Clinical study protocol

project name： **Tongyuan acupuncture on consciousness disorder after stroke**

version number/date： V2.0/2023-10-8

major investigators

applicant： **Nanfang Hospital, Southern Medical University**

Summary of research scheme

scheme name	Study on the effect of Tongyuan acupuncture on consciousness disorder after stroke
applicant	Nanfang Hospital, Southern Medical University
major investigators	
research center	Department of Rehabilitation, Nanfang Hospital, Southern Medical University
research object	Stroke patients with conscious disturbance
purpose of research	Objective: To investigate whether Tongyuan acupuncture can improve the consciousness disorder after stroke Secondary objective: To investigate the possible mechanism of action
Research grouping	Trial group: Tong Yuan acupuncture, once a day, 5 days a week for 4 consecutive weeks.Twenty days in total. Control group: pseudoacupoint method, once a day, 5 days a week for 4 consecutive weeks.Twenty days in total.
study design	This study was a randomized, placebo-controlled, single-blind study.Patients with post-stroke consciousness disorder hospitalized in the rehabilitation Department of Southern Hospital were randomly included into the experimental group and the control group, and the experimental group was treated with Tongyuan acupuncture on the basis of routine rehabilitation treatment and drug treatment.The control group was treated with 1cm acupuncture at the same depth beside the selected points of the experimental group. Before intervention, treatment for 1 week, treatment for 2 weeks, treatment for 3 weeks, and treatment for 4 weeks (after completion), follow-up:GCS score, CRS-R scale (Modified Coma Recovery Scale) were performed 4 weeks after discharge to assess the conscious state of the patients, and EEG, brainstem evoked potential and brain fluctuation map were examined before intervention and 4 weeks after treatment.The baseline data of the experimental group and the control group showed no statistical difference through statistical analysis. Conventional rehabilitation treatment and drug treatment were adopted by the current guidelines, and the distribution of cases in the two groups was also random.
Study duration	2023.1.1-2025.12.31
sample size	174
inclusion criteria	(1) It met the diagnostic criteria of Chinese and Western medicine for stroke, and the Glasgow coma score was between 3 and 9 points (the score was scored by the rehabilitation physician, and the patient had not used sedatives and anesthetics on the day of the score);

	(2) The patient's condition is stable, the vital signs are stable, and the onset time of consciousness disorder caused by stroke is confirmed not more than 6 months; (3) Clinical and auxiliary examination confirmed that cerebral infarction or cerebral hemorrhage is the only factor leading to consciousness disorders, excluding other diseases caused by consciousness disorders; (4) Aged between 18 and 85; (5) Family members or authorized clients are informed and sign informed consent; (6) Did not enter other clinical studies at the same time.
exclusion criteria	(1) People with consciousness impairment mainly due to changes in consciousness content or special types; (2) Those confirmed by examination to have carbon monoxide poisoning, brain tumor, brain trauma, brain parasitic disease, metabolic disorders; (3) Patients with severe primary diseases such as liver, kidney, blood system and endocrine system and other diseases with poor prognosis and mental illness; (4) Patients with severe complications such as upper gastrointestinal bleeding and secondary epilepsy; (5) Those who have venous thrombosis and are currently on anticoagulant therapy.
efficiency analysis	Main outcome measure: GCS score Secondary outcome measures: CRS-R Scale
security analysis	In this experiment, acupuncture treatment was used to exclude patients with serious primary diseases of liver, kidney, blood system and endocrine system, and other diseases with poor prognosis and mental illness;If the patient's condition deteriorates during treatment and dangerous events may occur, the clinical observation of the case shall be terminated to ensure the safety of the patient.
statistic analysis	Analysis set Statistical analysis was carried out using full analysis set, coincidence scheme set and security analysis set. Full analysis set (FAS) : Included all randomised participants who had received at least one study intervention and had a measurable baseline stroke. Per Protocol Set (PPS) : In the FAS population, participants with at least one post-intervention awareness scale assessment, good adherence, and no significant violations or deviations from the trial protocol. Safety Set (SS) : defined as subjects who received at least one intervention and were subsequently evaluated for safety. Sample size determination: The sample size is estimated according to

	the group design of two sample rates compared sample size estimation formula $$n = \frac{2\times(U_\alpha + U_\beta)^2 \times P\ (1-P)}{(P_1 - P_2)^2}$$ $$P = \frac{(P_1 * n_1 + P_2 * n_2)}{(n_1 + n_2)}$$ Where, Uα is the first type of error probability U value, Uβ is the second type of error probability, when bilateral α=0.05, unilateral β=0.1, Uα=1.96, uβ =1.28, P1 is the effective rate of the treatment group, P2 is the effective rate of the control group, and P is the rate of the two combinations.According to previous research literature [1], P1 and P2 are estimated to be 79.4% and 54.8%, resulting in n≈76, and the minimum sample size of each group is about 76 cases.As shedding cases were not excluded during the study, the shedding rate was 15%. For the successful completion of the experiment, 87 cases were assigned to each group based on various factors, and 174 cases were required to be included in the two groups. Statistical analysis: All data in the experiment were tested and analyzed for normality, and sPSS 25.0 statistical software was used for analysis and processing.
follow-up	Telephone and video follow-up
statistical method	Baseline data were analyzed by Chi-square test.Measurement data are expressed as mean SD.Univariate analysis of variance was used to compare the difference between groups at the same time point, the difference at different time points in the group, and the difference before and after between the two groups.P < 0.05 was considered statistically significant, and multiple comparisons were performed by Dunnett-t test.
Expected progress	Clinical cases will be collected from 2023.1.1 to 2024.12.30, and insufficient cases due to shedding will be added from 2025.1.1 to 2025.12.30.

List of abbreviations and term definitions

abbreviation	definition
CRS-R	Coma Recovery Scale-Revised
GCS	glasgow coma scale
NIHSS	National Institutes of Health Stroke Scale
FOUR	Full Outline of Unresponsiveness Scale

Test flow chart

item	Screening period		Duration of treatment (weeks)				Four weeks after discharge	Quit
	4weeks~-2days	baseline /-1day	1	2	3	4	Phone or video follow-up	
Informed consent	X							
Demography	X							
Inclusion/exclusion criteria	X							
Medical history	X							
CRS-R scale		X	X	X	X	X	X	
GCS score		X	X	X	X	X	X	
NIHSS score		X	X	X	X	X	X	
FOUR score		X	X	X	X	X	X	
Electroencephalogram		X				X		
brainstem auditory evoked potentials		X				X		
encephalofluctuograph		X				X		

1.research background

1.1 Post-stroke disturbance of consciousness

The development of emergency medicine and neuroscience has enabled more and more patients to survive after stroke, but a considerable number of severe patients remain with impaired consciousness.

1.1.1 The definition and classification of consciousness disorder: consciousness, including the level of consciousness and the content of consciousness. The normal level of consciousness is different from hyper alertness, wakefulness, sleepiness, light sleep, deep sleep, and dream. Awakening state refers to a physiological process of the human brain, which is a periodic alternating waking state with sleep, and depends on the integrity of the so-called "switch" system-the brain stem network structure ascending activation system. The content of consciousness, the so-called higher neural function activities, refers to the psychological processes (mental activities) such as human perception, thinking, memory, emotion and volitional activity, as well as the alertness of maintaining contact with the external environment through speech, hearing, vision, skilled movements and complex reactions. It is a function of the cerebral cortex, which depends on the integrity of the higher neural activities of the cerebral cortex .When the brain stem reticular structure ascending activation system is inhibited or the bilateral cerebral cortex is extensively damaged, the awakening state is weakened, the content of consciousness is reduced or changed, and the ability of the central nervous system to respond to internal and external environmental stimuli is reduced or disappeared, which can produce different degrees of consciousness disorders.

At present, the level of consciousness disorder is generally divided into: lethargy, lethargy and coma. According to the state of awakening, the content of consciousness and the evolution of the course of the loss of physical movement and the degree and breadth of brain function impairment, coma is usually divided into four stages: shallow coma: also called semi-coma, moderate coma, deep coma, excessive coma: also called irreversible coma or brain death. The common disorders of conscious content are: hazy state, hazy consciousness, delirium state,

waking coma. The common clinical types of waking coma are: de-cortical state, inactive silence, persistent vegetative state.

Although some patients have spontaneity or eye opening after stimulation, they lack perception and understanding of internal and external environment and cannot communicate effectively with the outside world, which is called vegetative state (VS) [1]. In recent years, some scholars believe that when patients with vegetative state present fluctuating consciousness, but it is insufficient for reliable communication, it is called minimally conscious state (MCS)[2].

1.1.2 The pathogenesis of disorders of consciousness:

Research on the pathogenesis of consciousness disorders in modern medicine: Intracranial lesions can directly or indirectly damage the cerebral cortex and the ascending activation system of reticular structure, such as widespread acute inflammation of the brain, supratentorial space occupying lesions resulting in uncal herniation pressing on the brain stem and brain stem hemorrhage, which can cause serious consciousness disorders. Extracranial diseases affect consciousness primarily by affecting neurotransmitters and energy metabolism in the brain. At present, the main causes of consciousness disorders are several categories: ① cerebrovascular accident;② Toxic metabolic encephalopathy: such as diabetic coma, carbon monoxide poisoning coma, hepatic encephalopathy coma, etc.; Meningitis, encephalitis;④ Brain trauma;⑤ Brain tumor, epilepsy, schizophrenia, etc. Among them, cerebrovascular accident is the cause of the highest incidence of consciousness disorders.

1.1.3 Assessment of disturbance of consciousness:

The commonly used consciousness assessment methods include behavioral scale assessment, neuroelectrophysiology assessment, neuroimaging assessment and serum marker assessment.

1.1.3.1 Behavioral scale assessment: For patients with consciousness disorders, the most commonly used clinical scales mainly include Glasgow Coma Scale (GCS) and Full Outline of Unresponsiveness scale (Full Outline of Unresponsiveness).FOUR) and revised Coma Recovery Scale-R (CRS-R).GCS

scale is the best choice for consciousness assessment of patients with acute brain injury. CRS-R scale is divided into 6 parts, including auditory (0-4 points), visual (0-5 points), motor (0-6 points), speech (0-3 points), communication (0-2 points) and arousal (0-3 points) assessment, with a total score of 0-23 points, is currently an internationally recognized measurement tool for identifying vegetative state (VS) and minimal state of consciousness (MCS).When patients communication =2 points or movement =6 points, that is, emergence from minimally conscious state (EMCS) [3].MCS was assessed on the following criteria: visual > 1 or auditory > 2 or verbal response > 2 or motor > 2 or communication > 0 or arousal > 2;The evaluation criteria of VS were: vision ≤1 score, hearing ≤2 score, speech response ≤2 score, movement ≤2 score, communication = 0 score and arousal ≤2 score; Clarity of mind was assessed on a scale of exercise = 6 points or communication = 2 points [4-5].However, it is not sensitive to the identification of MCS patients, and it cannot accurately assess patients with closed eye disorder caused by other reasons such as eye trauma [6].FOUR patients with locked-in syndrome can be identified by removing speech ability from GCS [7].The revised Coma Recovery Scale can be used to distinguish subtle differences in the level of consciousness and to monitor the return of consciousness [8].The scale consists of 6 subscales covering auditory, verbal, visual, communication, motor, and arousal levels, and includes 23 hierarchical grading scales. CRS-R and its operation manual are available in Chinese and have been verified for reliability and validity.

1.1.3.2 Neuroelectrophysiological assessment: The most commonly used neuroelectrophysiological evaluation methods are: Electroencephalo Graphic (EEG), Evoked Potential (EP) and transcranial magnetic stimulation combined with electroencephalographic (TMS-EEG).Conventional EEG is widely used to evaluate the prognosis of coma patients by analyzing the frequency, amplitude and waveform of brain waves [9] to evaluate brain function. When the brain tissue is damaged, the rhythm of the brain will change correspondingly, the brain activity slows down, and is proportional to the severity of the injury, mostly from the normal rhythm of α waves into the slower frequency of δ waves and θ waves. EP

has strong objectivity and can avoid the disturbance caused by sleep. Clinically, Brainstem Auditory Evoked Potentials (BAEP) and Somatosensory Evoked Potentials, SEP) and Event Related Potential (ERP) are the most commonly used evoked potentials and can be used to evaluate the prognosis of patients with DOC.BAEP stimulates the ear through sound and induces electrical activity of nerve cells through electrode conduction, which is not affected by physiological changes or drug factors of patients, and can directly reflect the function of the brain stem, but cannot show the function of the cerebral cortex. However, a few coma patients have no brain stem damage and their auditory function can still work normally, and BEAP may be normal at this time. However, in patients with prolonged latency and reduced wave amplitude, or disappearance of wave V, about 90% of these patients will have a severe poor prognosis or death, or a long-term VS state.

1.1.4 Treatment of consciousness disorders:

1.1.4.1 Drug treatment: Naloxone, an opioid receptor antagonist, is a common sedative drug in clinical practice. By inhibiting the production of anti-B-endorphins in the central nervous system, naloxone can quickly release the inhibitory effect of anti-B-endorphins on brain cells, reverse brain cell damage and neurological dysfunction, improve cerebral blood perfusion, and alleviate the hypoxia of edema brain cells.The use of calcium channel antagonists, exogenous gangliosides and free radical scavengers in acute stage of brain injury may help alleviate secondary brain damage, protect brain function, promote disease recovery and improve prognosis, but all of them are grade III clinical evidence.

1.1.4.2 physical agents therapy

1.1.4.2.1： Median nerve stimulation is also used to treat disorders of consciousness, but treatment must be started early and for long enough.Some studies have shown that deep brain stimulation can produce repeatable and sustained improvement in consciousness in MCS patients, and only patients with good brain network preservation through neuroimaging and neuroelectrophysiological examination can be selected for treatment.

1.1.4.2.2：In recent years, neuroregulatory therapy technology is often used in clinical treatment of coma, in which repetitive transcranial magnetic stimulation is a new biological technology that generates local function and electrical activity of neurons at the site of magnetic stimulation under the action of induction magnetic field caused by induction current. It is widely used in the treatment of nervous system diseases because of its advantages of easy operation, non-destructive, painless and high safety. Repetitive transcranial magnetic stimulation mainly applies pulsed magnetic field to scalp, induces induced current in the brain tissue of patients, and induces neuronal depolarization through neuronal stimulation, thus generating evoked potential. Other methods include transcranial electrical stimulation, high cervical posterior cord electrical stimulation, and acupuncture, which have only been studied in small or clinical studies with limited evidence. Although hyperbaric oxygen is widely used, there is a lack of grade I clinical evidence, and there is no study that clearly applies to the pressure, duration and other indicators required for patients with consciousness disorders.

1.1.4.3：Neurosurgical treatment: persistent vegetative state (PVS) surgical rehabilitation and awakening, mainly including spinal cord stimulation (SCS) and deep brain stimulation (DBS)[10].

SCS and DBS are invasive electrical stimulation with high cost and need surgical intervention, so it is difficult to promote them in basic hospitals. Other complications may occur, such as electrode displacement, electrode fracture, superficial infection, and epidural abscess.

At present, the clinical treatment of patients with consciousness disorder is still mainly comprehensive rehabilitation, including somatotherapy strategies and treatment measures to promote consciousness improvement.

1.2. Application status of acupuncture in the treatment of consciousness disorders:

Acupuncture has been used to treat the sequelae of stroke in China for more than 2000 years. Some modern Chinese medicine home acupuncture treatment of brain injury after consciousness disorder, found to have a certain effect.

Bao Yingcun et al. [11] randomly divided 100 patients with vegetative state of traumatic brain injury into observation group and control group. Both groups were given routine clinical treatment. The control group was given rehabilitation and hyperbaric oxygen therapy. Observation group was given "Xingnaokaiqiao" acupuncture method on the basis of control group, and the points were Neiguan, Shuigou, Sanyin Jiao, Qize, Weizhong, Hegu and Taichong. All patients were treated once a day for 5 days and rested for 2 days a week for 30 days. The scores of Glasgow Coma Scale (GCS) and Modified International Coma Recovery Scale (CRS-R) were observed before treatment and at 10, 20 and 30 days after treatment, and the wakefulness rate of the two groups was compared after treatment. Results After 10, 20 and 30 days of treatment, GCS score and CRS-R score of 2 groups were increased compared with before treatment ($P < 0.01$), and observation group was higher than control group ($P < 0.01$).After treatment, the wakefulness rate of the observation group was 16.7% (8/48), which was higher than that of the control group (12.0% (6/50, $P < 0.01$).

Ma Liang et al. [12] took 60 patients with consciousness disorder after craniocerebral injury as research objects. The control group was treated with routine awakening promotion method, and the observation group was treated with Tongdu Xingnao acupuncture method on the basis of the control group. It was found that the total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$).The waking time, feeding time, getting out of bed time and discharge time of observation group were shorter than those of control group ($P < 0.05$).After treatment, the scores of the revised Coma Recovery Scale (CRS-R) and Total non-responsiveness Scale (FOUR) in the observation group were higher than those in the control group ($P < 0.05$).After treatment, the levels of neuron-specific enolase (NSE) and astroglia-derived protein (S100β) in observation group were lower than those in control group, and the levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in observation group were higher than those in control group ($P < 0.05$).

Ma Qian et al. [13] included 91 cases of acute stroke patients with

consciousness disorder for study, and the acupuncture group was given the treatment of wakefulness and resuscitation acupuncture. There was significant difference in Glasgow scores between the acupuncture group and the control group at 10 and 20 days of treatment.

Xu Junfeng et al. [14] applied head electroacupuncture across the Central Line, used high-intensity stimulation combined with amplitude modulation, frequency conversion, instantaneous stimulation and continuous stimulation, and combined with integrated rehabilitation programs of traditional Chinese and Western medicine, Western medicine, exercise therapy, sensory stimulation and other traditional Chinese and western medicine, and achieved certain effects on the awakening of patients with persistent vegetative state.

1.3. Point selection and application of Tongyuan needle method:

Tongyuan acupuncture method was created by Professor Lai Xinsheng in more than 40 years of clinical practice. It has the characteristics of regulating Yin and Yang, regulating yuan and treating God, unique acupoint group, wide indication and remarkable curative effect. Tongyuan needle method is short for the dichotomy of Tongduyangshen and qi qi. According to different diseases or symptoms, the dichotomy can be used in combination or alone, or combined with syndrome differentiation and disease differentiation, or combined with acupuncture and medicine. It breaks through the limitations of the limbs meridian points used in the past, integrates the various forms of acupoint compatibility such as Shu Mu matching, upper and lower matching, left and right matching, and takes the two veins of Ren Du as the focus of meridian point selection, giving full play to the meridians' therapeutic effect of guiding the brain through the channel and regulating the yuan God and Ren pulse connecting the kidney as the return of qi. It is a new acupuncture and moxibustion prescription system of "Fuzhengdispelling evil" and "treating disease must seek the original".

The acupuncture method of Tongyuan includes two parts: Tongdu, qi and yuan.The main points of the head Baihui, the front top, the back top, the seal hall, the middle, the Dazhui, the back of the five viscera are selected; The qi Guiyuan is

mainly composed of Tianshu, Qi Hai, Hui Hui, Guanyuan, Shanzhong, Zhongwan abdominal Ren pulse and Mu points. The two can be used separately and combined, and most of the matching points are five transfusion points below the elbow and knee. Acupuncture and acupoint prescription composed under the guidance of this principle is suitable for many internal injury diseases and difficult diseases, such as female infertility, male infertility and other urogenital diseases, stroke and related encephalopathy, spinal limbs and neuromotor function diseases, dementia, depression, headache, insomnia, intellectual disability, epilepsy and other psychiatric diseases. Chronic cough, bronchial asthma, urticaria, hepatitis, colitis, gastritis, chronic prostatitis, polycystic ovary syndrome and so on have obtained satisfactory curative effect. Some scholars have found that Tongyuan acupuncture can significantly improve the cough reflex ability of patients with tracheotomy after stroke, control lung infection, improve swallowing function, and thus improve the success rate of clinical extubation.

It has been confirmed that scalp acupuncture based on Baihui can improve the volume and area of cerebral infarction [15].

1.4 Research status of acupuncture comfort control design

The design of acupuncture placebo control in clinical trials has always been a difficult point. The ideal acupuncture placebo control should have the following characteristics: first, it has no or very little physiological therapeutic effect; The second is that it is no different or as similar as possible to the trial intervention in every other respect, so that its psychological impact on the patient is minimal, and it is not easy to destroy the blind method. Acupuncture consolation control generally adopts false acupuncture point method or false acupuncture method. The depth of acupuncture can be divided into three degrees: shallow acupuncture, the same depth and non-transdermal. The general requirements of shallow needling are to Pierce the needle body only into the superficial surface of the body about 3~5mm, do not twist and other techniques to avoid qi; The same depth means that the acupuncture body of the comfort acupuncture group and the treatment group have the same depth into the human body; Transdermal is the use of a certain method or needle,

giving people the illusion that the needle body into the human body but does not actually Pierce the skin. The selection of acupuncture sites can be divided into three categories: non-meridian point, different meridian point and the same point. Non-meridian point is no name, no function, no positioning point, including the selection of fixed non-acupoints or false acupoints near the original meridian point (the original acupoint is opened outward by 5~20mm);Different meridian points mean that although they are clear acupoints, they have no therapeutic effect on the disease under study. The same point means that the selected acupoints are consistent with the treatment group [16-17].From the perspective of practical clinical operability and the implementation of the blind method, the control group of this experiment selected the original acupuncture point to open outwards by 1cm, with the same depth of acupuncture.

As for the study on the physiological effects of fake acupuncture points, some scholars collected clinical trial literature that used functional magnetic resonance imaging (fMRI) as the observation index to compare the changes in brain activity after true point acupuncture and fake point acupuncture, and used SDM-PSI software to conduct a meta-analysis of voxel-based whole brain fMRI imaging. It was found that acupuncture at the true point had more significant effects on brain connection, higher nervous function and motor regulation than that at the false point [18].

1.5 Current research status of encephalofluctuograph:

Encephalofluctuograph (EFG) is a non-invasive electrophysiological technology used to detect the function of brain neurotransmitters. It collects 10 min brain waves and extracts ultra-slow waves for analysis (frequency range: 1~255 mHz). A large number of experiments have proved that dominant ultra-slow waves are related to the activity of neurotransmitters in brain. Each neurotransmitter has a one-to-one correspondence (cryptographic relationship) with ultra-slow waves of a particular frequency. Through experiments, the code of several common neurotransmitters has been deciphered, which are acetylcholine, norepinephrine, gamma-aminobutyric acid, glutamic acid, 5-hydroxytryptamine and dopamine

[19-20].At present, many domestic scholars have used brain fluctuation graph to study the changes of neurotransmitter power in different nervous system diseases, especially in the study of neurodegenerative diseases, cerebrovascular diseases, emotional disorders and other diseases, and have obtained similar results in different research groups.

He Renhong et al. [21] included 39 patients with brain injury, and then collected the neurotransmitters in the brain during EEG assessment (detected by brain fluctuation map). The detection indexes included the transmitter power, relative power and index analysis of γ-aminobutyric acid, 5-hydroxytryptamine, norepinephrine, dopamine and other transmitters. The results showed that the brain transmitter power of the poor outcome group was significantly lower than that of the good group. Logistic regression analysis showed that gamma-aminobutyric acid and serotonin were the factors that could significantly affect the outcome. The authors suggest that in the clinical rehabilitation of brain injury, therapeutic methods that can improve the efficacy of gamma-aminobutyric acid and serotonin transmitters should be considered.

At present, the study on the effect of acupuncture on awakening has been developed from behavior to molecular mechanism.

2.purpose of research

2.1 Main Objective: To confirm the effect of Tongyuan acupuncture on consciousness disorder after stroke;

2.2 Secondary objective: To explore the mechanism of acupuncture intervention in post-stroke consciousness disorder.

3.study endpoint

3.1 Primary endpoint: GCS score.

3.2 Secondary endpoints: CRS-R Scale (Coma Recovery Scale–Revised), EEG(electroencephalograph), BAEP (Brainstem Auditory Evoked Potential)，and EFG (Encephalofluctuography).

4.experiment design

This clinical study was a randomized (1:1), single-blind, single-center, parallel

controlled clinical study. Seventy-two patients were recruited. After signing the informed consent, patients meeting the inclusion/exclusion criteria will be randomly assigned to the experimental group (Tongyuan acupuncture) and the control group (fake acupoint method) in a 1:1 ratio, and a total of 72 patients will be recruited.

Subjects randomized to the trial group will be treated with regular rehabilitation therapy and drug therapy + acupuncture once a day, 5 days a week for 4 weeks. Twenty days in total.

Subjects randomized to the control group will be treated with regular rehabilitation and drug therapy + pseudoacupoint method once a day, 5 days a week for 4 weeks. Twenty days in total.

Safety and study compliance were assessed for each subject at 1, 2, and 3 weeks of initial treatment and at the end of the intervention, and treatment guidance was given by the investigator. A safety assessment and survival follow-up were conducted 4 weeks after discharge, and the corresponding consciousness scale was evaluated.

4.2 Randomization and blinding

4.2.1 randomize

In this study, patients meeting the inclusion criteria will be randomized into the trial group and the control group in a 1:1 ratio.

Random numbers generated by SPSS software were used to include eligible subjects.

4.2.2 Blind state/broken blind

Because of the particularity of acupuncture treatment, it is impossible to implement double blindness, so this study implemented single blindness. The realization of single blind conditions: false acupoint method, and Tongyuan acupuncture method are adopted acupuncture methods so that patients and family members do not know the grouping. Moreover, trial designers, scale evaluators, acupuncture operators, and data statisticians do not know the status of treatment groups of individual subjects.

Blindness is crucial to the integrity of this clinical study. However, in the event

of a medical emergency or pregnancy event in an individual subject, the information about the study treatment received by the subject is so important to the subject's management that the treating physician will need to de-blind the subject.

Before blinding a subject's treatment, the investigator should determine that this information is necessary, that it will change the subject's immediate treatment. In many cases, especially when the subject's emergency condition is clearly unrelated to the study protocol, it can be assumed that the subject is being treated with the active drug without the need for blind treatment.

The need for blindness should first be discussed with the responsible medical monitor before determining the best response.

After unblinding, the subjects will withdraw from the study and terminate treatment. Safety follow-up and survival follow-up are still required.

5. Subject population

The subjects of this study were patients with post-stroke consciousness disorder.

5.1 diagnostic criteria

(1) Patients diagnosed with cerebral hemorrhage and cerebral infarction according to the Chinese Guidelines for the Diagnosis and Treatment of Cerebral Hemorrhage 2019 and the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 authored by the Neurology Branch of the Chinese Medical Association;

(2) Disturbance of consciousness dominated by altered degree of arousal: refer to the patients diagnosed as disturbance of consciousness in the 8th edition diagnostic criteria of Neurology, the textbook of the 13th Five-Year Plan of the National Health Commission in 2018.

5.2 inclusion criteria:

(1) sign the informed consent voluntarily;

(2) met the above diagnostic criteria, and the GCS score was between 3 and 9 (the score was scored by a rehabilitation physician, and the patient had not used sedatives or anesthetics on the day of the score);

(3) The patient's condition is stable, vital signs are stable, and the onset time of consciousness disturbance caused by stroke is confirmed to be less than 6 months;

(4) Cerebral infarction or cerebral hemorrhage confirmed by clinical and auxiliary examination is the only factor causing consciousness disorder, excluding other diseases caused consciousness disorder patients;

(5) those aged between 18 and 85;

(6) Family members or authorized principals know and sign informed consent;

(7) did not enter other clinical studies at the same time.

5.3 exclusion criteria：

(1) People with consciousness impairment mainly due to changes in consciousness content or special types;

(2) confirmed carbon monoxide poisoning, brain tumor, brain trauma, brain parasitic disease, metabolic disorders;

(3) Patients with severe primary diseases of liver, kidney, blood system, endocrine system and other diseases with poor prognosis, mental diseases;

(4) have upper gastrointestinal hemorrhage, secondary epilepsy and other serious complications;

(5) Those who have venous thrombosis and are currently on anticoagulant therapy;

(6) patients judged by the investigator to be unsuitable for participation in this trial.

5.4 Exit criteria

Subjects withdrawing from the study for any reason are required to document their reasons, including, but not limited to, the following:

1) The subject withdraws the informed consent;

2) The sponsor terminates the study;

3) More serious adverse events affect participants' continued participation in the trial;

4) serious program violations/deviations;

5) pregnancy;

6) Poor compliance;

7) Loss of follow-up;

8) The investigator and/or sponsor considers that the subject's medical condition may endanger the subject's safety or that the continuation of the study will harm the subject's health;

9) Death;

10) Others.

5.5 Termination criteria

Test termination criteria (if any of the following tests are met, the trial is terminated) :

1) Serious safety problems occur during the test;

2) Major errors in the clinical trial protocol are found in the trial;

3) The Ethics committee requests the termination of the trial.

6. Research treatment techniques:

6.1 Test instrument: Tianxie brand 25mm× (25mm~40mm) millimeter needle produced by Suzhou Medical Supplies Factory Co., LTD.

6.2 Non-research drugs: common first-line drugs for the treatment of hypertension, such as amlodipine, nifedipine, nirendipine, metoprolol, valsartan, etc.; The commonly used first-line drugs for the treatment of diabetes such as metformin, acarbose, insulin aspartate, insulin glargine, etc.

6.3 Treatment methods:

experimental group selected points: Baihui, Zhongwan, Guanyuan, Qihai, Tianshu (double);Point selection criteria: the national standard "Name and Location of points" (GB/T12346-2006).Intervention time: once a day, 5 days a week for 4 consecutive weeks. Twenty days in total;

Point selection of the control group: acupuncture treatment was performed 1cm beside the point selection of the experimental group.

6.4 Intervention discontinuation Indicators: Subjects will withdraw from the study if they have the following indications during treatment:

(1) If the patient's condition deteriorates during treatment and there is a possibility

of dangerous events, the clinical observation of the case should be terminated according to the doctor's judgment;

(2) In the course of treatment, the patient's family members give up the clinical treatment halfway, request the doctor in charge to terminate the treatment, and terminate the clinical observation of the case;

(3) The treatment is effective, but the patient's family uses other treatment methods in order to speed up the therapeutic effect, and cannot determine the efficacy of the clinical study, and the clinical observation of the case is terminated.

6.5 drug combination： Information on all drug combinations during the study period (generic name, purpose of administration, dose, time of administration, etc.) must be recorded in detail in the case report form. Treatment with other investigational drugs is prohibited during the study period.

7. Research methods and procedures

All subjects need to sign informed consent before screening, and successful subjects can enter this study. According to the protocol, the experimental group and the control group were treated respectively, and the effectiveness and safety were evaluated at 1, 2, 3 and 4 weeks. Telephone and video follow-up were conducted 4 weeks after discharge for statistical analysis. Treatment continued until subjects completed the 4-week course or met any of the exit criteria. Participants are evaluated comprehensively by the investigator, and if it is determined that the continuation of the experimental treatment can bring clinical benefit to the subject, the treatment can be continued until the subject's PD, intolerance, or death.

7.1 screening machine

All subjects were required to complete relevant examinations during the screening period before enrollment, and were screened according to the admission criteria.

(1) Sign informed consent;

(2) Record demographic data: date of birth, gender, initials;

(3) Medical history and physical examination (including vital signs, height, weight, physical examination of the whole body system; Past and present history of HCC,

etiology;

(4) Other laboratory tests, such as blood routine (white blood cells, neutrophils, hemoglobin, platelets, etc.), urine routine (urine white blood cells, urine protein, red blood cells), stool routine (stool occult blood);

(5) Liver function (albumin, aminotransferase), kidney function (filtration rate, creatinine), neuron-specific enolase, interleukin 6, etc ;

(6) Consciousness level assessment: GCS score.

7.2 therapeutic session

(1) Treatment plan:

Test group: Subjects will use conventional rehabilitation therapy (exercise training, physical factor therapy, etc.) and drug therapy (such as controlling blood pressure, blood sugar, promoting microcirculation, nutritional nerve and other supportive treatment) + Tongyuan acupuncture method: point selection: Baihui, Zhongwan, Guanyuan, Qihai, Tianshu (double);Point selection criteria: the national standard "Name and Location of points" (GB/T12346-2006).Intervention time: once a day, 5 days a week for 4 consecutive weeks. Twenty days in total.

Control group: Subjects will receive conventional rehabilitation treatment (exercise training, physical factor therapy, etc.) and drug treatment (such as symptomatic support treatment for controlling blood pressure, blood sugar, promoting microcirculation, nutritional nerve, etc.) + pseudacupoint method (acupuncture treatment is performed 1cm apart from the selected points of the experimental group), once a day, 5 days a week, for 4 consecutive weeks. Twenty days in total.

(2) Evaluation:

Consciousness levels were assessed before intervention, at 1, 2, 3, and 4 weeks of treatment, and 4 weeks after discharge: GCS score, NIHSS score, CRS-R Scale (Modified Coma Recovery Scale), and FOUR scale score . Electroencephalogram, brainstem auditory evoked potentials and encephalofluctuograph were examined before intervention and at 4 weeks of treatment.

7.3 follow-up period

Consciousness level assessment: GCS score, NIHSS score, CRS-R scale, FOUR

scale score.

8. evaluation index

8.1 Evaluation of effectiveness: Before and after the intervention and at 4 weeks of treatment: GCS score.

8.1.1 Glasgow Coma Scale (GCS) : 3 to 15 points

Open eyes (E) : 1-4 points; Vocalization (V) : 1-5 points; Exercise (M) :1-6 points.

The consciousness improvement rate of each patient was calculated according to the following formula:

Consciousness improvement rate of each patient = (score after treatment - score before treatment)/score before treatment ×100%

Consciousness improvement rate ≥20% is effective, 15%≤ consciousness improvement rate < 20% is effective, good consciousness

Turnover rate < 15% is invalid

Efficiency = (obvious + effective)/(obvious + effective + ineffective) ✖100%

8.1.2 Revised Coma Recovery Scale (CRS-R) : 0-23 points

The minimum state of consciousness (MCS) was assessed as: visual > 1 or auditory > 2 or verbal response > 2 or motor > 2 or communication > 0 or arousal > 2;

The evaluation criteria of persistent vegetative state (VS) were: vision ≤1 score, hearing ≤2 score, speech response ≤2 score, movement ≤2 score, communication = 0 score and arousal ≤2 score;

Clarity of mind was assessed on a scale of exercise = 6 points or communication = 2 points.

A change from below MCS to MCS, or from MCS to VS, or from VS to clear consciousness, or an increase of one level or more in the state of consciousness is considered valid.

8.2 Safety evaluation: Events such as needle dizziness, hematoma and unstable vital signs were recorded in the case report and reported to the trial designer. After group discussion, the case was withdrawn from the study. Follow-up of subjects after adverse events: in-hospital monitoring, 1 week after discharge, 4 weeks back to the hospital for re-examination.

9. Safety monitoring, reporting and medical treatment

9.1 Adverse event (AE) definition

An adverse event is any adverse medical event that occurs after a patient or subject receives a drug that is not necessarily causally related to the treatment. Therefore, an adverse event can be any adverse physical sign (including abnormal laboratory results), symptom, or disease that has a time correlation with the use of the investigational drug, regardless of whether a causal relationship with the investigational drug is considered. Adverse events include Serious adverse events (SAE) and non-serious adverse events.

9.2 SAE definition

SAE refers to the occurrence of medical events during clinical trials that require hospitalization or prolonged hospitalization, disability, affect work ability, endanger life or death, and lead to congenital malformations. Includes the following medical events:

1) events leading to death;

2) life-threatening events (defined as subjects in immediate danger of death at the time of the event);

3) Events requiring hospitalization or prolonged hospitalization;

4) Events that can cause permanent or severe disability/disability/affect the ability to work;

5) Congenital abnormalities or birth defects;

Other medically important events (defined as events that endanger subjects or require intervention to prevent the occurrence of any of the above).

9.3. Adverse event recording, collection, reporting and handling

9.3.1 Collection, reporting and handling of AE

From the signing of the informed consent to the beginning of the test, all AE related to the operating procedures specified in the test protocol shall be recorded in the eCRF...

The recording of AE should include: description of the AE and all related symptoms, time of occurrence, severity, duration, correlation with the means of the

test, measures taken, and final results and outcomes. The recording of AE must use medical terminology, and if the subject's signs and symptoms can be summarized by a common cause, the diagnosis should be recorded as far as possible. In addition to indicators related to disease progression, all clinical events and clinically significant laboratory adverse events can be treated with reference to the Common Adverse Event Evaluation Criteria (CTCAE) version 5.0.Adverse reactions to treatment will be recorded by the investigator.

9.3.2 SAE collection and reporting

All SAE, regardless of cause or drug correlation, occurring from the time the subject signed the informed consent to the completion of the trial intervention within 4 weeks were to be reported using the SAE Report Form. In case of SAE, the researcher should immediately take appropriate treatment measures for the subject, ensure the safety of the subject, and report within 24 hours to the applicant for drug registration, the State Drug Administration, the provincial Food and Drug Administration, the ethics committee of the relevant clinical trial center and the medical Department of the Medical Administration Bureau of the Health Commission, and timely report to the ethics committee of the group leader. The first report should, as far as possible, include the following: source of the report, name of the trial intervention, name of the serious adverse event, time of occurrence, severity, duration, association with the trial drug, action taken, and outcome.

9.3.3 gestation

Pregnant patients were not included in this study. Since the included subjects were hospitalized patients with consciousness disorder, the possibility of pregnancy during the study period was excluded.

9.3.4 Criteria for judging the severity of AE

Researchers will evaluate severity according to the five-level criteria developed by the NCI CTCA version 5.0:

Grade 1, mild; Asymptomatic or with mild signs; For clinical or diagnostic observation only, without medical intervention;

Grade 2, moderate; Age-appropriate limited functions of daily living (such as

cooking, shopping, making phone calls, etc.);

Grade 3, serious or medically important but not immediately life-threatening; Resulting in hospitalization or prolonged hospitalization; Disability; Limited daily self-care activities (daily self-care activities refer to bathing, dressing, undressing, eating, toilet use, medication, etc., but not bedridden);

Level 4, life-threatening, requiring emergency treatment;

Level 5, AE-related death

9.3.5 Other investigator responsibilities during

follow-up of serious adverse events

Serious adverse events should be examined and treated according to clinical judgment, including necessary clinical laboratory examination and physical examination. The results of any inspection or other updated SAE-related information obtained must be reported in a follow-up report within the same time frame and process as the initial report.

10. Trial termination/suspension criteria

10.1 Sponsor reserves the right to terminate/suspend this trial. Before terminating/suspending a clinical trial, the sponsor must notify the investigator, the Ethics Committee and the State Food and Drug Administration and state the reasons. After the early termination/suspension of the study, the restart of the study must be reviewed and approved by the Ethics Committee;

10.2 Termination/suspension requested by the Ethics Committee.

11. Regulations to end clinical trials.

The trial ends when all subjects meet the following conditions:

1) All subjects completed at least 6 months of survival follow-up;

2) or the death, loss of follow-up, or withdrawal of informed consent of all subjects.

12.data administration

12.1 data administration

1) The researcher must ensure that the data is true, complete and accurate;

2) When any correction is made to the test record, the revised data can only be underlined, annotated by the margin, and the reason should be stated. The original

record should not be erased or overwritten.

3) Complete laboratory inspection items.

12.2. Data recording and file preservation

Subject data on the case report form should be recorded in subject code and subject can only be identified by subject code or their initials.

From data entry to the verification requirements of the source data to the question answer of the quality control data, and finally to the operation of data locking and export, after confirming that the data is no doubt, all parties sign the database locking application form, and the data administrator locks the database. After the database is locked, the data administrator exports the analysis database and sends it to statisticians for statistical analysis. The locked data cannot be edited again, and the problems found after the database is locked can be corrected in the statistical analysis program after confirmation.

13.statistic analysis

13.1 Sample size determination

In this study, 1:1 parallel control was used to estimate the sample size according to the group design of two sample rates comparison sample content estimation formula:

$$n = \frac{2\times(U_\alpha + U_\beta)^2 \times P\ (1-P)}{(P_1 - P_2)^2} \quad P = \frac{(P_1 * n_1 + P_2 * n_2)}{(n_1 + n_2)}$$

Where, Uα is the first type of error probability U value, Uβ is the second type of error probability, when bilateral α=0.05, unilateral β=0.1, Uα=1.96, uβ =1.28, P1 is the effective rate of the treatment group, P2 is the effective rate of the control group, and P is the rate of the two combinations.According to previous research literature, P1 and P2 are estimated to be 79.4% and 54.8%, resulting in n≈76, and the minimum sample size of each group is about 76 cases.As shedding cases were not excluded during the study, the shedding rate was 15%. For the successful completion of the experiment, 87 cases were assigned to each group based on various factors, and 174 cases were required to be included in the two groups.

13.2 Analysis set definition and selection

A Full Analysis Set (FAS) is a set of participants who have received the investigational drug at least once since enrollment and have been evaluated for effectiveness at least once.

Safety Set (SS) : The set of all subjects who received the investigational drug at least once after enrollment and were evaluated for safety at least once.

Per Protocol Set (PPS) : The set of cases in which all patients in the full analysis completed protocol treatment and did not seriously violate the protocol.

13.3 Statistical method

The analysis included case distribution, demographic data, baseline analysis and therapeutic effect analysis. Baseline data included sex, age, stroke type, stroke duration, underlying medical history (diabetes, hypertension, heart disease, chronic obstructive pulmonary disease), and history of smoking and alcohol use. Baseline data were tested by chi-square test. The end point data was the score of the State of Consciousness scale, and the measurement data was expressed as mean SD. Univariate analysis of variance was used to compare the difference between groups at the same time point, the difference at different time points in the group, and the difference before and after between the two groups. $P < 0.05$ was considered statistically significant, and multiple comparisons were performed by Dunnett-t test.

13.4 Statistical software and general requirements:

1)All statistical analysis was performed using SPSS25.0 statistical software.

2)Measurement data were described using mean, standard deviation, median, maximum and minimum values.

3)Counting data are described by frequency and percentage.

4)All data in the experiment were tested for normality.

5)Baseline data were analyzed using Chi-square test. Measurement data are expressed as mean SD. Univariate analysis of variance was used to compare the difference between groups at the same time point, the difference at different time points in the group, and the difference before and after between the two groups. $P < 0.05$ was considered statistically significant, and multiple comparisons were

performed by Dunnett-t test.

14.testing management

14.1 Comply with GCP requirements

Governing body and implementation of the GCP:

1) Drug registration applicants and investigators should adopt standard operating procedures to implement quality control and quality assurance systems for clinical trials;

2) The original data must meet the GCP requirements of our country;

3) Laboratory test results must be accurate and reliable;

4) The observations and findings used should be verified to ensure the reliability of the data;

5) Establish a complete test organization and clarify the responsibilities of personnel at all levels;

6) The main researcher shall be responsible for the overall quality control and carry out the responsibilities of personnel at all levels;

7) The main investigator shall be responsible for the design of the experimental protocol and informed consent, and the main investigator shall write the experimental summary report after the end of the experiment;

8) The designated researcher shall be responsible for developing the implementation rules and SOP for use in the test;

9) The study plan for all participants shall be organized by the test group before the experiment, and all participants shall undergo GCP training;

10) The doctors, nurses and therapists participating in the experiment shall strictly abide by the protocol and follow the procedure, and shall not change it at will;

11) Designated statisticians are responsible for the overall statistical processing of the data.

14.2 Protect the subject's privacy

All the data of the subjects during the experiment will be recorded into the computer for confidential storage and analysis. If necessary, the records may be reviewed by relevant institutions to confirm the truth, accuracy and completeness of

the data. The data obtained from the experiment may also be published in academic journals, but the names of the subjects will not be published and the privacy of the subjects will be kept confidential.

Extra precautions are taken to ensure confidentiality of documents and to prevent identification of subjects through genetic data. However, in exceptional circumstances, someone may see a subject's genetic data and personal identification number. For example, in the event of a medical emergency, the sponsor, its representative physician or investigator is aware of the subject identification number and has access to the subject's genetic data. In addition, the relevant regulatory authorities requested access to the relevant documents.

14.3 Problems arising in the test and their treatment measures

1) Revision of the protocol: After the protocol is approved by the Ethics Committee, if the protocol is to be revised, a "Protocol Revision Statement" shall be formulated and signed by the principal investigator. The scheme can only be revised with the consent of the researcher and the applicant for drug registration through consultation;

2) The revised plan shall be submitted to the Ethics Committee for review and approval before implementation;

3) Any adverse event (AE) or severe adverse event (SAE) that occurs during the test will be reported and handled in accordance with the requirements of the protocol and SOP.

14.3 Quality control and quality assurance

14.3.1 quality assurance：

The sponsor and the cooperating units entrusted by the sponsor to be responsible for all or part of the responsibilities and tasks related to this study (including CRO, SMO, statistical unit, clinical center, etc.) shall establish their own quality assurance systems, perform their respective duties, strictly follow the clinical trial protocol, and adopt the corresponding standard operating procedures. To ensure the implementation of clinical trial quality control and quality assurance system.

14.3.2 Quality assurance of clinical trial process

Before starting clinical trials, researchers should receive training on the trial protocol, so that researchers have a full understanding of the clinical trial protocol and the specific connotation of each indicator. Quality control personnel should check the basic conditions of clinical trials to ensure that clinical trial conditions can meet the requirements of the program. In the course of the trial, the investigator shall carefully perform the clinical operation and other work according to the institutional SOP and the requirements of the trial protocol, and record it in a true, timely, complete and standardized manner. Quality control personnel conduct quality verification of the test process and corresponding original records. After the end of the test, the research unit sorted out the corresponding project files, which were checked by the quality control personnel and archived. The quality assurance department of the clinical research unit shall check the feasibility of the trials conducted. When non-conforming items are found, timely notify the researcher and the head of the unit to correct, and track the correction.

14.4 The expected schedule and completion date of the clinical trial

1)2023.1.1~2024.12.30: Clinical cases were collected

2)2025.1.1~2025.12.30: Cases of deficiency due to supplementary Shedding

14.5 Sponsor's duties

The sponsor is responsible for initiating, applying for and organizing this clinical trial, and providing trial funds. The sponsor shall submit the application for clinical trial to the State Food and Drug Administration in accordance with the provisions of China's GCP, drug registration Administration and other regulatory documents, and may also entrust a contract research organization (CRO) to perform certain work and tasks in the clinical trial.

The sponsor selects the institution and investigator of the clinical trial and recognizes its qualifications and conditions to ensure the completion of the trial.

In providing experimental drugs to researchers, sponsors shall establish a management system and record system for experimental drugs.

14.5.1 Researcher responsibility

This clinical study will be conducted in accordance with the moral, ethical and

scientific principles as well as protocol design and regulations stipulated by the Declaration of Helsinki and the Chinese GCP.

The investigator is responsible for making medical decisions related to the clinical trial to ensure that the subject receives timely treatment if AE occurs during the trial. Researchers should be aware of the procedures and requirements for reporting SAE, and record and report these events as required.

The researcher shall accurately, completely, timely and legally load the data into the eCRF, and accept the supervision or audit of the sponsor or CRO company and the inspection and inspection of the drug regulatory department to ensure the quality of the clinical trial.

14.5.2 Sponsor research methods for data publication

The sponsor has exclusive rights to this research data. Individual contributions should not be published until the final report of the multi-centre study has been completed, except with the written consent of the sponsor. The Sponsor has the final say in respect of the manuscript and publication.

15. Ethics related to trials

15.1 Ethics committee

The investigator shall submit the Investigator Handbook, protocol, informed consent, CRF and test drug inspection Report (as submitted), and any other information to the subject to the Ethics Committee for approval prior to the commencement of the study. Any amendments to the protocol must be approved by the Ethics Committee.

15.2 Informed consent

In informed consent, a qualified investigator must explain in detail to each subject the nature, purpose, procedure, expected time, potential risks and benefits, and any discomfort that may arise. Each subject must be aware that participation in the trial is voluntary and that he/she may withdraw from the trial and withdraw informed consent at any time without affecting his/her subsequent treatment or relationship with the treating physician.

Informed consent should be given in a standard writing format and in

non-professional language as far as possible. Each informed consent form must include all of the above and include a voluntary declaration. Informed consent must be submitted to the Ethics Committee for approval.

After the basics of the trial have been explained and the investigator is satisfied that each subject understands the purpose of the trial, each subject should be asked to sign and date the informed consent form. Subjects should read and consider their statements before signing and dating them, and should obtain an informed consent form to keep after signing. Subjects are not allowed to enter the study without informed consent.

15.3 other

When the subject is unable to participate independently in informed consent, a reliable and fair witness/legal representative must be present throughout the informed consent process. The selection of fair witnesses/legal representatives shall not violate the subject's right to confidentiality. After the subject has given verbal consent, the fair witness/legal representative should sign and date the informed consent to certify that the information is accurate.

16. references

[1] Jennett B. The vegetative state [J]. J Neurol Neurosurg Psychiatry, 2002, 73(4): 355-357.

[2] Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria [J]. Neurology,2002, 58(3): 349-353.

[3] Thibaut A，Schiff N，Giacino J，et al. Therapeutic interven tions in patients with prolonged disorders of consciousness[J]. The Lancet Neurology，18（2019）600—614.

[4] Schnakers C. Update on diagnosis in disorders of consciousness[J]. Expert Rev Neurother, 2020，20(10)：997-1004.

[5] Hernandez M, Calderon G, Tejada P C, et al. Prolonged disorder of consciousness in children, an update[J]．Andes Pediatr, 2021, 92(1)：15-24.

[6] Li A，Atem FD，Venkatachalam AM，et al．Admission glasgow coma scale score

as a pre dictor of outcome in patients without traumatic brain injury［J］. Am J Crit Care，2021，30(5) :350－355.

[7] R amazani J，Hosseini M. Comparison of full outline of unresponsiveness score and Glasgow Coma Scale in Medical Intensive Care Unit［J］. Ann Card Anaesth，2019，22(2) : 143-148.

[8] Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility [J]. Arch Phys Med Rehabil, 2004, 85(12): 2020-2029.

[9] Wutzl B，Golaszewski SM，Leibnitz K，et al. Narrative review: Quantitative EEG in disorders of consciousness［J］. Brain Sci，2021，11(6) : 697.

[10] GIBSON W S，ROSS E K，HAN S R，et a1. Anterior Thalamic Deep Brain Stimulation：Functional Activation Patterns in a Large Animal Model[J]. Brain Stimul，2017，9(5)：770—730.

[11] Bao Yingxun, Zhang Fang, Li Qun et al. The effect of "awakening and resuscitation" acupuncture on vegetative state patients with brain trauma [J]. Chinese Acupuncture and Moximoxib，2021，11（41）：1225-1228.

[12] Ma Liang, Bi Lijie, ZHAO Lisha et al.Effect of Tongdu Xingnao acupuncture on consciousness disorder after craniocerebral injury and its influence on consciousness state and neurofactors [J].Journal of Clinical Medicine Research and Practice, 2012, 7 (30) : 120-124.

[13] Ma Qian, ZHAO Jianguo, Zheng Wei, et al.Effect of Xingnaokaiqiao acupuncture on awakening consciousness disorder of acute stroke [J], Chinese Journal of Clinical Rehabilitation, 2006,10 (11) : 142-143.

[14] Xu Junfeng, Zhang Hao, Wang Xiaoyan et al.Clinical effect of electroacupuncture as the main method for continuous plant state comprehensive awakening [J], World of Chinese Medicine, 2018,13(4) : 970-977.

[15] Wang, W.-w., Xie, C.-l., Lu, L. & Zheng, G.-q. A systematic review and meta-analysis of Baihui (GV20)-based scalp acupuncture in experimental ischemic stroke. Sci. Rep. 4, 3981; DOI:10.1038/srep03981 (2014).

[16] Yang Liansheng, Zhou Danfeng, Zhang Kun et al.Study on optimal design of

clinical trial of acupuncture therapy for facial palsy [J]. Modern Chinese Medicine, 202, 42 (1) : 53-59.

[17] Liu Jiahui, Ma Ning, Dong Xu et al.Research status and application of placebo acupuncture control design [J]. Shanghai Journal of Acupuncture and Moxibustion, 202, 41 (3) : 318-322.

[18] Mo Yuxiao, ZHENG Shuitiao, Chen Chuyun et al.Difference of brain effect between true and false acupuncture points: a meta-analysis based on fMRI [J]. Chinese Journal of CT and MRI, 202, 20 (9) : 15-18.

[19] Mei L.Beijing:Guofang Gongye Publishing House 1995:56. Mei Lei. New Technology of ET-Brain function detection [M]. Beijing: National Defense Industry Press,1995:56.

[20] Mei L.Zhongguo Kongjie Yanjiu. 1984;4(4):323. Mei Lei.Research on space brain science [J]. Chinese Space Research,1984,4(4):323.

[21] He Renhong Fan Jianzhong Qiu Ling et al.Relationship between brain function and neurotransmitters after brain injury based on EEG grading [J]. Chinese Journal of Practical Neurological Diseases, 2019,22 (17) : 1857-1863.