Efficacy of Perioperative Anesthesia care bundle on Prognosis in elderly undergoing Hip Fracture Surgery: a single-center randomized controlled trial

Acronym: EPAPHUS

PRAMARY INVESTIGATOR: TING LI

ORGANIZATION'S UNIQUE PROTOCOL ID: SAHOWMU-CR2017-03-110

Version Number: 1.0

CENTER: THE SECOND AFFILIATED HOSPITAL AND YUYING CHILDREN' S HOSPITAL OF WENZHOU MEDICAL UNIVERSITY

STATISTICIAN: THE SECOND AFFILIATED HOSPITAL AND YUYING CHILDREN' S HOSPITAL OF WENZHOU MEDICAL UNIVERSITY, CLINICAL RESEARCH CENTER

2018-1-29

温州医科大学附属第二医院
育英儿童医院|第二临床医学院
THE 2ND AFFILIATED HOSPITAL AND YUYING CHILDREN'S HOSPITAL OF WENZHOU MEDICAL UNIVERSITY

Study summery

Title	Efficacy of Perioperative Anesthesia care bundle on Prognosis in elderly undergoing Hip Fracture Surgery: a single-center randomized controlled trial
Objectives	1.To evaluate the efficacy of perioperative anesthesia care bundle on prognosis in elderly undergoing hip fracture surgery. 2.To assess the levels of compliance that current anesthesia management strategy of our hospital against the new “guidelines”. 3.To analyze the defects in the current anesthesia management strategy and collect data for further multi-center research.
Study setting	The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University
Study design	Prospective, single center, randomized controlled clinical trial.
Study subjects	Elderly patients with acute hip fracture on one side and need surgical treatment
Inclusion criteria	1.Patients ≥ 75 years old; 2.Patients with hip fracture purely and surgical treatment is scheduled.
Exclusion criteria	1.surgical treatment has been performed after entering hospital; 2. Multiple trauma: multiple fractures; chest, abdomen, pelvis and sacral trauma; severe head injury, etc. 3.Refuse to sign informed consent; 4. Investigator thinks he/she is inappropriate to carry out this study.
Study grouping	1.New “guideline” anesthesia strategy team (Group A) 2.Current anesthesia strategy team (Group B)
Primary outcome	Mortality in 6 months of postoperative
Secondary outcomes	1.The intensity of postoperative pain using Visual Analogue Scale (VAS) 2.The incidence of postoperative complications 3.Mortality for postoperative of 30 days and 1 year 4.Length of time after surgery to death

	5.The level of compliance of new “guideline”(from the ratio of (score:total score)) 6.Length of hospital stay 7.Total cost in hospital and expenditure for anesthesia 8.Cognitive function with Mini-Mental State Examination (MMSE) 9.Overall satisfaction of patients
Statistical analysis	See the statistical analysis scheme
Expected length of progress	Two years

Background

Hip fracture is commonly seen among elderly patients. The incidence of hip fracture in the aged 65 and older is 957.3: 100,000 and 414.4: 100,000 respectively. Most of the elderly hip fracture needs surgical treatment, and the operation can improve the prognosis of patients. The 30-day hospitalization death rate for non-surgical treatment patients was twice as high as those with surgical treatment. However, elderly hip fracture patients always combine a variety of systemic diseases such as cardiovascular diseases (35%), respiratory system diseases (14%), cerebrovascular disease (13%), diabetes (9%), malignant tumor (8%) and kidney diseases (3%), and about 70% of patients are Ⅲ ~ Ⅳ class of American Society of Anesthesiologists (ASA). Their death rate in 6 months of postoperative is still between 12%~23% according to the survey, and 6 ~ 15 times higher than elective hip replacement.

A meta-analysis combines 35 observational studies describes that early surgery (operates within 48 hours) may reduce the risk of postoperative death, odds ratio (OR) = 0.74, with 95% confidence interval (CI): (0.67, 0.81). In addition, the risk of complications such as lung infection or deep vein thrombosis can be significantly increased by missing the best surgical time. But observational studies cannot tell whether a patient has an operation delay due to illness, which in turn affects mortality. This study has reviewed more than 1000 patients in our hospital (complete the operation within 48 hours) and found a mortality of 27% (low), and the mortality after operation within one month is 0.5%; while the length of surgery over 48 hours, mortality at 3.5% within one month after operation. So further randomized controlled studies are needed.

A retrospective study in the United States involving 18158 patients found that compared with general anesthesia, regional anesthesia reduces the inpatient mortality and pulmonary complications, but the continuation of studies (involving 56729 patients) found that local anesthesia does not decrease inpatient

mortality and pulmonary complications, only slightly reduced the length of hospital stay (published in the journal JAMA).The effect of anesthesia on the prognosis of hip fracture remains to be confirmed by further randomized controlled study.

There are researches that adopted a system of perioperative multidisciplinary management strategy that can significantly reduce the mortality of six months after hip fracture, and also lower the stress ulcer, occupancy rate of ICU and hospital readmission rate within 30 days.

The anesthesia research associated with hip fracture have the following several noteworthy viewpoints: (1) Whether new drug xenon (NCT01199276) or low doses of intraoperative sedation (NCT00590707) can reduce the occurrence of postoperative delirium. (2) Whether Dexmedetomidine is useful to the postoperative treatment. (3) Whether the best analgesia method is nerve block (NCT01593319, NCT 1547468 and NCT01638845). (4) Whether perioperative nutrition management can improve the outcome. (5) Anesthesiologists may need more effective clinical evaluation method than ASA to predict the prognosis. But as an important medical treatment for the perioperative period of elderly hip fracture, anesthesia needs to improve the management strategy of itself in order to improve its prognosis. A single anesthetic method or measure may not be sufficient to affect its prognosis.

On April 10th, 2017, the Chinese medical association anesthesiology branch introduced the Chinese elderly hip fracture patients' anesthesia and perioperative management guidelines (hereinafter referred to as "guidelines"), which expounds anesthesia related management strategies for these patients systematically and comprehensively. This study conformed to the guidelines and combined with our clinical practice, as a result, the measures to "improve" summarized (see appendix 1). The clinical anesthesia management strategy will implement in accordance with the appendix 1. Therefore, the purpose of this study is to compare the effect of the new "guideline" with the actual clinical anesthesia management strategy of our hospital on the prognosis of recent elderly hip fracture.

Its significance lies in: (1) The results of this study can be a preliminary answer whether new version of "guidelines" can improve the recent prognosis of elderly hip fracture, and the necessity of the promotion for the new "guidance". (2) The level of compliance of anesthesia management strategy from our hospital with new “guideline”. (3) Analyzing whether the present defects of anesthesia management strategy exist, and collect data for further multicenter study.

References：

1. Moja L, Piatti A, Pecoraro V, Ricci C, Virgili G, Salanti G, Germagnoli L, Liberati A, Ban G: Timing matters in hip frac- ture surgery: Patients operated within 48 hours have bet- ter outcomes. A meta-analysis and meta-regression of over 190,000 patients. PLoS One 2012; 7:e46175
2. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA: Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. ANESTHESIOLOGY 2012; 117:72–92
3. Neuman MD, Rosenbaum PR, Ludwig JM, Zubizarreta JR, Silber JH: Anesthesia technique, mortality, and length of stay after hip fracture surgery. JAMA 2014; 311:2508–17
4. Boddaert J, Cohen-Bittan J, Khiami F, Le Manach Y, Raux M, Beinis JY, Verny M, Riou B: Postoperative admission to a ded- icated geriatric unit decreases mortality in elderly patients with hip fracture. PLoS One 2014; 9:e83795

Study protocol

1. Study assumption: To strengthen the comprehensive treatment of perioperative anesthesia is possible to improve the prognosis of patients with hip fracture and reduce mortality.
2. Study design: randomized controlled pilot study.
3. Subjects: elderly patients with hip fracture on one side and needing surgical treatment.
4. Inclusion criteria:

   (1) Patients ≥ 75 years old

   (2) Patients with hip fracture purely and surgical treatment is scheduled

   Exclusion criteria：

   (1) Surgical treatment has been performed after entering hospital;

(2) Multiple trauma: multiple fractures; chest, abdomen, pelvis and sacral trauma; severe head injury, etc.

(3) Refuse to sign informed consent;

(4) Investigator thinks he/she is inappropriate to carry out this study.

5. Randomized grouping：

The central random system was used to determine the stratification factor by age (whether > 80 years old), POSSUM score (whether more than 40 points), whether there was a tracheal intubation or the auxiliary ventilation of the laryngeal mask. Randomized grouping (1:1).

(1). New “guideline” anesthesia strategy team (Group A)

(2). Current anesthesia strategy team (Group B)

6. Primary outcome

Mortality of postoperative of 6 months.

7. Secondary outcomes

(1). The intensity of postoperative pain using Visual Analogue Scale (VAS) – collected within two days after surgery

(2). The incidence of postoperative complications – collected post-operation to discharge

(3). Mortality for postoperative of 30 days and 1 year – collected within 30 days and 1 year after surgery

(4). Length of time after surgery to death

(5). The level of compliance of new “guideline”(from the ratio of score：total score) – duration of hospital stay, an average of 2 weeks

(6). Length of hospital stay – up to discharge, an average of 2 weeks

(7). Total cost in hospital and expenditure for anesthesia – length of hospital stay, an average of 2 weeks

(8). Cognitive function with Mini-Mental State Examination (MMSE) – within two days after surgery

(9). Overall satisfaction of patients - collected no more than two weeks before discharge

8. Study withdrawal

(1) Subject can withdraw from the study at any time without giving any explanation, and will not lose the right to medical care in the future;

(2) The primary orthopedic physician or anesthesiologist believes that the patient's condition is not suitable for continuing the study;

(3) During the study, if two anesthesia management strategies were found significantly different in prognosis of patients and could be terminated in advance;

(4) The ethics committee demands that the study be terminated.

9. Implementation of anesthesia strategies and data collection

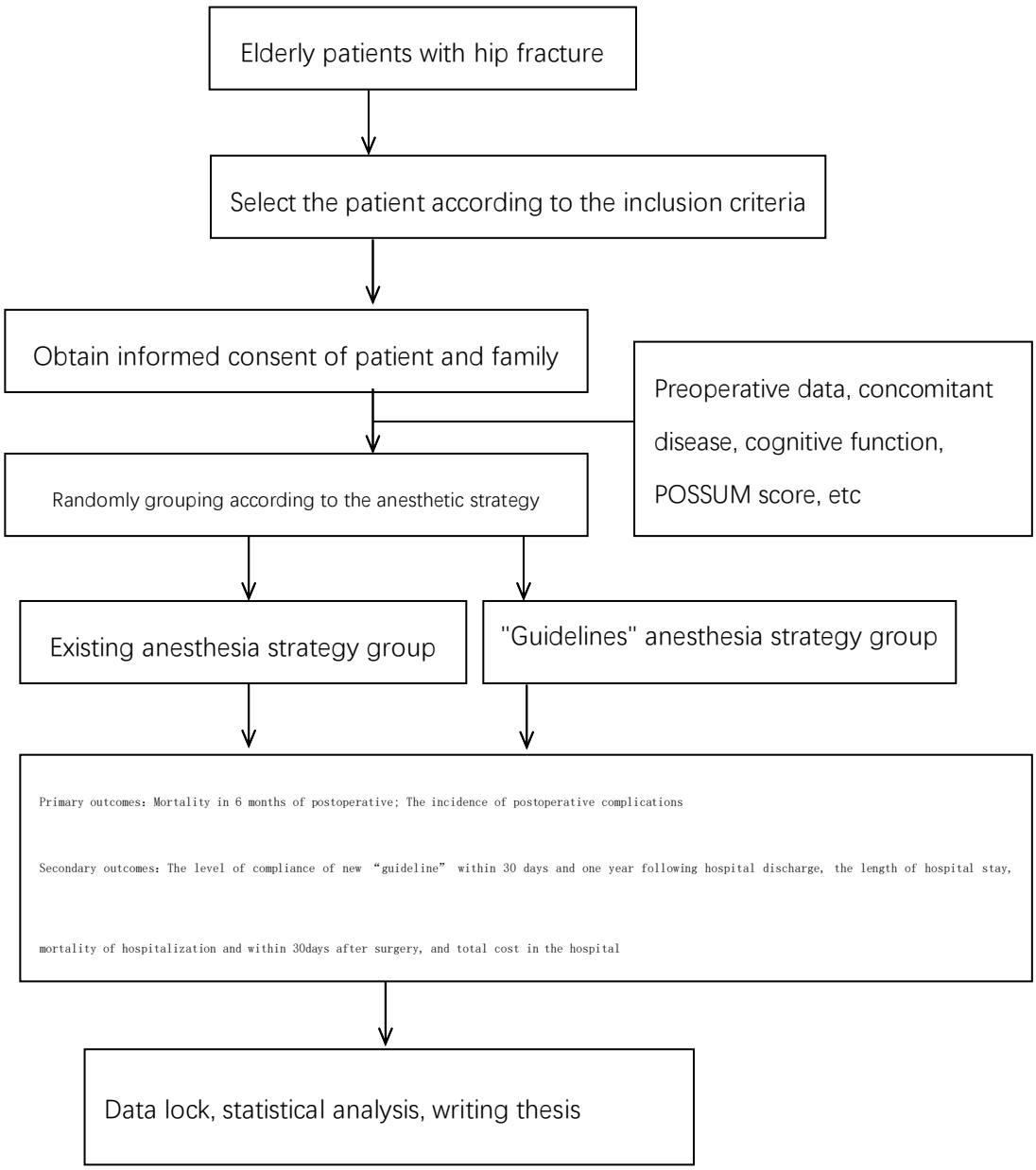
Three anesthesiologists were assigned to adopt the new "guideline" of the anesthetic strategy, and the anesthesia management of group A was carried out. Other anesthesiologists performed the management of group B in accordance with their own routine. A research nurse was assigned to collect data from preoperative and operative procedures and to complete random grouping. Another study nurse (who was blind of grouping condition) was assigned to collect the postoperative data to avoid subjective bias and to blind the observer. The data collection table is table 1 below.

Table1:data collection

Period	Variable	Approach
Preoperative data	Age, gender, address, type of fracture, past medical history, ASA grade, cognitive function(MMSE), POSSUM grade, VAS grade	Medical history, MMSE, visit
During operation	Type of surgery, level of surgeon, type of anesthesia, level of anesthetist, Narcotic drugs and dosage, hypotension, operation duration, estimated blood loss,	Medical history, anesthesia notes, visit

	transfusion volume	
Postoperation	Compliance degree to the new “guidelines”, length of hospital stay, cognitive function(MMSE), VAS grade, fee of hospitalization, fee of anesthesia, adverse event, mortality in hospital, mortality within 30 days, whether withdraw study	Medical history, visit
In 6 months and 12 months	Mortality, living quality	The telephone follow-up

10. **Flow diagram：**



Parameters	(a) Physiological score			
	1	2	4	8
Age	≤60	61-70	≥70	
Cardiac signs	No failure	Diuretic, digoxin, anti-anginal or hypertensive therapy	Peripheral oedema or warfarin therapy	Raised central venous pressure or cardiomegaly
Respiratory signs[a]	No dyspnoea	Dyspnoea on exertion, mild obstructive airway disease	Limiting dyspnoea (one flight) or moderate obstructive airway disease	Dyspnoea at rest (rate ≥30/min) fibrosis or consolidation
Systolic blood pressure (mmHg)	110-130	131-170 100-109	≥171 90-99	≤89
Pulse (rate/minute)	50-80	81-100 40-49	101-120	≥121≤39
Glasgow coma scale[a]	15	12-14	9-11	≤8
Haemogloblin (g/dl)	13-16	11.5-12.9 16.1-17.0	10.0-11.4	≤9.9≥18.1
White cell count[a] (10^9 cells/L)	4-10	10.1-20 3.1-4.0	≥20.1≤3.0	
Urea (mmol/L)	≤7.5	7.6-10	10.1-15.0	≥15.1
Sodium[a] (mmol/L)	≥136	131-135	126-130	≤125
Potassium[a] (mmol/L)	3.5-5.5	3.2-3.4 5.1-5.3	2.9-3.1 5.4-5.9	≥2.8≥6.0
Electrocardiogram[a]	Normal		Atrial fibrillation (rate 60-90)	Any abnormal rhythm or ≥5 ectopics/minute or Q waves or ST/T wave changes
			(b) Operativescore	
Operative severity	Minor	Moderate	Major	Major+
Multiple procedures[a]	1		2	>2
Total blood loss[a] (ml)	≤100	101-500	501-999	≥1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content
Malignancy	None	Minor (serous fluid)	Nodal metastasis	Distant metastasis
Mode of surgery	Elective		Urgent	Emergency

[a]Parameters which are not included in CR-POSSUM. P-POSSUM=Portsmouth-POSSUM; CR-POSSUM=Colorectal-POSSUM

Note: Total loss of blood, abdominal pollution, malignant tumor, type of operation, and lack of data are recorded as 1 point.

11. **Adverse events**

(1) Definition of adverse events and adverse reactions

(Adverse Event, AE) It refers to any adverse symptoms, abnormal signs and abnormal test results that occur after the intervention, whether or not there is a causal relationship with the intervention. Any adverse events, including the subjects offered, by researchers ask or by physical examination, laboratory examination, or other examination methods, medical records should be recorded in the research, and actively processing, strictly follow-up, till to alleviate or being in a stable condition.

(Adverse Drug Reaction, ADR)： The harmful, rather than expected, and causal relationship between the use of drugs in the prescribed dose of normal dosage of the drug.

(2) Records of adverse events

- All adverse events must be tracked. The investigator must document the corresponding parts of the case report and must record the adverse events in detail.

- Adverse event content: symptom name or sign name or disease diagnosis name or laboratory examination of an abnormal indicator.

- Start date of adverse event: the first occurrence of AE or AE related symptoms.

- End date of adverse event: the date of filling in AE or the symptoms associated with AE. If AE still exists, do not fill in the end date.

- Assess the severity of adverse events

    a. Mild: symptoms and signs are present, but can be tolerated and generally do not require treatment

    b. Moderate: symptoms or signs may cause discomfort, daily activities are limited, and appropriate treatment measures may be taken

    c. Severe: no ability to carry out work and daily activities, and should be actively treated

- Measures: to stop the related drugs or treatment, to adopt the treatment measures, and to take no measures.

- The result of adverse events: still exist, improve and have been relieved

- Correlation evaluation of adverse events and anesthesia:

  Evaluation criteria of the five levels:

    a. It must be related: the occurrence of adverse events corresponds to a reasonable time sequence after anesthesia;

       The production of adverse events is more reasonable than others;

The pattern of adverse events is consistent with the adverse reaction patterns produced by such anesthesia.

b. May be related: the occurrence of adverse events is in accordance with the reasonable time sequence after anesthesia;

The occurrence of adverse events is more reasonable than other causes by using anesthesia explanation;

But not for other reasons.

c. May not be related: the occurrence of adverse events does not accord with the reasonable time sequence after anesthesia;

The occurrence of adverse events may be caused by other causes, but it cannot be ruled out by anesthesia;

d. Irrelevant: adverse events are caused or excluded by other causes;

e. Cannot be determined: the occurrence of adverse events does not conform to the reasonable time sequence after anesthesia;

But it was impossible to tell whether it was related to anesthesia, or to explain it in other ways.

12. **SAE (Serious adverse event)**

(1) Severe adverse event definition (SAE)

During the clinical trial, the patient needs to be hospitalized, prolonged hospital stay, disability, affecting work ability, life or death, and congenital malformation.

(2) Serious adverse event handling procedures

When serious adverse events occur, all measures should be taken to avoid permanent damage. From the subjects began the trials to the observation period, any SAE appeared, the researchers must inform the principal investigator within 1 day, 5 days phone call or fax to inform clinical research center, the ethics committee, and fill in the part of the case report about the serious adverse events.

(3) The contact of serious adverse events is as follows: :

Table8 Contacts of SAEs

Center	Contact people	Contact information
The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University	Ting Li	13587876896
The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University	Medical ethics committee	0577-88002560 feykjkcy@126.com
The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University	Good Clinical Practice Institution Office/ Good Clinical Practice Institution Archives Room	0577-88002664、88002738 ywlcsy409@163.com

13. **Quality control and assurance**

(1) Qualification of the researcher

To participate in this clinical study, the researchers must have the corresponding professional technical position in medical institutions and practicing qualification, a testing scheme of the required professional knowledge and experience, has rich experience on clinical trials method or get this unit experienced researchers in academic guidance, familiar with the associated with the clinical trial data and literature that sponsor offered, have the right to control

personnel involved in the test, and handle the equipment needed for this test. Before the clinical trials, through training, the researchers can fully understand the specific contents of clinical trial protocol and indicators.

(2) Clinical trials supervision

This clinical study in inspection work completed by the quality controller that assigned by hospital clinical research center, to ensure the test record and data is accurate, complete and correct; to ensure the test comply with the relevant standard operating procedures, guidelines, manuals, the whole process is following the approved protocol and the relevant laws and regulations.

14. Ethical principles

(1) The ethical basis

The clinical trials follow the Helsinki declaration and our country's regulations and regulations on clinical trials.

(2) Ethics committee

Prior to the test, the test protocol, the prepared informed consent and other information to the patient shall be submitted to the ethics committee (IEC) to review. Prior to the commencement of the trial, the written approval of the ethics committee and the date shall be obtained. Any amendment to the programme shall be subject to the approval of the committee except for the amendments to the management.

(3) Informed consent

The researchers are responsible for obtaining a written informed consent form from each subject. The subject should not be programmed to conduct any experiments prior to the

subject's written informed consent. The researchers should identify the patient's autonomy and prevent some patients from participating in the study for possible benefits and lead to influence on study. These people should not be included in this study. The researchers should also not be treated differently from patients who did not participate in the study, and patients should be entitled to normal treatment.

Before obtaining the written informed consent, the researcher must explain to the prospective patient and his guardian the purpose, method, potential risks and possible discomfort of the study. Researchers should ensure that the participants in the group with plenty of time before asking the details of this study, this research has the responsibility to ensure that patients or their legal guardian all problems get a satisfactory answer.

Participants shall sign the two copies of informed consent and dated, researchers should be signed at the same time, both save a copy of the test. In the process of the test, the rights and interests of patients should be ensured, patients should follow the principle of confidentiality.

In the course of the study, patients can ask the researchers questions at any time, and the researchers have the obligation to introduce the information to the subjects in a timely manner. If there is a major adjustment in the research process, the informed consent form shall be signed from patients again.

15. **Data recording and management**

(1) Data entry and modification

According to the original observation records of the subjects, the researchers recorded the data in a timely, complete, correct and clearly recorded form in the original medical records. Each selected case had to complete the original medical record. The monitoring personnel of the clinical research center shall follow the test plan to confirm the completion of the

electronic case report and be consistent with the original data. Data administrator work on data entry and management. If there are errors or omissions, the researchers should be required to correct them in time and modify the retention of electronic tracks. The electronic case report should be properly saved and backed up.

All data is collected and stored in the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University research data platform. Data administrators designated by the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University are responsible for the data entry and management. The data administrator compiled the table of the electronic case report, work on data entry and management. The questions that exist in the case report form, data administrators should produce question answer sheets, send ask to the researchers, researchers should answer and return as soon as possible. Data manger will modify the data according to the responds from researchers, then confirm and entry again. Fill in and transfer of case report form.

(2) Preservation and summary of information Data audit and lock

All the data in the system questions resolved, "clean" data export to statisticians. Statistical audit by the principal investigator and statistician, and the data is locked. After locking the data, file will no longer be altered.

16. **File preservation and summary**

(1) Preservation of relevant materials

Clinical trials and amendment (signed), the ethics committee approval documents, signed informed consent form, the original medical records, case report form (already filled out, signed, dated) (reserved copy), serious adverse events, etc. Please file away after the study.

(2) Data preservation

The case report was completed by the researcher or the authorized person during the trial period and reviewed by the quality controller from the clinical research center. After the examination of all cases, the researchers will arrange the data entry, inquiry and statistics can

be completed by the clinical research center or statistician arranged by researchers. The original medical records were also saved by the clinical research center of the hospital.

17. Statistical analysis

(1) Sample size estimation: According to the results from literature review, elderly hip fracture had a 12%~23% mortality of 6 months, and the retrospective analysis of 2014 from our hospital found a mortality of 18.3% of 6 months. So under the existing anesthetic strategy, the mortality was 20% (alpha = 0.05, unilateral), and the relationship between the 6-month mortality and sample size of the new "guidance" anesthesia strategy group was as follows:

Mortality within 6 months	10%	12%	14%	16%	17%
1−β=0.8	*155*	*257*	481	1137	4749
1−β=0.9	*214*	355	667	1574	6577

The italic number needs 1 year to complete case collection; The underline numbers are required to complete the case collection in 1-2 years. The numbers on the box are required to complete the case collection by multi-center.

The new "guidelines" anesthesia strategy can decrease the anticipated mortality of 8% to 12% of 6 months, the required sample size of 257 cases, considering that withdraw or lost to follow-up, set the sample size of 300 cases, 1.5 years to complete the data collection.

(2) Analysis dataset

- Full analysis set（FAS）：A collection of all cases of random entry and anesthesia。

  In the analysis of the main curative effect indexes, the missing value of FAS is processed by the method of the current (LOCF), which was observed at the previous point of time.

  In the Case of secondary curative effect indexes, general situation and safety analysis, the Available Case Analysis principle is adopted to carry out missing value processing.

- Per Protocol Set(PPS)： Refers to the collection of cases that meet the inclusion criteria and complete the treatment according to the protocol, which is the case in which the test scheme, compliance and efficacy (at least the primary efficacy) are evaluated.

- Safety analysist set(SAS)：At least the anesthesia was carried out and the actual data were recorded with the safety index。

(3) Contents of statistical analysis

Primary statistical analysis：

- Distribution of two groups: the total shedding rate of the two groups and the loss of shedding rate due to adverse events.

- Comparability analysis: comparison of demographic data and other baseline values

to measure the comparability of the two groups.

- Compliance analysis: compare two groups of patients with the new "guideline" compliance.
- Effectiveness analysis: the main efficacy indexes were analyzed by PP and ITT.
- Factors: Age, sex, drug combination, preoperative complications, ASA grade, POSSUM grade and anesthesia type on each stage of mortality and postoperative complications, using chi-square test or CMH chi-square; to data that conform to the normal distribution, using analysis of covariance, otherwise with H test.
- Safety analysis: First, according to the requirements of adverse reaction correlation, listing table to describe two groups of adverse events and adverse reactions (including the number of cases of adverse events; laboratory examination indexes before and after the trial; the number of "normal turn abnormal" cases and variation rate).The frequency table was used to summarize the comparison between groups using the Chi-square test or Fisher exact test.

(4) Methods of statistical analysis

- The measurement data: The normal distribution was checked in the first place, then t test, paired t test, variance analysis and covariance analysis was adopted to test whether the data was normally distributed. Wilcoxon rank test, matching rank test, H test are used for data that do not conform to normal distribution.
- The enumeration data: Adjusted Chi-square test, Fisher exact test were adopted for enumeration data. The hierarchical data were analyzed by Ridit, CMH. The description of quantitative indicators included mean, standard deviation, median,

minimum and maximum value. The description of the classification index using counts and percentages. All statistical tests were carried out with unilateral test, and the P value was less than or equal to 0.05 was deemed to statistically significant.

(5) Data management and statistical software

- Data management and statistical software

  The integrated information platform of clinical research in our hospital is adopted. The statistical software included SAS9.4 and R 3.4.1 programming.

- Parameters in statistical analysis

  All the hypotheses were one side with 0.05 alpha. Therefore, it states significantly in statistics when p value is lower than 0.05.

Appendix 1 New elderly hip fracture anesthesia strategy

	The measurement of anesthesia	Implementation	Explanation
Preoperative management	是否 48 h 内实施手术 Surgery within 48 hours?		2 points: <48h, 1 point: <72h >48h, 0 point: >72h.
	Complete analgesia (12 hours in admission), VAS<4 points		2 points: <12h , 1 point: <24h and >12h, 0 point :>24h.
	Preoperative transfusion Hb<80～90 g/L, Patients with ischemic heart disease preoperative transfusion Hb<100 g/L.		2 points: complete comply, 1point: partly comply, 0 point: not follow
	Uptaking oxygen within 12 hours after injury, according to blood oxygen status to determine whether to continue to absorb oxygen after 12 hours. Target of SpO2 is 92% ~ 98%. Coexisting chronic respiratory disease or Ⅱ respiratory failure patients should maintain SpO2 in 88% ~ 92%		2 points: complete comply, 1 point: partly comply, 0 point: not follow
Management during operation	Arrange the degree of doctor in vice director or above		2 points: complete comply, 0 point: not follow
	Regional block technology analgesia		2 points: complete comply, 0 point: not follow
	Insulation measure		2 points: complete comply, 1 point: partly comply, 0 point: not follow
	Temperature monitoring		2 points: complete comply, 0 point: not follow
	Arterial Blood Pressure		2 points: complete comply, 0 point: not follow
	Preoperative, intraoperative and		2 points: complete comply, 1 point:

	postoperative blood volume optimization measures		partly comply, 0 point: not follow
术后管理	Maintain Hb no lower than 90 g/L		1 point: partly comply, 0 point: not follow
	Oxygen therapy lasts at least 24 hours, patients with hypoxemia continuously inhaling oxygen		2 points: complete comply, 1 point: partly comply, 0 point: not follow
	Postoperative analgesia		2 points：Nerve block analgesic technique, 1point：Epidural analgesia, 0 point：Only vein or oral or no analgesia

Note: 2 points: completely comply with the specified implementation as required (the desired index), 1 point: partly compliance (partly implemented, lack of time or (take measures not exceeding the expectation index), 0 point: did not comply with the corresponding measures (no measurement implemented).

Investigator declaration

I hereby sign that I have read this project and agree to the content, and will strictly follow this scheme, GCP and relevant national laws and regulations. I will discuss the study and relevant information with researchers I am responsible for to ensure that they are fully aware of this research medicine and how to conduct this clinical trial.

I will ensure that the subjects can receive proper treatment during the event of adverse events, ensure that the subjects take appropriate treatment measures and timely report the occurrence of serious adverse events.

Primary investigator: Ting Li

Primary investigator（signature）: _____ Date: _____