BMJ Open

Effect of head direction during prone positioning on postoperative delirium in elderly patients underwent thoracolumbar spine surgery: study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-083526
Article Type:	Protocol
Date Submitted by the Author:	21-Dec-2023
Complete List of Authors:	zhu, jixiang; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University; Xu Zhou Medical College, Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology Chen, Yongzhuang; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng Chen, Yangyang; The Affiliated Hospital of Xuzhou Medical University, Department of Anesthesiology; Xuzhou Medical University, Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology Liu, Fengyun; Xuzhou Medical University, Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology Ma, Hong; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng Chen, Qian; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng Wang, Fang; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng Chen, Xuetai; Xuzhou Medical University Xue, Zhouya; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng ni, kun; Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital, Department of Anesthesiology Li, Feng; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng Qian, Bin; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng

Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Posture, Thoracic surgery < SURGERY, Clinical Trial

Effect of head direction during prone positioning on postoperative delirium in elderly patients underwent thoracolumbar spine surgery: study protocol for a randomized controlled trial

Jixiang Zhu[1,2], Yongzhuang Chen[1], Yangyang Chen[2,4], Fengyun Liu[2], Hong Ma[1], Qian Chen[1], Fang Wang[1], Xuetai Chen[1,2], Zhouya Xue[1], Kun Ni[3], Feng Li[1,2], Bin Qian[1,2]

1. Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University; The First people's Hospital of Yancheng, Yancheng, 224006, China.
2. Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology, Xuzhou Medical University, Xuzhou, 221004, China.
3. Department of Anesthesiology, Drum Tower Hospital, Medical School of Nanjing University, 321 Zhongshan Road, Nanjing, 210008, China.
4. Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, 221001, China.

Jixiang Zhu, Yongzhuang Chen, and Yangyang Chen contributed equally to this work.

Correspondence to:

Bin Qian, Email: qianbin@ycsyy.com, Tel: +8613951489138

Feng Li, Email: 1226637852@qq.com, Tel: +8618351552626

Kun Ni, Email: lemonk_njumc@hotmail.com, Tel: +8615850582823

Keywords: delirium & cognitive disorders; posture; thoracic surgery; clinical trial.

Words statistics: 1684

Effect of head direction during prone positioning on postoperative delirium in elderly patients underwent thoracolumbar spine surgery: study protocol for a pilot randomized controlled trial

ABSTRACT

Introduction

Prone positioning with head rotation alters cerebral hemodynamics, potentially compromising brain perfusion and oxygenation. Elderly patients with Impaired brain perfusion and oxygenation are susceptive to postoperative delirium (POD). However, few studies have investigated whether head direction during prone positioning contributes to POD in elderly patients, which is often overlooked by clinicians. The present study aims to evaluate the effect of head direction during prone positioning on POD in elderly patients underwent thoracolumbar spine surgery.

Methods and analysis

This is a single-center, randomized, single-blind, pilot trial. Assessors will be blinded to the intraoperative head directions. Patients 65 years of age or older, undergoing elective thoracolumbar spine surgery will be eligible. 255 Patients will be randomly divided into group PC (prone with the head centered), group PL (prone with the head left rotated ~45 degrees), and group PR (prone with the head right rotated ~45 degrees). The primary outcome is the incidence of POD based on the 3 min diagnostic interview for Confusion Assessment Method (3D-CAM) until postoperative day 5. The secondary outcomes include the severity of POD based on the Memorial Delirium Assessment Scale (MDAS), alterations of postoperative cognitive impairment based on the Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), the intraoperative regional cerebral oxygen saturation (rSO2), alterations of the vertebrobasilar artery and the middle cerebral artery hemodynamics, and plasma concentrations of calcium channel binding protein S100 subunit beta (S100B) and neuron-specific enolase (NSE).

Ethics and dissemination

Ethical approval: Yancheng No.1 People's Hospital Ethics Examination Committee

(2023-K-120). Dissemination plans include presentations at annual conferences and publications in scientific journals.

Trial registration number: ChiCTR2300078839

Keywords: delirium & cognitive disorders; posture; thoracic surgery; clinical trial.

Introduction

Postoperative delirium (POD) is an acute and fluctuating confusion state manifesting disturbances in attention, awareness, and cognition. It is the most common postoperative complication, especially in elderly patients, and develops commonly within 5 days after surgery [1]. A recent meta-analysis revealed that the prevalence of POD in elderly patients undergoing spinal surgery ranged from 3.8% to 40.4% and the incidence of POD often brought poor prognostic [2]. Compared to patients without POD, patients with POD had a 2-4 times increase in perioperative mortality [3 4], a 2-3 times increase in readmission rates [5], and a 4-5 times increase in the incidence of dementia [6]. There is plenty of room for improvement against the development of POD, as so large span of the occurrence and necessity for patient well-being.

Different head directions during prone positioning, including neutral, left deviation, and right deviation, are optional depending on individual cases in thoracolumbar spine surgeries. However, some investigations suggested head rotation may alter cerebral hemodynamics and cerebral oxygenation. Among awake volunteers, vertebral artery flow was reduced when contralateral cervical rotation [7 8]. While another research debated the results [9]. Under general anesthesia in the prone position with the head rotated ~80 degrees to the right, the middle cerebral artery mean blood velocity (MCA V(mean)) reduces ~10% in young healthy volunteers [10]. Further, a recent study indicated that head right rotation in a prone position exhibited a statistical reduction in regional cerebral oxygen saturation (rSO2) earlier than neutral position and left deviation in elderly patients with spinal surgery, while the neutral position and left deviation showed a reduction in rSO2 over the same period [11]. Although the circle of Willis compensates for contralateral vascular dysfunction, complex clinical conditions exist, including level differs in atherosclerosis, long duration of operation, and general anesthesia without complaints and self-adjustment. It is elusive whether the

head direction in a prone position contributes to POD through altering cerebral hemodynamics and oxygenation.

Currently, no published research has investigated the effect of head direction during prone positioning on postoperative delirium in elderly patients. Based on previous literatures, we hypothesize that compared with neutral and left deviation in a prone position, right deviation contributes to POD via cerebral hemodynamic impairment. The primary aim of this study is to clarify the effect of head direction during prone positioning on the incidence and severity of POD among the elderly underwent thoracolumbar spine surgery. Our secondary aim is to identify the effect of head direction during prone positioning on cerebral hemodynamics and oxygenation.

METHODS AND ANALYSIS

Study design

This is a single-center, single-blinded, randomized controlled trial (Figure 1). Ethical approval has been granted by Yancheng No.1 People's Hospital Ethics Examination Committee (2023-K-120). Assessors are trained for homogenization.

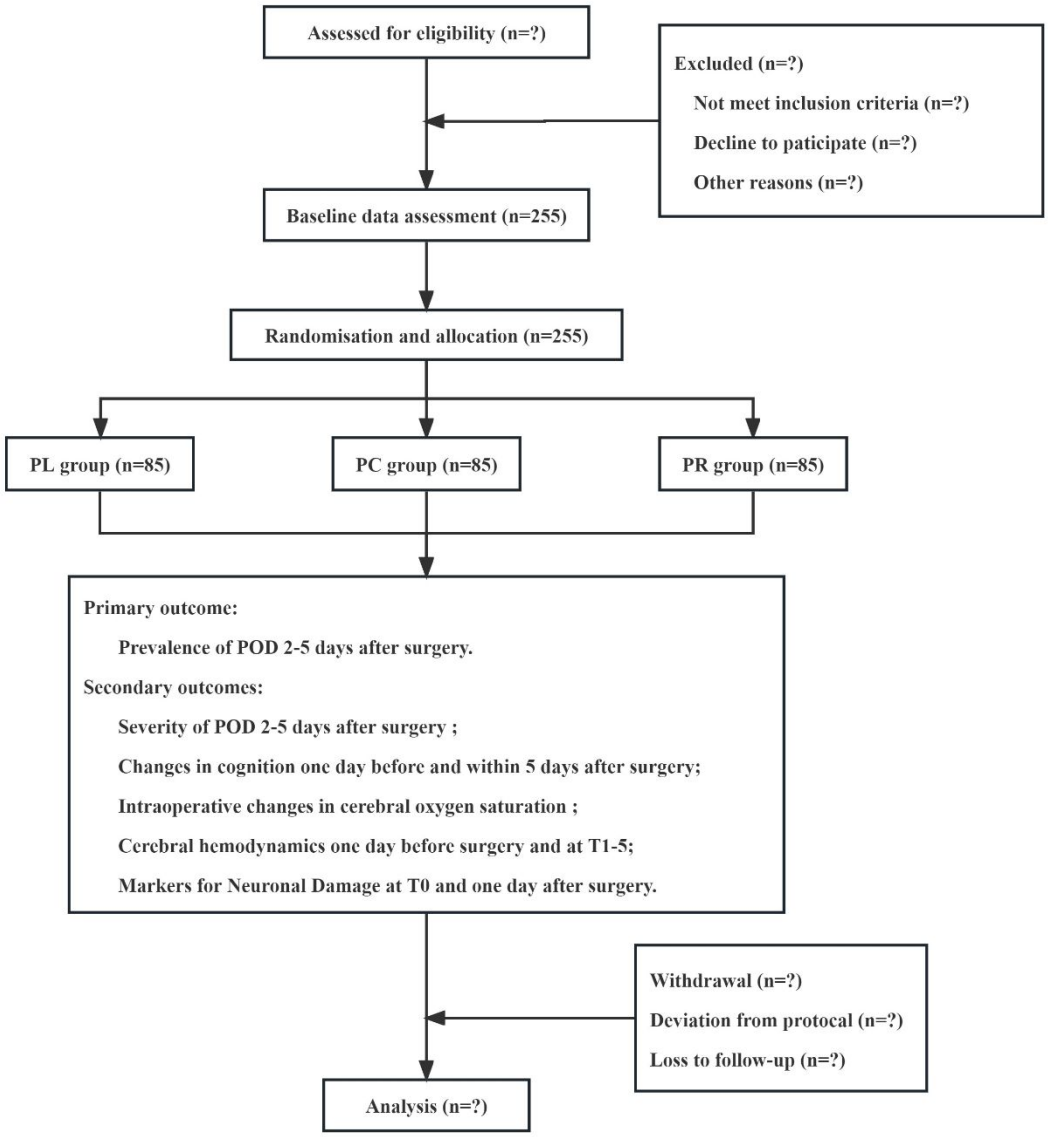


Figure 1

Study flow chart. PC: prone with the head centered; PL: prone with the head left rotated ~45 degrees; PR: prone with the head right rotated ~45 degrees; POD: postoperative delirium.

Patients and recruitment

The trial will be conducted at the First people's Hospital of Yancheng, Xuzhou Medical University. From 1 January 2024 to 31 December 2026, 255 patients who met the inclusion criteria will be enrolled. Written informed consent will be assigned before assessment.

Eligibility

Inclusion criteria

- Age ≥ 65 years.
- ASA class II–III.
- MMSE score > 23 points evaluated one day before surgery.
- Written informed consent was assigned.
- Projected operation time > 2 h.

Exclusion criteria

- Emerging or aging cervical spine trauma.
- Restricted position.
- Cervicogenic-related dizziness and vertigo.
- Comorbidities with clinical symptoms for central nervous system diseases
- Communication disability
- History of psychosis.

Discharge criteria

- The operation time < 2 h.
- Severe adverse reactions, such as severe anaphylactic reactions, and intraoperative blood loss > 800 ml.
- Interruption of study protocol.

ASA, American Society of Anesthesiologists; MMSE, baseline mini-mental state examination.

Standardized anesthetic protocol

Standardized anesthesia protocol will be applied to all volunteers. Vital signs will be monitored through ECG, oxygen saturation, and invasive blood pressure through upper limb arterial before anesthesia induction. Drugs for anesthesia induction include a combination of dexamethasone (10 mg), remimazolam tosylate (0.05–0.1 mg/kg), 1% propofol (1–1.5 mg/kg), fentanyl (0.1–0.15 μg/kg) and cis-atracurium (0.2 mg/kg). During the maintenance phase, 1-1.5% sevoflurane was administered by inhalation, and remifentanil was pumped intravenously (0.1 ug/kg/min) until the end of the operation. Fentanyl and cis-atracurium are intermittently added according to the concrete situation. Tropisetron Hydrochloride Injection (10 mg) and flurbiprofen axetil injection (50 mg)

will be applied intravenously 15 min before the end of surgery. The analgesic recipe for 48 hours after surgery consists of butorphanol tartrate injection (8-10 mg) and tropisetron hydrochloride injection (10 mg) in an analgesic pump.

Principles of intraoperative anesthesia management include the following:

- Bispectral index (BIS) value: 45-60;
- End-tidal carbon dioxide ($P_{ET}CO_2$): 40-55 mmHg;
- Body temperature: 36-37.5 ℃;
- Hemodynamic stability assisted by vasoactive drugs (Mean arterial pressure (MAP) changes within ±10% within 5 minutes);
- Pulse pressure variation (PPV) <10%;
- Acid-base and electrolyte homeostasis.

Randomization and blinding

Patients will be randomized into three groups based on a computer-generated table of random numbers. The allocation ratio is 1:1:1. Assessors responsible for preoperative and postoperative evaluations are blind to intraoperative head direction. Opaque randomized envelopes will be intraoperatively opened.

Interventions

Patients are randomly divided into three groups: group PC (prone with the head centered), group PL (prone with the head left rotated ~45 degrees), and group PR (prone with the head right rotated ~45 degrees).

Outcome measures

Primary outcome measure

The primary outcome is the prevalence of POD 2-5 days after surgery. 3 min diagnostic interview for Confusion Assessment Method (3D-CAM) will be taken to evaluate POD twice daily (08:00 to 10:00 and 18:00 to 20:00) [12].

Secondary outcome measure

Secondary outcomes include delirium severity, changes in cognition, changes in cerebral oxygen saturation, cerebral hemodynamics, and markers for neuronal damage. The severity of POD will be evaluated based on the Memorial Delirium Assessment

Scale (MDAS) together with the evaluation of 3D-CAM [13]. Assessment of perioperative cognition is based on the Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) one day before and within 5 days after surgery [14]. The baseline of rSO2 will be calculated by averaging values within 2 minutes before anesthesia induction. Further, intraoperative rSO2 values will be continuously recorded at the following timepoint: T_0: before anesthesia induction; T_1: 60 minutes after turning over; T_2: 90 minutes after turning over; T_3: 2 hours after turning over; T_4: 5 min before operation ending; T_5: before leaving the resuscitation room. The vertebrobasilar artery and the middle cerebral artery hemodynamic parameters will be quantified by transcranial doppler ultrasound at $T_{1\text{-}5}$. Serum concentrations of calcium channel binding protein S100 subunit beta (S100B) and neuron-specific enolase (NSE) will be determined by ELISA kits. Blood samples will be collected before anesthesia induction (T0) and one day after surgery.

Data collection

The study schedule (Figure 2) presents data collections at indicated point points. The detailed date collections are shown as follows:

Preoperative assessments

We will conduct preoperative assessments by trained assessors one day before surgery. Preoperative evaluation factors include the following:

- General data: age, sex, education level, body mass index (BMI), ASA grades, and basal blood pressure.
- Major medical history of cardiovascular and cerebrovascular diseases, such as hypertension, diabetes, coronary heart disease, and stroke.
- Major laboratory results (eg, blood routine, coagulation tests, atherogenic index of plasma (AIP), serum concentration of S100B and NSE).
- Evaluation for cognitive function using MMSE, MoCA.
- Evaluation of pain using VAS.
- Evaluation of sleep using the Pittsburgh Sleep Quality Index (PSQI).

Anesthesia, surgery, and postoperative care

All participants will receive a standardized anesthetic protocol. Meanwhile, all

information of perioperative interventions, including prone duration, use of vasoactive medications and anticholinergics, and vital signs will be recorded in detail for post hoc analysis. In particular, intraoperative rSO2 values and the vertebrobasilar artery and the middle cerebral artery hemodynamic parameters will be recorded at indicated time points. Blood gas analysis will be performed per hour.

Postoperative assessments

- Participants will be evaluated twice daily within 5 days after surgery.
- Incidence and severity of delirium by 3D-CAM and MDAS, respectively.
- Serum concentration of S100B and NSE postoperative day 1.
- Blood pressure twice daily.
- Evaluation for cognitive function using MMSE, MoCA.
- Pain using VAS.
- Quality of sleep using PSQI.
- Complications and mortality.

STUDY PERIOD												
	Preoperative day 1	Surgery day						Postoperative days (twice daily)				
	Enrolment	T0	T1	T2	T3	T4	T5	1	2	3	4	5
ENROLMENT												
Eligibility screen	√											
Informed consent	√											
Randomizion	√											
INTERVENTIONS												
Group PL			←	—	—	→						
Group PC			←	—	—	→						
Group PR			←	—	—	→						
ASSESSMENTS												
Baseline data	√											
Major laboratory results	√											
Intraoperative data		√	√	√	√	√	√					
rSO2		√	√	√	√	√	√					
Cerebral hemodynamics parameters		√	√	√	√	√	√					
Blood gas analysis (per hour)		←	—	—	—	—	→					
3D-CAM									√	√	√	√
MDAS									√	√	√	√
S100B and NSE	√							√				
Blood pressure	√	√	√	√	√	√	√	√	√	√	√	√
MMSE, MoCA	√							√	√	√	√	√
VAS	√							√	√	√	√	√
PSQI	√							√	√	√	√	√
Adverse events								√	√	√	√	√
All-cause death								√	√	√	√	√

Figure 2

Data collection at each time point. T_0, before anesthesia induction; T_1, 60 minutes after turning over; T_2, 90 minutes after turning over; T_3, 2 hours after turning over; T_4, 5 min before operation ending; T_5, before leaving the resuscitation room; Group PC, prone with the head centered; Group PL, prone with the head left rotated ~45 degrees; Group PR, prone with the head right rotated ~45 degrees; rSO2, Regional cerebral Oxygen Saturation; 3D-CAM, 3 min Diagnostic interview for Confusion Assessment Method; MDAS, Memorial Delirium Assessment Scale; MMSE, Mini-mental State

Examination; MoCA, Montreal Cognitive Assessment; VAS, Visual Analogue Scale; PSQI, Pittsburgh Sleep Quality Index.

Sample size

In this study, we suppose that right deviation contributes to POD, compared with neutral and left deviation in a prone position. According to literatures, we assume the incidence of POD in group PR is 40.5%, while 13.0% in group PC and 14.5% in group PL [15-17]. With the significance set at 0.05 (two-sided) and the power set at 90%, the sample size per group requires 68 patients to detect the difference. Considering about 20% of the loss in follow-up, 255 (85 in each group) patients need to be enrolled.

In this study, a mid-term analysis is proposed to be conducted when the sample size reaches 50%, and the sample size will be corrected again based on the actual incidence of POD.

Data analysis

All statistical analyses will be conducted by SPSS V.20.0. Quantitative indicators will be listed as mean ± SD, median, maximum, and minimum. Frequency distribution tables will be listed in terms of qualitative or hierarchical indicators. Appropriate statistical analyses will be used for intra- or inter-group comparisons, depending on the conditions of application. The $\chi 2$ test or Fisher's exact test will be performed to determine differences between groups. $P < 0.05$ will be considered statistically significant. Further, subgroup analyses will be performed based on the following:

- Age (youngest-old (from 65 to 74 years), middle-old (from 75 to 84 years), and oldest-old (>85 years)).
- atherogenic index of plasma (AIP)

Strengths and limitations of this study

- This study will be the first prospective, randomized, and controlled clinical trial constructed to evaluate the effect of head direction during prone positioning on postoperative delirium in elderly patients underwent thoracolumbar spine surgery.
- The study will include the incidence and severity of postoperative delirium and assess multiple dimensions of pre- and post-operative cognition variation,

intraoperative cerebral hemodynamics, oxygenation, and neural damage levels.

- The study did not set grades of head direction angels.
- The single-center design of the study may limit the generalizability.

Trial status

We have not initiated this trial when submitting this manuscript. We will begin from 1/1/2024 to 31/12/2025.

Patient and public involvement

No patient is involved.

Ethics statements

Patient consent for publication:

Not applicable.

Author attributions

Bin Qian, Jixiang Zhu designed this study and reviewed the manuscript. Jixiang Zhu and Yangyang Chen drafted the manuscript. Yongzhuang Chen, Fengyun Liu, Xuetai Chen gave constructive suggestions. All authors have revised the manuscript and approved the final version.

Fundings

This work was supported by Yancheng Fundamental Research Program (YCBK202208) and The First Affiliated Hospital of Jiangsu Vocational College of Medicine Basic Research Program (QN2022001).

Conflicts of interest disclosure:

The authors declare that they have no conflict of interest.

References

1. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020;125(4):492-504. doi: 10.1016/j.bja.2020.06.063 [published Online First: 2020/08/17]
2. Zhang HJ, Ma XH, Ye JB, et al. Systematic review and meta-analysis of risk factor for postoperative delirium following spinal surgery. *Journal of Orthopaedic Surgery and Research* 2020;15:1-8.
3. Hamilton GM, Wheeler K, Di Michele J, et al. A Systematic Review and Meta-

analysis Examining the Impact of Incident Postoperative Delirium on Mortality. *Anesthesiology* 2017;127(1):78-88. doi: 10.1097/aln.0000000000001660 [published Online First: 2017/05/02]

4. Park EA, Kim MY. Postoperative Delirium is Associated with Negative Outcomes and Long-Term Mortality in Elderly Koreans: A Retrospective Observational Study. *Medicina (Kaunas)* 2019;55(10) doi: 10.3390/medicina55100618 [published Online First: 2019/09/25]
5. Haynes MS, Alder KD, Toombs C, et al. Predictors and Sequelae of Postoperative Delirium in a Geriatric Patient Population With Hip Fracture. *J Am Acad Orthop Surg Glob Res Rev* 2021;5(5) doi: 10.5435/JAAOSGlobal-D-20-00221 [published Online First: 2021/05/15]
6. Ruck JM, Chu NM, Liu Y, et al. Association of Postoperative Delirium With Incident Dementia and Graft Outcomes Among Kidney Transplant Recipients. *Transplantation* 2023 doi: 10.1097/tp.0000000000004779 [published Online First: 2023/08/29]
7. Arnold C, Bourassa R, Langer T, et al. Doppler studies evaluating the effect of a physical therapy screening protocol on vertebral artery blood flow. *Manual Therapy* 2004;9(1):13-21. doi: https://doi.org/10.1016/S1356-689X(03)00087-0
8. Haynes MJ. Doppler studies comparing the effects of cervical rotation and lateral flexion on vertebral artery blood flow. *J Manipulative Physiol Ther* 1996;19(6):378-84. [published Online First: 1996/07/01]
9. Yelverton C, Wood JJ, Petersen DL, et al. Changes in Vertebral Artery Blood Flow in Different Head Positions and Post-Cervical Manipulative Therapy. *J Manipulative Physiol Ther* 2020;43(2):144-51. doi: 10.1016/j.jmpt.2019.09.001 [published Online First: 2020/06/03]
10. Højlund J, Sandmand M, Sonne M, et al. Effect of head rotation on cerebral blood velocity in the prone position. *Anesthesiol Res Pract* 2012;2012:647258. doi: 10.1155/2012/647258 [published Online First: 2012/09/19]
11. Liu YY. Effect of different head positions on cerebral oxygen saturation during spinal surgery in elderly patients [Master]. Shanxi medical university, 2023.

12. Wang J, Lu S, Huang Y, et al. A nurse-administered 3-Minute diagnostic interview for CAM-defined Delirium (3D-CAM Chinese version) in hospitalized elderly patients: A validation study. *Int J Nurs Stud* 2020;110:103701. doi: 10.1016/j.ijnurstu.2020.103701 [published Online First: 2020/08/01]

13. Shi Z, Wu Y, Li C, et al. Using the Chinese version of Memorial Delirium Assessment Scale to describe postoperative delirium after hip surgery. *Front Aging Neurosci* 2014;6:297. doi: 10.3389/fnagi.2014.00297 [published Online First: 2014/11/22]

14. Jia X, Wang Z, Huang F, et al. A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry* 2021;21(1):485. doi: 10.1186/s12888-021-03495-6 [published Online First: 2021/10/06]

15. Brown IV CH, LaFlam A, Max L, et al. Delirium After Spine Surgery in Older Adults: Incidence, Risk Factors, and Outcomes. *Journal of the American Geriatrics Society* 2016;64(10):2101-08. doi: https://doi.org/10.1111/jgs.14434

16. Baek W, Kim YM, Lee H. Risk factors of postoperative delirium in older adult spine surgery patients: A meta-analysis. *AORN journal* 2020;112(6):650-61.

17. Pan Z, Huang K, Huang W, et al. The risk factors associated with delirium after lumbar spine surgery in elderly patients. *Quant Imaging Med Surg* 2019;9(4):700-10. doi: 10.21037/qims.2019.04.09 [published Online First: 2019/05/31]

BMJ Open

Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-083526.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Aug-2024
Complete List of Authors:	zhu, jixiang; Yancheng First Hospital Affiliated Hospital of Nanjing University Medical School, The Yancheng Clinical College of Xuzhou Medical University, The First people's Hospital of Yancheng; Xu Zhou Medical College, Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology Chen, Yongzhuang; Yancheng No 1 People's Hospital, The Yancheng Clinical College of Xuzhou Medical University, The First people's Hospital of Yancheng Chen, Yangyang; The Affiliated Hospital of Xuzhou Medical University, Department of Anesthesiology; Xuzhou Medical University, Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology Ma , hong ; The Fourth Affiliated Hospital of Nantong University, liu, fengyun; Xuzhou Medical University, chen, qian; Xuzhou Medical University, Wang, Fang; Yancheng First Hospital Affiliated Hospital of Nanjing University Medical School, The Yancheng Clinical College of Xuzhou Medical University Yancheng, The First people's Hospital of Yancheng chen, xuetai; Xuzhou Medical University, Xue, Zhouya; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng ni, kun; Medical School of Nanjing University, Department of Anesthesiology Li, Feng; Yancheng No 1 People's Hospital, The Yancheng Clinical College of Xuzhou Medical University Yancheng, The First people's Hospital of Yancheng Qian, Bin; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Nursing, Surgery

Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Posture, Thoracic surgery < SURGERY, Clinical Trial

Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a study protocol for a randomized controlled trial

Jixiang Zhu[1,2], Yongzhuang Chen[1], Yangyang Chen[2,4], Fengyun Liu[2], Hong Ma[1], Qian Chen[1], Fang Wang[1], Xuetai Chen[1,2], Zhouya Xue[1], Kun Ni[3], Feng Li[1,2], Bin Qian[1,2]

1. Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University; The First people's Hospital of Yancheng, Yancheng, 224006, China.
2. Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology, Xuzhou Medical University, Xuzhou, 221004, China.
3. Department of Anesthesiology, Drum Tower Hospital, Medical School of Nanjing University, 321 Zhongshan Road, Nanjing, 210008, China.
4. Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, 221001, China.

Jixiang Zhu, Yongzhuang Chen, and Yangyang Chen contributed equally to this work.

Correspondence to:

Bin Qian, Email: 985578655@qq.com, Tel: +8613951489138

Feng Li, Email: 1226637852@qq.com, Tel: +8618351552626

Kun Ni, Email: lemonk_njumc@hotmail.com, Tel: +8615850582823

Keywords: delirium & cognitive disorders; posture; thoracic surgery; clinical trial.

Words statistics: 3145

Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a study protocol for a randomized controlled trial

ABSTRACT

Introduction

Prone positioning with head rotation can influence cerebral hemodynamics, potentially affecting cerebral perfusion and oxygenation. Elderly patients with impaired brain perfusion and oxygenation are at an increased risk of developing postoperative delirium (POD). Despite this, few studies have explored whether head orientation during prone positioning contributes to POD in older adults, an aspect often overlooked by clinicians. This study aimed to evaluate the impact of head orientation during prone positioning on the incidence of POD in elderly patients undergoing thoracolumbar spine surgery.

Methods and analysis

This study is a single-center, randomized, single-blind trial, with the assessors blinded to the intraoperative head position. Eligible participants are patients aged ≥ 65 years undergoing elective thoracolumbar spine surgery. A total of 500 patients will be randomly assigned to either the prone position with the head centered, or the prone position with the head deviated. The primary outcome is the incidence of POD, measured using the 3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) until postoperative day 5. Secondary outcomes include the severity of POD assessed by the Memorial Delirium Assessment Scale (MDAS), postoperative cognitive impairment evaluated using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), intraoperative regional cerebral oxygen saturation (rSO_2), changes in vertebrobasilar artery and middle cerebral artery hemodynamics, and plasma levels of calcium channel-binding protein S100 subunit beta (S100B) and neuron-specific enolase (NSE).

Ethics and dissemination

Ethical approval was obtained from Yancheng No. 1 People's Hospital Ethics Examination Committee (2023-K-120). The findings will be disseminated through

presentations at annual conferences and publications in scientific journals.

Trial registration number: ChiCTR2300078839

Keywords: delirium & cognitive disorders; posture; thoracic surgery; clinical trial.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is the first randomized controlled trial to investigate the potential effects of head rotation on postoperative delirium and cognitive dysfunction in elderly patients undergoing thoracolumbar spine surgery.
- The study does not account for graded angles of head rotation.
- It does not differentiate between left and right head deviations.
- The single-center design may limit the generalizability of the findings.

INTRODUCTION

Postoperative delirium (POD) is an acute, fluctuating neuropsychiatric syndrome characterized by disturbances in attention, awareness, and cognition, typically manifesting within five days post-surgery. It is the most common postoperative complication in older adults[1]. Recent meta-analyses report that the incidence of POD in elderly patients undergoing spinal surgery ranges from 3.8% to 40.4%, often associated with adverse clinical outcomes[2].

Emerging evidence suggests that cerebral hypoperfusion, influenced by cerebral hemodynamics, plays a crucial role in the pathogenesis of POD. Significant reductions in regional cerebral blood flow have been observed in patients with delirium, affecting both cortical and subcortical regions, with improvements noted upon resolution of delirium[3]. Inadequate cerebral perfusion pressure has also been linked to a higher risk of POD following lung transplantation[4]. Additionally, intraoperative decreases in regional cerebral oxygen saturation (rSO_2) have been associated with POD during thoracotomy and endovascular procedures[5 6]. Furthermore, reduced mean flow velocity (MFV) in the middle cerebral artery has been correlated with cognitive impairment and delirium in non-surgical populations[7 8]. These findings highlight the importance of

monitoring perioperative factors that contribute to cerebral hypoperfusion.

In thoracolumbar spine surgeries, head positioning – whether neutral or with lateral deviation – is typically based on clinical considerations. However, studies suggest that head rotation may affect cerebral hemodynamics. For instance, contralateral cervical rotation in supine conscious volunteers has been shown to reduce vertebral artery flow in the extracranial segment[9] [10]. Similarly, intracranial vertebral artery blood flow velocities are significantly reduced with contralateral head rotation in prone, young volunteers[11]. Under general anesthesia in the prone position, head rotation of approximately 80° to the right has been observed to reduce MFV by ~10% in healthy young volunteers[12]. Despite these observations, the potential impact of head orientation in the prone position on POD, through its effect on cerebral hemodynamics and oxygenation, remains unclear. Based on existing literatures, we hypothesize that maintaining a neutral cervical spine position will result in a lower incidence of POD compared to a deviated position.

Epidemiological studies on POD have seldom considered the influence of head orientation during spinal surgery, and no research has specifically examined the effects of head orientation in the prone position on POD in older adults. Thus, the primary aim of this study is to assess the impact of head direction during prone positioning on the incidence of POD in elderly patients undergoing thoracolumbar spine surgery. Our secondary aim is to investigate the effects of head direction on cerebral hemodynamics and oxygenation during prone positioning.

METHODS AND ANALYSIS

Study design

This single-center, single-blind, randomized controlled trial aims to assess whether maintaining a neutral cervical spine position reduces the incidence of POD compared to a deviated position in older adults undergoing thoracolumbar spine surgeries. The trial design and follow-up process are detailed in Figure 1 and Table 1. The study will be conducted at the First People's Hospital of Yancheng, Yancheng, China. Assessors will undergo standardized training, and the protocol will adhere to the Standard

Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Online Supplementary Additional File 1).

Table 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Schedule for Enrollment, Interventions, and Assessments. Time points: T_0, before anesthesia induction; T_1, 60 min post-positioning; T_2, 90 min after post-positioning; T_3, 2 h post-positioning; T_4, 5 min before surgical completion; T_5, prior to discharge from the PACU.

STUDY PERIOD												
	One day before surgery	**Surgery day**						**Postoperative days**				
	Enrolment	T0	T1	T2	T3	T4	T5	1	2	3	4	5
ENROLLMENT												
Eligibility screen	√											
Informed consent	√											
Randomization	√											
INTERVENTIONS												
Group PD			√									
Group PC			√									
ASSESSMENTS												
Baseline data	√											
Major laboratory results	√											
rSO_2 measurement		√	√	√	√	√	√					
Cerebral hemodynamics parameters		√	√	√	√	√	√					
Blood gas analysis (per hour)		√										
3D-CAM (twice daily)								√	√	√	√	√
MDAS								√	√	√	√	√
S100B and NSE	√							√				

MAP measurement	√	√	√	√	√	√	√	√	√	√	√	√
MMSE, MoCA	√							√	√	√	√	√
VAS	√							√	√	√	√	√
PSQI	√							√	√	√	√	√
Blood loss (mL)						√						
Adverse events								√	√	√	√	√
All-cause death								√	√	√	√	√

Randomization and blinding

This trial design is single-blinded, with the attending anesthetist collecting intraoperative data and not blinded to group assignments. Patients will be randomized into either the neutral cervical spine position (PC) group or the deviated position (PD) group using a computer-generated randomization table. Group assignments will be concealed in opaque envelopes, which will be opened intraoperatively. The allocation ratio is 1:1, and assessors responsible for preoperative and postoperative evaluations will be blinded to the intraoperative head orientation.

Patients and recruitment

A total of 500 patients meeting the inclusion criteria will be enrolled from 20 December 2023 to 31 December 2025. Participants will receive written information about the study (see Online Supplementary Additional File 2), and written informed consent will be obtained the day prior to surgery.

Eligibility

Inclusion criteria

- Age ≥ 65 years.
- American Society of Anesthesiologists (ASA) physical status class II–III.
- Mini-Mental State Examination (MMSE) score > 23 points, assessed one day preoperatively.
- Expected duration of surgery > 2 h.

Exclusion criteria

- Cervical spine trauma.
- Restricted head positioning.
- Cervicogenic dizziness and vertigo.
- Central nervous system disorders with clinical manifestations.
- Communication impairments.
- Psychiatric disorders.

Discharge criteria

- Duration of surgery < 2 h.
- Severe adverse events, such as anaphylaxis or intraoperative blood loss > 800 ml.
- Protocol deviations requiring intervention.

Interventions

Vital signs, including electrocardiography (ECG), oxygen saturation, and invasive arterial blood pressure, will be recorded prior to anesthesia induction. Anesthesia will be induced with dexamethasone (10 mg), remimazolam tosylate (0.05–0.1 mg/kg), 1% propofol (1–1.5 mg/kg), fentanyl (0.1–0.15 μg/kg), and cis-atracurium (0.2 mg/kg). During the transition from supine to prone positioning, the head will be positioned according to the assigned group. Anesthesia maintenance will involve 1–1.5% sevoflurane inhalation and continuous intravenous remifentanil infusion (0.1 μg/kg/min) until the completion of the surgery. Fentanyl and cis-atracurium will be administered as needed. Postoperatively, patients will be transferred to the post-anesthesia care unit (PACU) for extubation and observation until fully awake. Tropisetron hydrochloride (10 mg) and flurbiprofen axetil (50 mg) will be administered intravenously 15 min before surgery. Postoperative analgesia for 48 h will include butorphanol tartrate injection (8–10 mg) and tropisetron hydrochloride (10 mg) via an analgesic pump.

Principles of intraoperative anesthesia management include:

- Bispectral index (BIS) value: 45–60

- End-tidal carbon dioxide ($P_{ET}CO_2$): 40–55 mmHg
- Body temperature: 36–37.5 ℃
- Hemodynamic stability assisted by vasoactive drugs (Mean arterial pressure [MAP] changes within 10% over 5 min)
- Pulse pressure variation (PPV) < 10%
- Acid-base and electrolyte homeostasis.

Outcome measures

Primary outcome measure

The primary outcome is the incidence of POD within 5 days post-surgery, assessed using the 3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM), conducted twice daily (08:00–10:00 and 18:00–20:00)[13].

Secondary outcome measures

Secondary outcomes include the severity of delirium, perioperative cognitive changes, cerebral oxygen saturation, cerebral hemodynamics, and markers of neuronal injury. The severity of POD will be assessed using the Memorial Delirium Assessment Scale (MDAS) together with the evaluation of 3D-CAM[14]. Cognitive function will be evaluated perioperatively using the MMSE and Montreal Cognitive Assessment (MoCA) one day preoperatively and daily for 5 days postoperatively[15]. Baseline rSO_2 will be calculated by averaging the values within 2 min before anesthesia induction (T0). Intraoperative rSO_2 values will be continuously recorded using a cerebral oximeter at the following time points: T_1 (60 min after turning over), T_2 (90 min after turning over), T_3 (2 h after turning over), T_4 (5 min before surgery ends), and T_5 (before leaving the PACU). Hemodynamic parameters of the vertebrobasilar and middle cerebral arteries will be quantified using transcranial Doppler ultrasound at T_1–T_5. Serum concentrations of S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) will be determined using enzyme-linked immunosorbent assay (ELISA) kits, with blood samples collected at T0 and one day postoperatively.

Data collection

Preoperative assessments

Preoperative assessments will be conducted by trained assessors one day before surgery and will include:

- General data: age, sex, education level, body mass index (BMI), ASA classification, and baseline blood pressure.
- Medical history: major cardiovascular and cerebrovascular diseases (hypertension, diabetes, coronary heart disease, stroke).
- Key laboratory results: complete blood count, coagulation profile, atherogenic index of plasma (AIP), and serum concentrations of S100B and NSE.
- Cognitive function: assessed using MMSE and MoCA.
- Pain assessment: evaluated using the Visual Analogue Scale (VAS).
- Sleep quality: assessed using the Pittsburgh Sleep Quality Index (PSQI).

Anesthesia, surgery, and postoperative care

Detailed records of all perioperative interventions, including the duration in the prone position, use of vasoactive medications and anticholinergics, and vital signs, will be maintained for post hoc analysis. Special attention will be given to the intraoperative rSO_2 values and hemodynamic parameters of the vertebrobasilar and middle cerebral arteries, recorded at specified time points. Blood gas analysis will be performed hourly.

Postoperative assessments

- Incidence and severity of delirium: assessed using 3D-CAM and MDAS.
- Serum concentrations of S100B and NSE: measured on postoperative day 1.
- Blood pressure: monitored twice daily.
- Cognitive function: evaluated using MMSE and MoCA.
- Pain levels: assessed using VAS.
- Sleep quality: evaluated using PSQI.
- Complications and mortality: recorded as part of the study follow-up.

Sample size

Sample size calculations were performed using PASS (version 15.0.5). Preliminary experiments involving 32 patients (8 in the PC group and 24 in the PD group) indicated that 1 in the PC group and 6 in the PD group were diagnosed with POD. To achieve a power of 90% with a two-sided significance level of 0.05, the required sample size was calculated to be 200 patients per group. To account for an anticipated 20% loss to follow-up, a total of 500 patients will be enrolled. A mid-term analysis will be conducted once 50% of the target sample size is reached, with adjustments made based on the observed incidence of POD.

Data analysis

Statistical analyses will be conducted using SPSS version 20.0. Data will be presented as mean ± standard deviation (SD) for normally distributed data and median (interquartile range) for non-normally distributed data. Comparisons will be made using independent-sample t-tests for normally distributed data and Mann–Whitney U-tests for non-normally distributed data. Categorical data will be expressed as numbers or percentages and analyzed using Fisher's exact test or chi-squared tests. Univariate repeated measures analysis of variance (ANOVA) will be used for intragroup comparisons, with post hoc tests and Bonferroni correction applied to control for Type I errors. A Mantel–Haenszel test, stratified by potential influencing factors such as age (youngest-old [65–74 years], middle-old [75–84 years], oldest-old [> 85 years]), AIP, gender (male and female), and head deviation (left or right), will be used to compare the risk of POD between groups. Statistical significance will be set at $P < 0.05$.

Data Monitoring

The Data Monitoring Committee (DMC) will consist of an independent researcher responsible for data collection and classification, as well as a statistician. The DMC will focus solely on data monitoring without involvement in other aspects of the study. The DMC will ensure data completeness and accuracy and assess the overall progress of the trial. Upon completion, the original data, final dataset, and outcomes will be

submitted to the Scientific Research Management Committee.

Safety evaluation

All adverse events (AEs) associated with head rotation will be closely monitored. AEs include hypotension, significant cardiac arrhythmias, pneumothorax, significant disability or incapacity, cerebrovascular accidents, and death. Researchers will conduct daily patient visits until discharge and meticulously record any AEs. Should an AE occur, the trial will be suspended immediately for investigation, and appropriate actions will be taken based on the findings.

DISCUSSION

POD is a common and serious complication in elderly patients, significantly affecting postoperative recovery. Patients with POD experience a 2–4 times higher perioperative mortality rate[16 17], a 2–3 times higher readmission rate[18], and a 4–5 times higher risk of developing dementia compared to those without POD[19]. Thus, understanding and preventing POD is crucial for improving patient outcomes and recovery.

Reduced cerebral perfusion has been linked to POD[4 20 21], with key markers for assessing cerebral perfusion, including MFV measured by transcranial Doppler and rSO_2[22]. Previous studies have reported that MFV and intracranial vertebral artery blood flow velocities decrease during head rotation in the prone position among young volunteers[11 12]. However, a prospective controlled study found no significant difference in rSO_2 between neutral head positions and rotations to the right or left[23]. This study did not focus on elderly patients, and the short duration of head positioning (< 30 min) may limit its applicability. Furthermore, rSO_2 measurements were obtained by adjusting pressure sensors during head positioning, which may have affected results. Our study addresses these limitations by using a Mayfield headrest in the prone position, which mitigates pressure build-up on the forehead during cervical rotation. Despite a reported 10% decrease in MFV and compromised jugular venous return during rotation[23], the impact on cerebral perfusion pressure and autoregulation remains unclear. Further research is needed to clarify whether head rotation affects cerebral perfusion

and oxygenation and subsequently influences the incidence of POD.

Atherosclerosis, prevalent among older adults, is often assessed using the AIP, with higher values indicating more severe atherosclerosis and a greater impact on blood flow[24]. Notably, both carotid and vertebral arteriosclerosis are manifestations of large-artery atherosclerosis. Research suggests that the left vertebral artery (LVA) is more susceptible to atherosclerosis than the right vertebral artery (RVA) due to higher blood flow velocity and pressure[25]. A prior study reported that in healthy adults, approximately 50% have a dominant LVA, 25% have a dominant RVA, and the remaining 25% have vertebral arteries of similar sizes[26]. Likewise, in a study of 1,414 stroke-free participants with a mean age of ≥ 45 years, plaques were found in both carotid arteries in 85% of cases, with a higher prevalence in the left carotid artery (67%) compared to the right (33%)[27]. These findings highlight the notable asymmetry between the left and right vessels. Our preliminary experiments did not show a significant effect of head lateralization on POD. Future analyses will stratify data based on AIP and head deviation to explore these factors further. Additionally, sex differences in vertebral artery blood flow during head rotation have been reported[11], with mild reductions in males but not females during ipsilateral rotation[11]. These sex differences will also be considered in our stratified analyses.

This study has two main limitations. First, all participants are recruited from a single center, which may limit the generalizability of the findings. Second, the study does not include graded angles for head direction, which would have complicated the experimental design.

Despite these limitations, we anticipate that this trial will provide valuable insights into whether maintaining a neutral cervical spine position reduces the incidence of POD compared to a deviated position.

Trial status

To date, 32 participants have been enrolled in the study; however, participant recruitment is still ongoing at the time of submission. This trial is scheduled to be conducted from 20 December 2023 to 31 December 2025.

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing.

Patient and public involvement statement

Patients and/or the public were not involved

Ethics and dissemination

Ethical approval was obtained from Yancheng No. 1 People's Hospital Ethics Examination Committee (2023-K-120). The findings will be disseminated through presentations at annual conferences and publications in scientific journals.

Ethics statements

Patient consent for publication:

Not applicable.

Authors' contributions

Bin Qian took responsibility for the integrity of the work as a whole and served as the primary investigator. Jixiang Zhu, Yongzhuang Chen, Yangyang Chen, Kun Ni, Feng Li, and Bin Qian were involved in the study's design. Jixiang Zhu, Kun Ni, Feng Li, and Bin Qian drafted the manuscript. Yangyang Chen, Fengyun Liu, and Hong Ma contributed to the calculation of the sample size and provided statistical consultation. Qian Chen, Fang Wang, Xuetai Chen, and Zhouya Xue developed the case report forms and conducted a preliminary trial. Jixiang Zhu, Yongzhuang Chen, Hong Ma, Qian Chen, Fang Wang, Zhouya Xue, Kun Ni, Feng Li, and Bin Qian were responsible for conducting the clinical trials. All authors contributed to revising the manuscript for important intellectual content. Jixiang Zhu, Yongzhuang Chen, and Yangyang Chen contributed equally to this study and are joint first authors. Bin Qian acted as guarantor.

Funding statement

This work was supported by Yancheng Fundamental Research Program (YCBK202208) and The First Affiliated Hospital of Jiangsu Vocational College of Medicine Basic Research Program (QN2022001).

Conflicts of interest disclosure:

The authors declare that they have no conflict of interest.

References

1. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020;125(4):492-504. doi: 10.1016/j.bja.2020.06.063 [published Online First: 2020/08/17]
2. Zhang HJ, Ma XH, Ye JB, et al. Systematic review and meta-analysis of risk factor for postoperative delirium following spinal surgery. *Journal of Orthopaedic Surgery and Research* 2020;15:1-8.
3. Yokota H, Ogawa S, Kurokawa A, et al. Regional cerebral blood flow in delirium patients. *Psychiatry and clinical neurosciences* 2003;57(3):337-39.
4. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced Cerebral Perfusion Pressure during Lung Transplant Surgery Is Associated with Risk, Duration, and Severity of Postoperative Delirium. *Ann Am Thorac Soc* 2016;13(2):180-7. doi: 10.1513/AnnalsATS.201507-454OC
5. Cui F, Zhao W, Mu DL, et al. Association Between Cerebral Desaturation and Postoperative Delirium in Thoracotomy With One-Lung Ventilation: A Prospective Cohort Study. *Anesth Analg* 2021;133(1):176-86. doi: 10.1213/ane.0000000000005489
6. Wang X, Feng K, Liu H, et al. Regional cerebral oxygen saturation and postoperative delirium in endovascular surgery: a prospective cohort study. *Trials* 2019;20(1):504. doi: 10.1186/s13063-019-3586-y [published Online First: 20190814]
7. Sabayan B, Jansen S, Oleksik AM, et al. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies. *Ageing Res Rev* 2012;11(2):271-7. doi: 10.1016/j.arr.2011.12.009 [published Online First: 20111227]
8. Caplan GA, Lan Z, Newton L, et al. Transcranial Doppler to measure cerebral blood flow in delirium superimposed on dementia. A cohort study. *Journal of the American Medical Directors Association* 2014;15(5):355-60.
9. Arnold C, Bourassa R, Langer T, et al. Doppler studies evaluating the effect of a physical therapy screening protocol on vertebral artery blood flow. *Manual Therapy* 2004;9(1):13-21. doi: https://doi.org/10.1016/S1356-689X(03)00087-0
10. Haynes MJ. Doppler studies comparing the effects of cervical rotation and lateral

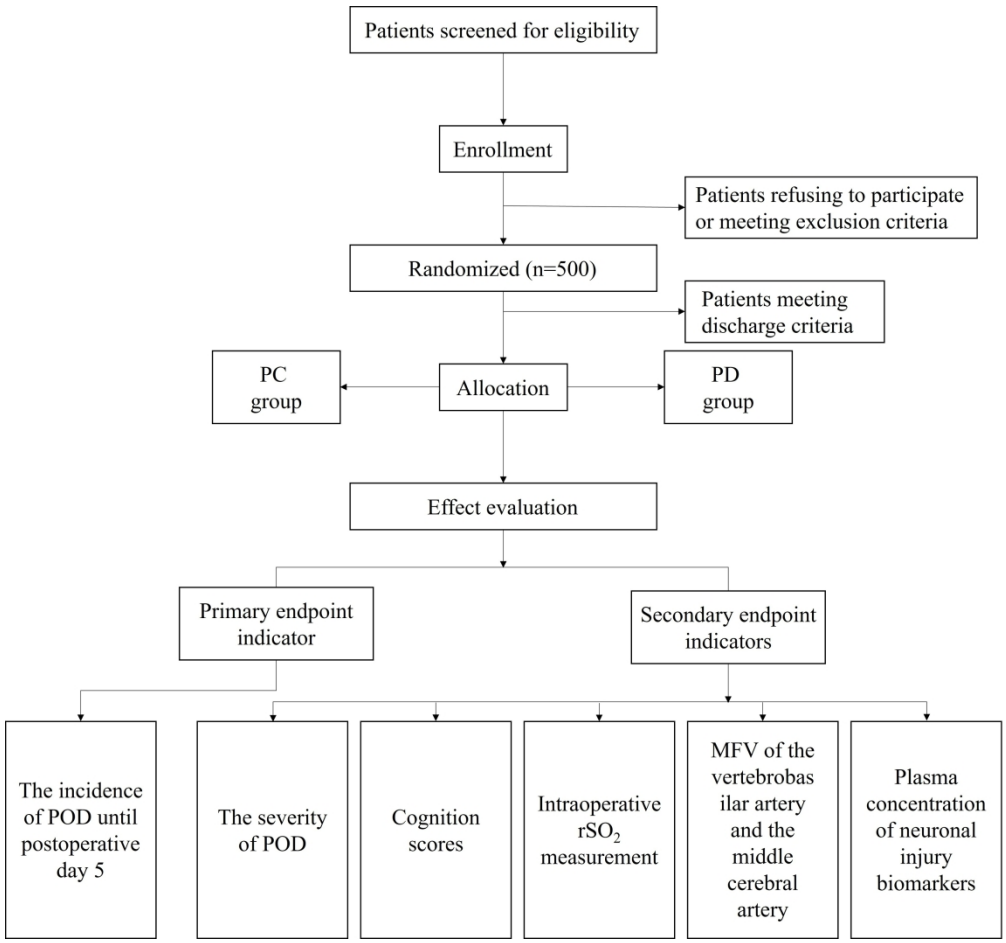
flexion on vertebral artery blood flow. *J Manipulative Physiol Ther* 1996;19(6):378-84. [published Online First: 1996/07/01]

11. Mitchell JA. Changes in vertebral artery blood flow following normal rotation of the cervical spine. *Journal of Manipulative and Physiological Therapeutics* 2003;26(6):347-51. doi: 10.1016/s0161-4754(03)00074-5
12. Højlund J, Sandmand M, Sonne M, et al. Effect of head rotation on cerebral blood velocity in the prone position. *Anesthesiol Res Pract* 2012;2012:647258. doi: 10.1155/2012/647258 [published Online First: 2012/09/19]
13. Wang J, Lu S, Huang Y, et al. A nurse-administered 3-Minute diagnostic interview for CAM-defined Delirium (3D-CAM Chinese version) in hospitalized elderly patients: A validation study. *Int J Nurs Stud* 2020;110:103701. doi: 10.1016/j.ijnurstu.2020.103701 [published Online First: 2020/08/01]
14. Shi Z, Wu Y, Li C, et al. Using the Chinese version of Memorial Delirium Assessment Scale to describe postoperative delirium after hip surgery. *Front Aging Neurosci* 2014;6:297. doi: 10.3389/fnagi.2014.00297 [published Online First: 2014/11/22]
15. Jia X, Wang Z, Huang F, et al. A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry* 2021;21(1):485. doi: 10.1186/s12888-021-03495-6 [published Online First: 2021/10/06]
16. Hamilton GM, Wheeler K, Di Michele J, et al. A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality. *Anesthesiology* 2017;127(1):78-88. doi: 10.1097/aln.0000000000001660 [published Online First: 2017/05/02]
17. Park EA, Kim MY. Postoperative Delirium is Associated with Negative Outcomes and Long-Term Mortality in Elderly Koreans: A Retrospective Observational Study. *Medicina (Kaunas)* 2019;55(10) doi: 10.3390/medicina55100618 [published Online First: 2019/09/25]
18. Haynes MS, Alder KD, Toombs C, et al. Predictors and Sequelae of Postoperative Delirium in a Geriatric Patient Population With Hip Fracture. *J Am Acad Orthop Surg Glob Res Rev* 2021;5(5) doi: 10.5435/JAAOSGlobal-D-20-00221 [published Online First: 2021/05/15]
19. Ruck JM, Chu NM, Liu Y, et al. Association of Postoperative Delirium With Incident Dementia and Graft Outcomes Among Kidney Transplant Recipients. *Transplantation* 2023 doi: 10.1097/tp.0000000000004779 [published Online First: 2023/08/29]
20. Anderson BJ, Diamond JM. Under Pressure: Reduced Cerebral Perfusion as a Risk Factor for Postoperative Delirium in Lung Transplant Recipients. *Ann Am Thorac Soc* 2016;13(2):156-7. doi: 10.1513/AnnalsATS.201512-796ED
21. Ma H, Ahrens E, Wachtendorf LJ, et al. Intraoperative Use of Phenylephrine versus Ephedrine and Postoperative Delirium: A Multicenter Retrospective Cohort Study. *Anesthesiology* 2024;140(4):657-67. doi: 10.1097/aln.0000000000004774

22. Soh S, Shim JK, Song JW, et al. Preoperative transcranial Doppler and cerebral oximetry as predictors of delirium following valvular heart surgery: a case-control study. *J Clin Monit Comput* 2020;34(4):715-23. doi: 10.1007/s10877-019-00385-x [published Online First: 20190903]
23. Andersen JD, Baake G, Wiis JT, et al. Effect of head rotation during surgery in the prone position on regional cerebral oxygen saturation: A prospective controlled study. *Eur J Anaesthesiol* 2014;31(2):98-103. doi: 10.1097/eja.0000000000000028
24. Huang Q, Liu Z, Wei M, et al. The atherogenic index of plasma and carotid atherosclerosis in a community population: a population-based cohort study in China. *Cardiovasc Diabetol* 2023;22(1):125. doi: 10.1186/s12933-023-01839-y [published Online First: 20230527]
25. Cagnie B, Barbaix E, Vinck E, et al. Atherosclerosis in the vertebral artery: an intrinsic risk factor in the use of spinal manipulation? *Surg Radiol Anat* 2006;28(2):129-34. doi: 10.1007/s00276-005-0060-1 [published Online First: 20060324]
26. Cloud G, Markus H. Diagnosis and management of vertebral artery stenosis. *Qjm* 2003;96(1):27-54.
27. Selwaness M, van den Bouwhuijsen Q, van Onkelen RS, et al. Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke* 2014;45(11):3226-30. doi: 10.1161/STROKEAHA.114.005202

Figure legend:

Study flow chart. PC: prone with the head centered; PD: prone with the head deviated; POD: postoperative delirium; MFV: mean flow velocity; rSO_2: regional cerebral oxygen saturation.



Study flow chart. PC: prone with the head centered; PD: prone with the head deviated; POD: postoperative delirium; MFV: mean flow velocity; rSO2: regional cerebral oxygen saturation.

319x297mm (300 x 300 DPI)

Informed Consent Form
(The original informed consent form is presented in Chinese. The English highlighted in red in the text is only used for peer review during the protocol publication process)

知情同意书

尊敬的先生/女士：

Project Title

我们邀请您参加盐城市基础研究计划批准开展的“胸腰椎手术术中俯卧位头偏侧对老年患者术后谵妄影响的前瞻性研究”课题研究。本研究由盐城市第一人民医院麻醉科主任医师钱斌负责，将在盐城市第一人民医院开展，估计将有 500 名研究参与者自愿参加。本研究已经得到盐城市第一人民医院医学伦理审查委员会的审查和批准，伦理审查编号：2023-K-120 。

Objectives and Descriptions

为什么要开展本项研究？

术后谵妄（postoperative delirium, POD）是最常见的老年患者术后并发症。据统计，65 岁以上老年患者 POD 的总体发生率约为 12%。POD 的患者与周围环境接触障碍，认识自己的能力减退，思维、记忆、理解与判断力均减退，言语不连贯并错乱，定向力减退，胡言乱语，兴奋烦躁，有明显的幻觉、错觉和妄想。POD 的发生常导致住院时间延长、医疗支出增加、痴呆发生率增加等，是临床热点问题。

脊柱外科老年患者 POD 发生率可高达 40.5% ，是易于发生 POD 的手术类型。目前，我省各医疗单位胸腰椎手术俯卧位头位摆放朝向正侧不一。有限的研究提示，俯卧位头位偏侧可能影响术中脑血流动力学和脑氧合。但是大脑有强大的代偿机制，同时有些患者合并有不同程度的动脉粥样硬化，全麻术中俯卧位头位偏侧是否能够影响术中脑灌注和脑氧合，是否足以影响 POD 的发生尚未有研究。本研究拟通过前瞻性随机对照研究探索老年胸腰椎手术人群中俯卧位头偏侧对 POD 发生率的影响及老年胸腰椎手术俯卧位头偏侧对术中脑灌注、脑氧合的影响，为临床决策提供循证参考。

哪些人适（不）宜参加研究？

1. 入选标准：

① 年龄≥65 岁；② ASA II-III 级；③ 术前 1 天 MMSE 评分>23 分； ④ 预计手术时长超过 2h

2. 排除标准：

① 存在颈椎新发或陈旧性外伤者；② 存在限制性体位者；③ 存在颈性眩晕者；④ 具有症状性中枢神经系统并发症；⑤ 沟通障碍者；⑥ 精神病史

Procedures

如果参加研究，需要做什么？

如果您愿意参加本项研究，您将 1/2 的可能性接受以下 2 种治疗方案，包括俯卧位头偏向一侧、俯卧位头正位。我们会在您接受治疗的 1 周内定期对您进行认知功能评估及采集脑灌注、脑氧合相关数据，分别在术前 1 天、术中、术后 1-5 天。

Benefits

参加研究有哪些好处？

参加此项研究有可能使您的疾病得到及时诊断、治疗，但是无法作出保证。参加本研究对您没有直接获益。您参与此项研究中获得的信息可能对于以后病人接受相关治疗有指导意义。

Potential Risks

参加研究有哪些风险？

本研究为前瞻性随机对照研究。脊柱外科胸腰椎手术头位偏侧目前无指南共识参考，是否影响术后谵妄的发生和严重程度尚无定论。本研究中，除俯卧位头位偏侧作为研究变量外，其他麻醉及手术治疗和术后护理均采用标准化治疗。在研究期间，如果出现任何不适和不良反应，请及时与研究医生联系。此外，任何治疗都可能出现无效的情况，以及因治疗无效或者因合并其他疾病等原因而导致病情继续发展。

Compensation

参加研究需要支付有关费用吗？（具体说明补偿计划和金额）

为了补偿您参加本研究可能给您带来的不便，本研究将支付您参加本项研究期间所做的脑氧饱和度监测、经颅超声检查费用。一次性的脑氧饱和度监测探头费用不在免费范围之内。如果您同时合并其他疾病所需的治疗和检查，以及因治疗无效而改用其他治疗的费用，将不在免费的范围之内。本研究系住院期间

研究，没有交通费，误工费、营养费等补偿。如果出现试验相关的损害，将依据国家有关规定提供相应的治疗与补偿。

Confidentiality 个人信息是保密的吗？

您的医疗记录将保存在医院，研究者、研究主管部门、伦理审查委员会将被允许查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私。

如果不参与本研究还有哪些治疗方法？

您可以选择不参加本项研究，这对您获得常规治疗不会带来任何不良影响。

Voluntary Participation 我必须参加研究吗？

参加本项研究是完全自愿的，您可以拒绝参加研究，或在研究过程中的任何时间退出本研究，这都不会影响医生对您的治疗。如果您决定退出本研究，请与您的医生联系，您可能被要求进行相关检查，这对保护您的健康是有利的。

如您有涉及个人权益方面的问题可与本院伦理审查委员会联系，联系电话：0515-66696823。

研究参与者声明：我已经阅读了上述有关本研究的介绍，对参加本研究可能产生的风险和受益充分了解。我自愿参加本研究。我将获得一份签署姓名和日期的本知情同意书副本。

Signatures **我同意☐ 或拒绝☐** 其他研究利用我的与本研究相关的医疗记录和临床标本。

研究参与者签名：_____ 日期：__ __ __ __ 年 __ 月 __ 日

研究参与者的联系电话：_____ 手机号：_____

（适用时）法定监护人/见证人签名：_____ 日期：__ __ __ __ 年 __ 月 __ 日

法定监护人/见证人联系电话：_____ 手机号：_____

研究者声明：我确认已向研究参与者解释了本研究的详细情况，特别是参加本研究可能产生的风险和受益，并回答了研究参与者的所有有关问题，研究参与者是出于自愿同意参加本研究。此知情同意书一式两份，研究者与研究参与者各留一份已签字的知情同意书。

研究医生签名：_____ 日期：__ __ __ __ 年 __ 月 __ 日

研究医生的工作电话：_____ 手机号：_____

BMJ Open

Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-083526.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Nov-2024
Complete List of Authors:	zhu, jixiang; Yancheng First Hospital Affiliated Hospital of Nanjing University Medical School, The Yancheng Clinical College of Xuzhou Medical University, The First people's Hospital of Yancheng; Xu Zhou Medical College, Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology Chen, Yongzhuang; Yancheng No 1 People's Hospital, The Yancheng Clinical College of Xuzhou Medical University, The First people's Hospital of Yancheng Chen, Yangyang; The Affiliated Hospital of Xuzhou Medical University, Department of Anesthesiology; Xuzhou Medical University, Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology Ma , hong ; The Fourth Affiliated Hospital of Nantong University, liu, fengyun; Xuzhou Medical University, chen, qian; Xuzhou Medical University, Wang, Fang; Yancheng First Hospital Affiliated Hospital of Nanjing University Medical School, The Yancheng Clinical College of Xuzhou Medical University Yancheng, The First people's Hospital of Yancheng chen, xuetai; Xuzhou Medical University, Xue, Zhouya; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng ni, kun; Medical School of Nanjing University, Department of Anesthesiology Li, Feng; Yancheng No 1 People's Hospital, The Yancheng Clinical College of Xuzhou Medical University Yancheng, The First people's Hospital of Yancheng Qian, Bin; Yancheng No 1 People's Hospital, Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University Yancheng
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine, Nursing, Surgery

Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Posture, Thoracic surgery < SURGERY, Clinical Trial

Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a study protocol for a randomized controlled trial

Jixiang Zhu[1,2], Yongzhuang Chen[1], Yangyang Chen[2,4], Fengyun Liu[2], Hong Ma[1], Qian Chen[1], Fang Wang[1], Xuetai Chen[1,2], Zhouya Xue[1], Kun Ni[3], Feng Li[1,2], Bin Qian[1,2]

1. Department of Anesthesiology, The Yancheng Clinical College of Xuzhou Medical University; The First people's Hospital of Yancheng, Yancheng, 224006, China.
2. Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology, Xuzhou Medical University, Xuzhou, 221004, China.
3. Department of Anesthesiology, Drum Tower Hospital, Medical School of Nanjing University, 321 Zhongshan Road, Nanjing, 210008, China.
4. Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, 221001, China.

Jixiang Zhu, Yongzhuang Chen, and Yangyang Chen contributed equally to this work.

Correspondence to:

Bin Qian, Email: 985578655@qq.com, Tel: +8613951489138

Feng Li, Email: 1226637852@qq.com, Tel: +8618351552626

Kun Ni, Email: lemonk_njumc@hotmail.com, Tel: +8615850582823

Keywords: delirium & cognitive disorders; posture; thoracic surgery; clinical trial.

Words statistics: 3147

Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a study protocol for a randomized controlled trial

ABSTRACT

Introduction

Prone positioning with head rotation can influence cerebral hemodynamics, potentially affecting cerebral perfusion and oxygenation. Elderly patients with impaired brain perfusion and oxygenation are at an increased risk of developing postoperative delirium (POD). Despite this, few studies have explored whether head orientation during prone positioning contributes to POD in older adults, an aspect often overlooked by clinicians. This study aimed to evaluate the impact of head orientation during prone positioning on the incidence of POD in elderly patients undergoing thoracolumbar spine surgery.

Methods and analysis

This study is a single-center, randomized, single-blind trial, with the assessors blinded to the intraoperative head position. Eligible participants are patients aged ≥ 65 years undergoing elective thoracolumbar spine surgery. A total of 500 patients will be randomly assigned to either the prone position with the head centered, or the prone position with the head deviated. The primary outcome is the incidence of POD, measured using the 3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) until postoperative day 5. Secondary outcomes include the severity of POD assessed by the Memorial Delirium Assessment Scale (MDAS), postoperative cognitive impairment evaluated using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), intraoperative regional cerebral oxygen saturation (rSO_2), changes in vertebrobasilar artery and middle cerebral artery hemodynamics, and plasma levels of calcium channel-binding protein S100 subunit beta (S100B) and neuron-specific enolase (NSE).

Ethics and dissemination

Ethical approval was obtained from Yancheng No. 1 People's Hospital Ethics Examination Committee (2023-K-120-01). The findings will be disseminated through

presentations at annual conferences and publications in scientific journals.

Trial registration number: ChiCTR2300078839

Keywords: delirium & cognitive disorders; posture; thoracic surgery; clinical trial.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is the first randomized controlled trial to investigate the potential effects of head rotation on postoperative delirium and cognitive dysfunction in elderly patients undergoing thoracolumbar spine surgery.
- The study does not account for graded angles of head rotation.
- It does not differentiate between left and right head deviations.
- The single-center design may limit the generalizability of the findings.

INTRODUCTION

Postoperative delirium (POD) is an acute, fluctuating neuropsychiatric syndrome characterized by disturbances in attention, awareness, and cognition, typically manifesting within five days post-surgery. It is the most common postoperative complication in older adults[1]. Recent meta-analyses report that the incidence of POD in elderly patients undergoing spinal surgery ranges from 3.8% to 40.4%, often associated with adverse clinical outcomes[2].

Emerging evidence suggests that cerebral hypoperfusion, influenced by cerebral hemodynamics, plays a crucial role in the pathogenesis of POD. Significant reductions in regional cerebral blood flow have been observed in patients with delirium, affecting both cortical and subcortical regions, with improvements noted upon resolution of delirium[3]. Inadequate cerebral perfusion pressure has also been linked to a higher risk of POD following lung transplantation[4]. Additionally, intraoperative decreases in regional cerebral oxygen saturation (rSO_2) have been associated with POD during thoracotomy and endovascular procedures[5 6]. Furthermore, reduced mean flow velocity (MFV) in the middle cerebral artery has been correlated with cognitive impairment and delirium in non-surgical populations[7 8]. These findings highlight the importance of

monitoring perioperative factors that contribute to cerebral hypoperfusion.

In thoracolumbar spine surgeries, head positioning – whether neutral or with lateral deviation – is typically based on clinical considerations. However, studies suggest that head rotation may affect cerebral hemodynamics. For instance, contralateral cervical rotation in supine conscious volunteers has been shown to reduce vertebral artery flow in the extracranial segment[9] [10]. Similarly, intracranial vertebral artery blood flow velocities are significantly reduced with contralateral head rotation in prone, young volunteers[11]. Under general anesthesia in the prone position, head rotation of approximately 80° to the right has been observed to reduce MFV by ~10% in healthy young volunteers[12]. Despite these observations, the potential impact of head orientation in the prone position on POD, through its effect on cerebral hemodynamics and oxygenation, remains unclear. Based on existing literatures, we hypothesize that maintaining a neutral cervical spine position will result in a lower incidence of POD compared to a deviated position.

Epidemiological studies on POD have seldom considered the influence of head orientation during spinal surgery, and no research has specifically examined the effects of head orientation in the prone position on POD in older adults. Thus, the primary aim of this study is to assess the impact of head direction during prone positioning on the incidence of POD in elderly patients undergoing thoracolumbar spine surgery. Our secondary aim is to investigate the effects of head direction on cerebral hemodynamics and oxygenation during prone positioning.

METHODS AND ANALYSIS

Study design

This single-center, single-blind, randomized controlled trial aims to assess whether maintaining a neutral cervical spine position reduces the incidence of POD compared to a deviated position in older adults undergoing thoracolumbar spine surgeries. The trial design and follow-up process are detailed in Figure 1 and Table 1. The study will be conducted at the First People's Hospital of Yancheng, Yancheng, China. Assessors will undergo standardized training, and the protocol will adhere to the Standard

Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Online Supplementary Additional File 1).

Table 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Schedule for Enrollment, Interventions, and Assessments. Time points: T_0, before anesthesia induction; T_1, 60 min post-positioning; T_2, 90 min after post-positioning; T_3, 2 h post-positioning; T_4, 5 min before surgical completion; T_5, prior to discharge from the PACU.

STUDY PERIOD												
	One day before surgery	**Surgery day**						**Postoperative days**				
	Enrolment	T0	T1	T2	T3	T4	T5	1	2	3	4	5
ENROLLMENT												
Eligibility screen	√											
Informed consent	√											
Randomization	√											
INTERVENTIONS												
Group PD			√									
Group PC			√									
ASSESSMENTS												
Baseline data	√											
Major laboratory results	√											
rSO_2 measurement		√	√	√	√	√	√					
Cerebral hemodynamics parameters		√	√	√	√	√	√					
Blood gas analysis (per hour)		√										
3D-CAM (twice daily)								√	√	√	√	√
MDAS								√	√	√	√	√
S100B and NSE	√							√				

MAP measurement	√	√	√	√	√	√	√	√	√	√	√	√
MMSE, MoCA	√							√	√	√	√	√
VAS	√							√	√	√	√	√
PSQI	√							√	√	√	√	√
Blood loss (mL)						√						
Adverse events								√	√	√	√	√
All-cause death								√	√	√	√	√

Randomization and blinding

This trial design is single-blinded, with the attending anesthetist collecting intraoperative data and not blinded to group assignments. Patients will be randomized into either the neutral cervical spine position (PC) group or the deviated position (PD) group using a computer-generated randomization table. Group assignments will be concealed in opaque envelopes, which will be opened intraoperatively. The allocation ratio is 1:1, and assessors responsible for preoperative and postoperative evaluations will be blinded to the intraoperative head orientation.

Patients and recruitment

A total of 500 patients meeting the inclusion criteria will be enrolled from 20 December 2023 to 31 December 2025. Participants will receive written information about the study (see Online Supplementary Additional File 2), and written informed consent will be obtained the day prior to surgery.

Eligibility

Inclusion criteria

- Age ≥ 65 years.
- American Society of Anesthesiologists (ASA) physical status class II–III.
- Mini-Mental State Examination (MMSE) score > 23 points, assessed one day preoperatively.
- Expected duration of surgery > 2 h.

Exclusion criteria

- Cervical spine trauma.
- Restricted head positioning.
- Cervicogenic dizziness and vertigo.
- Central nervous system disorders with clinical manifestations.
- Communication impairments.
- Psychiatric disorders.

Discharge criteria

- Duration of surgery < 2 h.
- Severe adverse events, such as anaphylaxis or intraoperative blood loss > 800 ml.
- Protocol deviations requiring intervention.

Interventions

Vital signs, including electrocardiography (ECG), oxygen saturation, and invasive arterial blood pressure, will be recorded prior to anesthesia induction. Anesthesia will be induced with dexamethasone (10 mg), remimazolam tosylate (0.05–0.1 mg/kg), 1% propofol (1–1.5 mg/kg), fentanyl (0.1–0.15 μg/kg), and cis-atracurium (0.2 mg/kg). During the transition from supine to prone positioning, the head will be positioned according to the assigned group. Anesthesia maintenance will involve 1–1.5% sevoflurane inhalation and continuous intravenous remifentanil infusion (0.1 μg/kg/min) until the completion of the surgery. Fentanyl and cis-atracurium will be administered as needed. Postoperatively, patients will be transferred to the post-anesthesia care unit (PACU) for extubation and observation until fully awake. Tropisetron hydrochloride (10 mg) and flurbiprofen axetil (50 mg) will be administered intravenously 15 min before surgery. Postoperative analgesia for 48 h will include butorphanol tartrate injection (8–10 mg) and tropisetron hydrochloride (10 mg) via an analgesic pump.

Principles of intraoperative anesthesia management include:

- Bispectral index (BIS) value: 45–60

- End-tidal carbon dioxide ($P_{ET}CO_2$): 40–55 mmHg
- Body temperature: 36–37.5 ℃
- Hemodynamic stability assisted by vasoactive drugs (Mean arterial pressure [MAP] changes within 10% over 5 min)
- Pulse pressure variation (PPV) < 10%
- Acid-base and electrolyte homeostasis.

Outcome measures

Primary outcome measure

The primary outcome is the incidence of POD within 5 days post-surgery, assessed using the 3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM), conducted twice daily (08:00–10:00 and 18:00–20:00)[13].

Secondary outcome measures

Secondary outcomes include the severity of delirium, perioperative cognitive changes, cerebral oxygen saturation, cerebral hemodynamics, and markers of neuronal injury. The severity of POD will be assessed using the Memorial Delirium Assessment Scale (MDAS) together with the evaluation of 3D-CAM[14]. Cognitive function will be evaluated perioperatively using the MMSE and Montreal Cognitive Assessment (MoCA) one day preoperatively and daily for 5 days postoperatively[15]. Baseline rSO_2 will be calculated by averaging the values within 2 min before anesthesia induction (T0). Intraoperative rSO_2 values will be continuously recorded using a cerebral oximeter at the following time points: T_1 (60 min after turning over), T_2 (90 min after turning over), T_3 (2 h after turning over), T_4 (5 min before surgery ends), and T_5 (before leaving the PACU). Hemodynamic parameters of the vertebrobasilar and middle cerebral arteries will be quantified using transcranial Doppler ultrasound at T_1–T_5. Serum concentrations of S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) will be determined using enzyme-linked immunosorbent assay (ELISA) kits, with blood samples collected at T0 and one day postoperatively.

Data collection

Preoperative assessments

Preoperative assessments will be conducted by trained assessors one day before surgery and will include:

- General data: age, sex, education level, body mass index (BMI), ASA classification, and baseline blood pressure.
- Medical history: major cardiovascular and cerebrovascular diseases (hypertension, diabetes, coronary heart disease, stroke).
- Key laboratory results: complete blood count, coagulation profile, atherogenic index of plasma (AIP), and serum concentrations of S100B and NSE.
- Cognitive function: assessed using MMSE and MoCA.
- Pain assessment: evaluated using the Visual Analogue Scale (VAS).
- Sleep quality: assessed using the Pittsburgh Sleep Quality Index (PSQI).

Anesthesia, surgery, and postoperative care

Detailed records of all perioperative interventions, including the duration in the prone position, use of vasoactive medications and anticholinergics, and vital signs, will be maintained for post hoc analysis. Special attention will be given to the intraoperative rSO_2 values and hemodynamic parameters of the vertebrobasilar and middle cerebral arteries, recorded at specified time points. Blood gas analysis will be performed hourly.

Postoperative assessments

- Incidence and severity of delirium: assessed using 3D-CAM (incidence) and MDAS (severity).
- Serum concentrations of S100B and NSE: measured on postoperative day 1.
- Blood pressure: monitored twice daily.
- Cognitive function: evaluated using MMSE and MoCA.
- Pain levels: assessed using VAS.
- Sleep quality: evaluated using PSQI.
- Complications and mortality: recorded as part of the study follow-up.

Sample size

Sample size calculations were performed using PASS (version 15.0.5). Preliminary experiments involving 32 patients (8 in the PC group and 24 in the PD group) indicated that 1 in the PC group and 6 in the PD group were diagnosed with POD. To achieve a power of 90% with a two-sided significance level of 0.05, the required sample size was calculated to be 200 patients per group. To account for an anticipated 20% loss to follow-up, a total of 500 patients were required. A mid-term analysis will be conducted once 50% of the target sample size is reached, with adjustments made based on the observed incidence of POD.

Data analysis

Statistical analyses will be conducted using SPSS version 20.0. Data will be presented as mean ± standard deviation (SD) for normally distributed data and median (interquartile range) for non-normally distributed data. Comparisons will be made using independent-sample t-tests for normally distributed data and Mann–Whitney U-tests for non-normally distributed data. Categorical data will be expressed as numbers or percentages and analyzed using Fisher's exact test or chi-squared tests. Univariate repeated measures analysis of variance (ANOVA) will be used for intragroup comparisons, with post hoc tests and Bonferroni correction applied to control for Type I errors. A Mantel–Haenszel test, stratified by potential influencing factors such as age (youngest-old [65–74 years], middle-old [75–84 years], oldest-old [> 85 years]), AIP, gender (male and female), and head deviation (left or right), will be used to compare the risk of POD between groups. Statistical significance will be set at $P < 0.05$.

Data Monitoring

The Data Monitoring Committee (DMC) will consist of an independent researcher responsible for data collection and classification, as well as a statistician. The DMC will focus solely on data monitoring without involvement in other aspects of the study. The DMC will ensure data completeness and accuracy and assess the overall progress

of the trial. Upon completion, the original data, final dataset, and outcomes will be submitted to the Scientific Research Management Committee.

Safety evaluation

All adverse events (AEs) associated with head rotation will be closely monitored. AEs include hypotension, significant cardiac arrhythmias, pneumothorax, significant disability or incapacity, cerebrovascular accidents, and death. Researchers will conduct daily patient visits until discharge and meticulously record any AEs. Should an AE occur, the trial will be suspended immediately for investigation, and appropriate actions will be taken based on the findings.

DISCUSSION

POD is a common and serious complication in elderly patients, significantly affecting postoperative recovery. In-hospital mortality was considerably higher among individuals with delirium (7.2%) compared to those without (0.9%). Additionally, post-operative 30-day mortality was also notably greater in patients with delirium (5.7%) than in those without (1.8%) [16]. Thus, understanding and preventing POD is crucial for improving patient outcomes and recovery.

Reduced cerebral perfusion has been linked to POD[4 17 18], with key markers for assessing cerebral perfusion, including MFV measured by transcranial Doppler and rSO_2[19]. Previous studies have reported that MFV and intracranial vertebral artery blood flow velocities decrease during head rotation in the prone position among young volunteers[11 12]. However, a prospective controlled study found no significant difference in rSO_2 between neutral head positions and rotations to the right or left[20]. This study did not focus on elderly patients, and the short duration of head positioning (< 30 min) may limit its applicability. Furthermore, rSO_2 measurements were obtained by adjusting pressure sensors during head positioning, which may have affected results. Our study addresses these limitations by using a Mayfield headrest in the prone position, which mitigates pressure build-up on the forehead during cervical rotation. Despite a reported 10% decrease in MFV and compromised jugular venous return during

rotation[20], the impact on cerebral perfusion pressure and autoregulation remains unclear. Further research is needed to clarify whether head rotation affects cerebral perfusion and oxygenation and subsequently influences the incidence of POD.

Atherosclerosis, prevalent among older adults, is often assessed using the AIP, with higher values indicating more severe atherosclerosis and a greater impact on blood flow[21]. Notably, both carotid and vertebral arteriosclerosis are manifestations of large-artery atherosclerosis. Research suggests that the left vertebral artery (LVA) is more susceptible to atherosclerosis than the right vertebral artery (RVA) due to higher blood flow velocity and pressure[22]. A prior study reported that in healthy adults, approximately 50% have a dominant LVA, 25% have a dominant RVA, and the remaining 25% have vertebral arteries of similar sizes[23]. Likewise, in a study of 1,414 stroke-free participants with a mean age of ≥ 45 years, plaques were found in both carotid arteries in 85% of cases, with a higher prevalence in the left carotid artery (67%) compared to the right (33%)[24]. These findings highlight the notable asymmetry between the left and right vessels. Our preliminary experiments did not show a significant effect of head lateralization on POD. Future analyses will stratify data based on AIP and head deviation to explore these factors further. Additionally, sex differences in vertebral artery blood flow during head rotation have been reported[11], with mild reductions in males but not females during ipsilateral rotation[11]. These sex differences will also be considered in our stratified analyses.

This study has two main limitations. First, all participants are recruited from a single center, which may limit the generalizability of the findings. Second, the study does not include graded angles for head direction, which would have complicated the experimental design.

Despite these limitations, we anticipate that this trial will provide valuable insights into whether maintaining a neutral cervical spine position reduces the incidence of POD compared to a deviated position.

Trial status

To date, 32 participants have been enrolled in the study; however, participant

recruitment is still ongoing at the time of submission. This trial is scheduled to be conducted from 20 December 2023 to 31 December 2025.

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing.

Patient and public involvement statement

Patients and/or the public were not involved

Ethics and dissemination

Ethical approval was obtained from Yancheng No. 1 People's Hospital Ethics Examination Committee (2023-K-120-01). The findings will be disseminated through presentations at annual conferences and publications in scientific journals.

Ethics statements

Patient consent for publication:

Not applicable.

Authors' contributions

Bin Qian took responsibility for the integrity of the work as a whole and served as the primary investigator. Jixiang Zhu, Yongzhuang Chen, Yangyang Chen, Kun Ni, Feng Li, and Bin Qian were involved in the study's design. Jixiang Zhu, Kun Ni, Feng Li, and Bin Qian drafted the manuscript. Yangyang Chen, Fengyun Liu, and Hong Ma contributed to the calculation of the sample size and provided statistical consultation. Qian Chen, Fang Wang, Xuetai Chen, and Zhouya Xue developed the case report forms and conducted a preliminary trial. Jixiang Zhu, Yongzhuang Chen, Hong Ma, Qian Chen, Fang Wang, Zhouya Xue, Kun Ni, Feng Li, and Bin Qian were responsible for conducting the clinical trials. All authors contributed to revising the manuscript for important intellectual content. Jixiang Zhu, Yongzhuang Chen, and Yangyang Chen contributed equally to this study and are joint first authors. Bin Qian acted as guarantor.

Funding statement

This work was supported by Yancheng Fundamental Research Program (YCBK202208) and The First Affiliated Hospital of Jiangsu Vocational College of Medicine Basic Research Program (QN2022001).

Conflicts of interest disclosure:

The authors declare that they have no conflict of interest.

References

1. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020;125(4):492-504. doi: 10.1016/j.bja.2020.06.063 [published Online First: 2020/08/17]
2. Zhang HJ, Ma XH, Ye JB, et al. Systematic review and meta-analysis of risk factor for postoperative delirium following spinal surgery. *Journal of Orthopaedic Surgery and Research* 2020;15:1-8.
3. Yokota H, Ogawa S, Kurokawa A, et al. Regional cerebral blood flow in delirium patients. *Psychiatry and clinical neurosciences* 2003;57(3):337-39.
4. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced Cerebral Perfusion Pressure during Lung Transplant Surgery Is Associated with Risk, Duration, and Severity of Postoperative Delirium. *Ann Am Thorac Soc* 2016;13(2):180-7. doi: 10.1513/AnnalsATS.201507-454OC
5. Cui F, Zhao W, Mu DL, et al. Association Between Cerebral Desaturation and Postoperative Delirium in Thoracotomy With One-Lung Ventilation: A Prospective Cohort Study. *Anesth Analg* 2021;133(1):176-86. doi: 10.1213/ane.0000000000005489
6. Wang X, Feng K, Liu H, et al. Regional cerebral oxygen saturation and postoperative delirium in endovascular surgery: a prospective cohort study. *Trials* 2019;20(1):504. doi: 10.1186/s13063-019-3586-y [published Online First: 20190814]
7. Sabayan B, Jansen S, Oleksik AM, et al. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies. *Ageing Res Rev* 2012;11(2):271-7. doi: 10.1016/j.arr.2011.12.009 [published Online First: 20111227]
8. Caplan GA, Lan Z, Newton L, et al. Transcranial Doppler to measure cerebral blood flow in delirium superimposed on dementia. A cohort study. *Journal of the American Medical Directors Association* 2014;15(5):355-60.
9. Arnold C, Bourassa R, Langer T, et al. Doppler studies evaluating the effect of a physical therapy screening protocol on vertebral artery blood flow. *Manual*

Therapy 2004;9(1):13-21. doi: https://doi.org/10.1016/S1356-689X(03)00087-0

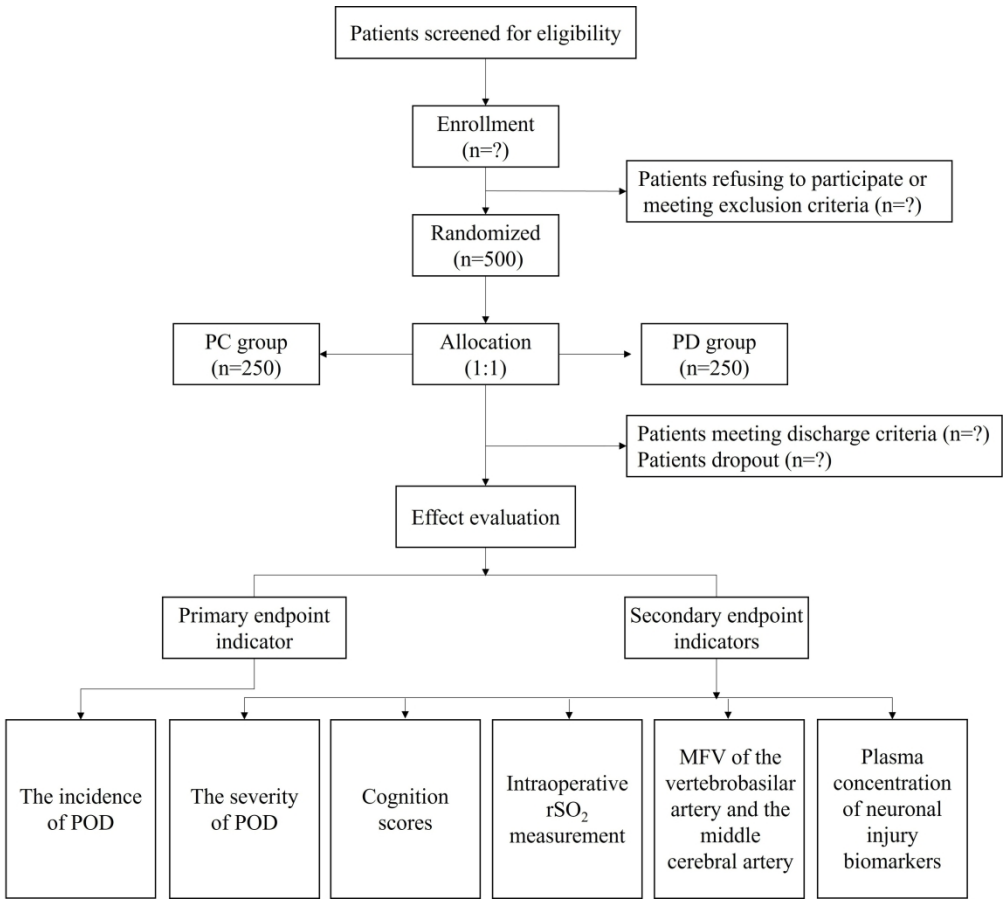
10. Haynes MJ. Doppler studies comparing the effects of cervical rotation and lateral flexion on vertebral artery blood flow. *J Manipulative Physiol Ther* 1996;19(6):378-84. [published Online First: 1996/07/01]
11. Mitchell JA. Changes in vertebral artery blood flow following normal rotation of the cervical spine. *Journal of Manipulative and Physiological Therapeutics* 2003;26(6):347-51. doi: 10.1016/s0161-4754(03)00074-5
12. Højlund J, Sandmand M, Sonne M, et al. Effect of head rotation on cerebral blood velocity in the prone position. *Anesthesiol Res Pract* 2012;2012:647258. doi: 10.1155/2012/647258 [published Online First: 2012/09/19]
13. Wang J, Lu S, Huang Y, et al. A nurse-administered 3-Minute diagnostic interview for CAM-defined Delirium (3D-CAM Chinese version) in hospitalized elderly patients: A validation study. *Int J Nurs Stud* 2020;110:103701. doi: 10.1016/j.ijnurstu.2020.103701 [published Online First: 2020/08/01]
14. Shi Z, Wu Y, Li C, et al. Using the Chinese version of Memorial Delirium Assessment Scale to describe postoperative delirium after hip surgery. *Front Aging Neurosci* 2014;6:297. doi: 10.3389/fnagi.2014.00297 [published Online First: 2014/11/22]
15. Jia X, Wang Z, Huang F, et al. A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry* 2021;21(1):485. doi: 10.1186/s12888-021-03495-6 [published Online First: 2021/10/06]
16. Ruck JM, Chu NM, Liu Y, et al. Association of Postoperative Delirium With Incident Dementia and Graft Outcomes Among Kidney Transplant Recipients. *Transplantation* 2023 doi: 10.1097/tp.0000000000004779 [published Online First: 2023/08/29]
17. Anderson BJ, Diamond JM. Under Pressure: Reduced Cerebral Perfusion as a Risk Factor for Postoperative Delirium in Lung Transplant Recipients. *Ann Am Thorac Soc* 2016;13(2):156-7. doi: 10.1513/AnnalsATS.201512-796ED
18. Ma H, Ahrens E, Wachtendorf LJ, et al. Intraoperative Use of Phenylephrine versus Ephedrine and Postoperative Delirium: A Multicenter Retrospective Cohort Study. *Anesthesiology* 2024;140(4):657-67. doi: 10.1097/aln.0000000000004774
19. Soh S, Shim JK, Song JW, et al. Preoperative transcranial Doppler and cerebral oximetry as predictors of delirium following valvular heart surgery: a case-control study. *J Clin Monit Comput* 2020;34(4):715-23. doi: 10.1007/s10877-019-00385-x [published Online First: 20190903]
20. Andersen JD, Baake G, Wiis JT, et al. Effect of head rotation during surgery in the prone position on regional cerebral oxygen saturation: A prospective controlled study. *Eur J Anaesthesiol* 2014;31(2):98-103. doi: 10.1097/eja.0000000000000028
21. Huang Q, Liu Z, Wei M, et al. The atherogenic index of plasma and carotid

atherosclerosis in a community population: a population-based cohort study in China. *Cardiovasc Diabetol* 2023;22(1):125. doi: 10.1186/s12933-023-01839-y [published Online First: 20230527]

22. Cagnie B, Barbaix E, Vinck E, et al. Atherosclerosis in the vertebral artery: an intrinsic risk factor in the use of spinal manipulation? *Surg Radiol Anat* 2006;28(2):129-34. doi: 10.1007/s00276-005-0060-1 [published Online First: 20060324]
23. Cloud G, Markus H. Diagnosis and management of vertebral artery stenosis. *Qjm* 2003;96(1):27-54.
24. Selwaness M, van den Bouwhuijsen Q, van Onkelen RS, et al. Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke* 2014;45(11):3226-30. doi: 10.1161/STROKEAHA.114.005202

Figure legend:

Study flow chart. PC: prone with the head centered; PD: prone with the head deviated; POD: postoperative delirium; MFV: mean flow velocity; rSO_2: regional cerebral oxygen saturation.



Study flow chart. PC: prone with the head centered; PD: prone with the head deviated; POD: postoperative delirium; MFV: mean flow velocity; rSO2: regional cerebral oxygen saturation.

292x260mm (300 x 300 DPI)

Informed Consent

Dear Sir/Madam：

We invite you to participate in the research project titled “Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a randomized controlled trial”. This study is led by Chief Anesthesiologist, Qian Bin, at The First people's Hospital of Yancheng and will be conducted at this hospital, with an estimated 500 participants volunteering to take part. The study has been reviewed and approved by Yancheng No. 1 People's Hospital Ethics Examination Committee, with the diary number: 2023-K-120-01.

Why is this research being conducted?

Postoperative delirium (POD) is an acute, fluctuating neuropsychiatric syndrome characterized by disturbances in attention, awareness, and cognition, typically manifesting within five days post-surgery. It is the most common postoperative complication in older adults. Recent meta-analyses report that the incidence of POD in elderly patients undergoing spinal surgery ranges from 3.8% to 40.4%, often associated with adverse clinical outcomes.

In thoracolumbar spine surgeries, head positioning – whether neutral or with lateral deviation – is typically based on clinical considerations. However, some studies suggest that head rotation may affect cerebral hemodynamics, which may potentially affect the incidence of POD. Epidemiological studies on POD have seldom considered the influence of head orientation during spinal surgery. It is unknown whether the intraoperative head orientation in the prone position contributes to POD in older adults. Thus, the primary aim of this study is to assess the impact of head direction during prone positioning on the incidence of POD in elderly patients undergoing thoracolumbar spine surgery. Our secondary aim is to investigate the effects of head direction on cerebral hemodynamics and oxygenation during prone positioning.

Who is (not) suitable to participate in the study?

1. Inclusion criteria
   - Age ≥ 65 years.
   - American Society of Anesthesiologists (ASA) physical status class II–III.
   - Mini-Mental State Examination (MMSE) score > 23 points, assessed one day preoperatively.
   - Expected duration of surgery > 2 h.
2. Exclusion criteria
   - Cervical spine trauma.
   - Restricted head positioning.
   - Cervicogenic dizziness and vertigo.
   - Central nervous system disorders with clinical manifestations.
   - Communication impairments.
   - Psychiatric disorders.

If you participate in the study, what do you need to do?

If you are willing to participate in this study, you will have a 1/2 chance of receiving one of the following two treatment plans: prone positioning with the head turned to one side, or prone positioning with the head in a neutral position. We will regularly assess your cognitive function and collect data related to cerebral perfusion and oxygenation during the week you undergo treatment, at the following time points: one day before surgery, intraoperatively, and postoperatively on days 1 to 5.

What are the benefits of participating in a study?

Whether or not you participate in this study, your condition will be diagnosed and treated in a timely manner. There is no direct benefit to you from participating in this study. However, the information gathered from your participation may provide valuable insights for future patients undergoing similar treatments.

What are the risks of participating in a study?

This study is a prospective randomized controlled trial. There is currently no guideline consensus on the effect of head position during thoracolumbar spine surgery, and its impact on the incidence and severity of postoperative delirium is still inconclusive. In this study, apart from the prone positioning with head tilt as the research variable, all other anesthesia, surgical treatments, and postoperative care will follow standardized protocols. During the study, if you experience any discomfort or adverse reactions, please contact the study physician immediately. Additionally, any treatment may be ineffective, and there is a possibility that the condition may continue to progress due to treatment failure or the presence of other comorbid conditions.

Are there any costs associated with participating in the study?

To compensate for any inconvenience caused by your participation in this study, we will cover the costs of cerebral oxygen saturation monitoring and transcranial ultrasound examinations during the study. However, the cost of a one-time cerebral oxygen saturation monitoring probe is not included in the free coverage. Any treatment and examinations required for comorbid conditions, as well as costs for alternative treatments if the current treatment proves ineffective, will not be covered. This study is conducted during your hospitalization, and there will be no reimbursement for transportation, lost wages, or nutritional expenses. In the event of any trial-related harm, appropriate treatment and compensation will be provided in accordance with national regulations.

Is personal information confidential?

Your medical records will be kept at the hospital, and the researchers, research oversight bodies, and ethics examination committee will be allowed to access your medical records. Any public reports related to the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information to the fullest extent permitted by law.

What other treatment options are available if you choose not to participate in this study?

You may choose not to participate in this study, and this will not have any negative impact on your access to standard treatment.

Do I have to participate in the study?

Participation in this study is entirely voluntary. You have the right to decline participation or withdraw from

the study at any time during the research process, and this will not affect the treatment provided by your doctor. If you decide to withdraw, please contact your doctor, and you may be asked to undergo relevant examinations, which will be beneficial for protecting your health.

If you have any concerns regarding your personal rights, you may contact the Ethics Review Committee of this hospital at the following phone number: 0515-66696823.

Participant Statement:

I have read the above information regarding this study and fully understand the potential risks and benefits of participating. I voluntarily agree to participate in this study. I will receive a signed copy of this informed consent form with my name and the date.

☐ I agree to participate in the research project titled “Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a randomized controlled trial”.

☐ I agree that data about me is processed in the manner described in the information.

Place and date	Signature

Personal identification number	Name printed

Investigator's Statement:

I confirm that I have explained the details of this study to the participant, particularly the potential risks and benefits of participating, and have answered all questions raised by the participant. The participant has voluntarily agreed to participate in this study. This informed consent form is made in two copies, one for the investigator and one for the participant, each with a signed copy."

Place and date	Signature

Personal identification number	Name printed