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Research article

Efficacy and safety of compound porcine cerebroside and ganglioside injection (CPCGI) versus piracetam on cognition and functional outcomes for adults with traumatic brain injury: A study protocol for randomized controlled trial

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ABSTRACT

Background: Traumatic brain injury (TBI) is a common neurosurgical disease in emergency rooms with poor prognosis, imposing severe burdens on patients and their families. Evidence indicates that piracetam and compound porcine cerebroside and ganglioside injection (CPCGI) can improve cognitive levels in TBI patients to enhance functional prognosis, but there is still a research gap regarding the efficacy of CPCGI. This study aims to determine the effectiveness and safety of CPCGI in improving cognitive and functional outcomes in TBI patients.

Methods: This study is a multicenter, randomized, parallel-group, double-blind trial aiming to recruit 900 adult patients with mild to moderate TBI. After providing informed consent, 600 patients will be randomly assigned to the CPCGI group (20 ml/d, for 14 days), and 300 patients will be randomized to the piracetam group as a control (20 ml/d, for 14 days), followed up for 3 months after treatment. The primary outcome is the change in the Montreal Cognitive Assessment

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(MoCA) score from baseline after 3 months. The main secondary outcome measures include Mini-Mental State Examination (MMSE) scores, Glasgow Outcome Scale-Extended (GOS-E), and the Barthel Index at 1 and 3 months.
Discussion: This multi-center clinical trial aims to provide high-quality evidence on the efficacy and safety of CPCGI in improving cognitive and functional outcomes in mild to moderate TBI patients.
Trial registration: ChiCTR2000040466, date of registration: November 28, 2020.

1. Introduction

Traumatic brain injury (TBI) represents a predominant cause of mortality and morbidity globally across all demographics [1]. Despite over a century of extensive basic and clinical research, the medical community recognizes a dearth of efficacious treatments or pharmacological interventions for TBI [2]. Annually, an estimated sixty-nine million individuals worldwide incur a TBI, with survivors frequently enduring persistent symptoms that profoundly deteriorate their life quality especially its sequela from cognition impairments [3,4]. Cognitive impairments, manifesting as compromised attention, memory deficits, diminished executive functions, impulsivity, inadequate decision-making capabilities, and depression, serve as critical determinants of whether individuals with TBI can maintain autonomy or experience significant disability. Such disabilities impose a considerable toll on both the affected individuals and their families [5–8]. Therefore, the identification and recommendation of effective therapeutic strategies to mitigate cognitive impairments in TBI patients are of paramount importance.

The etiology and underlying mechanisms of TBI remain elusive. Prior research has established a correlation between severe outcomes in TBI and phenomena such as pronounced cerebral edema, neuronal apoptosis, inflammation, and diminished cerebral perfusion [9–11]. Our investigations have further substantiated that interventions targeting cerebral edema reduction and neuronal apoptosis prevention can enhance motor and cognitive outcomes post-TBI [12,13]. In the realm of clinical interventions for TBI, various pharmacological approaches have been evaluated for their prognostic benefits [14]. Amantadine, a dopamine agonist, has been recognized for its potential in mitigating cognitive deficits [15]. Methylphenidate, by inhibiting catecholamine reuptake, elevates levels of dopamine, noradrenaline, and serotonin, and has recently been applied in addressing cognitive impairments following TBI [16–20]. Furthermore, Piracetam, a cyclic GABA derivative, has been shown to bolster cerebral metabolism, alleviate intracranial pressure and edema, thereby improving cognitive and motor functions in TBI patients [21–23].

Approved by the China Food and Drug Administration in 2010, Compound Porcine Cerebroside and Ganglioside Injection (CPCGI)

Table 1
Medical centers in China participating in the study.

Number	Medical centers
1	Tianjin Medical University General Hospital
2	Tianjin First Central Hospital
3	The First People's Hospital of Tancheng
4	The Affiliated Hospital of Qingdao University
5	The First Affiliated Hospital of Nanyang Medical College
6	Taizhou Traditional Chinese Medicine Hospital
7	Taizhou Second People's Hospital
8	Taizhou Municipal Hospital
9	Suzhou Municipal Hospital
10	Xianyang Hospital of Yan'an University
11	Huainan first people's Hospital
12	Huai'an First People's Hospital
13	Xinxiang Central Hospital
14	The Second People's Hospital of Hefei
15	The Second Hospital Universi ty of South China
16	The First People's Hospital of Jinzhong
17	The Fourth Affiliated Hospital of Anhui Medical University
18	Qinghai Provincial People's Hospital
19	Qinghai University Affiliated Hospital
20	Yuncheng Central Hospital
21	Affiliated Hospital of Nantong Hospital
22	Nantong First People's Hospital
23	Jiangsu Taizhou People's Hospital
24	Yangzhou First People's Hospital
25	Wuxi People's Hospital
26	Wuxi Second People's Hospital
27	Yixing People's Hospital
28	The First People's Hospital of Changzhou
29	The Affiliated Hospital of Xuzhou Medical Hospital
30	Suqian First People's Hospital
31	Shuyang People's Hospital

is a neurotrophic medication employed in the experimental management of conditions such as stroke, Alzheimer's disease, and central and peripheral nerve injuries [24–27]. CPCGI comprises key components including polypeptides, gangliosides, and hypoxanthine [26]. Studies have illustrated that CPCGI administration markedly enhances cerebral blood flow and neurological function, reduces cellular apoptosis, and facilitates the restoration of synaptic and mitochondrial functionality in ischemic/reperfusion rats models [25, 26]. Additionally, clinical research indicates CPCGI's efficacy in enhancing cerebral metabolism, contributing to neuronal growth, differentiation, and regeneration, and augmenting cerebral circulation in Alzheimer's disease [28]. Despite several clinical trials investigating CPCGI's application in TBI within China [29–31], high quality evidence remain scarce, thus weakening the evidential basis for CPCGI's broad clinical adoption in TBI treatment. We therefore initiated a multicenter, randomized, active control, double-blind trial to determine the efficacy and safety of CPCGI in patients with TBI.

2. Methods and analysis

2.1. Design

This protocol delineates a prospective, multicenter, phase III/IV randomized, active control, double-blind clinical trial aimed at assessing the efficacy and safety of CPCGI in patients with TBI, with piracetam serving as the comparator. This trial is planned to be conducted in 31 hospitals across China (Table 1). Participants shall not be enrolled in this study without obtaining informed consent from the subjects and/or their guardians/legal representatives. This study protocol is registered with the China Clinical Trial Registry (Registration number: ChiCTR2000040466; Registration date: November 28, 2020). Ethical approval has been granted by the ethics boards of Tianjin Medical University General Hospital and other involved institutions, adhering to the Declaration of Helsinki's ethical

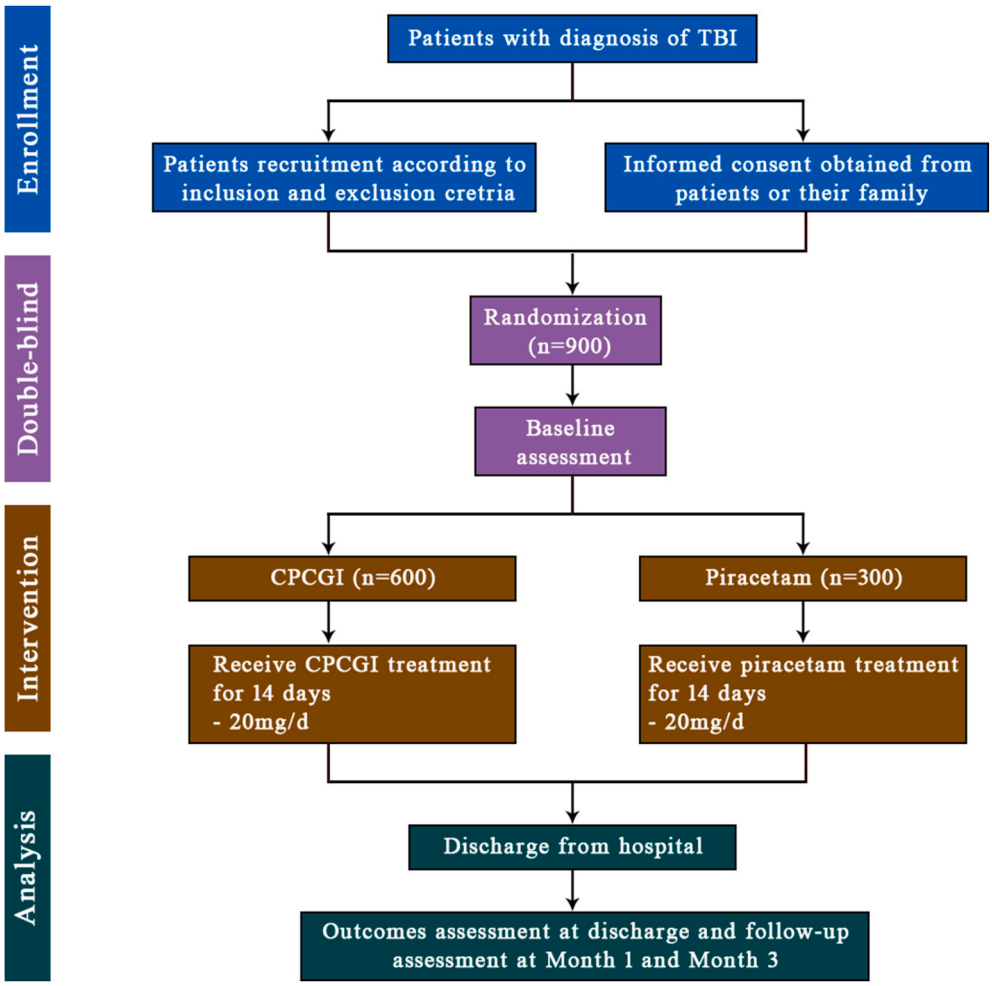

Fig. 1. Flow chart to illustrate the design of the trial.
TBI traumatic brain injury, CPCGI compound porcine cerebroside and ganglioside injection, MoCA Montreal Cognitive Assessment, MMSE Mini-Mental State Examination, GCS Glasgow Coma Scale, NIHSS National Institutes of Health Stroke Scale, GOS-E Glasgow Outcome Scale-Extended, AEs adverse events, ECG electrocardiogram.

guidelines. During the implementation process, we strive to avoid some common mistakes [32]. The flowchart of this study is shown in Fig. 1, and the evaluation time points are presented in Table 2.

2.2. Inclusion criteria

1) Ages 18–75 years old (inclusive of boundary values), irrespective of gender;
2) TBI patients meeting all of the following conditions:
   - Clear head trauma in the current diagnosis, including closed brain injuries or those accompanied by cerebrospinal fluid otorrhea and/or rhinorrhea and/or pneumocephalus;
   - Confirmed by MRI or CT to have supratentorial intracranial hemorrhage (including cerebral contusion, subarachnoid hemorrhage, epidural hematoma, subdural hematoma, intracerebral hematoma, etc.), pneumocephalus, skull fractures, or transient loss of consciousness;
3) TBI classified as mild to moderate (Glasgow Coma Scale (GCS) score $\geq$9 and $\leq$ 15);
4) Conservative treatment, non-craniotomy surgery (invasive intracranial pressure monitoring may be included);
5) Life signs and condition stable within 72 h post-TBI, with a Mini-Mental State Examination (MMSE) score below normal; diagnostic thresholds vary by educational level: illiterate (uneducated) $\leq$19, primary education $\leq$22, junior high school and above $\leq$26;
6) Agreement to participate in this clinical trial and signing of the informed consent form.

2.3. Exclusion criteria

1) Known or suspected allergy to the trial medication or its components;
2) Guillain-Barre syndrome, extrapyramidal disorders, Huntington's disease;
3) History of severe TBI, structural brain lesions, cognitive impairments, or intellectual disabilities;
4) Conditions such as speech/hearing impairments that hinder completion of cognitive function assessments;
5) Secondary brain injury post-current TBI;
6) Need for craniotomy or external ventricular drainage;
7) Concurrent severe major organ injury or serious complications potentially life-threatening;
8) Active epilepsy with seizures within the past year;
9) Severe cardiac, pulmonary, hepatic, or renal disease (ALT or AST$\geq$2.0 times the upper limit of normal, Scr $>$ upper limit of normal), hematopoietic or blood disorders, gastrointestinal diseases, malignant tumors, or other severe or progressive systemic diseases, assessed as having severely abnormal coagulation functions;
10) Concurrent neurological or psychiatric diseases making cooperation difficult or unwillingness to cooperate;
11) Suspected or confirmed history of alcohol or drug abuse, or tendency towards drug dependence;

Table 2
Visit and assessment schedule of this trial.

Activities	Screening or baseline	Day 7–14 (treatment end)	Month 1 ± 3 D	Month 3 ± 3 D
Informed consent	✓			
Inclusion/exclusion criteria	✓			
General information	✓			
Medical history	✓			
Personal history	✓			
Head CT/MRI	✓			
Pregnancy test	✓			
Concomitant medication[a]	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓
Neurological symptoms	✓	✓	✓	✓
MoCA[b]	✓			✓
MMSE	✓	✓		✓
GCS/NIHSS	✓	✓		
GOS-E		✓		✓
Barthel index			✓	✓
Vital signs	✓	✓		
Laboratory tests[c]	✓	✓		
Electrocardiogram	✓	✓		
Adverse events		✓	✓	✓
Drug dispensing	✓			
Drug recovery[d]		✓		

D day, *CT* computerized tomography, *MRI* magnetic resonance imaging, *MoCA* Montreal Cognitive Assessment, *MMSE* Mini-Mental State Examination, *GCS* Glasgow Coma Scale, *NIHSS* National Institutes of Health Stroke Scale, *GOS-E* Glasgow Outcome Scale-Extended.

[a] Records of combination therapy are required until the end of the trial.

[b] An additional MoCA test will be completed at 7 ± 1 days after treatment as baseline.

[c] Laboratory tests include blood routine, urinalysis, liver and renal function electrolyte, lipids, coagulation.

[d] The remaining drugs need to be recovered.

12) Pregnant or breastfeeding women or those with recent plans for pregnancy;
13) Participation in another clinical trial within the past three months;
14) Deemed by the researcher as unsuitable for participation in the clinical trial.

2.4. Randomization

This trial employs block randomization to divide successfully screened participants into two groups randomly. Random number tables are provided by Beijing Excellence Future International Pharmaceutical Technology Development Co., Ltd., using SAS9.4. Researchers at each participating trial center will obtain a random number for each eligible participant as they are screened, in chronological order of enrollment. This random number also serves as the drug number, which is used to distribute the corresponding trial medication according to the drug number.

2.5. Blinding

To ensure double-blinding during the clinical trial, each participating unit must appoint a dedicated unblinded research nurse. Throughout the trial, this unblinded nurse is prohibited from disclosing any medication dispensing information to anyone involved in the trial and does not participate in trial evaluations, being solely responsible for preparing the medications.

In the event of a serious adverse event, deterioration, or progression of a participant's condition, an emergency letter can initiate the unblinding process.

Step 1: After the researcher determines that a participant meets the protocol requirements, a random number is generated based on the enrollment sequence at the center. The drug administrator then issues the trial medication corresponding to the drug number to the unblinded research nurse, without selecting the medication. This drug number remains unchanged throughout the study.

Step 2: The unblinded research nurse prepares the medication according to its dosage and administration instructions.

Step 3: After preparation, a blinded nurse administers the medication to the participant.

After administration, the medication packaging is handed over by the unblinded research nurse to the drug administrator for storage.

During the trial, research physicians, participants, data management and statistical personnel, and monitors remain blinded, with only the drug administrator and the unblinded research nurse knowing which trial medication is used by each participant. All related personnel must strictly adhere to the blinding regulations to prevent information leakage.

2.6. Intervention

Trial Group: CPCGI 2 ml per vial. Approval number: H22026472. (Each 1 ml contains peptides 3.2 mg, monosialoganglioside (GM1) 0.24 mg, hypoxanthine 0.125 mg). Produced and supplied by Jilin Tiancheng Pharmaceutical Co., Ltd.

Control Group: Piracetam Injection, specification: 5 ml:1 g per vial. Approval number: H20054824, manufactured by Shanghai Modern Hasen (Shangqiu) Pharmaceutical Co., Ltd. Supplied by Jilin Tiancheng Pharmaceutical Co., Ltd.

All participants will undergo a 20 ml for 14-day treatment with CPCGI or Piracetam.

2.7. Standard care

Participants enrolled in the study will undergo standard therapeutic interventions for TBI, encompassing monitoring of vital signs, airway management, administration of analgesics and sedatives, and management of hemostasis and coagulopathies. Concurrent medication usage throughout the treatment duration, including the medication name, dosage, indication, and duration, will be meticulously documented.

The administration of Traditional Chinese Medicines (TCMs) purported to enhance cognitive function, including Congsheng Decoction and Herba Cistanche, is expressly prohibited during the study period [33,34]. Similarly, hormone replacement therapy is strictly disallowed.

2.8. Strategies to enhance adherence to intervention protocols

To optimize adherence to intervention protocols, strategies will encompass the provision of experimental drugs and laboratory assessments at no cost, and simplifying the regimen to a once-daily medication intake as opposed to multiple daily dosages. It is imperative that both patients and their familial guardians possess a comprehensive understanding of the trial's prerequisites and furnish informed consent accordingly. Additionally, during follow-up consultations, patients will be instructed to present all concurrently used medications for the purpose of evaluating their ancillary pharmaceutical consumption.

2.9. Efficacy outcomes

The primary outcome is the change in the MoCA score at 3 months post-medication relative to the baseline. Secondary outcomes include: 1) The change in the MMSE score at post-medication and 3 months relative to the baseline; 2) The percentage of participants in each Glasgow Outcome Scale-Extended (GOS-E) category at post-medication and 3 months post-medication; 3) The change in the GCS

score at post-medication relative to the baseline; 4) The Barthel Index scores for activities of daily living at 1 month and 3 months post-medication; 5) The difference in the National Institutes of Health Stroke Scale (NIHSS) score at post-medication compared to the baseline.

Note: The MoCA score will be assessed by medical staffs who have the certificate. Other scales will be evaluated by neurologists with expertise in professional scale assessment. Unified training on the scales will be provided to personnel at all centers before the trial begins to ensure consistency in scale assessment.

2.10. Safety outcomes

1) Vital signs; 2) Laboratory tests: complete blood count, urinalysis, liver function tests, renal function tests; 3) 12-lead electrocardiogram (ECG); 4) Adverse events, serious adverse events, drug adverse reactions, suspected and unexpected serious adverse reactions.

2.11. Sample size

The sample size calculation of the study is based on the published data that mean ± SD of MoCA score change from baseline was 3.0 ± 4.5 after 3 months piracetam treatment for cute cerebral infarction [35]. We assume that mean ± SD of MoCA score change from baseline is 4.0 ± 4.5 after 3 months CPCGI treatment for TBI. Using the PASS11.0 application software, employing a one-tailed test with $\alpha = 0.025$, $\beta = 0.2$ and a 2:1 sample ratio, we need to recruit 479 patients in experimental group and 240 in control group. Accounting for a 20 % dropout rate at each participating center, the sample size is expanded to 600:300 patients.

2.12. Data analysis

Statistical analysis will be performed after data collection is completed. A 2-tailed test will be implemented and a p value < 0.05 is considered to indicate statistical significance. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) will be used for statistical analysis. Analysis of covariance (ANCOVA) model will be used to compare the change of MoCA score from baseline after 3 months of medication. A model taking group as fixed effect and baseline MoCA score as covariate will be used. According to the model, the least squares mean of the change in MoCA score from baseline to 3 months after treatment will be calculated for both groups, as well as the difference of the corrected mean between experimental group and control group and its 95 % confidence interval. The parameters of continuous variable include cases, means, standard deviation, median, minimum value and maximum value. The MMSE score, GCS score, Barthel index score and NIHSS score will be analyzed via the same statistical analysis method as MoCA score. The percentage of subjects in each grade of GOS-E will be calculated after treatment and 3 months after the intervention, and a single ordered CMH chi-square test will be employed to compare the difference between two groups.

It should be noted that the study included patients aged 18–75. To minimize bias, we will divide the age groups into 18–60 and 60–75 for data analysis.

2.13. Interim analysis

No interim analysis will be conducted.

2.14. Auditing

A series of quality control audits for the database will be conducted before the end of the trial.

3. Methodology

The study is designed based on published trials in treating TBI patients with CPCGI in China, demonstrating that administration of CPCGI has therapeutic effects and high safety [29–31]. However, effects of CPCGI on clinical TBI treatment is not confirmed worldwide, thus we limit our recruitment to patients who are classified as mild or medium TBI ($9 \leq GCS \leq 15$), and with no need for surgery. To prevent adverse risks, all patients will be closely monitored for acute neurological degradation. In case neurological symptoms or other vital signs change for the worse during the trial, patients will receive an emergency head CT scanning and surgery if necessary, and such patients will be excluded from the trial instantly.

CPCGI and piracetam are considered to be generally very safe, with this in mind, we decide not to waive SAE for this trial protocol. On the occasion a patient experiences any suspected related side effects, he or she will be removed from the trial immediately. If CPCGI or piracetam-related side effects are confirmed, treatment will be terminated and affected patients will be followed up for 3 months.

4. Discussion

We hold the belief that this trial is of great necessity because strategies for cognition improvement of TBI are very limited. Edaravone is a free radical scavenger that can mitigate damage induced by oxidative stress, and the potential mechanism may be resulted from activation of the Nrf 2/ARE pathway [36,37]. Unfortunately, clinical research on edaravone is still sparse, and its overall

safety and efficacy in TBI patients remain uncertain [37]. Attention deficit hyperactivity disorder agonists such as MPh are increasingly applied to improve cognitive dysfunction after TBI by addressing underlying neurotransmitter imbalances [38–40]. However, the benefits of MPh on executive function and the associated mechanisms have not been firmly evaluated in patients with TBI [41]. Combining repetitive transcranial magnetic stimulation (rTMS) and cerebrolysin is another novel option to improve cognitive function in TBI patients, but the universality, optimal dosage and treatment protocol of this method have not been identified [42].

CPCGI has been widely assessed in China for central nervous system (CNS) disease via experimental animal model and no adverse reaction has been discovered during the administration [25], [26], [43]. In clinical studies, it is demonstrated that CPCGI can significantly shorten the time of fracture healing and improve the curative effect of fracture healing [44]. Besides, application of CPCGI has also been tested in clinical therapy for TBI, Alzheimer's disease, cerebral infarction, and found to have positive effects on promote cognitive function [28–30,45]. This trial is based on the above experience, and we aim to explore and summarize the significance of CPCGI profound enough for its application in clinical strategy for TBI.

This CPCGI treatment trial for TBI, to our knowledge, is the first clinical trial that taking another administration widely used as control group, as compared to previous trials focusing on different efficacy between CPCGI and blank control. Besides, due to the extensive distribution of participating medical centers throughout China, the scientific randomization and sample size calculation, we believe our conclusion that whether put CPCGI into clinical therapy for TBI is feasible and beneficial will be more convincing, and more conductive to promotion in China and even around the world.

Trial status

This trial began in November 2020, and is still conducted.

Ethics approval and consent to participate

The trial was approved by the Ethics Committee of Tianjin Medical University General Hospital (IRB2020-124-01). All the participants will provide written informed consent.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Tao Liu: Writing – review & editing, Visualization, Software, Project administration, Formal analysis, Data curation. **Yunhu Yu:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Liang Mi:** Writing – original draft. **Zhihao Zhao:** Methodology. **Mingqi Liu:** Methodology. **Jiao Wang:** Formal analysis. **Xin Wang:** Investigation. **Zhuang Sha:** Data curation. **Meng Nie:** Investigation. **Weiwei Jiang:** Investigation. **Chenrui Wu:** Investigation. **Jiangyuan Yuan:** Investigation. **Chuanxiang Lv:** Methodology. **Biao Zhao:** Conceptualization. **Kun Lin:** Methodology. **Zhanying Li:** Methodology. **Zhenyu Luo:** Investigation. **Xuanhui Liu:** Investigation. **Yu Qian:** Investigation. **Rongcai Jiang:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

TBI	traumatic brain injury
CPCGI	Compound porcine cerebroside and ganglioside injection
MoCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Examination
GOS-E	Glasgow Outcome Scale-Extended

GCS	Glasgow Coma Scale
NIHSS	National Institutes of Health Stroke Scale
MPh	Methylphenidate
GMP	good manufacturing practice
CFDA	China Food and Drug Administration
ECG	Electrocardiogram
ANCOVA	Analysis of covariance
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
SAEs	Severe adverse drug reaction/events
rTMS	repetitive transcranial magnetic stimulation
CNS	central nervous system

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