The Efficacy and Safety of Tropisetron in Preventing Emergence Delirium

Study Protocol

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# Key Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| BIS          | the Bispectral Index |
| CAM-ICU      | The Confusion Assessment Method for The Intensive Care Unit |
| CRF          | case report form |
| DSMB         | Data Safety Monitoring Board |
| ECG          | electrocardiogram |
| EEG          | Electroencephalography |
| GAD-7        | 7-item Generalized Anxiety Disorder Scale |
| ISI          | Insomnia Severity Index |
| ITT          | intention to treat analysis |
| MoCA         | The Montreal Cognitive Assessment |
| NCT          | National Clinical Trial |
| PACU         | post anesthesia care unit |
| PHQ-9        | 9-item Patient Health Questionnaire |
| POCD         | postoperative cognitive dysfunction |
| PONV         | postoperative nausea and vomiting |
| PP           | per protocol analysis |
| RASS         | Richmond Agitation Sedation Scale |
| RCT          | randomized controlled trial |
| VAS          | Visual analogue scale |
1 BACKGROUND

Postoperative delirium (POD) is a highly prevalent, costly and risky neuropsychiatric complication needed to be solved. In patients after anesthesia and surgery, approximately 11 to 51% of the population suffer from postoperative delirium,\(^1\) which is characterized by cognitive decline, inattention and a change in level of consciousness.\(^2\) It is a common neuropsychiatric complication of surgery, especially in the elderly.\(^3\) Patients could present delirium early at post anesthesia care unit (PACU),\(^4\)-\(^6\) with an incidence of 3.7% to 22.2%.\(^7\)-\(^9\)

Fluctuating mental status of delirium are associated with delayed postoperative recovery, longer hospital stay, increased morbidity and mortality.\(^10\)-\(^12\) Patients experienced postoperative delirium are more likely to develop permanent cognitivedisturbances.\(^13,14\) Thus, pharmacological prevention is needed in order to lower the risk of postoperative delirium and improve prognosis of related patients.

The underlying molecular mechanisms of POD includes central cholinergic deficiency, neuroinflammation, oxidative stress and apoptosis. Acetylcholine plays an important role in regulating synaptic transmission and modulating cognitive performances.\(^15\) Aging induces neurodegeneration, accompanied by decreased acetylcholine level and cholinergic dysfunction in cerebral cortex and hippocampus, and profoundly affects learning and memory processes.\(^16\) The impaired cholinergic nervous system may predispose the patients to develop delirium.\(^17\) Postoperative delirium may be caused by microglia activation, neuroinflammation and disruption of the blood-brain barrier (BBB).\(^1,18,19\)

Microglia activation triggers inflammatory cascade by release of proinflammatory cytokines, and results in the development of POD.\(^17\) Accumulating evidence indicates that POD is correlated with elevated levels of multiple inflammatory cytokines such as IL-6, IL-2, TNF-a and IL-12.\(^20\) Isoflurane exposure may induce neurotoxicity and increase risk of cognitive impairment for surgery patients.\(^21\)

Activation of \(\alpha/7\)nicotinic acetylcholine receptor (\(\alpha/7\)nAChR) can inhibit inflammation, reduce the production of toxic A\(\beta\)-protein and lessen
neuronal apoptosis. α7nAChR is widely expressed in brain and its physiological functions have been demonstrated including cognition, sensation, analgesia, transmitter release and neurons protection. Nicotine, choline and other α7nAChR agonist have been shown to attenuate inflammatory responses by reducing the release of pro-inflammatory cytokines.

α7nAChR stimulation may activate signaling associated with neuroprotection which represent one approach for cognitive impairment treatment. α7nAChR bind Aβ1-42 with high affinity, and Aβ1-42 inhibits alpha7nAChR-dependent acetylcholine release which involves in cognitive functions. Bitner suggested that α7nAChR agonist induced activation of phosphatidylinositol 3-kinase/ serine-threonine kinase (PI3K/AKT) pathway and showed a neuroprotective property by inhibition of glycogen synthase kinase 3β (GSK3β) activity and the concomitant reduction of tau phosphorylation attenuating tau hyperphosphorylation. The protection effect of nicotine and galantamine against neurotoxicity has also been observed in the primary rat cortical neurons. All these findings point out that α7nAChRs agonist may offers a potential approach for cognitive deficits.

As a partial agonist of α7nAChR, tropisetron is a feasible method that may participate in the regulation of cognitive function and provide neuroprotective benefits for POD in clinic. Tropisetron is a serotonin (5-hydroxy-tryptamine, 5-HT) 3 receptor antagonist and is frequently used in prevention and treatment of postoperative nausea and vomiting (PONV). Additionally, this drug is also a high-affinity partial agonist of α7 nicotinic acetylcholine receptors (α7 nAChRs). Triggering α7 nAChRhhas been demonstrated neuroprotective effects in various cognitive deficiency diseases. Most recently, beneficial effects in cognitive function such as memory performance have been reported of tropisetron in animals. In Alzheimer’s disease (AD) mouse models, tropisetroninduced greater improvements in spatial and working memory. The mechanism involves increased the sAPPα/A β1-42 ratio and protection against Aβ-induced neurotoxicity. In a randomized double-blind study, schizophrenia patients who received tropisetron were found
to have overall cognitive deficits improved compared to patients received placebo. In perioperative settings, only a published hypothesis is available, showing that tropisetron could act as potential therapeutic drug for postoperative cognitive dysfunction (POCD) considering the sharing identical mechanisms between POCD and Alzheimer’s disease. Taken together, evidence suggests that tropisetron comprises a promising approach in preventing delirium. However, there are no large clinical trials that have studied the effect of tropisetron for emergence delirium.

The aim of the study is to provide evidence on the effect of tropisetron in preventing delirium. This study based on a large sample, randomized, double-blind, placebo-controlled trial, combined scale evaluation with molecular biology measurement to investigate the efficacy and safety of POD prevention by tropisetron. The aim of this study is firstly to determine the effect of tropisetron on the incidence of emergence delirium. Secondly, to better understand beneficial effects of tropisetron on the incidence of postoperative delirium and other delirium related outcome measures compared with placebo. Once tropisetron was proved can reduce the incidence of POD, we will be pioneered in provide a new approach for preventing POD, which has important economic and social benefits for reducing postoperative complications and improving the prognosis of patients in the future.

2 HYPOTHESIS AND STUDY OBJECTIVE

2.1 Hypothesis

Tropisetron will lead to lower risk of emergence delirium for patients undergoing non-cardiac surgery.

2.2. Study Objective

To perform a randomized clinical trial with aim of determining the efficacy and safety of tropisetron on prevention of emergence delirium in patients undergoing non-cardiac surgery.
3 STUDY METHODS

3.1 Overall Study Design

We will conduct a double-blinded, randomized placebo-controlled trial that includes 1508 patients undergoing non-cardiac surgery. Potential participants undergoing non-cardiac surgery will be screened for eligible criteria and sign the informed consent form before recruitment in this trial. All enrolled patients will be randomly divided into either Tropisetron group or placebo group at a 1:1 ratio. The patients will receive a screening visit, a pre-intervention visit, an intraoperative visit and five follow-up visits. The primary endpoint is the incidence of emergence delirium. We will also examine important outcomes such as incidence of postoperative delirium within 3 days after surgery, nausea and vomiting, postoperative pain, adverse events, and length of hospital stay.

3.2 Participant selection

3.2.1 Inclusion Criteria

- Age 18 years or older
- Written consent given
- Scheduled to undergo elective non-cardiac surgeries under general anesthesia
- American Society of Anesthesiologists physical status score I-III

3.2.2 Exclusion Criteria

- History of neurological disease (e.g., dementia, or Parkinson’s disease)
- Patients undergoing neurosurgery
- History of psychiatric disease (e.g., schizophrenia)
- Patients with a medication history of anti-psychiatric drugs over the last 30 days prior to enrollment
- Unable to complete neuropsychological tests including patients with severe visual or hearing impairment
- The Montreal Cognitive Assessment (MoCA) scores below 10
• Patients with severe intraoperative adverse events (e.g., cardiac arrest)
• Patients with contraindication to tropisetron.

3.3 Recruitment

Participants are recruited in hospital ward one day before surgery at Beijing Chao-Yang Hospital. Team members will screen and visit patients who meet the eligibility criteria and invite them to join the study.

3.4 Informed Consent

All participants signed written informed consent forms before enrollment. During the consent process, investigators will: (1) give an introduction about the study; (2) explain the trial in detail including all collected data; (3) inform of benefits and risks during trial procedure; (4) explain the nondisclosure agreements with participants; (5) answer participants’ questions; (6) given a contact information for study investigator. Consent forms will be locked in a research cabinet.

3.5 Randomization and Blinding

Participants will be randomly assigned to tropisetron group or placebo group with a 1:1 ratio with a block size of 4 (SAS software, version 9.4, SAS institute Inc, USA). A statistician who is not involved in data collection or analysis produced the randomization list which is printed out and sealed in an opaque envelope for each participant’s assignment. A study nurse (Dan Wu) who is blinded to the participants’ characteristics assigned the participants to treatment by telephoning a contact in Beijing Chao-Yang hospital. The contact is not involved in the number generation and recruitment process. Participants will be then randomly allocated to identical ampoules with 5 mg tropisetron or 0.9% saline solution. The syringe with a total volume of 1 mL will be given to anesthesiologists prior to entering the operating room. Both participants and anesthesiologists are blinded to randomization assignments. Unblinding is permissible if necessary for safety reasons.
3.6 Intervention and Study Visits

3.6.1 Baseline Hospital Ward Visit

Baseline assessments are conducted in the hospital ward. Demographic information, medical history, health history (e.g., chronic alcohol use and smoking status), hearing and vision condition, baseline laboratory tests and electrocardiogram are collected from electronic medical record. Participants receive assessments, including pain measured by Visual Analogue Scale (VAS; pain assessment),\(^{39,40}\) depression by 9-item Patient Health Questionnaire (PHQ-9; depression assessment),\(^{41}\) anxiety by 7-item Generalized Anxiety Disorder Scale (GAD-7),\(^{42}\) insomnia by Insomnia Severity Index (ISI)\(^{43}\) and cognitive functions by the Montreal Cognitive Assessment (MoCA),\(^{44}\) with aim of identifying risk factors of emergence delirium.

3.6.2 Baseline Operating Room Visit

Electroencephalography (EEG) monitor (the Bispectral Index, BIS) is applied in participants in both groups during preoperative period (5 min with eyes closed). A blood sample is drawn prior to intervention for identifying potential biomarkers including IL-1\(\beta\), IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, IFN-\(\gamma\), MCP-1, RAGE, TNF-\(\alpha\), CRP, Tau, Tau[pT231], A\(\beta1-42\), VEGF-D, UCHL1, BDNF, \(\alpha\)-Synuclein, SAA.

3.6.3 Intervention and Control

Following randomization, patients enrolled in this trial come to the operating room and are applied with standard monitoring, including electrocardiogram (ECG), blood pressure and oxygen saturation. Intravenous access is then established. The intervention group receives tropisetron in a dosage of 5 mg as a bolus intravenously once prior to induction of anesthesia, while the control group receives placebo of 0.9% saline solution. Patients in both groups receive general anesthesia and tracheal intubation. Mean artery blood pressure (MAP) is maintained more than 65 mmHg during surgery, BIS value is maintained between 40 and 60. EEG data is acquired by the BIS monitoring system for the
entire duration of the operation. Information is collected on surgical and anesthesia techniques used (e.g., intraoperative medication, anesthesia methods, type of surgery, laparoscopic or open, duration of surgery, estimated blood loss during surgery, intraoperative infusion, blood transfusion during surgery and patient-controlled analgesia). Patients are transferred to post-anesthesia care unit (PACU) after surgery. Patients of both group receive non-drug intervention in the postoperative period. The Enhanced Recovery After Surgery (ERAS) pathway is not applied in our study.

3.6.4 Follow-up Visits

In the PACU, participants will be screened by The Confusion Assessment Method for The Intensive Care Unit (CAM-ICU)\(^{45-47}\) at 15mins, 30mins after tracheal extubation, and at discharge from PACU (within 1 hour after tracheal extubation). Delirium will be defined as a positive CAM-ICU test at either of these three time points. Richmond Agitation Sedation Scale (RASS) will be performed before CAM-ICU test in order to assess depth of sedation.\(^{48}\) If RASS scores is -4 or -5, the patient is insufficiently aroused for delirium assessment. Researchers will repeat an independent assessment at next predetermined time point. If RASS scores is >-4, the patients will receive following CAM-ICU test. If RASS scores remain -4 or -5 beyond 1 hour after tracheal extubation, the patient will no longer receive CAM-ICU test at PACU, and the primary outcome will be recorded as missing data.

In the hospital wards, participants are reassessed for delirium from postoperative day one to day 3, twice a day, in the morning and afternoon. Visual Analogue Scale is performed to measure level of postoperative pain at postoperative day 1-3. Participants will complete measures of depression (9-item Patient Health Questionnaire, PHQ-9),\(^{41}\) anxiety (7-item Generalized Anxiety Disorder Scale, GAD-7)\(^{42}\) and insomnia (Insomnia Severity Index, ISI)\(^{43}\) at postoperative day 3. Trained researchers will conduct assessment blinded to the allocation.

3.7 Data Collection and Management
3.7.1 Outcome Measurements

*Montreal cognitive assessment (MoCA).* The MoCA will be used to evaluate cognitive function. The MoCA is a multi-dimension cognitive assessment that evaluate visuospatial, executive, naming, memory, attention, language, abstraction, delayed recall and orientation. The total score is 30 and score lower than 26 indicates cognitive impairment. MoCA has comparable sensitivity and specificity to diagnose mild cognitive impairment.\(^4\)

*Richmond agitation-sedation scale (RASS).* The RASS is a reliable and valid sedation scale which will be used to detect changes in sedation status. It has 10 scale representing discrete criteria for different levels of sedation and agitation. And the scale is measured according to duration of eye contact aroused by stimulation (verbal or physical).\(^5\)

*Confusion assessment method intensive care (CAM-ICU).* The CAM-ICU is a reliable assessment with high level of sensitivity and specificity, and will be used to measure delirium. It is valid for both verbal and nonverbal patients. The contents focus on acute onset of mental status changes or fluctuating course, inattention, disorganized thinking and altered level of consciousness.\(^6\)

*9-item patient health questionnaire (PHQ-9).* The PHQ-9 will be used to measure depressive disorder and the grade of depressive symptom severity. It is completely self-administered and has been commonly used in clinical evaluation. The total score range from 0 to 27, with 0 to 3 points for each item. The thresholds for mild, moderate, moderately severe and severe depression are 5, 10, 15 and 20.\(^7\)

*7-item generalized anxiety disorder (GAD-7).* The GAD-7 will be used to screen anxiety and measure its severity. The participant rates each item using scale from 0 (not at all) to 3 (nearly every day). And the degree of anxiety which is defined as minimal, mild, moderate and severe is based on the total score for 7 items.\(^8\)

*Insomnia severity index (ISI).* The ISI will be used to assess subjective insomnia. It
is a self-report instrument measuring insomnia symptoms and consequences. The items on the were designed to assess the severity of sleep-onset, sleep maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, notice ability impairment and degree of distress or concern caused by sleeping problems.  

Visual analogue score (VAS). The VAS is an easy and reliable assessment that will be used to measure the intensity of pain. A ruler is provided, which has picture of faces showing none to extremely pain on one side and continuous scale on the reverse side. The participant will be asked to point out the status of pain and the corresponding score will be acquired. The pain intensity can be categorized as none, mild, moderate and severe.

3.7.2 EEG Data Acquisition and Processing

EEG data is acquired by the BIS monitoring system for the entire duration of the operation and recorded whether or not burst suppression is present. The baseline eyes closed period (5 min), and the recovery period after extubation (5 min) are extracted from the data for each patient.

Data is reviewed in EEGLab to assess for quality and the presence of motion and eye movement artifact. Spectral analysis is performed with Chronux Toolbox and MATLAB (MathWorks, USA) scripts. Spectral power is computed with multitaper spectral analyses (mtspecgramc function; time window: 6 s, overlap: 0 s, number of tapers: 3, time-bandwidth product: 5, spectral resolution: 0.25 Hz). The median absolute power ($10\times\log_{10}[\mu V^2/Hz]$) is calculated for the recovery period at each of three frequency bands (delta: 1 to 4 Hz, theta: 4 to 8 Hz, alpha: 8 to 13 Hz) for frontal channels.

3.7.3 Blood Biomarker

Intravenous blood samples are collected in 5ml tube, centrifuged at 4,000×g for 10 min. Supernatants are stored at −80 °C prior to the determination of IL-1β, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, IFN-γ, MCP-1, RAGE, TNF-α, CRP, Tau, Tau[pT231], Aβ1-42, VEGF-D, UCHL1, BDNF, α-Synuclein, SAA.
3.7.4 Demographic Assessments

Demographics. Baseline assessments will be conducted in preoperative visit in hospital wards. The information collected include age, gender, BMI, education status, living status, ethnic, history of physical diseases, smoking and alcohol consumption. And laboratory tests such as blood routine, blood biochemistry, blood pressure and electrocardiogram will be obtained from electronic medical record.

Surgery and anesthesia information. The information of surgery and anesthesia including the grade of ASA, anesthesia methods, intraoperative anesthetic, type of surgery, laparoscopic or open, duration of surgery, estimated blood loss during surgery, intraoperative infusion, blood transfusion during surgery and patient-controlled analgesia. All the information will be acquired from electronic medical record.

Follow-up information. Participants will be asked about VAS and postoperative nausea and vomiting for 3 days after surgery. If the participant suffers from unbearable postoperative pain, additional analgesia such as tramadol and flubiprofen will be used for pain management. Name and dosage of additional analgesia will be recorded. The adverse events such as shiver, hypertension, hypotension, hypoxia, major adverse cardiac events, atelectasis, pulmonary edema, acute kidney injury, death are also screened for 3 days.

3.7.4 Data Management

A study database with all included patients will be generated, and the study specific randomization module and study specific variables from separate case report forms (CRFs) will be entered into an electronic dataset based on EpiData software. Consent forms and CRFs will be locked in a research cabinet accessible to study researchers only, and will be retained for 15 years after trial completion at Beijing Chao-Yang Hospital. Quality control procedures will apply. All data will be merged at study end and exported to an analysis database for further analysis.
3.8 Outcomes

3.8.1 Primary Outcome

The primary outcome in this study is the incidence of emergence delirium within 1h after tracheal extubation measure using the validated Chinese version of the CAM-ICU. The positive CAM-ICU test requires the presence of (1) acute changes in mental status of a fluctuating course and (2) inattention, with either (3) disorganized thinking or (4) altered level of consciousness. Patients with delirium may display hyperactive signs or hypoactive signs. Hyperactive delirium is defined as RASS scores between +1 and +4, and hypoactive delirium is defined as RASS scores between -3 and 0.

3.8.2 Secondary Outcomes

Secondary outcomes include: (1) incidence of postoperative delirium within 3 days after surgery (defined as positive CAM-ICU test); (2) nausea and vomiting; (3) postoperative pain, measured using VAS (Score ranges from 0 to 10, with higher scores indicating greater pain); (4) adverse events (cardiac arrhythmias, cardiogenic shock and other unexpected adverse events); (5) length of hospital stay; (6) all-cause mortality.

3.9 Sample Size Calculation

The sample size calculation is based on the primary outcome. According to previous studies, incidence of delirium diagnosed in the PACU ranged between 3.7% and 22.2%. We assumed emergence delirium incidence of 15% in the control and a 6% reduction (the clinical limit of superiority) in the intervention group. With a power of 80% and one-sided alpha level of 0.05, using superiority tests for two proportions, 640 patients per group are required. Considering a dropout rate of 15%, the final planned total sample size is 754 randomized patients in each group. The sample size calculation was performed on PASS 14.0 Software (Number Cruncher Statistical Software, USA).

4 STATISTICAL ANALYSES
4.1 Intention to Treat Analysis

The primary analysis will be according to the intention to treat (ITT) principle and complemented with a per protocol (PP) analysis. Non-compliance refers that patients fail to receive intervention or placebo after randomization, such as cancelled operation and refusing to participate on surgery day. To control bias from non-compliance, sensitivity analyses will be conducted among participants without non-compliance.

4.2 Baseline Analyses

To comparing baseline characteristics, continuous variables will be given as mean (standard deviation [SD]) for normal distribution or median (interquartile range [IQR]) for skewed distribution. Categorical variables will be given as numbers and percentages. Clinical characteristics were compared between the two groups of patients with the use of an analysis of Student’s t-test or the Mann–Whitney U test for continuous variables and with the use of the $\chi^2$ test or Fisher exact test for categorical variables.

4.3 Primary Outcome Analysis

The primary outcome of our analysis is the incidence of emergence delirium. Comparisons in delirium incidence between two groups will be assessed with a $\chi^2$ test, and 95% CI will be calculated for the difference in delirium incidence.

4.3.1 Priori Subgroup Analyses

To explore the results differences amongst different patients, subgroup analyses will be conducted by comparisons of prespecified subgroups: a. Age (older than 65 years versus 65 years or younger); b. Surgery type (major surgery versus minor surgery); c. preoperative MoCA scores (>26 versus 18-26 versus 10-17).

4.4 Secondary Outcome Analysis

For secondary outcome analyses, the Mann–Whitney U test will be used for length of hospital stay, while $\chi^2$ test or Fisher exact test will be used for
categorical variables, including incidence of postoperative delirium within 3 days after surgery, nausea and vomiting, postoperative pain, adverse events. For all-cause mortality during hospitalization, we will conduct Kaplan-Meier curves, with a log-rank test for between-group comparison. Cox proportional hazard model will be used to estimate the hazards ratio among patients in tropisetron group compared with those with placebo with adjusting for potential confounding factors.\textsuperscript{56,57}

All tests will be two-sided and statistical significance will be defined as a $P$ value less than 0.05. Statistical analysis will be performed with SPSS 22.0 software (SPSS Inc, USA).

\section*{5 PRESPECIFIED SUB-STUDIES}

The primary purpose of this study is to determine whether tropisetron can lower the risk of emergence delirium and other delirium or treatment related outcomes. In addition, we collect data on changes of blood biomarkers, EEG behaviors and clinically relevant outcomes. Sub-studies derived from this trial are encouraged, with aim of providing more evidence on clinically relevant outcomes as below:

\begin{itemize}
  \item[a.] EEG behaviors and postoperative delirium
    \begin{itemize}
      \item It remains inconclusive on the role of EEG patterns for delirium prediction and detection.\textsuperscript{58-60} The current study allows for this investigation, as EEG data is collected on baseline, intraoperative period and postoperative period. We will explore the relationship between EEG behaviors and postoperative outcomes (e.g., emergence delirium and postoperative delirium).
    \end{itemize}
  \item[b.] Association between blood biomarkers and postoperative delirium
    \begin{itemize}
      \item Previous study has evaluated the molecular levels of biomarkers related to detection and/or predicting prognosis of postoperative delirium.\textsuperscript{20,61} In the current study, preoperative and postoperative blood samples were measured
to explore for the association of potential biomarkers with the risk of
postoperative delirium.

c. Effect of preoperative psychiatric and cognitive status on postoperative
delirium

The cognitive status has impact on development of postoperative
delirium. We will explore the association between preoperative psychiatric
and cognitive status (e.g. anxiety, depression, insomnia and cognitive
impairment) and postoperative delirium.

d. Perioperative depressive symptoms outcomes

Depressive symptoms are a common and important complication of major
surgery and associated with worse quality of life and even morality. Depressive symptoms at postoperative day 3 will be assessed and
mechanisms would be explored including: risk factors, pain and general
health status.

e. Anxiety symptoms outcomes

The occurrence of anxiety has been shown to be associated with high levels
of pain, prolonged hospital stays and long-term dissatisfaction. Preoperative and postoperative anxiety symptoms will be assessed to
determine clinical factors associated with presenting anxiety symptoms, and
postoperative outcomes (pain and general health status) associated with
anxiety.

f. Association between insomnia and postoperative outcomes

Insomnia have previously been associated with clinically relevant outcomes. The study will assess the effect of preoperative insomnia on postoperative
outcomes (pain and general health status).

6 SAFETY AND ADVERSE EVENT REPORTING
The research team is monitoring the study for adverse events. Since tropisetron 5mg is commonly used to prevent PONV in perioperative period, it would be less likely that serious adverse events attributable to tropisetron treatment would occur in the current study. The following adverse events will be reported: adverse events possibly related to the study drug, such as headache, dizziness, diarrhea and anaphylaxis, and serious adverse event including death and life-threatening. Study oversight is performed by an independent Data Safety Monitor Board (DSMB), which is composed of two physicians and a statistician. Interim analyses will be performed for safety concerns after including 500, 1000 participants respectively.

7 STRENGTHS AND LIMITATIONS

As far as we are aware, this is the first randomized controlled study powered to investigate tropisetron as a prevention drug for emergence delirium in adults scheduled for non-cardiac surgery.

There are several strengths of this study. The broad inclusion of this study strengthens the external validity and clinical applicability. Predetermined subgroup analysis, such as age, surgery type, smoke history and other disturbance in cognitive function (anxiety, depression and insomnia) will mitigate these potential confounders which could influence outcomes of our study.

This study has limitations which must be addressed. First, the trial is conducted at only one medical center, which restricts generalizability of the results. Second, symptoms of delirium fluctuate over times. It may be difficult to accurately identify delirium at the assessing time. We will perform delirium assessments at various times to ensure better detection.

8 ETHNIC

This protocol will be reviewed and approved by the Medical Ethics Committee of the Chaoyang Hospital. This protocol will be registered in Clinicaltrials.gov. All study members involved in the conduct of this research will receive the required education on the protection of human participant rights.
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