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**Clinical Trial Official Document**

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# Research Protocol: Effects of Enhanced Bispectral Index (BIS) Control with Ciprofol on Early Postoperative Recovery Quality in Elderly Patients Undergoing Knee and Hip Arthroplasty

## (I) Research Content, Research Objectives, and Key Problems to be Solved

### 1. Research Objectives

To clarify whether enhanced BIS control with ciprofol can improve early postoperative recovery quality in elderly patients undergoing knee and hip arthroplasty.

### 2. Research Content

This study adopts a randomized block design. Patients scheduled for knee or hip arthroplasty will be randomly divided into two groups: a group with BIS maintained at 35–50 and a group with BIS maintained at 50–65. The Charlson Comorbidity Index (CCI) is used as the blocking factor, with a block length of 4, and a random allocation sequence is generated using SPSS software.

**Deep anesthesia group: BIS 35–50**

Under continuous EEG monitoring, ciprofol is used to regulate the depth of anesthesia, with a target value of 35–50. BIS is recorded every 1 minute; if the BIS remains outside the target range for 1 consecutive minute, the medication is adjusted immediately. During this period, the BIS value is recorded every 1 minute until it returns to within the target range. The maintenance dose of ciprofol is 0.4–2.4 mg/kg/h, with a recommended starting maintenance dose of 0.8 mg/kg/h. If BIS < 35, the concentration gradient of ciprofol is set at 0.1 mg/kg/h and the ciprofol infusion rate is reduced by 0.7 mg/kg/h; if the BIS remains unchanged, the rate is further reduced to 0.6 mg/kg/h until the BIS returns to above 35. If the ciprofol maintenance dose falls to 0.4 mg/kg/h and the BIS is still below 35, the infusion rate of the analgesic drugs may be reduced until the BIS returns to above 35. If BIS > 50, the ciprofol infusion rate is increased to 0.9 mg/kg/h; if the BIS still shows no response, the ciprofol infusion rate is further increased, up to a maximum of 2.4 mg/kg/h. When the maximum is reached and the BIS is still above 50, ciprofol 0.4 mg/kg may be slowly administered as an intravenous bolus every 2 minutes (with reference to the half-life of ciprofol) until the BIS returns to within the target range, after which adjustment of the drug infusion rate is stopped.

Hemodynamic management: MAP is maintained at 65–120 mmHg to ensure adequate blood supply to the vital organs (especially cerebral perfusion) and to avoid tissue ischemia caused by hypotension.

Postoperative recovery quality assessment tools and indicators:

1. Quality of Recovery-15 (QOR-15 scale): (see Appendix 1) Assessment time points: Day 1, Day 2, and Day 3 after surgery.

**Light anesthesia group: BIS 50–65**

Continuous EEG monitoring is still performed, and ciprofol is used to regulate the depth of anesthesia, with a target value of 50–65. BIS is recorded every 1 minute; if the BIS remains outside the target range for 1 consecutive minute, the medication is adjusted immediately. During this period, the BIS value is recorded every 1 minute until it returns to within the target range. If the BIS value exceeds the target range, the operating procedure is the same as that for the BIS 35–50 group.

Hemodynamic management: MAP is likewise controlled at 65–120 mmHg. The management method is the same as that for the intervention group.

Postoperative recovery assessment: Postoperative recovery quality is assessed using the QOR-15 scale on Day 1, Day 2, and Day 3 after surgery.

**3. Key Problems to be Solved**

By using ciprofol to enhance BIS control, one group of patients will have BIS controlled at 35–50 and the other group at 50–65; the QOR-15 scale is used for assessment to investigate the effect on postoperative recovery quality in elderly patients undergoing knee and hip arthroplasty.

## (II) Research Methods and Technical Route to be Adopted

### 1. Research Methods

### 1.1 Trial Design

This study is a prospective, single-center, randomized, double-blind controlled trial. This study enrolls elderly patients aged 60 years and above, who constitute a special population. All enrolled patients sign a written informed consent form. The informed consent is explained face-to-face by the investigator and includes the research purpose, the group allocation method, differences in the anesthesia regimens, potential risks, additional monitoring items, voluntary participation without compensation, and the right to withdraw unconditionally at any time. For patients with normal cognition but of

advanced age and relatively weak comprehension, the immediate family members are also informed, and the informed consent form is signed jointly by the patient and the family members.

### 1.2 Trial Subjects

Patients requiring elective knee or hip arthroplasty are selected from the Third Department of Orthopedics, General Hospital of Ningxia Medical University.

#### 1.2.1 Inclusion criteria:

- Patients scheduled for elective knee or hip arthroplasty;
- ASA classification I–III;
- Aged 60 years or above;
- Able to answer questionnaires;
- Able to understand and sign the informed consent form.

#### 1.2.2 Exclusion criteria:

Patients meeting any one of the following conditions are excluded:

- A definite history of allergy to anesthetic drugs;
- Pre-existing cognitive impairment;
- Concurrently scheduled for other surgery in addition to knee or hip arthroplasty;
- Severe hepatic dysfunction (Child–Pugh class C or above);
- Long-term regular use before surgery of drugs that affect EEG activity and anesthetic sensitivity, such as benzodiazepines, antidepressants, and antipsychotics;
- Long-term heavy alcohol use;
- Language or communication difficulties, or inability to cooperate with follow-up.

#### 1.2.3 Elimination criteria:

- Mean BIS value exceeding the target range by 5 BIS units;
- Use of sedative drugs other than ciprofol (e.g., midazolam, remimazolam);
- Signal quality index (SQI) < 50;
- Unexpected cancellation of surgery;
- Patients who refuse to participate in this trial.

### 1.3 Research Protocol

#### 1.3.1 Randomization and Blinding

#### 1.3.1.1 Randomization

This study adopts a randomized block design. Patients scheduled for knee or hip arthroplasty are divided into two groups: a group with a BIS target of 35–50 and a group with a BIS target of 50–65. CCI is used as the blocking factor, with a variable or fixed block length of 4, and a random allocation sequence is generated using SPSS 26.0. Group allocation information is sealed in opaque, sealed envelopes in order of enrollment. The random sequence is kept strictly confidential to prevent disclosure of the block allocation pattern. The envelopes are opened by the anesthesiologist on the day of surgery before the induction of anesthesia, thereby achieving allocation concealment. After all cases have been enrolled and all data collection has been completed, and the database has been locked, unblinding is performed centrally by designated personnel. Cases that are emergently unblinded are marked separately and are not included in the primary analysis set.

#### 1.3.1.2 Blinding

All patients and all researchers who assess the outcomes and adverse events are blinded to the group allocation. The anesthesiologist can see the group allocation on the day of surgery. In the deep anesthesia group (BIS: 35–50), the anesthesiologist adjusts the drug dosages in a timely manner based on the information provided by the EEG to maintain the BIS value between 35 and 50. In the light anesthesia group (BIS: 50–65), the anesthesiologist adjusts the drug dosages in a timely manner based on the information provided by the EEG to maintain the BIS value between 50 and 65. To reduce subjective bias of the anesthesiologists, all intraoperative BIS values, drug doses, and vital signs are recorded in real time and objectively in electronic form, without allowing post-hoc alteration. Drugs are adjusted strictly according to the standardized procedure, and arbitrary manual changes to the BIS target are prohibited.

### 1.3.2 Anesthesia Management

#### 1.3.2.1 Pre-anesthesia Preparation

Preoperative assessment: One day before surgery, a professionally trained researcher conducts a preoperative visit to the patients who meet the inclusion criteria, explains the purpose, methods, and confidentiality principles of this study to the patients and their family members, and communicates the anesthetic procedure and related risks. The researcher prepares a general information questionnaire and collects the patients' general information.

Equipment and monitoring preparation: After the patient enters the operating room, the electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NBP), and pulse oximetry (SpO2) are monitored immediately. After cleaning the skin of the forehead with alcohol, the EEG sensor is applied to the patient's forehead, and the equipment is adjusted to ensure stable BIS signal acquisition (signal quality index ≥ 80).

#### 1.3.3.1 General Anesthesia Induction, Maintenance, and Emergence

Anesthesia induction: Anesthesia is induced by the sequential intravenous administration of ciprofol 0.4 mg/kg, sufentanil 0.2–0.4 μg/kg, and rocuronium 0.6 mg/kg. After adequate muscle relaxation, a laryngeal mask airway is inserted and the patient is connected to the ventilator for assisted ventilation, with ventilation parameters set to maintain the end-tidal carbon dioxide partial pressure at 35–45 mmHg.

Anesthesia maintenance: Continuous intravenous infusion of ciprofol 0.6–1.2 mg/kg/h combined with remifentanil 0.1–0.2 μg/kg/min is used to maintain the depth of anesthesia. During the operation, vital signs (HR, NBP, SpO2, PetCO2) are recorded every 5 minutes, and the EEG waveform and BIS are continuously monitored to dynamically assess the state of anesthesia.

Anesthesia emergence: After surgery is completed and the wound is closed, all anesthetic drug infusions are stopped immediately, and sugammadex sodium is administered for reversal of the neuromuscular blockade (the dose is adjusted according to the total amount of rocuronium used and the results of neuromuscular monitoring). When spontaneous breathing has recovered, the patient is awake, hemodynamically stable (HR and NBP fluctuations < baseline ± 20%), and able to perform command-driven movements, the laryngeal mask airway is removed, and the patient is transferred to the post-anesthesia care unit for observation for at least 30 minutes.

### 1.3.3 Analgesia Protocol

Preoperative nerve block: Before surgery, for patients undergoing hip arthroplasty, a femoral nerve combined with lateral femoral cutaneous nerve block is performed using 40 mL of 0.25% ropivacaine; for patients undergoing knee arthroplasty, a sciatic nerve combined with adductor canal block is performed using 50 mL of 0. 1875% ropivacaine. Anesthesia induction is performed after successful blockade, in order to reduce intraoperative anesthetic drug consumption and postoperative pain stress.

Postoperative analgesia management: Immediately after surgery, the patient is connected to a patient-controlled intravenous analgesia pump to provide continuous

postoperative analgesia. If the patient still experiences intolerable pain during analgesia (Visual Analogue Scale, VAS score ≥ 4), additional intravenous nonsteroidal anti-inflammatory drugs (e.g., parecoxib sodium 40 mg) may be given for rescue analgesia.

The nerve block drugs, analgesia pump formula, drug doses, rescue analgesia criteria, and medications are exactly the same between the two groups, thereby excluding interference from different analgesia protocols on the outcome indicators.

**1.4 Interventions**

This study targets elderly patients undergoing knee and hip arthroplasty and uses a random number table method to divide the subjects into a deep anesthesia group and a light anesthesia group.

**Deep anesthesia group: BIS 35–50**

- After induction (successful insertion of the laryngeal mask airway), the anesthesia maintenance phase begins. Ciprofol is administered by intravenous infusion, with a maintenance dose of 0.4–2.4 mg/kg/h and a recommended starting maintenance dose of 0.8 mg/kg/h, titrated in real time according to the BIS index. Remifentanil is simultaneously infused at a rate of 0.1–0.2 μg/kg/min.
- BIS target range: The BIS value is monitored via frontal four-lead EEG, with a target of 35–50. BIS is recorded every 1 minute; if the BIS remains outside the target range for 1 consecutive minute, the medication is adjusted immediately. During this period, the BIS value is recorded every 1 minute until it returns to within the target range. The maintenance dose of ciprofol is 0.4–2.4 mg/kg/h, with a recommended starting maintenance dose of 0.8 mg/kg/h. If BIS < 35, the concentration gradient of ciprofol is set at 0.1 mg/kg/h and the ciprofol infusion rate is reduced by 0.7 mg/kg/h; if the BIS remains unchanged, the rate is further reduced to 0.6 mg/kg/h until the BIS returns to above 35. If the ciprofol maintenance dose falls to 0.4 mg/kg/h and the BIS is still below 35, the infusion rate of the analgesic drugs may be reduced until the BIS returns to above 35. Once EEG burst suppression is detected intraoperatively, regardless of the BIS value, the ciprofol infusion rate is reduced immediately according to the "excessive depth of anesthesia" procedure until the burst suppression disappears, and the duration of occurrence and the management process are recorded in detail. If BIS > 50, the ciprofol infusion rate is increased to 0.9 mg/kg/h; if the BIS still shows no response, the ciprofol infusion rate is further increased, up to a maximum of 2.4 mg/kg/h. When the maximum is reached and the BIS is still above

50, ciprofol 0.4 mg/kg may be slowly administered as an intravenous bolus every 2 minutes (with reference to the half-life of ciprofol) until the BIS returns to within the target range, after which adjustment of the drug infusion rate is stopped.

- Hemodynamic management: MAP is 65–120 mmHg, which is consistent with the recommended thresholds of the perioperative blood pressure management guidelines. If MAP < 65 mmHg (after excluding blood loss and hypovolemia), the sedative/analgesic drugs are first reduced while maintaining the BIS target (e.g., slowing the ciprofol and remifentanil infusions); if the blood pressure still does not recover, norepinephrine is continuously infused at 0.01–0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and adjusted dynamically according to MAP. If MAP > 120 mmHg, the sedative/analgesic drugs are moderately increased without affecting the BIS (e.g., appropriately increasing the ciprofol or remifentanil infusion rate); if the blood pressure remains high, urapidil 12.5–25 mg is administered as an intravenous bolus per dose, repeated at intervals of 10–15 minutes, with a single maximum dose of ≤ 50 mg; continuous infusion of 2–8 $mg \cdot h^{-1}$ may be given if necessary.
- Postoperative recovery quality assessment: Postoperative recovery quality is assessed using the QOR-15 scale on Day 1, Day 2, and Day 3 after surgery.

**Light anesthesia group: BIS 50–65**

- BIS target range: BIS is set at 50–65, and the anesthesiologist adjusts the anesthetic drugs according to the BIS range. BIS is recorded every 1 minute; if the BIS remains outside the target range for 1 consecutive minute, the medication is adjusted immediately. During this period, the BIS value is recorded every 1 minute until it returns to within the target range. If the BIS exceeds the target range, the management is the same as that for the BIS 35–50 group.
- Hemodynamic management: The MAP target is the same as that of the intervention group, 65–120 mmHg, and the principles of blood pressure management are consistent with those of the intervention group.
- Postoperative assessment: Postoperative recovery quality is likewise assessed using the QOR-15 scale on Day 1, Day 2, and Day 3 after surgery, in order to allow horizontal comparison with the intervention group.

### 1.5 Observation Objectives

#### 1.5.1 Primary Observation Indicators

The QOR-15 scale score on Day 1 after surgery.

The scale consists of 15 self-assessment items covering physical comfort, emotional state, self-care, pain, nausea, and other aspects. Each item is scored 0–10, with a total score of 0–150. The higher the score, the better the recovery quality. It is simple and quick, and is commonly used for assessment at time points such as 24 hours after surgery, and is frequently used in clinical and research practice.

### 1.5.2 Secondary Observation Indicators

- QOR-15 scores on Day 2 and Day 3 after surgery;
- The occurrence of intraoperative awareness (assessed using the Brice questionnaire);
- The occurrence of postoperative delirium (assessed using CAM or CAM-ICU);
- The incidence of intraoperative hypotension and hypertension;
- The use of vasoactive drugs;
- The incidence of nausea and vomiting within 48 hours after surgery;
- Length of hospital stay (from admission to discharge);
- Postoperative pain (assessed using the VAS pain scale);
- Postoperative sleep status (assessed using the RCSQ scale).

## 1.6 Statistical Analysis

### 1.6.1 Sample Size Calculation

The QOR-15 score is used as the primary outcome indicator. With $\alpha = 0.05$ (two-sided), a statistical power $(1-\beta)$ of 0.80, an expected mean difference in QOR-15 scores of 8 points between the two groups, and a standard deviation of 15 points, 56 patients are required per group by calculation. Considering a 10% dropout rate, at least 63 patients are needed per group. To ensure the stability of the study and prevent data bias, 65 patients per group are ultimately enrolled, for a total of 130 patients in the two groups.

### 1.6.2 Statistical Analysis

The data are analyzed using SPSS 25. The Shapiro–Wilk test is used to examine the normality of the distribution of continuous data. Normally distributed continuous variables are reported as mean (standard deviation) and are analyzed using the two-sample independent-samples t test. Non-normally distributed data are reported as median (interquartile range) and are compared using the Mann–Whitney U test. The difference in medians and the 95% confidence interval (CI) are calculated using the Hodges–Lehmann method. Categorical variables are compared using the chi-square test

or Fisher's exact test, and the results are expressed as numbers (percentages). In two-sided tests, $P < 0.05$ is considered statistically significant.

### 1.7 Data Collection

#### 1.7.2 Preoperative Routine Data Collection

The researcher prepares a general information questionnaire and collects the patients' general information, including name, sex, age, place of origin, ethnicity, clinical diagnosis, past medical history, complete blood count, liver and kidney function, medication history, food allergy history, surgical history, and anesthesia history, as well as the preoperative VAS pain score, the SAS anxiety self-assessment scale, the preoperative RCSQ (Richards Campbell Sleep Questionnaire), the list of long-term preoperative medications, and the preoperative CAM score. All of the above results are derived from the patients' medical records and the assessments performed during the preoperative visit one day before surgery.

#### 1.7.3 Intraoperative Data Collection

Duration of surgery, total blood loss, total ciprofol consumption, total remifentanil dose, duration of burst suppression, and total duration of hypotension.

#### 1.7.4 Postoperative Data Collection

Length of hospital stay; the occurrence of nausea and vomiting within 48 hours after surgery; the occurrence of intraoperative awareness; the occurrence of postoperative delirium; length of hospital stay; postoperative pain; and postoperative sleep status.

### 1.8 Data Management

(1) The researcher enters the data into the case report forms in a timely, complete, and accurate manner based on the original observations and follow-up results; the principal investigator monitors whether the trial is conducted in accordance with the protocol. After the case report forms are signed by the monitor, they are promptly submitted to the clinical trial data custodian.

(2) After data entry and verification are completed as required, the case report forms are archived and preserved in order of number.

(3) The project leader is responsible for data management.