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The neuroprotective effect of electro-acupuncture on cognitive recovery for patients with mild traumatic brain injury

A randomized controlled clinical trial

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Abstract

Background: Traumatic brain injury (TBI) is a major health and socioeconomic problem that affects all societies. Consciousness disorder is a common complication after TBI while there is still no effective treatment currently. The aim of this study was to investigate the protective effect of electro-acupuncture (EA) on cognitive recovery for patients with mild TBI.

Methods: A total of 83 patients with initial Glasgow coma scale score higher than 12 points were assigned into this study. Then patients were randomly divided into 2 groups: EA group and control group (group C). Patients in group EA received EA treatment at Neiguan and Shuigou for 2 weeks. At 0 minute before EA treatment (T_1), 0 minute after EA treatment (T_2), and 8 weeks after EA treatment (T_3), level of neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), hypoxia inducible factor-1α (HIF-1α), and malondialdehyde were tested by enzyme-linked immunosorbent assay. The score of Montreal Cognitive Function Assessment (MoCA) and mini-mental state examination (MMSE) as well as cerebral oxygen saturation (rSO2) were detected at the same time.

Results: Compared with the baseline at T_1, the level of NSE, GFAP, HIF-1α, MDA, and rSO2 decreased, and the score of MoCA and MMSE increased in the 2 groups were significantly increased at T_{2-3} ($P < .05$). Compared with group C, the level of NSE, GFAP, HIF-1α, MDA, and rSO2 decreased, and the score of MoCA and MMSE increased were significantly increased at T_{2-3} in group EA; the difference were statistically significant ($P < .05$).

Conclusions: EA treatment could improve the cognitive recovery for patients with mild TBI and the potential mechanism may be related to improving cerebral hypoxia and alleviating brain injury.

Abbreviations: EA = electro-acupuncture, GFAP = glial fibrillary acidic protein, HIF-1α = hypoxia inducible factor-1α, MDA = malondialdehyde, MMSE = mini-mental state examination, MoCA = Montreal Cognitive Function Assessment, NSE = neuron-specific enolase, rSO2 = cerebral oxygen saturation, TBI = traumatic brain injury.

Keywords: cerebral oxygen metabolism, cognitive recovery, electro-acupuncture, traumatic brain injury

1. Introduction

Traumatic brain injury (TBI) is a common and multifaceted disease that seriously endangers human health. In the United States, it is the leading cause of death and disability among people under 45 years of age, and its incidence has been on the rise for some time.[1–3] TBI-affected brain tissue has a high metabolic rate and is more susceptible to hypoxia, which can result in irreversible damage to the central nervous system.[4,5] Studies have found that more than 90% of patients with TBI are accompanied by ischemia and hypoxia of local brain tissue, which cause abnormal brain metabolism, cerebral perfusion and brain tissue damage.[6] According to Elder GA, there are approximately 558 people in every hundred thousand will suffered from TBI, and a quarter of these patients will also have cognitive impairments, such as memory, attention, thinking abilities, and executive functions.[7] Cognitive impairment after TBI may accompany patients for life, making it one of the most important socio-economic and public health problems.[8]

Over 2000 years ago, acupuncture was developed in China as a special treatment for systemic diseases through the conduction of meridians and acupoints.[9] Electro-acupuncture (EA) is a new therapeutic method developed by increasing electric current of different frequency and intensity on the basis of traditional

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

This study was approved by the institutional review board of the Cangzhou Central Hospital in compliance with the Helsinki and declaration and consent were waived for its retrospective nature.

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acupuncture. Wong showed EA has a unique therapeutic effect on the treatment and rehabilitation of TBI patients.[10] The parameters of waveform, time, frequency, and intensity can be adjusted to produce different treatment effects based on the acupoint and electrical stimulation combined. The research from Liu J[11] showed EA intervention can effectively promote the recovery of consciousness after TBI with initial Glasgow coma scale score of less than 8 points, but the exact protective mechanism of EA is still unclear.

Given that this aim of our study was to explore the protective effect of EA on cognitive recovery for patients with mild TBI, so as to provide a potential choice for cognitive recovery in patients with TBI.

2. Methods

This prospective, randomized, controlled trial has been approved by the Ethics Committee of Cangzhou Central Hospital and complies with the Helsinki Declaration. Obtained written informed consent from each participating patient before randomization.

2.1. Participants

Between February 2019 and July 2022, patients suffered from mild TBI in the department of neurosurgery, Cangzhou Central Hospital were eligible for the study. The inclusion/exclusion criteria for subject enrollment have been reported previously.[12] The inclusion criteria were as follows: Meet the diagnostic criteria for TBI (confirmed by MRI and brain CT examination); Patients aged 18 to 70 years old, male or female; Initial Glasgow coma scale score higher than 12 on the beginning day; MRI shows head has no obvious shift, missing, large necrosis of brain structure change and obvious brain stem (not including pyramidal tract) or thalamic lesions, each lobe lesions range cannot exceed 30% of the scope of 1 side of the brain; No primary consciousness disorder and limb functional activity disorder; All patients or their family members signed informed consent; Able to receive oral drug and EA treatment. The exclusion criteria were as follows: Cognitive impairment of patients were not induced by TBI; Suffered from TBI more than 1 years; Combined with heart, liver or kidney failure endanger the safety of life at any time; Patients were younger than 18 years or older than 70 years; Refused to receive treatment of EA or not receiving a full course of treatment; Skin infection occurs at the corresponding points of EA intervention; Women with pregnancy and lactation; History of drug or alcohol addiction; Need for any operation. The trial will be ceased if one of the following conditions appeared a serious poststroke complication arises or recurrent stroke or any other severe condition occurs leaving the patient in a critical condition.

2.2. Randomization and blinding

Eighty-three individuals completed a baseline assessment and were randomly divided into 2 groups using the random number table method: control group (group C, n = 43) and EA group (n = 40). All patients were blinded to the group allocations. The physicians who conducted EA intervention, evaluated and analyzed the patients knew nothing about the grouping.

2.3. Assessment and intervention procedures

Figure 1 shows the schematic of the intervention timeline. In the 2-weeks treatment phase after eligibility, participants in both groups received conventional treatment including the prescription of coma arousal and neuroprotective medicines. In addition to conventional treatment, patients in the group EA received a 2-weeks EA treatment at Neiguan (PC 6) and Shuigou (GV 26) with disperse-dense wave, 2 Hz/100 Hz in frequency, 0.1 to 5 mA in intensity by EA stimulator instrument (Model G6805; SMIF, Shanghai, China) according to the method of previous research for 30 minutes once daily,[11] while patients in group C were not received EA treatment. Neiguan is located between the palmaris longus tendon and the flexor carpi radialis tendon, 2 inches above the wrist striation.

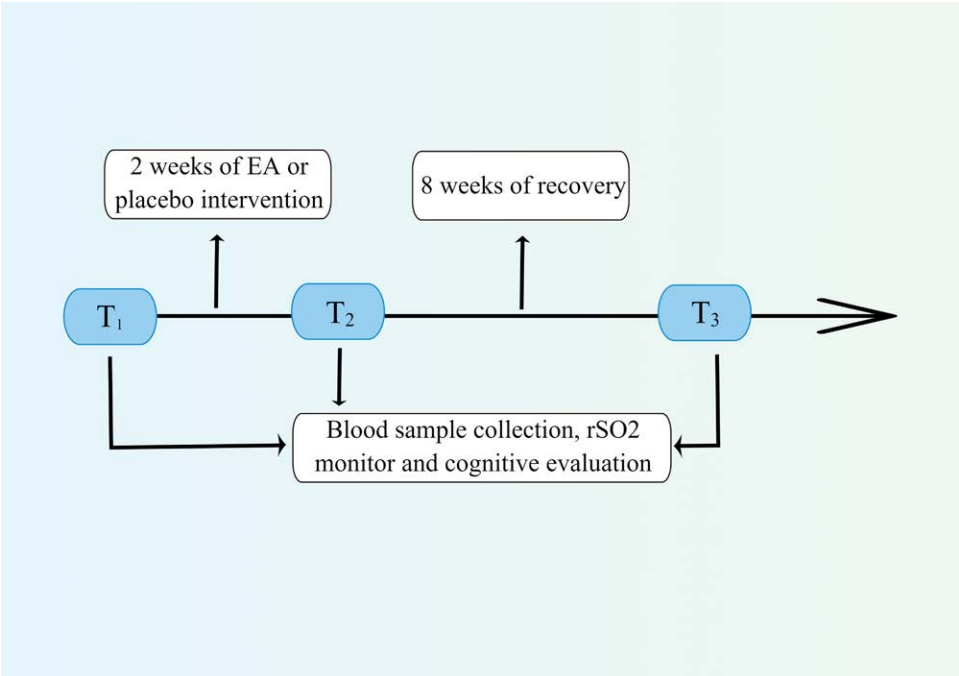

Figure 1. Schematic of the intervention timeline (drawn by Figdraw, ID:TRPWO2c2ee).

Shuigou is located at the intersection of upper and middle 1/3 of Renzhong ditch.

2.4. Sample collection and detection

Blood samples of 4 mL were collected from the 2 groups 0 minute before EA treatment (T_1), 0 minute after EA treatment (T_2), and 8 weeks after EA treatment (T_3). After centrifugation at 3000 × g for 15 minutes, the collected serum was stored at −80°C. Serum concentrations of neuron-specific enolase (NSE) (Item No. EPX010-12335-901, Thermo Scientific, Waltham), GFAP (Item No. ab114149, Abcam, Cambridge, UK), hypoxia inducible factor-1α (Item No. ab111577, Abcam, Cambridge, UK), and malondialdehyde (Item No. ab287797, Abcam, Cambridge, UK) were detected by enzyme-linked immunosorbent assay according to the manufacturer's instructions.

Cerebral oxygen saturation (rSO2) detector (Covidine II) was used to monitor rSO2. Two electrodes were placed on the left and right forehead, 4 cm away from the eyebrow arch. At $T_{1–3}$, rSO2 were recorded.

2.5. Cognitive function evaluation

Cognitive function was assessed using the Montreal Cognitive Function Assessment (MoCA)[13] scale and the mini-mental state examination (MMSE)[14] scale at $T_{1–3}$. MoCA mainly includes cognitive assessment of visual spatial executive ability, naming, memory, attention, language fluency, abstract thinking, delayed memory, orientation, etc. MMSE is a scale of cognitive function which could evaluate patients' time-directed force, site directed force, immediate memory, attention and computing power, delayed memory, language, and visual space. MoCA and MMSE contains 30 questions, and patients will obtain 1 point if answer is correct, but 0 point if the answer is wrong. The total scores less than 27 indicate cognitive dysfunction.

2.6. Sample size estimation and statistical analyses

The sample size of the study was calculated using the G*Power program (V.3.1.9) (gpower.hhu.de/). We aimed to show a significant difference in cognitive function. According to preliminary experimental results,[12] the required sample size was thus 36 subjects per group with 80% power and a 2-tailed α error of 5%. Considering a high incidence of dropout, we decided to include 40 patients in each group at least.

SPSS 21.0 software (SPSS, Inc., Chicago, IL) was applied to statistical analysis of all experimental data, and normally distributed measurement data were represented as mean ± standard deviation. Categorical variables are analyzed by χ^2 test or Fisher exact test and presented as frequencies and percentages. One-way analysis of variance was used to compare the data between groups and within groups. $P < .05$ was regarded as statistically significant.

3. Results

3.1. Demographic characters of patients

As shown in flow diagram of this study, there were 208 individuals evaluated for eligibility; 68 participants did not meet eligibility criteria, and of the 140 eligible participants, 57 patients declined participation. Of the patients who declined participation, 30 participants were "not interested," 19 participants reported they worried about affecting recovery, and 8 participants reported "other reasons." During this study period, there were no participants refused to be followed up. Finally, a total of 83 patients were enrolled in this study and assigned into 2 groups: group C (n = 43) and group EA (n = 40).

As shown in Table 1, the demographic data of the 2 groups, such as: age, gender, body mass index (BMI), education years, Glasgow coma scale score, course of disease after injury, as well as the cause of injury, and the differences were no statistically significant ($P > .05$).

3.2. NSE, GFAP, HIF-1α, and MDA levels

As shown in Figure 2, there was no significant difference in level of NSE, GFAP, HIF-1α and MDA between 2 groups at T_1 ($P > .05$). Compared with the baseline at T_1, the level of NSE, GFAP, HIF-1α, and MDA in both 2 groups were significantly increased at $T_{2–3}$ ($P < .05$). The level of NSE, GFAP, HIF-1α, and MDA in group EA at $T_{2–3}$ were significantly decreased compared with group C, and the difference was statistically significant ($P < .05$).

3.3. Cerebral oxygen saturation

Throughout the observation, the rSO2 of the 2 groups fluctuated within the normal range. As shown in Table 2, compared with T_1, the values of rSO2 on 2 sides increased in 2 groups at $T_{2–3}$, the values of rSO2 on 2 sides increased in group EA at $T_{2–3}$ compared with group C ($P < .05$).

3.4. Cognitive function

As shown in Table 3, the score of MoCA and MMSE increased at T_2 and T_3 in both 2 groups compared with T_1 ($P < .05$). Compared with, group C, the score of MoCA and MMSE increased at T_2 and T_3 in group EA ($P < .05$).

Table 1

Demographic data of patients between 2 groups (χ ± s).

Characteristics	Group C (n = 43)	Group EA (n = 40)	*P* value
Age (yr)	50.84 ± 6.17	51.92 ± 6.50	.562
Gender			.668
Male [(n) %]	26 (60.47%)	25 (62.5%)	
Female [(n) %]	17 (39.53%)	15 (37.5%)	
BMI (kg/m^2)	25.19 ± 2.67	24.88 ± 2.91	.652
Education years (yr)	8.81 ± 2.64	7.69 ± 2.35	.481
GCS score	13.85 ± 1.34	14.02 ± 1.51	.269
Course of disease after injury (d)	10.49 ± 2.03	11.35 ± 2.41	.389
Cause of injury			
Car accident injury [(n) %]	19 (44.19%)	16 (40%)	.447
Falling injury [(n) %]	11 (25.58%)	10 (25%)	.782
Hit injury [(n) %]	7 (16.28%)	6 (15%)	.519
Other reason [(n) %]	6 (19.95%)	8 (20%)	.681

BMI = body mass index, EA = electro-acupuncture, GCS = Glasgow coma scale.

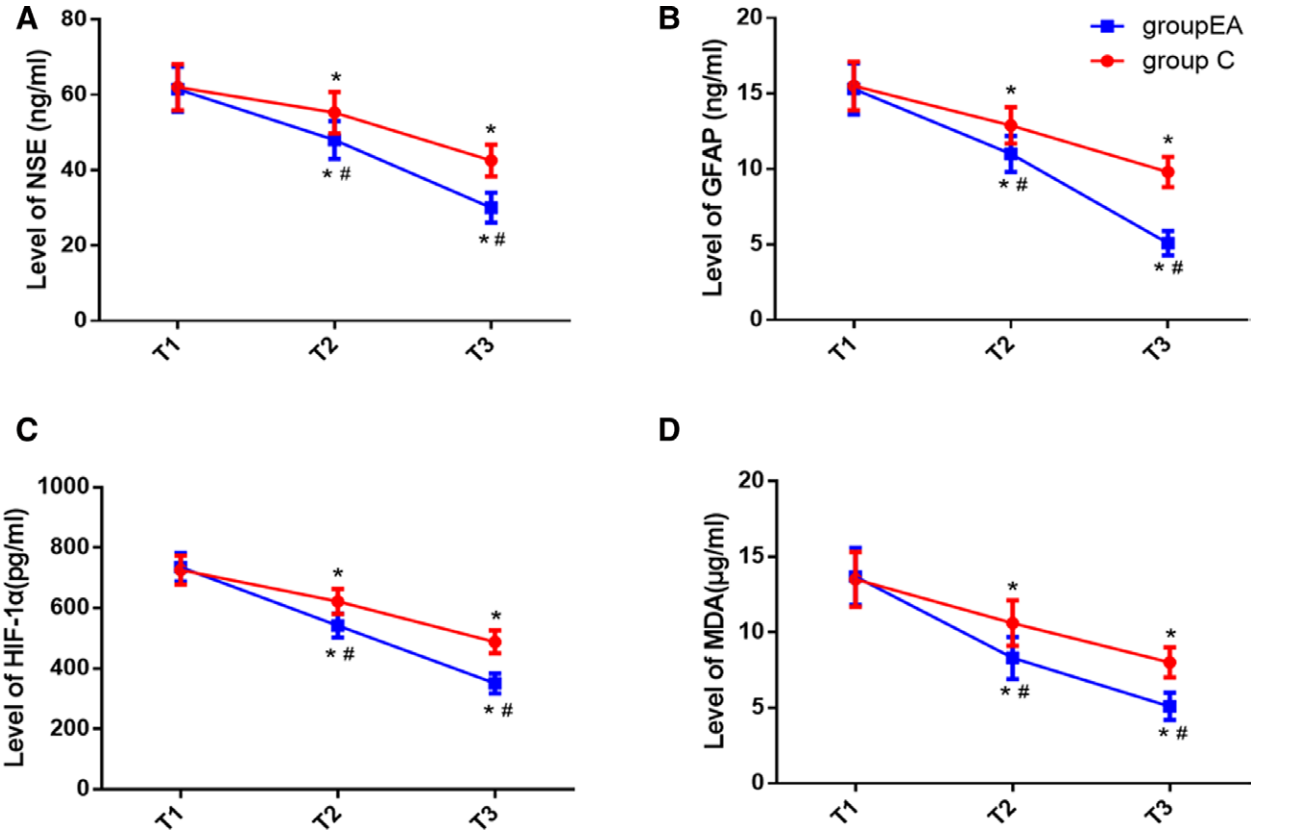

Figure 2. Concentrations of serum NSE (A), GFAP (B), HIF-1α (C), and MDA (D). Compared with T_1, *$P < .05$; compared with Group C, #$P < .05$. Flow diagram of study. Group C (red) and Group EA (blue). EA = electro-acupuncture, GFAP = glial fibrillary acidic protein, HIF-1α = hypoxia inducible factor-1α, MDA = malondialdehyde, NSE = neuron-specific enolase.

Table 2

Comparison of cerebral oxygen saturation between 2 groups (χ ± s).

Time	Group	Group C (n = 43)	Group EA (n = 40)	*P* value
T_1	Left	58.22 ± 5.72	59.17 ± 5.52	.374
	Right	59.17 ± 4.98	59.55 ± 5.41	.525
T_2	Left	66.28 ± 6.03*	74.68 ± 6.42*,#	.008
	Right	66.92 ± 6.15*	75.24 ± 6.64*,#	.027
T_3	Left	74.58 ± 6.81*	83.29 ± 7.78*,#	.016
	Right	75.14 ± 6.93*	84.12 ± 7.89*,#	.021

EA = electro-acupuncture, T_1 = 0 min before EA treatment, T_2 = 0 min after EA treatment, T_3 = 8 weeks after EA treatment.
*$P < .05$, compared with T_1.
#$P < .05$, compared with group C.

Table 3

Comparison of cognitive function score between 2 groups (χ ± s).

Time		Group C (n = 43)	Group EA (n = 40)	*P* value
T_1	MoCA	15.74 ± 2.66	16.02 ± 2.79	.618
	MMSE	16.89 ± 2.35	17.25 ± 2.58	.592
T_2	MoCA	18.06 ± 2.34*	20.55 ± 2.18*#	.014
	MMSE	18.67 ± 2.20*	20.13 ± 2.470*,#	.026
T_3	MoCA	19.15 ± 2.13*	22.47 ± 2.64*,#	.008
	MMSE	20.33 ± 2.05*	22.99 ± 2.15*,#	.019

EA = electro-acupuncture, T_1 = 0 min before EA treatment, T_2 = 0 min after EA treatment, T_3 = 8 weeks after EA treatment, MMSE = mini-mental state examination, MoCA = Montreal Cognitive Function Assessment.
*$P < .05$, compared with T_1.
#$P < .05$, compared with group C.

4. Discussion

With the characteristics of high energy consumption, high metabolism, and high oxygen consumption, the brain is very sensitive to ischemia and hypoxia. But the TBI destroy the normal homeostasis of the brain and the automatic regulation of cerebral blood flow which easily lead to cognitive impairment. Previous study showed EA treatment can effectively promote the recovery of consciousness after TBI, but the potential mechanism is still unclear. In the present research, we found that EA treatment could improve the cognitive recovery for patients with mild TBI and the potential mechanism may be related to improving cerebral hypoxia and alleviating brain injury.

There is a close relationship between TBI and cerebral oxygen metabolism disorder.[15] Verweij BH et al found that body energy metabolism, especially cerebral oxygen metabolism was impaired after TBI, which induced a series of adverse events, such as cognitive dysfunction.[16] Cerebral metabolism is highly dependent on cerebral blood flow and brain oxygen supply,[17] and Khellaf A et al have shown that the brain tissue ischemia and hypoxia rate of TBI patients after TBI can reach 92%.[18] Partly because head trauma can directly cause primary brain damage, such as brain contusion, subarachnoid hemorrhage and cerebrovascular injury, which arouse damage to the blood-brain barrier and the dysfunction of cerebrovascular autonomic regulation, resulting in insufficient brain tissue perfusion, reduced oxygen supply, and cerebral tissue ischemia and hypoxia.[19,20] And professor Salehi had also pointed out that there would emerge cerebral vasospasm and vascular regulation disorders after brain injury, which reduced cerebral perfusion to regions of the brain.[21] On the other hand, by causing brain tissue energy metabolism disorder, excitatory transmitter release, cell apoptosis and other secondary brain damage, aggravates cerebral edema and cerebral microcirculation disorders.[22] The interaction between the 2 forms a vicious circle of increased intracranial pressure, decreased cerebral perfusion pressure, and nerve cell ischemia and hypoxia. Rockswold SB et al found that improvement of cerebral oxygen metabolism could decrease markers of oxidative metabolism in relatively uninjured brain as well as pericontusional tissue, reduced intracranial hypertension.[23] LuY et al found that hyperbaric oxygen treatment can improve the prognosis of TBI patients by improving cerebral oxygen metabolism.[24] Therefore, the intervention of cerebral oxygen metabolism is the key point of TBI treatment.

EA has an protective effect on the nervous system and immune system, which has analgesic effect, immune regulation, and Organ function protection.[25,26] Regional rSO2 is a commonly used indicator for monitoring rSO2 in clinical practice, which can timely and accurately reflect the balance between oxygen supply and oxygen demand in patients' brain tissue, and the decrease of rSO2 index indicates insufficient cerebral tissue perfusion.[27] The study from Ning JQ showed EA stimulation can increase rSO2 levels in patients with diabetes.[28] The results of this study showed that EA treatment could decrease rSO2 level and increase the score of MoCA and MMSE, indicating that EA treatment could improve the recovery of consciousness after TBI by decreasing cerebral oxygen metabolism.

HIF-1α is a common transcription factor closely related to hypoxia in humans and other mammals, but it is easy to be degraded under the condition of normal oxygen and hardly be detected.[29] Only under hypoxia conditions can HIF-1α be expressed stably and the abnormal expression of it is involved in the development of ischemic and hypoxic diseases. A large number of domestic and foreign studies have found that the levels of HIF-1α and its mRNA in the body are significantly increased after brain injury, which promoted the cerebral vascular repair and regeneration.[30,31] TBI can make patients in a continuous stress state, increase brain oxygen consumption, stimulate the body to release a large number of inflammatory factors, cause brain edema, and aggravate brain hypoxia. Cerebral ischemia and hypoxia can promote the accumulation of a large number of oxygen free radicals and toxic substances in the body, membrane lipid peroxidation reaction, significantly increase the content of oxidative stress products. MDA is the end product of the peroxidation of free radicals and lipids, and is a sensitive index of damage.[32] It can reflect the content of oxygen free radicals and the degree of oxidative damage. The results of the current study showed that, compared with group C, the serum HIF-1α and MDA concentrations of patients in group EA at T_{2-3} were decreased, suggesting that EA could reduce cerebral oxidative stress.

TBI can directly cause cerebral hemorrhage to damage the blood-brain barrier, and can also through calcium overload, oxygen free radical damage, inflammatory factor release and other secondary damage to increase the blood-brain barrier permeability, so as to enable macromolecular substances to pass through the barrier.[33] NSE and GFAP are important neurobiological markers of brain injury. NSE is mainly found in nerve tissue and neuroendocrine tissue. It is a marker of neuronal cell body damage and a sensitive indicator of nerve cell death. GFAP is a highly specific marker of astrocytes and central nervous system. It is currently the most stable biological indicator of TBI, and its plasma concentration is not affected by multiple injuries.[34] Under physiological conditions, NSE and GFAP are very low in plasma, however, when the structural and functional integrity of nerve cells is destroyed and the permeability of the blood-brain barrier increases, its plasma concentration increased significantly. In the present study, the serum NSE and GFAP concentrations of patients in group EA decreased at T_{2-3} compared with group C, suggesting that EA can protect neurons and improve brain injury in patients with TBI.

It is undeniable that there are still some limitations in the current study. In this study, we only collected the blood sample at the intervention stage and 8 weeks after intervention, frequency of assessment needs to be increased and the follow-up time needs to be extended to obtain more accurate results.

5. Conclusion

In conclusion, EA treatment could improve the cognitive recovery for patients with mild TBI and the potential mechanism may be related to improving cerebral hypoxia and alleviating brain injury.

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