combined General and Epidural Anesthetic Technique. Anaesth Analg. 2016 Apr;122(4):1202-10

23. Cao JL, Pei YP, Wei JQ, et al. Effects of intraoperative dexmedetomidine with intravenous anesthesia on postoperative emergence agitation/delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy: A CONSORT-prospective, randomized, controlled clinical trial. Medicine (Baltimore). 2016 Dec; 95(49): e5566.

24. Sun Y, Liu J, Yuan X, et al. Effects of dexmedetomidine on emergence delirium in pediatric cardiac surgery. Minerva Pediatr. 2017 Jun; 69(3): 165-173.

25. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial.

PLoS One. 2017 Feb 9; 12(2): e0170757.

26. Yang X, Li Z, Gao C, et al. Effect of dexmedetomidine on preventing agitation and delirium after microvascular free flap surgery: a randomized, double-blind, control study. J Oral Maxillofac Surg. 2015 Jun; 73(6): 1065-72.

27. Deiner S, Luo X, Lin HM, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. JAMA Surg. 2017 Aug 16; 152(8): e171505.

28. Collin C, Wade DT, Davies S, et al. The Barthel ADL Index: a reliability study. Int Disabil Stud. 1988; 10: 61-3.

29. Katzman R, Zhang MY, Ouang-Ya-Qu, et al. A Chinese version of the Mini-Mental State Examination; impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol. 1988; 41: 971-8.

30. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The Confusion Assessment Method. A new method for detecting delirium. Ann Intern Med 1990; 113:941-8

31. Mu DL, Zhang DZ, Wang DX, et al. Parecoxib Supplementation to Morphine Analgesia Decreases Incidence of Delirium in Elderly Patients After Hip or Knee Replacement Surgery: A Randomized Controlled Trial. Anaesth Analg. 2017 Jun; 124(6):1992-2000.

32. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001 Jul; 29(7): 1370-9.

33. Liu P, Li YW, Wang XS, et al. High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a

prospective cohort study. Chin Med J (Engl). 2013;126(19):3621-7.

34. Jl L, Vc L, Leung CM, et al. Clinical utility and validation of two instruments (the Confusion Assessment Method Algorithm and the Chinese version of Nursing Delirium Screening Scale) to detect delirium in geriatric inpatients. Gen Hosp Psychiatry. 2008; 30: 171-6.

35. Wang C, Wu Y, Yue P, et al. Delirium assessment using Confusion Assessment Method for the Intensive Care Unit in Chinese critically ill patients. J Crit Care. 2013; 28: 223-9.

Figure legend

Figure 1. Flowchart of this study.

Figure 1 Flow chart of this study

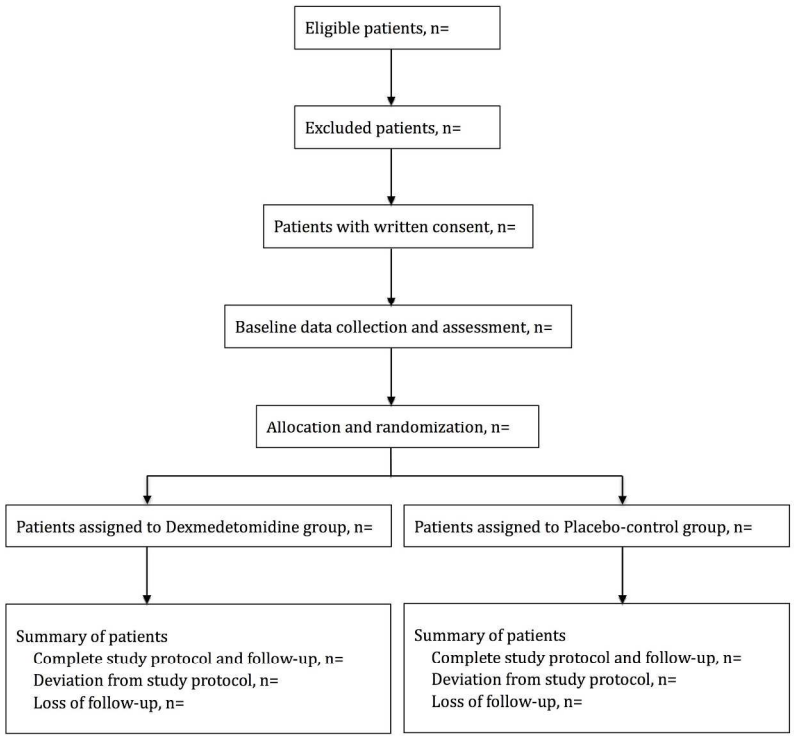

Figure1 Flow chart of this study

209x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/L1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P4/L7-8; P8/L14-16; P19/L4-7
	2b	All items from the World Health Organization Trial Registration Data Set	P8/L3-L17
Protocol version	3	Date and version identifier	P8/L11
Funding	4	Sources and types of financial, material, and other support	P19/L18-21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1/L5-16, P19/L23-P20/L2
	5b	Name and contact information for the trial sponsor	P19/L18-21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P19/L18-21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P6-7
	6b	Explanation for choice of comparators	P7/L8-22; P10/L12-22
Objectives	7	Specific objectives or hypotheses	P7/L23-25
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P8/L3-9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P8/L7-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P8/L21-P9/L6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10/L12-22
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P10/L11-24, P11/L1-2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P12/L20-P14/L8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P14/L24-P15/L7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P9/L7-17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P9/L18-24
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P9/L18-P10/L9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9/L21-24
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P10/L1-4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P10/L5-9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P12/L6-P15/L20
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P12/L25-P13/L3

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P14/L9-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P14/L23-P15/L20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P15/L9-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P11/L7-9; P12/L25-P13/L3
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/L9-22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P14/L19-22
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P13/L16-P14/L8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14/L16-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P8/L11-14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P8/L11-14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8/L16-17 P19/L3-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P14/L10-11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P19/L12-16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P14/L11-14; P20/L12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	P14/L6-8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P4/L4-5; P19/L9-10
	31b	Authorship eligibility guidelines and any intended use of professional writers	P19/L23-P20/L2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P20/L12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.