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Fluoxetine for reducing postoperative cognitive dysfunction in elderly patients after total knee replacement: study protocol for a single-centre, double-blind, randomised, parallel-group, superiority, placebo-controlled trial

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ABSTRACT

Introduction Postoperative cognitive dysfunction (POCD) is a common complication following major surgical procedures. The underlying pathophysiology is poorly understood, but the role of neuroinflammation is strongly implicated. Given the antineuroinflammatory and neuroprotective effects of fluoxetine, we hypothesise that fluoxetine may reduce the cumulative incidence of POCD in elderly patients undergoing total knee arthroplasty (TKA).

Methods and analysis This is a prospective, randomised, double-blind, parallel-group, placebo-controlled, superiority trial. Five hundred elderly patients undergoing unilateral TKA will be randomly assigned to the fluoxetine and placebo groups. The fluoxetine group will receive fluoxetine 20 mg daily 8 weeks preoperatively, and the placebo group will receive placebo capsules daily 8 weeks preoperatively. The primary outcome is the cumulative incidence of POCD at 1 month postoperatively. The secondary outcomes include the occurrence of delirium, the area under the curve of the Numeric Rating Scale pain scores over time, and sleep disturbance. Data on all the results, risk factors and adverse events will also be collected and analysed.

Ethics and dissemination The Fujian Provincial Hospital Ethics Board has approved the protocol for this trial (identifier number: K2021-01-009). All participants will be required to provide written informed consent before any protocol-specific procedures.

Trial registration number ChiCTR2100050424.

INTRODUCTION

Background Postoperative cognitive dysfunction (POCD) is a common complication following major surgical procedures, especially in elderly patients.1 2 Most patients affected by POCD experience a decline in various cognitive domains, including attention, recent memory, executive ability and social integration that can last for months or even be permanent.3 4 It has been shown that POCD is present in 41.4% at 1 month and 12.7% at 3 months postoperatively in patients over 60 years old after major non-cardiac surgeries.5 POCD is associated with delays in return to work and early retirement and a significantly higher death rate.3 6

Despite extensive research conducted in recent years, the exact pathogenesis of POCD remains unknown. Recently, a neuroinflammatory response has been suggested as a possible aetiological factor leading to cognitive decline after operations.6–9 Vacas et al reported that the inflammatory processes of the central nervous system were influenced by peripheral inflammation resulting from surgical trauma and associated systemic inflammatory mediator release.10 Meanwhile, some preclinical studies found that proinflammatory cytokines, such as interleukin 1β (IL-1β) and tumour necrosis factor-α, are central to surgery-induced neuroinflammation.11

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study has significant social and clinical implications, given the ageing trend of the population, the increase in the number of geriatric surgical groups, and the risk of postoperative cognitive dysfunction (POCD).

⇒ This is the first study to investigate whether 8 weeks of oral fluoxetine intervention could reduce the cumulative incidence of POCD in elderly patients after total knee replacement by multidimensional neurocognitive function evaluation.

⇒ This study did not include elderly patients with low preoperative cognitive function, and it is not clear whether fluoxetine can reduce the cumulative incidence of POCD in this group.

⇒ The mortality of the elderly and other force majeure will result in some patients being lost to follow-up.
Incidentally, patients with total knee arthroplasty (TKA) have neuroinflammation, which may be associated with the higher incidence of POCD.12

Fluoxetine, a classical selective serotonin reuptake inhibitor (SSRI), has been widely prescribed for depression and anxiety disorders due to its less toxic and adverse effects.13 It has been demonstrated that fluoxetine is clinically effective for cognitive decline and behavioural abnormalities in mild cognitive impairment patients.14 For example, fluoxetine has been reported to protect cognitive function in neurodegenerative conditions, such as Alzheimer’s and Parkinson’s diseases.15 16 Moreover, preclinical experiments have indicated that fluoxetine exhibits neuroprotective profiles due to its antineuroinflammatory properties.17 Based on its anti-inflammatory effect, and preclinical and clinical evidence, we hypothesised that fluoxetine could prevent POCD in elderly patients. Therefore, we designed this single-centre, prospective, randomised, double-blind, parallel-group, placebo-controlled, superiority study to test this hypothesis.

Objectives
This trial aims to determine whether 8 weeks of preoperative oral fluoxetine reduces the cumulative incidence of POCD in elderly patients undergoing TKA.

Trial design
We will perform a single-centre, prospective, randomised, double-blind, parallel-group, placebo-controlled, superiority trial at Fujian Provincial Hospital. All procedures will follow the guidelines outlined in the Declaration of Helsinki and Good Clinical Practice. The Ethical Committees of Fujian Provincial Hospital approved the protocol (K2021-01-009). A researcher will randomly assign 500 patients to the fluoxetine group or the placebo group in a ratio of 1:1 using a computer-generated list. The study schema is presented in figure 1.

METHODS
Recruitment and study setting
We will enrol patients who undergo elective unilateral TKA under general anaesthesia at the Fujian Provincial Hospital. It is possible to follow-up carefully with patients returning for regular postoperative appointments at defined intervals of 1, 3, 6 and 12 months postoperatively. Before study inclusion, patients will be preoperatively screened for neuropsychological deficits. The researchers will follow good clinical training and ensure that participants are fully aware of the study before obtaining written consent.

Inclusion criteria
Participants need to meet the following criteria:
► ≥65 years of age.
► American Society of Anesthesiologists (ASA) physical status I to III.

Exclusion criteria
Patients with the following conditions will be excluded:
► A Mini-Mental State Examination (MMSE) score ≤23.
► Severe language, visual or auditory deficiency.
► Unable to adhere to study procedures or follow-up visits.
► History of allergy to SSRIs.
► Recent drug administration may lead to drug interactions, such as monoamine oxidase inhibitors and SSRIs.
► Hepatic impairment (alanine transaminase or aspartate transaminase >three times the upper standard limit) or renal impairment (glomerular filtration rate ≤60 mL/min/1.73 m²).
► Other conditions that the researcher considers inappropriate for inclusion in the study.

Randomisation, allocation concealment and blinding
Patients will be randomly allocated to fluoxetine or placebo groups at a 1:1 ratio using a computer-generated list of random numbers. Group allocations will be concealed in consecutively numbered, sealed, opaque envelopes by a researcher not connected to the study team. Eight weeks before surgery, an independent research nurse (who is not involved in the patient’s care) will open the envelope and prepare the investigational drugs. Patients, research personnel and others involved in caring for the patients or data collection will be blinded to the treatment throughout the whole observation period.

To adjust the practice effect from repeated neuropsychological evaluation, we will enrol 164 control subjects who are not exposed to surgery. These subjects will be mainly relatives of patients of similar age who applied
the same inclusion and exclusion criteria except that they were not exposed to surgery. The evaluation dates of control subjects will overlap with those of surgical patients in the study. These control subjects will be recruited exclusively for this study.

**Intervention**

The fluoxetine group will receive oral fluoxetine 20 mg capsules daily in the morning for 8 weeks before surgery. The placebo group will receive the same appearance of placebo capsules daily in the morning 8 weeks preoperatively.

**General anaesthesia and postoperative analgesia protocol**

All participants will be provided with standardised general anaesthesia and postoperative analgesia regimen. On arrival in the operating room, standardised ASA monitoring, including non-invasive blood pressure, ECG, peripheral pulse oximetry, capnography and temperature, will be continuously monitored. We will induce anaesthesia with 0.6 µg/kg sufentanil, 2.0 mg/kg propofol and 0.15 mg/kg cisatracurium followed by laryngeal mask airway (LMA) insertion. All patients will receive sevoﬂurane (0.8 age-adjusted minimal alveolar concentration) and intravenous infusion of remifentanil titrated to maintain the haemodynamic parameters (heart rate and mean arterial blood pressure) within 20% of preoperative values and the target bispectral index of 40–60. Muscle relaxation will be achieved by intermittent injections of cisatracurium 5 mg as needed. At the end of the procedure, the residual neuromuscular blockade will be antagonised by 1 mg neostigmine and 0.5 mg atropine. After removing the LMA, all patients will be admitted to the postanaesthesia care unit (PACU) for 2 hours of observation.

Postoperative multimodal analgesia includes local anaesthetic using 0.5% ropivacaine 20 mL, patient-controlled intravenous analgesia (PCIA) with sufentanil 1.0 µg/hour and intravenous parecoxib 40 mg every 12 hours. If the Numeric Rating Scale (NRS) is higher than three or patients needed, an intravenous bolus injection of 2 µg sufentanil with a 10 min lockout interval would be administered as a rescue analgesic by the patient using the PCIA pump (REHN II; Renxian Medical Corporation, Jiangsu, China).

**OUTCOMES**

**Primary outcome**

The primary outcome of this trial is the cumulative incidence of POCD at 1 month postoperatively. An investigator will be responsible for performing the neuropsychological assessment without knowing the patients’ group assignment. The neuropsychological evaluation will be a test battery recommended by the International Study of Postoperative Cognitive Dysfunction 1.18 19. The average practice effect (ΔXcontrol) and SD (ΔScontrol) of each neuropsychological test will be determined by comparing the test scores of control subjects at baseline with those at the same evaluation time point. The Z score value will be calculated for each neuropsychological test: Z score=(ΔX−ΔXcontrol)/SD (ΔXcontrol). ΔX refers to the difference between the baseline and postoperative scores in the surgical patients. A composite Zcombined will be calculated as the mean of the Z score of all tests: Zcombined=(iZ)/ (SD[Zcontrol]). The composite Zcombined will be calculated based on control subjects of all tests. POCD is defined if two or more individual Z scores or Zcombined≥1.96.

**Secondary outcomes**

The secondary outcomes include the cumulative incidence of POCD 3, 6 and 12 months postoperatively, the incidence of delirium, the area under the curve (AUC) of the NRS pain scores over time, postoperative recovery quality, postoperative anxiety and depression, postoperative cumulative opioid consumption over 24 hours, sleep disturbance, adverse events during the perioperative period, the length of PACU stay, hospitalisation time and the blood concentrations of C reactive protein (CRP) and IL-1β. The Confusion Assessment Method scale will be used two times a day (between 08:00 and 10:00 and between 18:00 and 20:00) in the first five postoperative days to evaluate the incidence of postoperative delirium.24 The diagnosis of delirium requires the presence of features 1 and 2 and either 3 or 4. The postoperative pain at rest and movement will be assessed using a self-reported 11-score NRS score (no pain=0; maximum pain=10) at 0.5, 1, 2, 4, 8, 24 and 48 hours postoperatively. Postoperative recovery quality will be tested using the Chinese version of the 15-item Quality of Recovery questionnaire at preoperative (baseline), postoperative 24 hours, day 7 and day 30.25 The Self-rating Anxiety/Depression Scale will be used to screen the symptoms of anxiety and depression 1 day before surgery and on postoperative day 7 and day 30.26 A standard score below 50 is normal, 50–59 points indicates mild anxiety or depression, 60–69 points indicates moderate anxiety or depression, and more than 70 points indicate severe anxiety or depression. Sleep and disturbance will be assessed by the 6-item Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance short form 1 day before surgery (baseline) and on postoperative day 7 and day 30.27–29 The items relate to overall sleep quality, whether sleep was refreshing, difficulty falling asleep, had or words recalled from visual verbal learning trials after a 20 min delay; (3) distractibility: Stroop colour word interference test;21 (4) cognitive flexibility: trail making test part A and B;22 (5) working memory: letter-digit coding.23 Assessment procedures will be in a particular test room when the condition is limited, the location of the test selection is quiet, and there is no outside interference in the ward.

POCD diagnostic criteria are based on the International Study of Post-Operative Cognitive Dysfunction 1.18 19. The average practice effect (ΔXcontrol) and SD (ΔScontrol) of each neuropsychological test will be determined by comparing the test scores of control subjects at baseline with those at the same evaluation time point. The Z score value will be calculated for each neuropsychological test: Z score=(ΔX−ΔXcontrol)/SD (ΔXcontrol). ΔX refers to the difference between the baseline and postoperative scores in the surgical patients. A composite Zcombined will be calculated as the mean of the Z score of all tests: Zcombined=(iZ)/ (SD[Zcontrol]). The composite Zcombined will be calculated based on control subjects of all tests. POCD is defined if two or more individual Z scores or Zcombined≥1.96.
a sleep problem, restless sleep and trying hard to get to sleep. Each item is rated on a 5-point Likert scale, with scores ranging from 6 to 30 and higher scores are associated with greater sleep disturbance. A higher PROMIS scores will indicate more sleep disturbances. Patient blood samples from both groups will be collected to determine CRP and IL-1β concentrations preoperatively and at 0.5 hour after surgery. The Case Report Form (CRF) will be used to accurately record adverse events and treatment actions during the study. Adverse events include but are not limited to the following conditions: hypertension, hypotension, tachycardia, bradycardia, nausea, vomiting, dizziness, respiratory depression, diarrhoea and so on.

**Participant timeline**
The participant timeline is demonstrated in [table 1](#).

**Study monitoring**

**Data monitoring and quality assurance**
The Fujian Provincial Hospital Ethics Committee is responsible for monitoring the trial’s adverse event response variables and supervising participants’ safety in the trial. The primary investigator will conduct data analysis. An independent statistician (not involved in the research) will regularly monitor this study and quality control. The Fujian Provincial Hospital Ethics Committee will meet once a year to discuss the research and receive safety reports and data reports. The safety reports will include any compliance issues, adverse events and withdrawal from the study. Serious adverse events will be monitored so that patients can stop the study promptly. Investigators must faithfully fill out the CRF by item for all cases according to the design requirements. Research medical records and CRF shall be regarded as original records and shall not be changed. The laboratory data during the clinical trial should be recorded, and the original report (or a copy) should be affixed to the medical report form.

**Harm**
The adverse effects commonly reported for fluoxetine are headache, nausea, insomnia, fatigue and diarrhoea. The sufentanil used in this study may induce opioid-related adverse effects, such as constipation, respiratory depression, vomiting and nausea. From the time patients sign the informed consent to the end of the study, participants will be asked about adverse events or serious adverse events at every visit and all adverse events will be recorded in the medical case. The incidence of adverse events will be summarised for each group and compared using the χ² test or Fisher’s exact test.

**Follow-up and withdrawal**
All participants will carry out a 12-month follow-up. Patients returning for regular postoperative appointments can be followed up thoroughly at defined intervals of 1, 3, 6 and 12 months. The battery of validated neuropsychological tests is designed to evaluate POCD. Other patients will not replace participants who do not meet the 1-year follow-up process due to deviation from intervention, discontinuation for personal reasons, or contact failure. All patients can decide to withdraw at any time. All data monitored will be analysed and corrected if necessary.

**Statistics**

**Loss to follow-up**
Although we have designed to take steps to reduce the loss of the follow-up of patients, given the possibility of all-cause death in the elderly and other unavoidable situations, we are in the process of sample size calculation considering a 20% loss of follow-up. If patients withdraw from the study prematurely, data will be collected on the premise of informed consent and until the timing of the lost follow-up. All data collected in the trial will be analysed.

**Sample size**
The sample size calculation for the influence of fluoxetine on POCD is based on the reported incidence of POCD at 1 month after major non-cardiac elective surgery of approximately 41.4%. According to power analysis (a type I error rate of 5% and a power of 0.8), we needed 225 participants in each group to detect a 30% reduction in the incidence of POCD. Considering approximately a 20% inflation for dropout and loss of participants to follow-up, 500 participants were required in this study. In addition, the sample size of control subjects was 164, which was based on previous studies.

**Data analysis**
All analyses will be performed using IBM SPSS Statistics V.25.0 (IBM Corporation) in an intention-to-treat (ITT) fashion. We will test the normality distribution of continuous variables using the Shapiro-Wilk test and the Q–Q plot. Homogeneity of variance will be tested using Levene’s test. According to the normality tests, Gaussian distribution data will be reported as the mean (SD) and compared using independent Student’s t-tests; skewed distribution data will be reported as the median (IQR) and compared using Mann-Whitney U tests. Categorical variables will be summarised as numbers (proportions, %) and compared using the χ² test or Fisher’s exact test as appropriate. The absolute intergroup difference will be presented via the 95% CI. A two-sided p value will be calculated, and the significance level will be 5%.

The primary outcome in this study is the cumulative incidence of POCD at 1 month postoperatively, which will be analysed as ‘ITT’. Additionally, a per-protocol analysis will be performed as a supplement to the ITT analysis to reveal the effect of treatment as actually received. As a sensitivity analysis, for patients who were lost to follow-up or had protocol violations, we defined them as POCD or defined them as non-POCD and analysed them with worst-case and best-case scenarios separately. The intergroup comparison will be performed using the χ² test or Fisher’s exact test as appropriate with no adjustment for
## Table 1  Participant timeline

| Study period          | Enrolment | Allocation | In-hospital | Postoperative follow-up |
|-----------------------|-----------|------------|-------------|-------------------------|
| **Timepoints**        | Preoperative | −8 weeks | −1 days | 0.5 hours | 2 hours | 4 hours | 8 hours | 24 hours | 48 hours | 3 days | 4 days | 5 days | 7 days | 1 month | 3 months | 6 months | 12 months |
| **Enrolment**         |           |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| Eligibility screening | X         |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| Informed consent      | X         |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| Random allocation     |           |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| **Interventions**     |           |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| Baseline data         | X         | X         |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| Fluoxetine            |           |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| **Assessments**       |           |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| MMSE                  | X         |           |           |           | X        | X        | X        |          |          |        |        |        |        |          |          |          |          |
| Neuropsychological evaluation | X      |           |           |           |          |          |          |          | X        |        |        |        |        |          |          |          |          |
| Postoperative delirium| X         | X         | X         | X         | X        | X        | X        | X        | X        |        |        |        |        | X        | X        | X        | X        |
| AUC of the NRS at rest| X         | X         | X         | X         | X        | X        | X        |          |          |        |        |        |        |          |          |          |          |
| AUC of the NRS on movement| X     | X         | X         | X         | X        | X        | X        |          |          |        |        |        |        |          |          |          |          |
| Sleep disturbance     | X         |           |           |           |          |          |          |          | X        |        |        |        |        |          |          |          |          |
| QoR-15                | X         |           |           |           |          |          |          |          | X        |        |        |        |        |          |          |          |          |
| Anxiety and depression| X         |           |           |           |          |          |          |          | X        |        |        |        |        |          |          |          |          |
| Postoperative opioid consumption | X    |           |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| CRP                   | X         | X         |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| IL-1β                 | X         | X         |           |           |          |          |          |          |          |        |        |        |        |          |          |          |          |
| Adverse events        | X         | X         | X         | X         | X        | X        | X        | X        | X        |        |        |        |        | X        | X        | X        | X        |

AUC, area under the curve; CRP, C reactive protein; IL, interleukin; MMSE, Mini-Mental State Examination; NRS, Numeric Rating Scale; QoR-15, 15-item Quality of Recovery.
multiplicity. The relative risk and associated 95% CI will be calculated to assess the independent contribution of fluoxetine in preventing POCD.

Secondary outcomes including the cumulative incidence of POCD at 3, 6 and 12 months, the incidence of delirium, the AUC of the NRS pain scores over time, postoperative recovery quality, postoperative cumulative opioid consumption over 24 hours, sleep disturbance, anxiety and depression scores, the length of PACU stay and hospitalisation time will be analysed as ‘per protocol’. The AUCs of NRS pain scores over time will be determined by the trapezoidal rule using GraphPad Prism V.8.0 (GraphPad Software, California, USA). Two-way repeated-measures analysis of variance will be used to analyse the effect of fluoxetine on postoperative NRS pain scores at different time points. We will define the NRS pain score as the dependent variable, and the treatment, time and treatment multiplied by the time as independent variables. The treatment-by-time interaction will be tested first. If not significant, the main effect of fluoxetine will be tested next. Otherwise, intergroup differences at different time points will be tested with Bonferroni adjusted p values. Adverse events during the perioperative period will be analysed in the safety set. The incidence of adverse events will be compared using the χ² test or Fisher’s exact test. Univariate logistic regression analysis will be used as an initial step to identify possible risk factors for POCD, such as age, ASA physical status classification, sex, preoperative MMSE score, duration of anaesthesia, CRP concentrations, IL-1β concentrations and duration of hospitalisation. These variables with a p value of <0.05 from this analysis will be included in the multiple regression analysis with forced entry. The variance inflation factor will be used to evaluate the multicollinearity of the enrolled variables, the Hosmer-Lemeshow test will be used to examine the goodness of fit of the model, and the discrimination of the models will be estimated by using analysis of the AUC.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data management

Acute postoperative pain intensity, postoperative opioid consumption and face-to-face interviews postoperatively are planned to be performed by a research assistant. To ensure adequate follow-up of participants, we will record home and mobile phone numbers, WeChat (the most commonly used social networking software in China) ID and email addresses for postoperative interviews. All participants will be identified with a unique ID number. Participants’ identification data will be kept confidential until the study results are published. Our data collection and management will use CRF and ResMan (an electronic data capture) software. Another researcher will double check the entered data to ensure the accuracy of the data. For continuous variables, multiple imputations will be used for missing data at random with M=5 and adjustment for the imputation model based on age, sex and body mass index. For categorical variables, missing values will be imputed based on the last-observation-carried-forward approach.

Ethical approval and dissemination

The Fujian Provincial Hospital Ethics Board approved the protocol for this study on 13 January 2021 (Ref: K2021-01-009). The study period is planned from May 2022 to March 2024. The results of this study will be disseminated via manuscript publication and peer-reviewed journals.

DISCUSSION

This trial, to our knowledge, is the first randomised controlled trial to determine the effectiveness of fluoxetine on POCD, which has important clinical and social implications as the incidence of POCD in elderly patients undergoing orthopaedic surgery is relatively high with a negative impact on return to daily activities and work. The expected result is that 8 weeks of preoperative oral fluoxetine administration may reduce the cumulative incidence of POCD.

TKA is one of the most frequently performed orthopaedic surgeries globally for end-stage knee osteoarthritis when non-surgical treatment is no longer efficient. Therefore, TKA surgery mainly adopts the appointment system, which facilitates our enrolment of participants according to the criteria. Patients will return for regular postoperative appointments at defined intervals of 1, 3, 6 and 12 months. Thus, we can minimise the risk of loss to follow-up.

Fluoxetine is a safe and well-tolerated drug, and its cost is reasonable. In this trial, fluoxetine is 20mg once daily for 8 weeks preoperatively, similar to the FLAME (fluoxetine in motor recovery of patients with acute ischaemic stroke) trial. Neuronal apoptosis induced by neuroinflammation induced by surgery is considered one of the possible causes of POCD. The neuroprotective effect of fluoxetine has been confirmed in some studies. Shan et al reported that fluoxetine could protect against IL-1β-induced neuronal apoptosis. Fluoxetine could also reduce microglial activation, which is essential for preventing neuroinflammation. Therefore, fluoxetine may have potential value in preventing and treating POCD. Additionally, we chose the neuropsychological testing battery based on the International Studies of POCD 1 and 2 supplemented by motor skills and verbal fluency evaluation. This battery has recently been used in many clinical trials and has proven reliable and effective.

At present, the influence of anaesthesia on POCD is controversial. Both general anaesthesia and neuraxial anaesthesia are used safely for TKA. However, taking different types of antithrombotic drugs simultaneously, common in elderly patients, will significantly increase
the risk of spinal haematoma in neuraxial anaesthesia. Moreover, neuraxial anaesthesia can be challenging in patients with anatomical alterations of the lumbar spine, such as scoliosis or previous lumbar spinal surgery. Multiple insertion attempts caused by anatomical alterations of the lumbar spine in neuraxial anaesthesia may be associated with several complications, including epidural/spinal haematoma, neural damage, patient discomfort and dissatisfaction, increasing the possibility of patient withdrawal. In contrast, general anaesthesia exhibits better applicability in ensuring patient comfort and improving patient compliance than neuraxial anaesthesia with equal effect. Thus, we administered a standard general anaesthesia regimen in this trial.

This study is also subject to some limitations. First, we did not intend to recruit patients with preoperatively declining cognitive function, and therefore could not study whether fluoxetine treatment would reduce the incidence of POCD in these patients. Second, our hypothesis is based on the anti-inflammatory and neuroprotective properties of fluoxetine, but the pathogenesis of POCD remains unclear. Neuroinflammation caused by surgery may be only part of the pathogenesis of POCD. Third, the possibility of all-cause death in elderly patients and several confounding factors, such as the quality of the living environment and medications the patient received at home, may result in a potential bias in analysing the results.

In conclusion, if fluoxetine 20 mg given daily for 8 weeks can reduce the cumulative incidence of POCD after TKA in elderly patients, this will provide a promising strategy to lessen the incidence of POCD clinically.

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Contributors DL, LY and YD designed the study. LY and JC drafted the manuscript. YD critically revised the manuscript. DL, LY, JC, HY and YW participated in the conduct of the study. All authors have read and given consent to the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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