Efficiency of Donepezil in Elderly Patients Undergoing Orthopaedic Surgery Due To Underlying Post-Operative cognitive Dysfunction: Study Protocol for A Multicentre Randomised Controlled Trial

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Study protocol

Keywords: Donepezil, post-operative cognitive dysfunction, randomised controlled trial

Posted Date: June 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-182572/v1

Abstract

Background

Post-operative cognitive dysfunction (POCD) is an overarching term used to describe cognitive impairment identified in the preoperative or post-operative period. After surgical operations, older patients are particularly vulnerable to memory disturbances and other types of cognitive impairment. However, the pathogenesis of POCD remains unclear and no confirmed preventable or treatment strategy avilable. Our previous study demonstrated that the concentration of choline acetyl transferase in the cerebral spinal fliud was a predictive factor of POCD, and donepezil is an acetylcholinesterase inhibitor which was used in clinical for the treatment of alzheimer's disease can prevent the learning and memory impairment after anesthesia/surgery in aged mice. This study aimed to determine the critical role of donepezil in preventing cognitive impairment in elder patients undergoing orthopaedic surgery.

Methods

A multicentre, double-blind, placebo-controlled, crossover clinical trial will be performed to assess the efficacy of donepezil in elderly patients undergoing orthopaedic surgery. Participants (n = 360) will receive donepezil (5 mg once daily) or placebo from 1 day prior to surgery until 5 days after surgery. Neuropsychological tests will be measured at 1 day before the operation and 1 week, 1 month, 6 months and 1 year after the operation.

Discussion

This research project mainly aimed to study the effects of donepezil in elderly patients undergoing orthopaedic surgery due to underlying POCD and to investigate the underlying physiological and neurobiological mechanisms of these effects. The results may provide important implications for the development of effective interfering strategies, specifically regarding cognitive dysfunction therapy using drugs.

Trial registration:

ClinicalTrials.gov, NCT04423276. Registered on 14 June 2020.

Background

Post-operative cognitive dysfunction (POCD) has been described as an objectively measurable decline in cognitive function at varying intervals after anaesthesia and surgery, up to 3 months to 7.5 years after surgery [1, 2]. Severely affected individuals may experience personality changes and a reduced capacity for social interaction. Some patients even develop irreversible cognitive impairment [3]. Monk et al. reported that POCD leads to increased mortality in the first year after surgery [4]. Steinmetz et al. not only confirmed the results by Monk et al. but also showed that POCD after noncardiac surgery is highly associated with the risk of leaving the labour force prematurely [5]. Although POCD is a common clinical complication, its aetiology and mechanism remain elusive.

The cholinergic system of the central nervous system is widely considered to be essential in learning and memory, including the modulation of the acquisition, encoding, consolidation, reconsolidation, extinction and the retrieval of

memory [6]. This system degenerates during ageing [7] and in neurodegenerative diseases such as Alzheimer's disease (AD) [6]. In the normal human hippocampus, a striking and highly significant age-related decline in ChAT occurs from middle to old age (between 40 and 100 years) [7]. Donepezil is a highly selective and reversible acetylcholinesterase inhibitor that improves cognition and memory by increasing the concentration of acetylcholine at the neuronal synaptic cleft [8–10]. Donepezil is mainly used for the treatment of mild to moderate AD [11]. Our previous studies have shown that the concentration of choline acetyl transferase in the cerebral spinal fliud was a predictive factor of POCD and donepezil administration prevents isoflurane-induced learning and memory impairment in aged mice [12–14]. Therefore, a large randomised controlled trial is indicated to assess the efficiency of donepezil in elderly patients undergoing orthopaedic surgery due to underlying POCD.

Aims and objectives

We aim to investigate the effect of donepezil on the improvement of cognitive function in elderly patients undergoing orthopaedic surgery. Our primary objective is to evaluate the incidence of POCD 7 days (or before leaving hospital) after surgery. Our secondary objective is to evaluate the incidence of POCD at 1 month, 6 months and 1 year after surgery and post-operative delirium during the hospital stay. We predict that the donepezil intervention will alleviate post-operative cognitive impairment in elderly patients undergoing orthopaedic surgery. We aim to provide reliable clinical evidence for reducing the rate of POCD.

Trial design

This is a protocol for a multicentre, double-blind, randomised, two-arm parallel-group, placebo-controlled, interventional clinical study. We will observe the effects of the perioperative administration of donepezil on the post-operative cognitive function of elderly patients undergoing orthopaedic surgery.

Methods

Participants, interventions and outcomes

Study setting. This study will enrol approximately 360 participants from the Renji Hospital Shanghai Jiao Tong University School of Medicine, Tenth People's Hospital of Tongji University and Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine. This clinical trial has been approved and supported by the ethics committee of the Renji Hospital Shanghai Jiao Tong University School of Medicine (RJ17189).

Eligibility criteria. Patients will be recruited primarily from three centres. Table 1 presents a summary of the inclusion and exclusion criteria.

Table 1
Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
1) Elder than 60 years old	1) Existing cerebral disease, or have a history of neurological and psychiatric diseases including Alzheimer Disease, stroke, epilepsy and psychosis
2) Speak Chinese Mandarin	2) Existing cognitive impairment as evidenced by Mini-Mental State Examination scores below 24
3) Scheduled to undergo hip or knee replacement surgery	3) Several audition or vision disorder
4) The operation time is more than 2 hours	4) Patients with tumors or infections
5) Signed the inform consent	5) Unwillingness to comply with the protocol or procedures
6) American Society of Anesthesiologists (ASA) classification I-II	6) Can not communicate normally in Mandarin Chinese
	7) Existing bradycardiac arrhythmia (Heart rate < 60 bpm for any reasons)
	8) Existing gastrointestinal ulcer
	9) Existing urinary incontinence
	10) Existing asthma or chronic obstructive pulmonary disease
	11) Postoperative admission to ICU
	12) Allergic to donepezil

Recruitment and informed consent. Table 2 presents the schedule of the major study events for each study visit. Elderly patients who are scheduled to undergo orthopaedic surgery will be included in this study. Participants will receive a detailed description of the trial and provide informed consent. Patients who are interested to participate will be screened based on the inclusion and exclusion criteria. Eligible participants will sign an informed consent form. Participants will be informed that study participation is voluntary and that they will be free to withdraw at any time. Recruitment and consenting of study participants by the members of the research team is in-line with Good Clinical Practice (GCP). During the clinical trial, if any serious adverse events occur to the subjects, regardless of whether it is related to the drug under study, the researchers should immediately report to the director in charge of the clinical trial of the research institution, and contact Professor Diansan Su or Dr. Huichen Zhu.

Table 2
Schedule of major study events

	Screening	Visit 0 (1day before surgery)	Visit 1 (surgery day)	Visit 2 (1-5days after surgery)	Visit 3 (7 days after surgery)	Visit 4 (1month after surgery)	Visti 5 (6 months after surgery)	Visit 6 (1year after surgery)
Informed Consent	X							
Checking Inclusion/exclu-sion criteria	X							
Demographics	X							
Medical history and Review of Medications	X							
Mini Physical Exammination (Height, Weight and BMI)	X							
Randomization	X							
MMSE	X							
Visual Reproduction		X			X			
STROOP (Stroop Color and Word Test)		X			X			
Digit Span Test		X			X			
Digit Symbol Substitution Test		X			X			
Color Trail Test 1		X			X			
Color Trail Test 2		X			X			
CAM				X				
TICS-m						X	X	X
Study drug dispensed		X	X	X				
Adverse event		X	X	X	X	X	X	X
Concomitant Medication Assessment		X	X	X	X	X	X	X

Allocation. Subjects will be randomly assigned to one of the following two groups: donepezil group or control group (placebo). Randomisation will be performed as a block randomisation, stratified by the centre with 1:1 allocation, using SAS software. A random code will be generated between the donepezil group and the control group from each centre, in a 1:1 ratio. Envelopes containing the random codes will be generated and distributed to each centre. Drugs will be allocated according to these random numbers by personnel who are unrelated to the trial, and a code will be assigned to each drug. Upon entering the study, each subject will be assigned to either the donepezil group or the control group with an equal probability according to the random code at each centre.

Intervention. Subjects will receive 5 mg of donepezil or placebo once every night starting from 1 day before surgery until 5 days after surgery. On the day of surgery, patients will have a peripheral vein opened as a routine procedure. After measuring pulse oximetry, electrocardiogram and noninsive blood pressure, general anaesthesia will be induced with 0.05 mg/kg midazolam, 1 mg/kg propofol, 0.6 mg/kg rocuronium and 0.5 μg/kg sufentanyl. Anaesthesia will be maintained with intravenous cisatracurium, sevoflurane, remifentanil and propofol. The drug dosage will be adjusted according to the patients' hemodynamic response to maintain stable haemodynamics. To ensure that the patient's haemoglobin level remains > 8 g/dL, blood will be transfused when the haemoglobin level drops to < 8 g/dL. Succinylcholine will be avoided during surgery. Post-operative analgesia will be given through patient-controlled intravenous analgesia. Patients will be returned to the general ward once they recover from anaesthesia.

Interventions modifications and adherence

The assigned intervention will only be discontinued in response to participant request. No modification of the interventions is planned during the trial. Adherence to interventions mainly refers to patientsp self-management adherence. No concomitant care or intervenions are permitted during this trial.

Outcomes

Primary outcome measures. The primary outcome is the incidence of POCD 7 days after surgery (or before leaving hospital).

Secondary outcome measures. Secondary outcomes comprise the following:

1. POCD incidence 1 month after surgery
2. POCD incidence 6 months after surgery
3. POCD incidence 1 year after surgery
4. Incidence of post-operative delirium after surgery

Participant timeline

Table 2 presents the schedule for enrolment, interventions, assessments and visits for participants.

Cognitive function will be assessed 1 day before surgery, in the first 7 days or before leaving hospital and at 1 month, 6 months and 1 year after surgery.

The evaluation of cognitive function will also include Visual Reproduction, Stroop Colour and Word Test (STROOP), Digit Span Test, Digit Symbol Substitution Test, Colour Trail Test 1 and Colour Trail Test 2.

Post-operative delirium will be assessed using the Confusion Assessment Method (CAM). The CAM includes acute onset, inattention, disorganised thinking and abnormal consciousness. The diagnosis of delirium by the CAM requires the presence of features 1 and 2 and either 3 or 4. Table 3 presents the specific content.

Table 3
Specific content of the Confusion Assessment Method

The Confusion Assessment Method (CAM)	
Feature 1	Acute change in mental status with a fluctuating course Is there evidence of an acute change in mental status from the patient's baseline? Did this behavior fluctuate during the past day, that is, tend to come and go or increase and decrease in severity? This feature is usually obtained from a family member or nurse and is shown by positive responses.
Feature 2	Inattention Dose the patients have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3	Disorganized thinking This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4	Altered level of consciousness Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])
The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4	

Long-term cognitive function will be assessed using a modified version of the Telephone Interview for Cognitive Status-modified (TICS-m) at 1 month, 6 months and 1 year after surgery. TICS-m has been used to screen for dementia and mild cognitive impairment. TICS-m scores range from 0 to 48, with higher scores indicating better function.

Evaluators will comprehensively assess the status of the patients according to their medical history, clinical observation, current psychiatric examination and information provided by family members, especially care providers [15].

Sample size

As a result of the intervention, the power analysis for the primary outcome of POCD prevalence assumes a reduction from 25–12.5% in the outcome. The results of a conventional analysis to detect differences in proportions (POCD) between the intervention and control groups, using PASS19.0, led to a total of 300 patients with a 1:1 randomisation, given a power of $1 - \beta = 0.80$ and a two-side α level of 5%. Assuming a dropout rate of 10%, this results in a requirement of about 360 total patients.

Allocation masking

This study is planned to follow a double-blinded method. In all cases, the investigator, intraoperative attending anaesthesiologist, evaluator, data analyser and patient will not be aware of the treatment allocation, as the

medication will be encapsulated and provided by an independent nurse.

Unblinding procedures

In the event of a medical emergency, which requires identification of an individual patient's treatment, the investigators will be permitted to open the respective emergency envelope. A justification must be documented in the patient's medical record and in the case report form (CRF). Serious adverse events will be collected and recorded for further analysis at the end of the trial, and investigators will explore the correlation between these events and patients' healthcare records.

Plans for communicating important protocol modifications to relevant parties

All changes to the study protocol will be reviewed by the ethical committee, then reported to the sponsor, participating care providers, and investigators.

Data management

All patient data collected during this clinical study will be entered and/or filed in the respective patient's CRF. The patient's study participation must be documented appropriately in the patient CRF with study number, subject number, date of subject information and informed consent and date of each visit. Source data should be filed according to the GCP guidelines. The data manager will be responsible for data processing, according to the sponsor's standard operating procedures., and conduct regular monitoring to ensure that the date are adequate, accurate, and complete. Database lock will occur only after the completion of quality assurance procedures.

Statistical analysis

Statistical analysis will be conducted using SPSS 20.0 (IBM Inc., Armonk, NY, USA). Continuous variables will be analysed using the unpaired t test or Mann–Whitney U test. Categorical variables will be analysed using the χ^2 test, continuity correction χ^2 test or Fisher exact test. The definition of POCD is determined using the Z score recommended by the International Study of Post-operative Cognitive Dysfunction studies [16]. We will compare the patients' preoperative with post-operative scores 1 week later and divide the result by the standard deviation of the preoperative score of all patients to obtain a Z score for each individual test. Patients will be regarded as developing POCD if the Z score is ≥ 1.96 on ≥ 2 individual cognitive tests. A P value of < 0.05 will be considered statistically significant. The statistical code generated during the current study will be available from the corresponding author on reasonable request after the trial is finished.

Dissemination plans

The study results will be disseminated via articles published in peer-reviewed journals.

Discussion

POCD is generally believed to indicate the degeneration of the central nervous system and the decline of nervous system function induced or aggravated by anaesthesia, surgery and other factors. A number of animal studies have shown that surgery has different effects on the cognitive function of animals of different ages [17, 18]. Our previous studies have also shown that adult mice and aged mice respond differently to isoflurane anaesthesia. The learning and memory ability of adult mice can be improved under repeated isoflurane anaesthesia [19], but the

opposite is true for elderly mice. After isoflurane anaesthesia, learning and memory ability were shown to decrease significantly [13, 14]. We noticed that the central cholinergic state is different between adult mice and elderly mice and that the number of central cholinergic nerves in elderly mice decreased significantly. Before the age of 40 years, the activity of the central cholinergic system is continuously enhanced in healthy individuals, but it gradually degenerates after 40 years of age until the end of life [7]. The central cholinergic nervous system plays an important role in learning and memory as well as against central nociceptive responses. Studies have shown that nicotine or cholinesterase inhibitors can counteract cognitive impairment caused by AD [20, 21]. Additionally, in vitro studies have shown that nicotine can antagonise the neurotoxicity mediated by N-methyl-D-aspartate and β-amyloid protein [22]. Moreover, nicotine can reduce neurologic damage, behavioural changes and brain injury caused by stroke, Parkinson's disease and Huntington's disease [23–26]. The degeneration of the central cholinergic system that results from ageing is an important cause of cognitive dysfunction in elderly animals.

Donepezil is a specific acetylcholinesterase inhibitor that is widely used for the treatment of mild to moderate AD. It can improve cognitive and memory functions by increasing the concentration of acetylcholine in the synaptic spaces of neurons and slow the rate of AD progression. Donepezil has been shown to slow the progression of hippocampal atrophy in patients with AD as compared with untreated patients [27–29]. In addition to inhibiting acetylcholinesterase hydrolysis of acetylcholine, donepezil also antagonises the inhibition of N-methyl-D-aspartate receptors in the brain, improves blood circulation and reduces the neurotoxic effects of β-amyloid. It has been used in the clinical setting for the treatment of cognitive dysfunction caused by craniocerebral injury, senile vascular dementia and other diseases [27, 30]. Our previous research has found that donepezil prevent the learning and memory impairment after isflurane exposure in aged mice [13].

In a previous study, test results from the normative population revealed that four tests were highly correlated with both age and IQ: Letter-Digit Coding, Stroop Colour Word Test, Concept Shifting Task and Visual Verbal Learning. Additionally, high test–retest reliability coefficients were obtained. Consequently, these tests were chosen to evaluate cognitive function [16]. Our previous study using these cognitive test battery to evaluate the association between the biomarker in the cerebral spinal fliud and the cognitive function after surgery [12]. Our present study will also use the Z score to define POCD. The advantage of the Z score method is that it reflects subtle changes in test scores.

This will be the first led to multicentre randomised controlled trial to examine the effect of perioperative administration of donepezil on post-operative cognitive impairment in elderly patients after orthopaedic surgery. Our previous studies have shown that the administration of donepezil in elderly mice reduces perioperative ChAT protein expression, leading to improved cognitive function in the perioperative period [13]. We predict that the donepezil intervention will alleviate post-operative cognitive impairment in elderly patients undergoing orthopaedic surgery. We aim to provide reliable clinical evidence for reducing the rate of post-operative cognitive impairment.

Trial status

This study started in June 2020, and the recruitment phase will last until December 2021.

There will be three follow-up examinations after 1, 6 and 12 months, with the final examination planned for December 2022. We plan to complete the evaluations and analysis by December 2022.

Abbreviations

POCD
post-operative-cognitive dysfunction; AD:Alzheimer's disease; ChAT:Choline acetyltransferase; GCP:Good Clinical Practice; STROOP:Stroop Colour and Word Test; CAM:Confusion Assessment Method; TICS-m:Telephone Interview for Cognitive Status-modified; CRF:case report form;

Declarations

Acknowledgements

Our team would like to thank all of the staff at all participating sites and the patients who have participated in the trial to date

Authors' contributions

HZ and LC shared first authorship and contributed to the final manuscript. YC, SC, ZH, JZ and JX participated in performing the experiement and collection of data. LC contributed to the sample size estimations and statistical design of the RCT. YH and DS were responsible for the conception and design of the study. All authors have read and approved the final manuscript.

Funding

This study was supported by grants from the National Natural Science Foundation of China (Nos.81970995). The funders had no role in the analyses and interpretation of the results or writing of the manuscript.

Availability of data and materials

The participant-level data set cannot be made publicly available because of Chinese data protection rules and regulations. The statistical code is available upon request.

Ethics approval and consent to participate

This clinical trial was approved and supported by the Ethics Commission of Renji Hospital Shanghai Jiao Tong University School of Medicine (2017-189). The study was registered on the Clinical Trials Register (No. NCT04423276) on 14 June 2020.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Received: 28 January 2021

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