Clinical Research Protocol

Clinical Study Protocol for Efficacy and Safety Evaluation of Remote Ischemic Conditioning (Intermittent Pressure Stimulation) in the Treatment of Post-Stroke Insomnia

Research Type: Intervention studies

Research Establishment： The Second Affiliated Hospital of Nanchang University

DATE: April 28,2025

1. Study Protocol Summary

Study Objectives: To preliminary evaluate the efficacy and safety of remote ischemic conditioning (RIC) technology (intermittent pressure stimulation) in the treatment of post-stroke insomnia disorder.

Key Scientific Question: Can remote ischemic conditioning (intermittent pressure stimulation) effectively treat post-stroke insomnia?

Study Content:

2.1 Inclusion and Exclusion Criteria

2.1.1 Inclusion Criteria

[1] Aged 18-80 years;

[2] Meets the diagnostic criteria for ischemic stroke, confirmed in accordance with the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke;

[3] Despite adequate sleep opportunity, the patient has difficulty falling asleep or maintaining sleep, occurring at least 3 times per week for at least 3 months, resulting in distress or daytime functional impairment;

[4] PSQI score ⩾6 and ISI score ⩾8;

[5] Has understood all study content and signed the informed consent form.

2.1.2 Exclusion Criteria

[1] Pre-stroke insomnia;

[2] Comorbid mental disorders (e.g., bipolar disorder, depression, generalized anxiety disorder) or other psychiatric conditions;

[3] Pregnant or lactating women;

[4] Other reasons deemed inappropriate by the researcher.

Withdrawal Criteria: All subjects who signed the informed consent form, passed screening, and were randomized are considered withdrawn if they fail to complete the full clinical trial observation for any reason. Subjects will be classified as withdrawn if: 1) They voluntarily request to withdraw from the study and revoke the informed consent form; 2) They are lost to follow-up.

Handling of Withdrawn Cases: After a subject withdraws, the researcher must record the

reason in the case report form (CRF) for future reference. The withdrawal rate of this clinical trial shall not exceed 20%.

Exclusion criteria : those who meet one of the following conditions after randomization should be excluded : 1) those who do not meet the inclusion criteria or meet the exclusion criteria ; 2) without any test data records ; 3) The test instrument is provided for others to use.

Treatment of excluded cases : The researchers must fill out the reasons for the exclusion in the patient registration form and keep it for future reference.

2.2 Entry time : The entry time of clinical samples should start after the ethical approval of the product is obtained and the clinical agreement is signed, and end after the expected sample size is reached.

2.3 Research methods

2.3.1 Design : Single-center, randomized, double-blind, sham-controlled trial. Experimental group : control group = 1 : 1.

2.3.2 Randomized grouping :

The patients who met the criteria were randomly divided into experimental group (RIC treatment group) and control group (sham-RIC treatment group) according to the ratio of 1 : 1. Allocation sequences of random variable block lengths (e.g., 4 or 6) are generated by independent statisticians. In order to achieve allocation concealment, an envelope numbered in order, sealed, and opaque will be used. Each envelope contains the corresponding group assignment information. The envelope will be kept by a neutral person unrelated to the study. When the subjects were eligible for enrollment, the researchers would receive the next envelope open in order from the neutral custodian to perform the grouping.

3.3.3 Treatment :

On the basis of regular secondary prevention of acute ischemic stroke, all patients were given the following interventions : The experimental group received RIC treatment : The patients ' upper arms were pressurized with a fully automatic ischemic preconditioning therapy instrument (patent number : ZL200820123637.X, model : IPC-906) (pressure = 200 mmHg in the experimental group). The pressure lasted for 5 minutes, followed by a 5-minute rest after deflation, which was an ischemia-reperfusion cycle. Each training was performed for 5 consecutive cycles, once in the morning and once in the afternoon, twice a day, at least 5 days a week, for a total of 4 weeks. The control group received sham-RIC treatment (pressure = 60 mmHg).

2.3.4 Follow-up observation

RIC therapeutic instrument can automatically record the use of patients to ensure treatment compliance. The researchers followed up the patients by telephone every month, and recorded the patient 's condition, treatment and clinical endpoint events to ensure that the patients were treated as required. The patients were followed up at the 4th week after randomization. The patients were

provided with a treatment record sheet as required, and the patients completed PSG, clinical scale evaluation, hematological indicators, carotid ultrasound, TCD, and head MRI / CT review. The assessment scale, hematological indicators, ultrasound, MRI sequence / CT were consistent with the baseline, and the emotional state, neurological deficit, daily living ability, cognitive ability, clinical endpoint events, biological indicators and imaging changes were evaluated. The patients were followed up by telephone at 3 months and 6 months after treatment, and the patients were evaluated for emotional state, neurological deficit, daily living ability and cognitive ability.

2.3.5 Observation indicators

2.3.5.1 Clinical data collection : All patients were recorded in detail before enrollment socio-demographic data, depression-related risk factors, combined medication and family history. The neurological examination and symptom evaluation were performed, and the occurrence of clinical endpoint events was recorded.

Video-guided sleep monitoring (if any) : video-guided sleep monitoring was performed at baseline and at the end of the fourth week after enrollment ;

2 Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI) ;

3 Emotional state assessment : Hamilton Depression Rating Scale (HDRS-17), Hamilton Anxiety Scale (HAMA).

The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) were used to evaluate the functional recovery results and the degree of disability after stroke.

Assessment of activities of daily living : Barthel index (BI), Functional Independence Measurement (FIM).

(5) Cognitive ability assessment : Mini-mental state examination (MMSE) and Montreal cognitive assessment scale (MoCA) were used for overall rapid assessment.

Clinical endpoint events : ischemic events include transient ischemic attack (TIA), ischemic cerebral infarction, myocardial infarction and all-cause death ; bleeding events include skin mucosal bleeding, gastrointestinal bleeding, intracranial hemorrhage and so on.

2.3.5.2 Laboratory index detection : Routine blood routine, biochemical and coagulation indexes were detected. Peripheral venous blood of the subjects was taken, serum plasma was extracted and packaged, and stored in a refrigerator at-80 ° C.

2.3.5.3 Laboratory index detection

1 Inflammatory factors : C-reactive protein (CRP), IL 1 / 4 / 6 / 8 / 10, TNF- α ;

2 Metabolic indicators : blood glucose, blood lipids (biochemical items-total cholesterol, triglycerides, LDL-L, HDL-L, apolipoprotein-AI, apolipoprotein-B), homocysteine, folic acid, Vit-B12 ;

3 Hypothalamus-pituitary-adrenal axis (HPA axis) : cortisol, CRH, ACTH ;

2.3.5.4 Other relevant checks (if any) :

1 Image data : carotid ultrasound, TCD, magnetic resonance : resting state, DTI, MRS, structure image ;

2 24-hour ambulatory blood pressure monitoring : systolic blood pressure coefficient of variation (SBPV), diastolic blood pressure coefficient of variation (DBPV).

2.4 Outcome of the study :

2.4.1 Main Outcomes

1 The sleep efficiency of polysomnography in the fourth week was changed compared with the baseline value.

2 The change of insomnia severity index (ISI) score at the end of the 4th week compared with the baseline value.

2.4.2 Secondary study outcomes

1 The change of PSQI score compared with baseline value ;

(2) Polysomnography monitoring indicators compared with the baseline value changes (sleep latency, sleep efficiency, total sleep time, N1 %, N2 %, N3 %, REM %)

3 clinical symptom score (emotional state, degree of neurological deficit, daily living ability, cognitive function) ;

4 The occurrence of clinical endpoint events : ischemic events included transient ischemic attack (TIA), ischemic stroke, myocardial infarction and all-cause death ; bleeding events include skin mucosal bleeding, gastrointestinal bleeding, intracranial hemorrhage and so on.

2.4.3 Safety evaluation index :

Observe the local skin damage caused by RIC physical therapy, including subdermal hemorrhage at the treatment site, redness and swelling of the upper limbs, weakened arterial pulsation, and withdrawal from RIC physical therapy that cannot be tolerated ;

subcutaneous hemorrhage : ecchymosis (diameter not more than 2mm), purpura (diameter 3-5mm) and ecchymosis (diameter greater than 5mm).

6 The changes of plasma myoglobin after RIC physical therapy.

2.4.4 Sample Size Calculation

This study intends to use video-guided sleep monitoring indicators as the main outcome. Based on the complexity of the previous literature estimation and completion, the sample size of this study was tentatively set to 40 cases (20 cases in the control group and 20 cases in the RIC group), and the sample size was increased according to the later research.

2.Research background information

Stroke is the second leading cause of death and one of the main causes of disability. The incidence of stroke is increasing worldwide. In 2010, the number of patients with first stroke increased by 68 % compared with 1990 [1]. The long-term effects of stroke sequelae include movement ability, cognitive ability, language and communication disorders, as well as emotional problems, difficulties in daily life activities, and social disorders. [2] Sleep often changes after stroke. Insomnia disorder is a risk factor for stroke [3] and an independent predictor of life satisfaction 6 months after stroke [4]. Insomnia disorder is a sleep disorder characterized by frequent and persistent difficulty in falling asleep and / or difficulty in maintaining sleep and leading to poor sleep quality. Insomnia disorder can exist in isolation, or with mental disorders, physical diseases or substance abuse comorbidity, can be accompanied by a variety of functional impairment during awakening [5]. It is reported that in the general population, the prevalence of insomnia is 6 % to 48 % according to different definitions of insomnia [6]. The prevalence of insomnia is higher in stroke patients [7-8]. Insomnia after stroke has a high correlation with depression, disability and fatigue [7,9-10], and has a greater impact on returning to work one year after stroke [10]. Therefore, actively dealing with the insomnia symptoms of stroke patients is conducive to improving the prognosis of stroke patients and improving the quality of life of stroke patients. The current treatment methods are divided into drug therapy and non-drug therapy. Drug therapy mainly includes benzodiazepines and barbiturates, but its clinical application and long-term use are limited due to many adverse reactions, contraindications, and strong dependence [11]. In addition to drug therapy, other treatments for post-stroke depression and insomnia include psychotherapy, strong light therapy, transcranial magnetic stimulation and acupuncture. Some evidence shows that these methods are beneficial to insomnia, fatigue, mood and quality of life. [12] However, the current conclusions are inconsistent and the quality of evidence is low.

Remote ischemic condition (RIC), also known as intermittent pressure stimulation, is a non-invasive and easy-to-use physical therapy that has been used in clinical trials to protect the brain (including ischemic and hemorrhagic stroke), heart and many other organs. Studies have shown that RIC also has the effect of treating depression, insomnia and anxiety, but the research

reports on the treatment of insomnia after stroke are still limited. At present, the mechanism of insomnia after stroke is unknown, and there may be many factors involved, such as inflammatory stress, stroke location, environmental factors, etc. The potential mechanisms of RIC include anti-inflammatory, anti-oxidative stress, immune system regulation and other potential pathways. Therefore, RIC can be used as a promising non-invasive physical therapy for post-stroke insomnia.

Therefore, this study takes patients with post-stroke insomnia as the research object, uses RIC technology to treat patients with post-stroke insomnia, and observes its therapeutic effect and adverse reactions.

References:

[1]FEIGINL，FOROUZANFARH，KRISHNAMURTHIR，et al. Global and regional burden of stroke during 1990-2010：findings from the global burden of disease study 2010[J]. Lancet，2014，383（9913）：245-255.

[2]WUMP，LINHJ，WENGSF，et al. Insomnia subtypes and the subsequent risks of stroke：report from a nationally representative cohort[J]. Stroke，2014，45（5）:1349-1354.

[3] HACKETTML，PICKLESK. Part I：frequency of depression after stroke：an updated systematic review a nd met a-a nalysis of obser vat ional studies[J]. Int J Stroke，2014，9（8）：1017-1025.

[4] PALOMAKIH，BERGA，MERIRINNEE，et al. Complaints of poststroke insomnia and its treatment with mianserin[J]. Cerebrovasc Dis，2003，15（1/2：56-62.

[5] SATEIAMJ. Inter national classif ication of sleep disorders-third edition：highlights and modifications[J]. Chest，2014，146（5）：1387-1394.

[6] OHAYONMM. Epidemiology of insomnia：what we know and what we still need to learn[J]. Sleep Med Rev，2002，6（2）：97-111.

[7] LEPPÄVUORA，POHJASVAARAT，VATAJA R，et al. Insomnia in ischemic stroke patients[J]. Cerebrovasc Dis，2002，14（2）：90-97.

[8] RIEMANND，BAGLIONIC，BASSETTIC，et al. European guideline for the diagnosis and treatment of insomnia[J]. J Sleep Res，2017，26（6）：675-670.

[9] CHENYK，LUJY，MOKVCT，et al. Clinical and radiologic correlates of insomnia symptoms in ischemic stroke patients[J]. Int J Geriatr Psychiatry，2011，26（5）：451-457.

[10] GLOZIERN，MOULLAALITJ，SIVERTSENB，et al. The course and impact of poststroke insomnia in stroke survivors aged 18 to 65 years： results from the psychosocial outcomes in stroke （POISE） study[J]. Cerebrovasc Dis Extra，2017，7（1）：9-20.

[11] Richardson, K, Savva, GM, Boyd, PJ, et al. Non-benzodiazepine hypnotic use for sleep disturbance in

people aged over 55 years living with dementia: a series of cohort studies. HEALTH TECHNOLASSES. 2021; 25 (1): 1-202

[12] YANGJL. Acupuncture treatment for post-stroke insomnia：a systematic review and meta-analysis of randomized controlled trials[J/OL]. Complement Ther Clin Pract，2021，44：101396

3. Objectives and endpoints of the study

Objective : To preliminarily evaluate the efficacy and safety of remote ischemic adaptation (intermittent pressure stimulation) in the treatment of post-stroke insomnia disorder.

Research endpoint

Main endpoints and definitions :

In the fourth week, the sleep efficiency of polysomnography was changed compared with the baseline value.

Changes in the Insomnia Severity Scale (ISI) score at the end of the 4th week compared with the baseline value.

Secondary endpoints and definitions :

1 The change of PSQI score compared with the baseline value ;

(2) Polysomnography monitoring indicators compared with the baseline value changes (sleep latency, sleep efficiency, total sleep time, N1 %, N2 %, N3 %, REM %)

3 Clinical symptom score (emotional state, degree of neurological deficit, daily living ability, cognitive function) ;

the occurrence of clinical endpoint events : ischemic events include transient ischemic attack (TIA), ischemic stroke, myocardial infarction and all-cause death ; bleeding events include skin mucosal bleeding, gastrointestinal bleeding, intracranial hemorrhage and so on.

Safety evaluation indicators :

1 Observe the local skin damage caused by RIC physical therapy, including subdermal hemorrhage, upper limb swelling, decreased arterial pulsation, and intolerance to RIC physical therapy.

Subcutaneous hemorrhage : ecchymosis (diameter not more than 2mm), purpura (diameter 3-5mm) and ecchymosis (diameter greater than 5mm).

2 The changes of plasma myoglobin after RIC physical therapy.

Sample Size Calculation

This study intends to use video-guided sleep monitoring indicators as the main outcome. Based on the complexity of the previous literature estimation and completion, the sample size of this study was tentatively set to 40 cases (20 cases in the control group and 20 cases in the RIC group), and the sample size was increased according to the later research.

4. Research Design

1. Overall research design :

Single-center, randomized, double-blind, sham-control trial. Experimental group : control group = 1 : 1.

2.Randomized grouping :

The patients who met the criteria were randomly divided into experimental group (RIC treatment group) and control group (sham-RIC treatment group) according to the ratio of 1 : 1. Allocation sequences of random variable block lengths (e.g., 4 or 6) are generated by independent statisticians. In order to achieve the distribution of hidden, will be used in order to number, sealed, opaque envelope. Each envelope contains the corresponding group assignment information. The envelope will be kept by a neutral person unrelated to the study. When the subjects are eligible for enrollment, the researcher will receive the next envelope from the neutral custodian in order to open it to perform the grouping.

5.Research Program

Study Objectives: To preliminary evaluate the efficacy and safety of remote ischemic conditioning (RIC) technology (intermittent pressure stimulation) in the treatment of post-stroke insomnia disorder.

Key Scientific Question: Can remote ischemic conditioning (intermittent pressure stimulation) effectively treat post-stroke insomnia?

Study Content:

2.1 Inclusion and Exclusion Criteria

2.1.1 Inclusion Criteria

[1] Aged 18-80 years;

[2] Meets the diagnostic criteria for ischemic stroke, confirmed in accordance with the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke;

[3] Despite adequate sleep opportunity, the patient has difficulty falling asleep or maintaining sleep, occurring at least 3 times per week for at least 3 months, resulting in distress or daytime functional impairment;

[4] PSQI score ⩾6 and ISI score ⩾8;

[5] Has understood all study content and signed the informed consent form.

2.1.2 Exclusion Criteria

[1] Pre-stroke insomnia;

[2] Comorbid mental disorders (e.g., bipolar disorder, depression, generalized anxiety disorder) or other psychiatric conditions;

[3] Pregnant or lactating women;

[4] Other reasons deemed inappropriate by the researcher.

Withdrawal Criteria: All subjects who signed the informed consent form, passed screening, and were randomized are considered withdrawn if they fail to complete the full clinical trial observation for any reason. Subjects will be classified as withdrawn if: 1) They voluntarily request to withdraw from the study and revoke the informed consent form; 2) They are lost to follow-up.

Handling of Withdrawn Cases: After a subject withdraws, the researcher must record the

reason in the case report form (CRF) for future reference. The withdrawal rate of this clinical trial shall not exceed 20%.

Exclusion criteria : those who meet one of the following conditions after randomization should be excluded : 1) those who do not meet the inclusion criteria or meet the exclusion criteria ; 2) without any test data records ; 3) The test instrument is provided for others to use.

Treatment of excluded cases : The researchers must fill out the reasons for the exclusion in the patient registration form and keep it for future reference.

2.2 Entry time : The entry time of clinical samples should start after the ethical approval of the product is obtained and the clinical agreement is signed, and end after the expected sample size is reached.

2.3 Research methods

2.3.1 Design : Single-center, randomized, double-blind, sham-controlled trial. Experimental group : control group = 1 : 1.

2.3.2 Randomized grouping :

The patients who met the criteria were randomly divided into experimental group (RIC treatment group) and control group (sham-RIC treatment group) according to the ratio of 1 : 1. Allocation sequences of random variable block lengths (e.g., 4 or 6) are generated by independent statisticians. In order to achieve allocation concealment, an envelope numbered in order, sealed, and opaque will be used. Each envelope contains the corresponding group assignment information. The envelope will be kept by a neutral person unrelated to the study. When the subjects were eligible for enrollment, the researchers would receive the next envelope open in order from the neutral custodian to perform the grouping.

3.3.3 Treatment :

On the basis of regular secondary prevention of acute ischemic stroke, all patients were given the following interventions : The experimental group received RIC treatment : The patients ' upper arms were pressurized with a fully automatic ischemic preconditioning therapy instrument (patent number : ZL200820123637.X, model : IPC-906) (pressure = 200 mmHg in the experimental group). The pressure lasted for 5 minutes, followed by a 5-minute rest after deflation, which was an ischemia-reperfusion cycle. Each training was performed for 5 consecutive cycles, once in the morning and once in the afternoon, twice a day, at least 5 days a week, for a total of 4 weeks. The control group received sham-RIC treatment (pressure = 60 mmHg).

2.3.4 Follow-up observation

RIC therapeutic instrument can automatically record the use of patients to ensure treatment compliance. The researchers followed up the patients by telephone every month, and recorded the patient 's condition, treatment and clinical endpoint events to ensure that the patients were treated as required. The patients were followed up at the 4th week after randomization. The patients were

provided with a treatment record sheet as required, and the patients completed PSG, clinical scale evaluation, hematological indicators, carotid ultrasound, TCD, and head MRI / CT review. The assessment scale, hematological indicators, ultrasound, MRI sequence / CT were consistent with the baseline, and the emotional state, neurological deficit, daily living ability, cognitive ability, clinical endpoint events, biological indicators and imaging changes were evaluated. The patients were followed up by telephone at 3 months and 6 months after treatment, and the patients were evaluated for emotional state, neurological deficit, daily living ability and cognitive ability.

2.3.5 Observation indicators

2.3.5.1 Clinical data collection : All patients were recorded in detail before enrollment socio-demographic data, depression-related risk factors, combined medication and family history. The neurological examination and symptom evaluation were performed, and the occurrence of clinical endpoint events was recorded.

Video-guided sleep monitoring (if any) : video-guided sleep monitoring was performed at baseline and at the end of the fourth week after enrollment ;

2 Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI) ;

3 Emotional state assessment : Hamilton Depression Rating Scale (HDRS-17), Hamilton Anxiety Scale (HAMA).

The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) were used to evaluate the functional recovery results and the degree of disability after stroke.

Assessment of activities of daily living : Barthel index (BI), Functional Independence Measurement (FIM).

(5) Cognitive ability assessment : Mini-mental state examination (MMSE) and Montreal cognitive assessment scale (MoCA) were used for overall rapid assessment.

Clinical endpoint events : ischemic events include transient ischemic attack (TIA), ischemic cerebral infarction, myocardial infarction and all-cause death ; bleeding events include skin mucosal bleeding, gastrointestinal bleeding, intracranial hemorrhage and so on.

2.3.5.2 Laboratory index detection : Routine blood routine, biochemical and coagulation indexes were detected. Peripheral venous blood of the subjects was taken, serum plasma was extracted and packaged, and stored in a refrigerator at-80 ° C.

2.3.5.3 Laboratory index detection

1 Inflammatory factors : C-reactive protein (CRP), IL 1 / 4 / 6 / 8 / 10, TNF- α ;

2 Metabolic indicators : blood glucose, blood lipids (biochemical items-total cholesterol, triglycerides, LDL-L, HDL-L, apolipoprotein-AI, apolipoprotein-B), homocysteine, folic acid, Vit-B12 ;

3 Hypothalamus-pituitary-adrenal axis (HPA axis) : cortisol, CRH, ACTH ;

2.3.5.4 Other relevant checks (if any) :

1 Image data : carotid ultrasound, TCD, magnetic resonance : resting state, DTI, MRS, structure image ;

2 24-hour ambulatory blood pressure monitoring : systolic blood pressure coefficient of variation (SBPV), diastolic blood pressure coefficient of variation (DBPV).

2.4 Outcome of the study :

2.4.1 Main Outcomes

1 The sleep efficiency of polysomnography in the fourth week was changed compared with the baseline value.

2 The change of insomnia severity index (ISI) score at the end of the 4th week compared with the baseline value.

2.4.2 Secondary study outcomes

1 The change of PSQI score compared with baseline value ;

(2) Polysomnography monitoring indicators compared with the baseline value changes (sleep latency, sleep efficiency, total sleep time, N1 %, N2 %, N3 %, REM %)

3 clinical symptom score (emotional state, degree of neurological deficit, daily living ability, cognitive function) ;

4 The occurrence of clinical endpoint events : ischemic events included transient ischemic attack (TIA), ischemic stroke, myocardial infarction and all-cause death ; bleeding events include skin mucosal bleeding, gastrointestinal bleeding, intracranial hemorrhage and so on.

2.4.3 Safety evaluation index :

Observe the local skin damage caused by RIC physical therapy, including subdermal hemorrhage at the treatment site, redness and swelling of the upper limbs, weakened arterial pulsation, and withdrawal from RIC physical therapy that cannot be tolerated ;

subcutaneous hemorrhage : ecchymosis (diameter not more than 2mm), purpura (diameter 3-5mm) and ecchymosis (diameter greater than 5mm).

6 The changes of plasma myoglobin after RIC physical therapy.

2.4.4 Sample Size Calculation

This study intends to use video-guided sleep monitoring indicators as the main outcome. Based on the complexity of the previous literature estimation and completion, the sample size of this study was tentatively set to 40 cases (20 cases in the control group and 20 cases in the RIC group), and the sample size was increased according to the later research.

2.5 Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) software. The statistical significance test of this study was performed using a two-sided test. The test level was statistically significant at $P < 0.05$.

2.5.1 Descriptive statistical analysis

The treatment of outliers and missing values : according to statistics and professional analysis to determine the choice ; when there are missing values in individual subjects, it is up to the statistics and profession to decide whether to drop out or carry forward the data.

Descriptive statistics : measurement data list mean, standard deviation, extreme value, median, percentage, etc. ; count data lists frequency, percentage.

2.5.2 Statistical test

The measurement data were described by mean ± standard deviation, and compared with the baseline data at the time of enrollment. The repeated measurement analysis method was used (repeated measurement analysis of variance was used for continuous data, and the corresponding repeated measurement analysis method was used for categorical data). The differences between groups and within groups before and after treatment were compared.

Count data using the percentage of statistical description before and after treatment were compared using the 2 test.

Safety analysis : a detailed list of adverse events and adverse reaction cases ; the incidence of adverse events and adverse reactions was calculated between the two groups using the chi-square or Fisher 's exact probability method.

2.6 Key technologies

In this study, patients with first-ever acute anterior circulation ischemic stroke (4 points ≤ NIHSS < 25 points) were randomly divided into experimental group (RIC treatment group) and control group (sham-RIC treatment group) by RIC technique to preliminarily evaluate the efficacy and safety of remote ischemic adaptation (intermittent pressure stimulation) in preventing post-stroke depression.

2.7 Quality control measures

2.7.1 Training : Unified organization scale evaluation and endpoint evaluation training.

2.7.2 Build a randomized system and electronic data / data registration system.

2.7.3 Strengthen follow-up : telephone follow-up twice a week to monitor patients ; rIC real-time monitoring.

2.7.4 Establish a quality control work group, determine the project leader, and organize regular meetings.

2.8 Definition of the end of the study :

End afer reaching the expected sample size.

6. Security Judgement

The ischemic adaptation therapy instrument is a non-invasive training device. During use, there may be local bleeding points at the cuff contact skin or ecchymosis in the forearm and numbness in the arm. These conditions may cause you to be nervous, causing panic, nausea and other symptoms. The above symptoms will gradually recover with your habit of using the device. If there is a small bleeding point in the upper limb skin, the use of the instrument can be suspended (up to 7 days of continuous suspension, 7 days to continue to use), and the towel hot compress bleeding point, generally within a week will be absorbed by itself, and then continue to treat ; if there is a large area of ecchymosis in the upper limb, the treatment can be suspended (for up to 7 consecutive days, continue to use after 7 days) and contact the doctor in time to conduct relevant examinations in a timely manner. The doctor can adjust the relevant drug treatment according to the needs, and can continue to use after the symptoms and signs disappear.

7.Data collection and management

The subjects ' data were collected and managed using the White Tower database.

8.quality control program

The remote ischemic preconditioning therapeutic instrument applied in this study is a patented product of Capital Xuanwu Hospital. It has the basis of early clinical application, can ensure the standardization of treatment technology, and can ensure the safe and smooth progress of the test. And the ischemic preconditioning therapy instrument in the process of this experiment is unified production, with technical support. The distal limb ischemic preconditioning is a non-invasive operation. The instrument is easy to operate and easy to master. It can ensure the application effect of the research object, so as to avoid the technical error of the operation to the greatest extent. During the use of the ischemic adaptation therapy instrument, there may be local bleeding points or forearm ecchymosis at the cuff contact skin, arm numbness, panic and nausea caused by tension caused by the subject 's lack of understanding of the equipment operation. The symptoms will gradually recover with the habit of using the research equipment. Mild symptoms can continue to use the symptoms will gradually ease and disappear, if there is a persistent severe symptoms can not tolerate the situation, the researchers can be given according to the specific circumstances to reduce the number of treatment or stop using the decision, if necessary, to give symptomatic treatment, but these changes need to be recorded in detail in the CRF table. We intend to use the adverse reactions of the limb remote ischemic adaptation therapy instrument as a safety indicator to ensure the smooth progress of the test.

This study will sign informed consent with all patients during the study. Patients participate in the study voluntarily, and patients can voluntarily withdraw at any time of the study, and this will not affect the patient 's relationship with the doctor and will not affect the patient 's medical interests.

The main risks of this clinical study are patient compliance, how to control the quality of the study and how to reduce the loss of follow-up in the cohort study. We will conduct quality control, management and planning of the study through timely mid-term summary to ensure the effective progress of the study. In order to ensure the safety rights and interests of patients, after one month of research, the program and related data of this study were preliminarily analyzed and summarized, and corresponding modifications were made after the defects were found to ensure the smooth progress of this study.

9.Pre-assessment of project risk benefit and risk control plan

1.Benefit / risk assessment

Such benefits include that the patient 's condition may be improved, the risk of insomnia may be reduced, and the patient will be given 14 days of free use of the remote ischemic adaptation device. At the same time, the participation of patients will also contribute to the exploration of a method to prevent this disease. This study may help develop a new prevention method for other patients with similar conditions.

2. Moral ethics

(1) Ethics Committee (should describe how to get the plan approved by the Research Ethics Committee / Institutional Review Board)

Any changes in the clinical trial protocol and document modifications related to the protocol must be approved by the independent ethics committee before they can be implemented.

(2) Patient information and informed consent (sets out who will obtain informed consent from the subject or guardian and how to obtain it, and the terms of compensation for harm caused by participation in the trial ; if you need to collect and use the subject 's data and biological specimens for other studies, additional notes should be made)

The ethical principles of this experiment : This experiment strictly abides by the ethical principles of the World Medical Association 's ' Helsinki Declaration ', including the principle of no harm, the principle of benefit, the principle of respect and the principle of justice.

Subjects ' informed and informed consent : All subjects were informed of the trial and signed the informed consent form in writing, and had the right to withdraw from the study at any time during the trial.

10.Relevant information on human genetic resources

The peripheral venous blood of the subjects was taken, and the serum plasma was extracted from the biological sample bank of our hospital and stored in the refrigerator at-80 ° C.