Quantitative Measurement of Brain State and Neurofeedback Intervention Techniques for the Treatment of Perioperative Neurocognitive Disorders in Elderly Patients

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I. Background of the study

Perioperative neurocognitive disorders (PND) have a prevalence rate of up to 40% in elderly surgical patients and are closely associated with decreased quality of life, long-term cognitive impairment and increased mortality in the first year postoperatively, including postoperative delirium (POD) and delayed neurocognitive recovery (DNR). PND includes postoperative delirium (POD) and delayed neurocognitive recovery (DNR). Currently, neuropsychological tests are the "gold standard" for the diagnosis of PND, but the results are greatly affected by the type of test and the judgement criteria, especially for the elderly, whose basic cognitive function is poor and compliance is not good, and there is an urgent need to develop an objective and rapid test to quantitatively assess the brain state of these patients. In addition to the relative lack of diagnostic techniques, research in the field of PND prevention and treatment has also reached a bottleneck, and no clinical interventions have yet been found that can effectively improve PND. EEG signals can comprehensively reflect the electrical activity of neuronal cells in the cerebral cortex, and contain a large amount of rich information on human physiology, psychology and diseases, which can

assist in the diagnosis and treatment of neurological diseases. With the continuous development of bioelectricity acquisition technology and artificial intelligence technology, through in-depth analysis of EEG signals, brain function/emotional state can be quantitatively assessed, and data-guided brain health promotion training can be achieved.

It has been found that improving the basal cognitive reserve of elderly patients through interventions of different intensities, durations and techniques may have positive implications for the prevention and treatment of PND. An observational study of elderly orthopaedic surgery patients found that encouraging preoperative activities such as reading, singing and writing emails reduced the incidence of PND. A study also confirmed that using a special mobile phone APP to receive 10 hours of "brain exercise" (cognitive rehabilitation training) before surgery can effectively reduce the incidence of postoperative delirium in elderly patients undergoing non-cardiac major surgery. Currently, domestic and international research on "cognitive rehabilitation training" is in its infancy and lacks uniform training tools and assessment methods, but its value in improving perioperative brain health in elderly patients is worth exploring in depth.

The principle of quantitative brain state measurement technology is to use multiple biomedical sensors to amplify and filter biomedical signals through a signal acquisition system, convert them into analogue electrical signals of a certain amplitude, and convert them into digital signals suitable for computer

processing through an A/D converter. Relying on patented algorithms, we dynamically analyse cortical and subcortical brain electricity and use the latest wavelet algorithms in signal processing algorithms to extract and quantify data related to emotional stress, brain habits, brain development, brain capacity, etc., in order to understand the emotional state of the subjects, clarify their brain habits, and assess their brain capacity. In terms of neurofeedback intervention training, we collect physiological data of brain electrical activity in the cerebral cortex through the use of EEG signal acquisition terminals, and extract quantitative values reflecting a variety of specific states of the brain, such as excitation, inhibition, concentration, relaxation, energy consumption, etc., which are then transformed into the corresponding commands in the brain-controlled game, guiding the user to focus on their attention and proactively adjusting their own state. The core of the game is to apply time-varying stimuli under the condition of immediate quantitative reflection of the brain's functional state, so that the brain understands the process of its own state change in real time, and thus learns the explicit regulation of the brain's inhibition and excitation through the brain's self-adaptation and learning ability. Through training, subjects will learn to regulate the brain thinking according to the needs (fast relaxation, continuous relaxation; fast concentration, continuous concentration), reduce irrational chaotic thinking, achieve the purpose of deep brain learning, and then ease the state of tension and anxiety, reduce brain fatigue, improve microcirculation, and gradually restore the brain capacity.

II. Objectives of the study

To evaluate the role of perioperative active rehabilitation training of brain function in elderly patients through a randomised controlled trial using quantitative brain state measurement and neurofeedback intervention system for data guidance in reducing the incidence of perioperative neurocognitive disorders in elderly oncology patients, and ultimately to achieve an integrated solution for assessing and improving perioperative brain state in elderly patients to reduce the incidence of PND and provide new ideas and methods of prevention and control of the disease. methods.

III.Research design

1. Study design: This study is a prospective, multi-centre, randomized parallel-controlled trial.

2. Sample size calculation: Referring to the results of the previous study, assuming that the incidence of POD in the intervention group is 8%, and the incidence of POD in the control group is 18%, and according to the statistical efficacy of 80%, the test level of unilateral 0.025, and the test of superiority using the PASS 15 software Tests for Two Proportions, the calculation of the intervention group: the control group = 1:1, each group needs 177 cases, a total of 354 cases, and each group needs 177 cases, a total of 354 cases. 177 cases were needed, totalling 354 cases. Considering the dropout rate of about 10% (20%) during the clinical trial, the minimum number of cases in the intervention group and the control group were 195 cases each, and a total of 390 cases were

expected to be needed.

Randomisation and blinding: the enrolled patients were randomly divided into intervention and control groups using a random coding table. Each case was enrolled strictly according to the corresponding random code. Brain status measurements and neuropsychiatric examination scales were assessed by different researchers, and the researcher who conducted the scale assessment was not aware of the grouping of the subjects, and the grouping was blinded to the statistician.

3. Inclusion and exclusion criteria

Inclusion criteria: a) patients undergoing elective major surgery (colorectal, pancreatic-gastric, hepatobiliary, thoracic, gynaecological and urological) under general anaesthesia; b) expected duration of the operation was >2 hours; c) age ⩾65 years;

Exclusion criteria: a) refusal to participate in the study; b) preoperative Brief Mental State Examination score <26 or MMSE <24 if the patient's educational level is below high school and active depressive state (GDS-15 score >9); c) undergoing neurosurgery or the surgery itself interferes with the patient's postoperative communication (e.g., tracheotomy); d) severe organ dysfunction; e) undergoing cardiac surgery, neurosurgery, or neurosurgery; and f) undergoing postoperative hospital stay ⩾7 days; and gynecology and urology. (e) Undergoing cardiac surgery or neurosurgery; (f) ASA grade IV or above.

4. Cognitive function assessment

The Montreal Cognitive Assessment (MoCA) was used in this study.

The Montreal Cognitive Assessment (MoCA) was used in this study to assess preoperative and postoperative cognitive function, and the CAM scale was used to assess perioperative delirium (POD).The diagnosis of PND was made using the same criteria as in the ISPND1 study. The Z-scores of all test items in a single patient were summed and divided by the standard deviation of the sum of the Z-scores of all test items in the control group to obtain a total Z-score. PND was diagnosed if a patient had Z-scores of ⩾1.96 for two or more tests or a total Z-score of ⩾1.96.

5. Research process

a) 2 weeks before the operation, the researcher screened the patients according to the nadir criteria and signed the informed consent form;

b) Random numbers were assigned according to the order of enrolment, and according to the study protocol, the Neuropsychiatric Examination Scale (State of Trait Anxiety (STAI) questionnaire, Pittsburgh Sleep Quality Index (PSQI) scale, and Montreal State of Cognitive Abuse (MoCA) scale) were used to examine the patients according to the study protocol, and a baseline brain Functional status test;

c) Patients in the intervention group underwent preoperative brain training using a closed-loop neurofeedback training system (at least 1 hour per day, cumulative preoperative brain training recommended).

d) One day before anaesthesia, the patients will be examined again with the

scale and brain function test, and the anaesthesia will be carried out.

e) The patients were continuously observed for 7 days after the operation, and brain status tests were conducted at a fixed time every day to assess the incidence of POD during the 7-day period, and cognitive function tests were conducted on the 7th and 30th days after the operation, and the diagnosis was made according to the criteria of DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition);

f) Record the number of days of hospitalisation, medical expenses during hospitalisation, non-delirium complications within 30 days after surgery and mortality rate within 30 days after surgery.

6. Anaesthesia programme

Induction of anaesthesia: After the patients were admitted to the room, electrocardiogram, blood pressure, heart rate, oxygen saturation were monitored, intravenous access was established, and the depth of anaesthesia was monitored by the bispectral index (BIS) of electroencephalogram (EEG), and the patients' depth of anaesthesia was induced by intravenous rapid sequential induction using midazolam, sufentanil, propofol and rocuronium bromide, and the dosage of the following medications were administered: midazolam 0.04-0.06 mg/kg, propofol The dosage: midazolam 0.04-0.06 mg/kg, propofol 1-2.5 mg/kg, sufentanil 0.2-0.4ug/kg, and after the patient's consciousness disappeared, rocuronium bromide was slowly injected intravenously at a dose of 0.6-0.9 mg/kg, and after the patient's depth of anaesthesia was reached, the

anaesthesiologist inserted a single-lumen endotracheal tube through the mouth under the clear vision and the position of the catheter was confirmed by auscultation and then connected to the respiratory machine on the end for mechanical ventilation. Ventilation mode: choose volume control mode. The parameters were set as follows: fresh gas flow 2L/min, FiO2 60%, frequency 12 times/min, inspiratory/expiratory ratio (I/E) 1:1.5, tidal volume (Vt) 8 ml/kg, and EtCO2 control at 35-45mmHg.

Anaesthesia maintenance: additional 0.1ug/kg sufentanil IV at the beginning of surgery. Intraoperative anaesthesia maintenance was performed with total intravenous anaesthesia, TCI propofol and remifentanil. The BIS was maintained in the range of 50±5 by adjusting the plasma propofol target-controlled concentration; the initial dose of remifentanil was 1ng/ml, which was adjusted according to the haemodynamic parameters. If the target-controlled infusion of remifentanil reaches 5 ng/mL but the heart rate and blood pressure are still 20% above the basal value, sufentanil is given intravenously at 0.1 μg /kg. If the patient develops hypertension that cannot be corrected with sufentanil, uradil 5 mg is given intravenously to lower the blood pressure and can be repeated after 5 min. Rocuronium bromide 0.2-0.3mg/kg was added intermittently to maintain muscle relaxation until 30min before the end of surgery.

Anaesthesia resuscitation: all anaesthetics were stopped at the end of the surgical suturing of the muscular layer, and the time of stopping was recorded. When the patient showed spontaneous respiration, the muscle relaxation

antagonist neostigmine 2mg and atropine 1mg were given. the time of eye opening was recorded, and the tracheal intubation was removed when the extubation criteria were met, and the time of extubation was recorded. Intraoperative sufentanil and remifentanil dosages (converted to morphine equivalents according to their relative potency), propofol, vasoactive drugs, and muscle relaxant dosages were recorded. The patients were then transferred to the post-anaesthesia care unit (PACU). All patients were administered PCIA for adjunctive analgesia postoperatively. PCIA formula: 2ug/kg sufentanil diluted with saline to 100 ml. PCIA parameter setting: 2mcg/kg sufentanil diluted with saline to 100 ml. PCIA parameter setting: Background 2ml/h, Bolus 0.5ml, Lock-on 15min, PCIA retained for 48 hours. If the postoperative PCIA process is intolerable due to side effects and other reasons, the analgesic mode can be changed after evaluation by the surgeon and recorded accordingly.

PACU: Record the patient's PACU stay, postoperative side effects and their extent in the PACU, nausea and vomiting scores when leaving the room, and pain NRS scores.

7. Primary and secondary endpoints

Primary observation index: incidence of POD within 7 days after surgery.

Secondary endpoints: a) incidence of DNR at 30 days postoperatively; b) non-delirium complications within 30 days postoperatively; c) length of postoperative hospitalisation and medical expenditure during hospitalisation; (d) brain function status measurements in PND patients; (e) 30-day postoperative mortality.

8. Statistical analysis of data

Continuous data were presented as mean ± standard deviation or median (interquartile spacing), and categorical data were presented as number of cases (percentage). （Categorical data were described by the number of cases (percentage). The t-test or Mann-Whitney U-test was used for the comparison of continuous variables. Comparisons of count data were made using the chi-square test or Fisher's exact test, and survival status was analysed using Kaplan-Meier analysis.

9. Exploratory/additional analyses

a) The EEG and brain functional status measurements of patients with clinical diagnosis of PND were extracted and compared with those of normal patients.

The results were compared with those of normal patients to describe their characteristics and to draw the brain state pattern of PND;

(b) Compare the results of the brain function state test with those of the preoperative sleep and anxiety scales to determine the reliability of the test in assessing the perioperative neuropsychiatric state of elderly surgical patients.

10. Definition and management of perioperative adverse events:

1) Definition of intraoperative adverse events:

Bradycardia: defined as HR <50bpm, or if the basal heart rate <69bpm, a decrease in heart rate of 20% of the baseline value;

Hypotension: defined as SBP <90 mmHg, or if basal blood pressure <119 mmHg, a decrease in blood pressure of 20% of the baseline value;

Tachycardia: defined as HR >100bpm, or a rise in heart rate of 20% of the baseline value if the basal heart rate is >83bpm;

Hypertension: defined as SBP > 160 mmHg, and a rise in blood pressure of 20% of the baseline value if the basal blood pressure is > 133 bpm;

Hypoxaemia: SPO2 < 94% for more than 10 min with a decreasing trend;

Intraoperative hypothermia: patient's intraoperative temperature <35.8°C for more than 30 min.

2) Adverse event management:

Bradycardia: single administration of atropine 0.25-0.5mg iv;

Hypotension: single administration of ephedrine 6-12mg iv or phenylephrine 25-50mcg iv;

Tachycardia: correct aggressively after clarifying the etiology (e.g. surgically related blood loss, CO2 pneumoperitoneum, etc.). Intensify analgesia if inadequate analgesia is considered by first giving 0.1mcg/kg sufentanil iv. If no improvement or persistently elevated heart rate give esmolol 20mcg iv post evaluation;

Hypertension: intensify analgesia by first giving 0.1mcg/kg sufentanil IV. If there is no improvement or the blood pressure continues to rise give uradil 5mg iv, after 5min of observation if the patient's blood pressure does not return to normal level then give nitroglycerin 50mcg-100mcg iv until the patient's blood pressure returns to normal level;

Hypoxaemia: firstly, check whether the depth of intubation is too deep leading

to one-lung ventilation and correct it, and secondly, carry out sputum suction to eliminate airway obstruction. If the patient is in the pneumoperitoneum and Trendelenburg position then communicate with surgery to try to reduce the pneumoperitoneum pressure or reduce the patient's head-down angle. If there is no improvement, then oxygen ventilation is performed and pulmonary resuscitation is performed. If the patient's oxygen saturation continues to fall, refer to Serious Adverse Events and remove the patient from the trial;

Perioperative hypothermia: treat with a warming fan or intravenous fluid warming, and continuously monitor the patient's temperature until the patient's temperature is >35.8°C.

3) Serious Adverse Event Definition:

Refers to adverse events that may affect the patient's life safety. The content includes but is not limited to: perioperative dramatic fluctuation of haemodynamic changes, severe hypoxaemia, postoperative severe liver and kidney function impairment. Once a serious adverse event occurs in a patient, the trial should be terminated immediately and reported to the clinical trial management organisation.