Regional or General Anesthesia for Post-operative Delirium in Patients Undergoing Hip Fracture Surgery

Abbreviations: RAGA-Delirium

Clinical trails No.: NCT02213380

Unit Leader: 01 Second Affiliated Hospital of Wenzhou Medical University

Participants:02 Tongji Hospital, Huazhong University of Science and Technology

03 West China Hospital, Sichuan University

First Affiliated Hospital of Third Military Medical University (Southwest Hospital)

05 First Affiliated Hospital of Wenzhou Medical University

06 Second Affiliated Hospital of Zhejiang University Medical College

07 Beijing Jishuitan Hospital

08 First Affiliated Hospital of Nanchang University

09 Second Affiliated Hospital of Anhui Medical University

10 Ningbo Second People's Hospital

11 Taizhou Hospital, Zhejiang Province

12 Lishui People's Hospital

Option number: 1.1 8 July 2014

Confidentiality statement

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Program summary

Name of study	Prospective, multicenter, large sample, randomized controlled study of the effect of local and general anesthesia on postoperative delirium in elderly patients with hip fractures
Purpose of the study	To evaluate the effect of two anesthetic methods on the incidence and prognosis of delirium in elderly hip fracture
Clinical trial units	Clinical trial leader: 01 Second Affiliated Hospital of Wenzhou Medical University Clinical trial participants: 02 Tongji Hospital, Huazhong University of Science and Technology 03 West China Hospital, Sichuan University First Affiliated Hospital of Third Military Medical University (Southwest Hospital) 05 First Affiliated Hospital of Wenzhou Medical University 06 Second Affiliated Hospital of Zhejiang University Medical College 07 Beijing Jishuitan Hospital 08 First Affiliated Hospital of Nanchang University 09 Second Affiliated Hospital of Anhui Medical University 10 Ningbo Second People's Hospital 11 Taizhou Hospital, Zhejiang Province 12 Lishui People's Hospital
Research Desigr	Prospective, multicenter, large sample, randomized controlled study design
Research population	Elderly patients with acute hip fractures on one side requiring surgical treatment
Selection criteria	1. age greater than or equal to 65 2.ASA Ⅰ~ IV 3. Voluntary signature of informed consent
Exclusion criteria	Complex 1. injuries: multiple fractures, chest, abdomen, pelvic and sacral trauma, head trauma, etc 2. contraindications of intraspinal anesthesia: coagulation dysfunction, thrombocytopenia, intraspinal space-occupying, infection of the puncture site, etc 3. relative contraindications of general anesthesia: known difficult airway, malignant hyperthermia, etc 4. nerve block taboo: puncture site infection, peripheral neuropathy, local anesthetic allergy, etc

	5. have participated in other clinical studies
Research Groups	1. local anesthesia group (RA group) 2. general anesthesia group (GA group)
Main indicators	Incidence of delirium within 7 days after the operation
Secondary indicators	Type, severity, duration of 1. delirium (DRS-R-98 scale diagnosis); 2. postoperative pain score (pain VAS score); 3. other related complications and outcomes: related complications: pulmonary infection, myocardial infarction, renal failure, gastrointestinal bleeding; 4. length of stay; 5. mortality rates during hospitalization and 30 days after surgery; 6. the total cost of hospitalization and anesthesia; Follow-up for 6 months and 1 year of 7. discharge: incidence, type, severity, cognitive function, quality of life, mental condition, the mortality of delirium.
Statistical analysis	Comparison of incidence of delirium, degree of delirium, type of delirium, and prognosis of patients
Expected test progress	2 years

Directory

1. Background and significance of the study

Delirium, also known as acute consciousness disorder, is an acute organic brain syndrome with attention, feeling, thinking, memory, mental exercise, and sleep cycle disorders occurring in a short period, characterized by restlessness, multilingualism, orientation disorders, and unanswered questions. Age (≥65) and hip fractures are major risk factors for delirium. The incidence of delirium in elderly inpatients was reported in 14%~56%, while in elderly patients with hip fractures, the incidence of delirium was 32%~53.3% higher. An incidence of postoperative delirium was reported in 11.1%~44.8% in elderly patients. The incidence of postoperative delirium was higher in 20.3%~60.9% in elderly patients with hip fractures. After delirium occurs, diazepam or psychotic drugs are often needed to increase nursing requirements and the risk of falling while delaying the time of autonomous activity and hospital stay and increasing medical costs. During recovery, delirium increases mortality (figure 1), and disability can also increase the incidence of dementia. Dysfunction also causes persistent depression or anxiety.

Elderly patients are prone to low-activity delirium, which is not easy to detect and is easily misdiagnosed as cognitive decline, depression, or dementia.Han results suggest that low activity type is very common in the emergency department,76% of which are missed by emergency doctors. Ouimet et al. found that delirium incidence was 70%, 2/3 of delirium was poor, mortality was higher, and high activity outcome was generally better, which was closely related to low activity type identification and misdiagnosis. Mixed delirium (alternate low activity and high activity) is severe, and cognitive impairment is more severe.However, some studies have suggested that the prognosis of low active delirium in elderly patients with hip fracture is higher than that of active delirium. There are many reasons for misdiagnosis or missed diagnosis of delirium, one of which is that clinicians pay less attention to delirium and often underestimate the incidence, severity, and delirium outcome. A British questionnaire found that young doctors lack the basic knowledge of diagnosis and management of delirium and lack understanding of the prevalence and clinical significance of delirium. Delirium is traditionally considered a temporary disease, but there is growing evidence that delirium is often persistent, poor after recovery, and increases dementia and cognitive impairment.Coler, a systematic review of 18 prospective studies, found continuous delirium common at discharge; the rate is 44.7%, The incidence of delirium was 32.8%,25.6%, and 21% in 1,3 and 6 months after discharge; poor prognosis in mortality, function, and consciousness in patients with persistent delirium. Dasgupta's systematic review found, Continuous delirium is

associated with hypoactive delirium, Can increase the severity of delirium, Cognitive impairment, Causes many kinds of complications and so on; Meanwhile, The author also believes that the existing information can not fully explain this problem .

One of the important medical interference methods in treating patients by anesthesia surgery is closely related to delirium occurrence and development. There are few studies on the relationship between anesthesia and delirium, which can reduce the incidence of delirium. Although simple local anesthesia avoids the disturbance of general anesthesia to patients' mental state, it has not been confirmed whether to reduce delirium. Sieber etcShallow sedation (BIS BIS<80) reduced the incidence and duration of postoperative delirium compared with deep sedation (BIS<50) in elderly patients with hip fractures. However, at home, Yue waitedIt was found that general anesthesia with different anesthetic depth and mode had no significant effect on early delirium incidence in patients with hip arthroplasty. Tan Gang, China,The results of epidemiological investigation of postoperative delirium in elderly patients with non-cardiac surgery showed that general anesthesia was not a risk factor for delirium; the risk factors related to anesthesia were the occurrence of perioperative hypotension, the use of scopolamine and pethidine. Abou-Setta etc. The results showed that local nerve block analgesia did not reduce postoperative delirium incidence. Mouzopoulos andA randomized controlled study of iliac fascia block and perioperative delirium in hip fracture showed that iliac fascia block reduced delirium incidence compared with placebo. Clegg and Young Studies on different drugs and delirium suggest that opioids, benzodiazepines, and blood pressure-lowering drugs dihydropyridine can increase delirium incidence. However, the authors also stress insufficient evidence to support it. Lonergan etc. A study of ICU patients suggested that lorazepam increased delirium interval compared with dexmedetomidine. The results did not suggest that benzodiazepines could be used to treat delirium.

Current Vague Assessment Scale of Consciousness (Confusion Assessment Method, CAM) It is still the most widely used delirium diagnostic tool for non-psychiatric specialists. Its items are simple, accurate, and easy to use. It is widely used in clinical and research. The limitation is that patients with language disorders can not be assessed, it is difficult to distinguish delirium from dementia, depression, or other mental illness, and the severity of delirium can not be assessed, so it is difficult to grasp the fluctuation of the condition dynamically. CAM-ICU scale. Has been shown to be used to diagnose delirium in patients with severe ICU tracheal intubation or verbal communication. Its multi-language translations, including Chinese versions, have also been shown to have high reliability and validity in clinical

applications. The CAM-ICU scale has been proved to be effective in the diagnosis of postoperative delirium in the recovery room (PACU) of anesthesiology. The recent review of delirium emphasizes that patients with delirium should be classified into exercise subtypes, the severity of delirium should be assessed, and the fluctuation of delirium should be dynamically monitored, which is beneficial to the diagnosis of etiology, treatment, cognitive impairment and outcome. At present, there is a delirium rating scale (Delirium Rating Scale, DRS), delirium rating scale-98 revised edition (DRS-R-98), memory delirium evaluation scale (Memorial Delirium Assessment Scale, MDAS) and so on. DRS-R-98 delirium scale. It is considered to be an effective and credible delirium severity scale; it can be used to distinguish delirium from other mental disorders such as Alzheimer's disease, schizophrenia, and depression, to classify delirium and to continuously observe the changes of delirium patients' condition. The scale has been translated into Chinese and confirmed to have high reliability and validity.

This study's significance is to observe and compare the effects of general anesthesia and local anesthesia on delirium and other related complications after hip fracture in the elderly through prospective, large sample, multicenter and randomized controlled clinical studies. The following questions are identified:

1) Is there any difference between general anesthesia and local anesthesia in the occurrence, severity, attack type, and delirium duration after hip fracture in the elderly? Which anesthetic method can reduce the incidence of postoperative delirium?

2) Is there a difference in the effect of the two anesthetic methods on postoperative delirium in different older people (elderly, dementia, or delirium)?

3) Do various factors (hypotension, drugs, pain, etc.) during anesthesia affect postoperative delirium and extent?

4) To analyze whether the control of anesthesia can reduce the medical expenses and related economic benefits caused by delirium.

5) The relationship between the classification and duration of delirium and patients' prognosis; does delirium lead to long-term cognitive dysfunction? How does it affect patients and their families' quality of life? The survival rate in patients with delirium?

2. Research topics

A randomized, controlled, multicenter, prospective study of the effect of local and general anesthesia on postoperative delirium in elderly patients with hip fractures

3. Purpose of the study

To evaluate the effect of two anesthetic methods on the incidence and prognosis of delirium in elderly hip fracture

4. Research Design

using prospective, multicenter, large sample, randomized controlled study design. Randomly enter local anesthesia group or general anesthesia group at 1:1.

According to the domestic literature report of postoperative delirium in elderly patients, the sample size estimation estimated that postoperative delirium incidence is about 26. Assuming that postoperative delirium incidence after local anesthesia is less than 30% of general anesthesia, the calculated sample size is 441 nα= each group. The provisional total sample size is 1000 cases. The sample size can be adjusted according to the progress of the study and the results in the medium term.

The number of cases in each center is 100. Because of the central random system, the number of cases in each center can be automatically adjusted according to the actual situation of the subjects recruited.

5. Case selection

5.1 Research population

Elderly patients with acute (≦3 weeks) hip fractures on one side need surgical treatment.

5.2 Selection criteria

1) Age greater than or equal to 65
2) ASA Ⅰ~ IV
3) Voluntary signature of informed consent

5.3 Exclusion criteria

1) Compound injury: multiple fractures, chest, abdomen, pelvic and

sacral trauma, head trauma, etc.

2) Intravertebral anesthesia contraindications: coagulation dysfunction, thrombocytopenia, intraspinal space-occupying, puncture site infection, etc.

3) relative contraindications of general anesthesia: known difficult airway, malignant hyperthermia, etc.

4) Nerve block contraindication: puncture site infection, peripheral neuropathy, local anesthetic allergy and so on.

5) Have participated in other clinical studies.

5.4 Termination criteria

5.4.1 Patient standard

5.4.1.1 Subject may withdraw from the study at any time without giving any explanation and without losing the right to future medical care;

5.4.2 Research Standards

5.4.2.1 Use of drugs in violation of program requirements during observation;

5.4.2.2 Other conditions that may increase the risk of the patient;

5.4.2.3 serious complications occurred during observation.

6. Random grouping

After obtaining informed consent, all selected patients were randomly grouped by network or telephone central random system (1：1):

1) local anesthesia group (RA group): epidural anesthesia, lumbar anesthesia, combined spinal anesthesia, nerve block (but the failure rate is high, not recommended).

2) General anesthesia group (GA group): general anesthesia + nerve block, general anesthesia, intraspinal anesthesia, simple general anesthesia.

7. Anesthesia:

Because of the particularity of senile anesthesia, experienced anesthesiologists are required to carry out anesthesia. They need to master nerve block, intraspinal anesthesia, and general anesthesia and be competent for anesthesia in elderly hip fracture surgery.

1) Preoperative, intraoperative, and postoperative patients were prevented from using any sedative drugs other than intravenous anesthetics (e.g., midazolam, dexmedetomazole, etc.) if surgical reasons for postoperative use of sedative drugs should be recorded in detail.

2) General anesthesia group, propofol or etomidate intravenous induction, anesthesia should be as simple as possible. Drugs such as ephedrine, opioids, atropine, and other drugs that have a certain impact on the spirit of consciousness should be used with clinical indications and recorded on the CRF table. All-body anesthesia can be performed before completing the nerve obstruction lag (or before), laryngeal mask, tracheal intubation, or mask can be passed through, mechanical ventilation, or spontaneous ventilation. Intraoperative use of intravenous analgesics, inhalation anesthesia (sevoflurane or isoflurane), or intravenous anesthesia to maintain general anesthesia. Iliac fascia block "3 in1" block, femoral nerve block, or posterior lumbar plexus block; single nerve block or a continuous nerve block can be used.

3) The local anesthesia group can use nerve block analgesia before operation (anterior femoral nerve or iliac fascia block is recommended to relieve pain in position) or opioid drugs (avoid pethidine), and then epidural anesthesia, lumbar anesthesia, or combined spinal anesthesia puncture. Do not use sedation techniques and related adjuvant sedation drugs. If sedative drugs

are used for surgical or other reasons, please record them in detail.

4) Intraoperative anesthesia management: if the anesthetic effect of the local anesthesia group can not complete the operation, the anesthesiologist can decide to use the drug or change the general anesthesia and record it in detail. This study does not make any provision for this situation. The general anesthesia group adjusted the depth of general anesthesia according to the surgical stimulation. Blood pressure reduction base value 30% or systolic blood pressure less than 90 mmHg is hypotension, recommended for vasoactive drugs or liquid treatment, the anesthesiologist can be appropriate according to personal experience.

5) Postoperative analgesia: various analgesia methods can be used (intravenous, epidural, nerve block sustained or self-controlled analgesia, or combined with oral medication), but both groups avoid using any sedative.

Considering the actual situation and the particularity of geriatric anesthesia, it is estimated that there will be some differences in the implementation of anesthesia, puncture technique, and intraoperative management among the research centers and anesthesiologists. The scheme does not provide for these differences or differences.

8. Main indicators:

Incidence of delirium within 7 days after surgery (CAM)

9. Secondary indicators:

1) Delirium type, severity, duration (diagnosed by DRS-R-98 scale)
2) Postoperative pain score VAS pain score）
3) Other related complications and outcomes: related complications: pulmonary infection, myocardial infarction, renal failure,

gastrointestinal bleeding;

4) Hospitalization time
5) The mortality rate during hospitalization and 30 days after surgery
6) The total cost of hospitalization and anesthesia.
7) 6 months and 1-year follow-up: incidence, type, severity, the cognitive function of delirium (mini-mental state examination, MMSE), quality of life (The MOS 36-item Short-Form Health Survey, SF-36)Hospital Anxiety and depression scale, HADS mental state), mortality.

Description:

The incidence of delirium before surgery includes (delirium from admission to surgery). CAM scale is used for the diagnosis of delirium in the ward; the CAM-ICU scale is used to diagnose delirium in the intensive care unit, that is, CAM-ICU is used when the CAM is not available. When there is a contradiction between the diagnosis obtained by the scale and the psychiatrist's diagnosis, when there are still differences after consultation, the diagnosis of the psychiatrist shall prevail. To prevent missed diagnosis, we should communicate with the medical staff in the ward on time. After the patient is selected, the family member or escort staff should be informed. The researcher should be informed of the evaluation of delirium when any abnormal performance of the patient's mood, consciousness, cognition and so on is found. When postoperative delirium is found, the subject should communicate with the competent physician and decide on further diagnosis and treatment if the patient's performance was normal 7 d after the operation, the visit ended, while the patient with continuous delirium was followed up until normal or discharged. Delirium patients were assessed by delirium rating scale 98 revised (DRS-R-98) for type and severity of delirium. The patient's assessment form was used as evidence of postoperative delirium and the duration of delirium.

10. Data collection

Arrange post-operative delirium assessment and data collection by a fixed staff member who should not know about the study design and purpose to reduce the error in the study report, assess the presence, type, severity of postoperative delirium daily, patient medical records and nurse records are also used to determine whether delirium occurs for a total of 7 days after surgery (delirium was observed and discharged). The data collection table is shown in Table 1. Besides, the mortality, hospitalization time, and discharge department were recorded. Table 2 summarizes other data to be collected.

Table 1 Data collected daily. P： days after surgery

Time points	Preoperative evaluation	P1	P2	P3	P4	P5	P6	P7
Temperature	✲	✲	✲	✲	✲	✲	✲	✲
Blood pressure	✲	✲	✲	✲	✲	✲	✲	✲
Heart rate	✲	✲	✲	✲	✲	✲	✲	✲
Oxygen saturation	✲	✲	✲	✲	✲	✲	✲	✲
Hemoglobin	✲	✲	✲	✲	✲	✲	✲	✲
Alanine aminotransferase	✲	✲	✲	✲	✲	✲	✲	✲
Alanine aminotransferase	✲	✲	✲	✲	✲	✲	✲	✲
Album	✲	✲	✲	✲	✲	✲	✲	✲
Urea nitrogen	✲	✲	✲	✲	✲	✲	✲	✲
Creatinine	✲	✲	✲	✲	✲	✲	✲	✲
PH	✲	✲	✲	✲	✲	✲	✲	✲
PO2	✲	✲	✲	✲	✲	✲	✲	✲
PCO2	✲	✲	✲	✲	✲	✲	✲	✲
HCO3	✲	✲	✲	✲	✲	✲	✲	✲
Na	✲	✲	✲	✲	✲	✲	✲	✲
K	✲	✲	✲	✲	✲	✲	✲	✲
Cl	✲	✲	✲	✲	✲	✲	✲	✲
Delirium CAM or not	✲	✲	✲	✲	✲	✲	✲	✲
DRS-R-98 of type and severity of delirium	✲	✲	✲	✲	✲	✲	✲	✲
VAS pain score	✲	✲	✲	✲	✲	✲	✲	✲

Table 2: Other data to be collected

Period	Data	Method
Preoperative general data	Age, sex, address, type of fracture History, ASA rating Cognitive function (MMES)	Medical records MMSE
Intraoperative	Methods of operation, level of the surgeon, manner of anesthesia Anesthesiologist level, anesthetic substance, and dosage Low blood pressure	Review of medical records and anesthesia records

	Duration of operation estimated blood loss	
Postoperative	Length of stay, hospitalization costs, anesthesia costs, adverse events, mortality during hospitalization,30-day mortality, withdrawal from the study	Telephone follow-up
6 months and 12 months later	Whether delirium occurs, type and severity Mortality Quality of life, anxiety or depression	Quality of life scale SF-36, anxiety and depression scale (HADS) Review of patients' families

11. Adverse event reports

11.1 Adverse events

11.1.1 Definition of adverse events and reactions

Adverse events (Adverse Event, AE) refer to any adverse symptoms, abnormal signs, and abnormal laboratory results after the intervention study, whether there is a causal relationship with the intervention. Any adverse events, including those provided by the subjects voluntarily or obtained through inquiry by the researcher or by physical examination, laboratory examination, or other examination methods, should be recorded on the CRF and actively handled, followed closely until remission or condition is stable.

Adverse reactions (Adverse Drug Reaction, ADR): harmful, rather than desirable, results in a causal relationship with drug use during the normal application of the drug at the prescribed dose.

11.1.2 Records of adverse events

(1) All adverse events must be tracked, and the researcher must record them in the corresponding section of the case report form and record the adverse events in detail.

(2) Adverse event content: name of symptom or sign or diagnostic name of disease or laboratory examination of an indicator abnormality.

(3) Date of onset of adverse events: date of the first occurrence of AE or related symptoms AE subjects.

(4) End date of adverse events: date of cessation of AE or AE-related symptoms. If the AE still exists, do not fill in the end date.

(5) Evaluation of the severity of adverse events

Mild: symptoms and signs present, but can tolerate, generally without treatment

Moderate: Symptoms or signs cause discomfort, daily activities are limited, appropriate treatment can be taken

Severe: no ability to work and daily activities, need active treatment

(6) Measures taken :discontinuation of the relevant medication or treatment ; use of therapeutic measures; and no measures are taken.

(7) Result of adverse events: persistence, improvement, mitigation

(8) Evaluation of the correlation between adverse events and anesthesia:

Five-level evaluation criteria:

Positive correlation: adverse events appear under a reasonable time order after anesthesia;

The anesthetic method used to explain adverse events is more reasonable than other causes;

The pattern of adverse events is consistent with the pattern of adverse reactions caused by such anesthesia.

Maybe relevant: adverse events appear under the reasonable time order after anesthesia;

The use of anesthesia to explain adverse events is more reasonable than other causes; but do not rule out other reasons.

It may not be relevant: the occurrence of adverse events does not conform to the reasonable time order after anesthesia; (Other causes may cause adverse events, but the possibility of anesthesia can not be ruled out;None: The possibility of adverse events resulting from or excluding from anesthesia by other causes);

Can not be determined: the occurrence of adverse events does not conform to the reasonable time order after anesthesia; However, it is impossible to determine whether it is related to anesthesia, nor can it be explained by other reasons.

11.2 Serious adverse events

11.2.1 Definition of serious adverse events (SAE)

In the course of clinical trials, such events as hospitalization, prolonged hospitalization, disability, affecting working ability, endangering life or death, causing congenital malformation, etc.

11.2.2 Serious adverse event handling process

When serious adverse events occur, we should make every effort to rescue and actively take various measures to avoid permanent damage. The SAE researcher must notify the applicant, clinical trial organization, ethics committee by telephone or fax within 24 hours from the beginning of the trial to the observation period, and fill in the section of the case report form on serious adverse events. SAE's medical information should also be reported to the applicant after 24 hours.

11.2.3 Reporting procedures for serious adverse events

(1) Applicant: Second Affiliated Hospital of Wenzhou Medical University

(2) Clinical Trial Institution/Ethical Committee of the Unit Leader

Second Affiliated Hospital of Wenzhou Medical University

Tel :057788002990 Fax :057788002925

11.2.4 Responsibilities of severe adverse events researcher

When a severe adverse event occurs, the researcher should actively take appropriate medical measures, carry out rescue treatment, and notify the above responsible person by telephone or fax within 24 hours.

11.2.6 Responsibility of applicants for serious adverse events

Assist researchers to report serious adverse events and take necessary measures to ensure the safety of subjects.

11.2.7 Responsibility of the Inspector for Serious Adverse Events

Assist researchers to report serious adverse events and take necessary measures to ensure the safety of subjects.

11.3 Adverse reactions recorded in (CRF) of the case report form

All adverse reactions should be recorded in the case report form (CRF) adverse events.

12. Data management and statistical analysis

12.1 Input of case report form and completion of original record form

This study adopts an electronic case report form; researchers should input in time to ensure accurate content and timely summary. The paper original record form is used to record the study's relevant data, generally should not be altered, if there is an error that needs to be modified, it should sign at the modification place and sign the date of modification. The completed original record form should be entered immediately into the electronic medical record report form.

12.2 Data entry and modification

12.2.1 Source file definitions

The source file is the first-hand information of clinical trial data recording. This clinical study's source documents refer to the research medical records, informed consent, physical and chemical examination reports, drug management documents, quality inspection documents, etc.

12.2.2 Data recording and reporting

Any observation and inspection results in the study should be recorded in the source file in a timely, accurate, complete, standardized, and true manner.

Changes to source files and source data must be sufficiently substantiated. Otherwise, the first judgment (a record) shall prevail.

Data reporting uses a network-based "electronic CRF and data management system. "

Data entry: independent double timely input.

The advantages of electronic CRF and data management system: to ensure that the organizer can grasp the dynamic of each center test in time; to facilitate the quality controller to review and question the data of each center in time through the network platform, to improve the working efficiency and reduce the cost of quality control; to set the data rules and ensure the quality of the data through the network CRF,; to input the CRF data from each center to help each center find

problems in time and correct them, and to export the data entered by the center for academic papers with the permission of the team leader; After the completion of the test, faster and more accurate completion of the statistical analysis report.

12.2.3 Data verification requirements

The Data Monitoring Committee will conduct a mid-term evaluation of the research data, monitor the data, and hold occasional meetings to evaluate the research data's security and effectiveness.

During site inspection (SDV), clinical research institutions shall provide convenience and consult in prescribed places.

Data audit method: the inspector logs in the data monitoring end of the electronic CRF and data management system in each center and uses the online method to confirm the inconsistent data input. 100% check the consistency of electronic CRF data with source data such as research medical records.

The reference of source documents should follow hospital medical documents' regulations and the regulations of archives of drug clinical research institutions.

12.2.4 Requirements for Data Questions and Answers

Issue of questions: questions issued in logical checks and questions issued during SDV are regularly logged into the system by the CRC- data entry officer, and the organization's questions are downloaded to generate a data clarification table (DCF).

Question answering: the CRC- data entry staff will DCF the corresponding researcher to answer questions; the data is modified on the DCF, DCF saved as the source file.

Online update: CRC- data entry will answer questions on the DCF online data update.

Solution: the inspector SDV, the DCF, checks its authenticity and rationality; the project data manager verifies the answer data," confirms the correct, "or" issues a new question "when there is still a problem or a new problem. The question is deemed to be resolved.

Data entry is the responsibility of the designated data administrator. In order to ensure the accuracy of the data, two data administrators should independently input and proofread.

The data manager will question the case report form (DRQ) questions and send questions to the researcher through the clinical inspector. The researcher should answer and return them as soon as possible. The data manager will modify, confirm, and input the data according to the researcher's answer and issue the DRQ. again if necessary

12.3 Data locking

After confirming that the established database is correct, the data is locked by the principal researcher, the applicant, and the statistical analyst. Locked data files are no longer changed in principle.

Statistical analysis

12.4.1 Analysis of data sets

(1) Total Analysis Set (FAS): A collection of all cases randomly enrolled and treated with at least one trial drug.

When analyzing the main curative effect index, the FAS concentration's missing value is processed by carrying the results observed at the last time point to the current (LOCF) method.

An Available Case Analysis principle is used to deal with the missing value in the analysis of secondary efficacy index, general condition, and safety.

(2) Conformity with program set (PPS): a collection of cases that meet the inclusion criteria and complete treatment in accordance with the provisions of the trial program, i.e., cases that meet the trial program, have good compliance, have not taken banned drugs, and have completed the evaluation of effectiveness (at least primary efficacy), if any.

(3) Security data set (SAS): at least one treatment and actual data recorded with a safety indicator evaluation.

12.4.2 Content of statistical analysis

The main analysis includes:

(1) Distribution of cases between the two groups: Comparing total abscission rate and abscission rate due to adverse events.

(2) Comparability analysis: Comparison of demographic data and other baseline indicators to measure comparability between the two groups.

(3) Compliance analysis: To compare whether the two groups of patients were using the test drugs on time and on time, and the drugs that were not banned in the unused regimen.

(4) Validity analysis: both PP and ITT analyzed the main efficacy indicators; since this study is a multicenter clinical trial, the effects of central effect and baseline on efficacy indicators should be considered.

The incidence of delirium was compared by chi-square test, chi-square test, CMH chi-square test, delirium exacerbation analysis, H analysis of data consistent with normal distribution; otherwise, H test, single-factor analysis of delirium aggravation, The data that do not conform to normal distribution are tested by rank sum test or Kruskal-Wallis test (H test).

(6) Safety analysis: First of all, according to the requirements of the correlation of adverse reactions, the list describes the adverse events and adverse reactions in the two groups (including the number of cases of various adverse events, the number of cases of "normally abnormal" before and after the test and the rate of variation). The adverse reactions were statistically analyzed by the chi-square test.

12.4.3 Statistical analysis methodology

Metrological data: First, the normal test is carried out, and the methods of t-test, pairing t-test, variance analysis, covariance analysis are used for those that conform to a normal distribution, and rank-sum test, paired rank-sum test, H test and so on are used for the data that do not conform to normal distribution.

Numbering data: using calibration chi-square test, Fisher accurate test, etc.; grade data using Ridit analysis, CMH method.

(3) Multi-center analysis of comprehensive efficacy: counting data using CMH method; measurement data using covariance analysis.

All the statistical tests were bilateral, and the P-value was less than or equal to 0.05.

12.4.4 Data management and statistical analysis software

1. Data management and statistical analysis software

Beijing Baiaozhi Information Technology Co., Ltd. clinical research integrated information platform (www.bioknow.net), using double independent input, check the correct statistical analysis. The statistical analysis adopts SAS9.13 software programming analysis.

(2) Setting of parameters in statistical analysis

The bilateral test (two-side test) was used for all hypothesis tests, and the α= was 0.05. P ≤0.05, the reliability of all confidence intervals was 95.

13. Test management

13.1 Programme compliance

The approved plan shall carry out the test, and any deviations from the plan shall be recorded.

13.2 Programme changes

13.2.1 Subject to the Ethics Committee's approval, this program shall be subject to developing a "program modification specification ", signed by the lead researcher. The proposal may be amended only with the consent of the applicant;

13.2.2 The program shall be amended and submitted to the Ethics Committee for approval before implementation;

13.2.3 Any person participating in the test shall follow the GCP principle and shall not violate the program. In the event of a breach of the program, it shall be recorded in the original record sheet.

13.3 Case report form (eCRF)

13.3.1 eCRF; completed by the researcher according to original records

13.3.2 Timely, accurate, complete, and reliable data recording;

13.3.3 The eCRF form shall be reviewed by the heads of the centers upon completion;

14. Test quality control

14.1 After the start-up of the project, the centers will hold in-hospital start-up meetings to train the pilot program, delirium assessment scale, and eCRF form;

14.2 Inclusion of cases in strict accordance with inclusion/exclusion criteria;

14.3 Both the applicant and the researcher shall implement a quality control and quality assurance system for clinical trials using standard operating procedures in the program:

a) (a) The recording and preservation of raw materials must meet the GCP requirements;
b) The laboratory must have inspection qualification to ensure that the inspection results are correct and reliable and can be properly preserved in the database;
c) All observations and findings should be verified to ensure the reliability of the data. Ensure that the conclusions of clinical trials are derived from raw data and that quality control must be used at each stage of data processing;
d) The applicant will monitor the research center on-site or by telephone during the middle and end of the study, when the sub-research center begins to be selected.
e) The designated researcher shall be responsible for formulating and implementing the test rules;
f) (b) Prior to the experiment, all the participants were trained in programs, operations, and GCP;
g) Participants in the test should strictly abide by the provisions of the program, according to the procedures can not be arbitrarily changed;
h) Designate statisticians to be responsible for the statistical processing of comprehensive data;
i) The original records shall be kept by a particular person and kept in each sub-research center after the test.

15. Data preservation

According to the Clinical Trial Management Standard, the researcher should keep the clinical trial data until 5 years after the clinical trial.

16. Publication of papers

All research participants shall strictly keep confidential all information provided by the second Affiliated Hospital of Wenzhou Medical University, and at the same time require other participants and ethics committees to take the same confidentiality measures, without written permission, Information shall not be leaked to others.

The researcher and the applicant own all the data and results of this experiment. The researcher may not publish himself without the consent of the applicant. The applicant reserves the right to sign the paper. The applicant unit is the unit to which the project results belong.