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Full Length Research Paper

A clinical study on the effects and mechanism of Xuebijing injection in the treatment of traumatic intracranial hematoma

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Xuebijing injection (XBJ) is one of Chinese materia medica standardized products which was extracted from *Salvia miltiorrhiza* Bge, *Carthamus tinctorius* L, *Paeonia lactiflora* Pall, *Ligusticum chuanxiong* Hort. and *Angelica sinensis*, has the actions of activating blood circulation and clear the meridians to melt away toxin factor. Our aim was to observe whether or not XBJ have neuroprotective effects on the patients with traumatic intracranial hematoma (TICH). If so, we would explain the mechanism involved. Forty patients with TICH were randomly assigned to trial group and a control group (20 patients per group). Routine medication was given to the patients of the two groups, and XBJ was administered intravenously to patients in the trial group additionally. The scores of GCS was recorded pre and post-treatment of the two groups, along with GOS after therapy. We also measured each patient' volume of the intracranial hematoma and coagulation indexes pre- and post-treatment. In addition, the activities of antioxidative enzymes were also evaluated in the study. XBJ could promote glasgow coma scale (GCS) and glasgow outcome scale (GOS) after therapy for the trial group compared with the control group ($p<0.01$). There was a significant post-treatment difference in the intracranial hematoma absorption between the two groups ($p<0.01$). The plasma levels of fibrinogen and D-dimer in the trial group were significantly decreased after therapy ($p<0.01$). XBJ also could decrease the serum level of malondialdehyde (MDA), increased the activities of superoxide dismutase (SOD), catalase (CAT) and the serum level of glutathione (GSH). These results suggest that XBJ exerts significant neuroprotective effects to the recovery of patients with TICH safely, which may be likely through the coagulation improvement and antioxidation and antilipid peroxidative properties of its action.

Key words: Xuebijing injection, traumatic intracranial hematoma, clinical study, coagulation, function, oxidative stress.

INTRODUCTION

Traumatic intracranial hematoma (TICH), which occurs in 45% of severe head trauma cases (Foulkes et al., 1991), is a common severe encephalopathy secondary to brain injury (Sun et al., 2009). Approximately 40% of patients with intracerebral hemorrhage die within 30 days, and the majority of survivors are left with severe disability (Counsell et al., 1995). Traumatic intracranial hematoma

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(TICH) can expand or develop late after head injury (Sawauchi et al., 2001). Furthermore, hemorrhage expansion is an independent determinant of death and disability (Davis et al., 2006). Identification of risk factors, early diagnosis and proper treatment of such lesion are important for improving the prognosis of these patients.

Recent studies (Wu et al., 2006; Lima et al., 2008) have reported that the pervasive action of oxidative stress on neuronal function and plasticity after traumatic brain injury (TBI) including TICH is becoming increasingly recognized.

Physiologic regulation keeps the dynamic balance between oxidant and antioxidant. However, in the bodies of patients with TICH a series of free radical chain reactions were gravely aggravated, the dynamic balance between oxidation and antioxidation was seriously disrupted, and oxidative stress was clearly exacerbated (Bakey et al., 1986), which is closely related to many disorders, such as brain edema, increased intracranial pressure, cerebral capillary spasm, increased vasopermeability, hemorheological changes, and so on (Sun et al., 2009). These factors may further accelerate cerebral ischemia and hypoxia which is the therapy key of TICH (Tang et al., 2006). So, antioxidant, that is scavenging free radicals, is a good strategy in clinics (Wu et al., 2010).

Computed tomography (CT) is central to acute TBI including TICH diagnostics, and millions of brain CT scans are conducted yearly worldwide (David et al., 2010), which is helpful to improve the diagnosis rate of TICH, make clinical tracing, observe absorption of small and moderate-sized hematomas in nonsurgical treatment. Symptomatic treatments such as dehydration therapy to reduce cranial pressure, pain relief, and so on are often adopted in neurosurgery for those having small and moderate-sized, non-life-threatening hematomas (Sun et al., 2009). Given its prognostic significance, mostly, there is no satisfactory clinical results obtained (Li et al., 2003).

However, studies have been completed to establish that TICH treated with additional Chinese materia medica in the early phase may result in satisfactory therapeutic effects with improved safety (Zhou et al., 2009; Wei et al., 2004). Xuebijing injection (XBJ) is one of Chinese materia medica standardized products which was extracted from *Salvia miltiorrhiza* Bge, *Carthamus tinctorius* L., *Paeonia lactiflora* Pall, *Ligusticum chuanxiong* Hort. and *Angelica sinensis*, has the actions of activating blood circulation and clear the meridians to melt away toxin factor.

Pharmacological studies show that XBJ can antagonize the disruptive effects of endotoxin (Zhang et al., 2006), regulate body immune functions (Dai et al., 2009), decrease the stress-induced organ or tissue damage (Li et al., 2006), and notably improve the survive rate of animals with systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome (MODS) (Wang et al., 2006). Moreover, according to some clinical researches, early Xuebijing injection treatment showed favorable therapeutic effects and reliable safety on the patients with sepsis (Wang et al., 2007) or MODS (Zhang et al., 2002). Meanwhile, it may also reduce the whole body and local inflammatory reaction degree and exhibit protection of brain tissue (Yuan et al., 2009b). The Safflor yellow A is the main chemical component in XBJ, and studies reported that the Safflor yellow A can protected rat brain (Ye et al., 2008) and cardiomyocytes (Liu et al., 2008) against I/R injury, exhibit neuroprotective effects after permanent middle cerebral artery occlusion in rats (Zhu et al., 2003) and antagonize binding of platelet activating factor to its receptor (Zang et al., 2002). XBJ has been applied extensively to the treatment of TICH and has showed significant therapeutic effect in our hospital. Therefore, the aim of the clinical study was to observe the short- and long-term therapeutic effects of XBJ in the treatment of acute TICH, and to explore its possible mechanisms.

MATERIALS AND METHODS

Selection of subject

Over the period from January 2010 to September 2011 in Xiangya Hospital, Changsha, China. Patients 18 years of age or older with TICH documented by CT scan within 3 h after causes ranged from traffic accident injury to falling from higher places, to being hit were eligible for enrollment. Subjects were randomly assigned to the trial group (XBJ treatment, twenty cases) and the control group (twenty cases) upon admission to the hospital. The diagnostic criteria and exclusion criteria referred to the previous study (Sun et al., 2009), as follows: those who were admitted within 24 h after a cerebral injury confirmed by CT; with an intracranial hemorrhage volume between 10 and 40 ml; with no continuously enlarged hematoma after consecutive head CT examinations within 3 days, but not scheduled for surgery; aged between 16 and 65 years; and all with Glasgow coma score (GCS) greater than 8. The exclusion criteria were: severe cardio-/cerebral vascular diseases; liver or renal diseases; diabetes mellitus; other severe organ injuries; coagulation disorders; obviously enlarged hematoma confirmed by head CT and/or aggravated symptoms indicating a need for surgery. The study was approved by the institutional ethics committee. Informed consent was obtained from all patients or from their guardians prior to inclusion.

The data were comparable between the two groups with no significant differences in gender, age, type, volume of intracranial hemorrhage in Table 1.

TREATMENT

Routine therapy (that is, dehydration therapy to reduce cranial pressure, pain relief, antinausea, antiinfection, neurotrophic activity, e t c.) anti-microbial and sputum elimination agents were given to patients of both the two groups. Xuebijing injection produced by Tianjin Hongri Pharmaceuticals Co. Ltd. was additionally used in the trial group, 50 ml of Xuebijing injection with 100 ml of normal saline administered through intravenous drip twice a day. The treatment course was 14 days for both the two groups.

Table 1. Subject demographic and baseline characteristics.

Variable		Trial Group (n = 20)	Control Group (n = 20)
Gender	Male	15	16
	Female	5	4
Age	Range (yr)	19-64	20-65
	Mean±SD (yr)	39.43±12.35	38.96±13.79
Type	Epidural hematoma	7	6
	Subdural hematoma	5	6
	TICH	5	6
	Multiple hematoma	3	2
Volume of intracranial hemorrhage	Range (ml)	15-36	14-35
	Mean±SD (ml)	28.12±7.96	27.46±8.07

Glasgow coma score (GCS) and glasgow outcome score (GOS)

GCS (Graham et al., 1974) and GOS were recorded pre-treatment and on the 14th day of the therapy. The intracranial hemorrhage volume and GCS was used to judge the short-term efficacies and GOS (Jennett et al., 1981): (1: death; 2: persistent vegetative state; 3: severe disability; 4: moderate disability; 5: good recovery) was used to evaluate the long-term efficacies in the two groups. 3 months post-treatment was set as the evaluation time (Sun et al., 2009).

Coagulation detection

Venous blood samples (withdrawn pre-treatment and on the 14th day of the therapy) were anticoagulated by the addition of 4.5 ml of whole blood to 0.5 mL of 0.105 mol/L citrate. Plasma samples were double centrifuged at 3000 g × 10 min and frozen at -80°C until analysis at a later date. Prothrombin time (PT), PT international normalized ratio (INR), activated partial thromboplatin time (APTT), thrombin time (TT), fibrinogen (Fbg), D-dimer (DD) were detected according to the protocols by the technicians in Xiangya Hospital affiliated to Central South University.

Intracranial hematoma volume determination

Intracranial hematoma volume was determined in the following manner (Broderick et al., 1994): On the CT slice with the largest area of intracranial hematoma, the largest diameter (A) of the hematoma was measured by use of the centimeter scale on the CT film. The diameter of the hemorrhage perpendicular to the largest diameter represented the second diameter (B). The height of the hematoma was calculated by multiplying the number of slices involved by the slice thickness, providing the third diameter (C). The three diameters were multiplied and then divided by 2 (A×B×C/2) to obtain the volume of intracranial hematoma. Head CT scan were conducted as pre-treatment, on the 7th and 14th days post-treatment to confirm the absorption of intracranial hematoma.

Biochemical estimation

Fasting blood samples of each patient in the two groups was drawn by medical officer between 6:00 to 8:00 a.m. pre-treatment and on the 14th day of the therapy. Serum was obtained by centrifugation at 1500 × g for 15 min of blood samples taken without anticoagulant. Serum was kept at -80°C until the biochemical estimation of different parameters. Malondialdehyde (MDA), superoxide dismutase (SOD) activity, catalase (CAT) activity, glutathione (GSH) estimation in the serum were performed by the method of Santanu et al. (2008)

Efficacy assessment and monitoring of adverse effects

The common adverse effects (that is, dizziness, cardiopalmus, fever, rash, etc.) of Chinese herbs were observed by a specifically appointed person according to the previous reports (Yang et al., 2011). Blood routine, alanine transferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, electrocardiogram were tested pre-treatment and on the 14th day of the therapy.

All the tests were operated according to the protocols provided by Xiangya Hospital affiliated to Central South University.

Statistical analysis

All the data in the experiment are expressed as mean ± standard deviation. All data were analyzed by SPSS 16.0 software. Comparisons between pre- and post- treatment was carried out using a paired t-test. An independent-samples t-test was used to compare the post-treatment data between the trial group and the control group, and a Chi-square test was taken for nonparametric data. The values of $p< 0.05$ were considered to be statistically significant.

RESULTS

Effect on GCS

Figure 1 showed that the pre-treatment GCS (9.76±1.24 and 9.83±1.31) of the two groups were comparable with no significant differences ($p>0.05$). The post-treatment score in trial group and control group was significantly

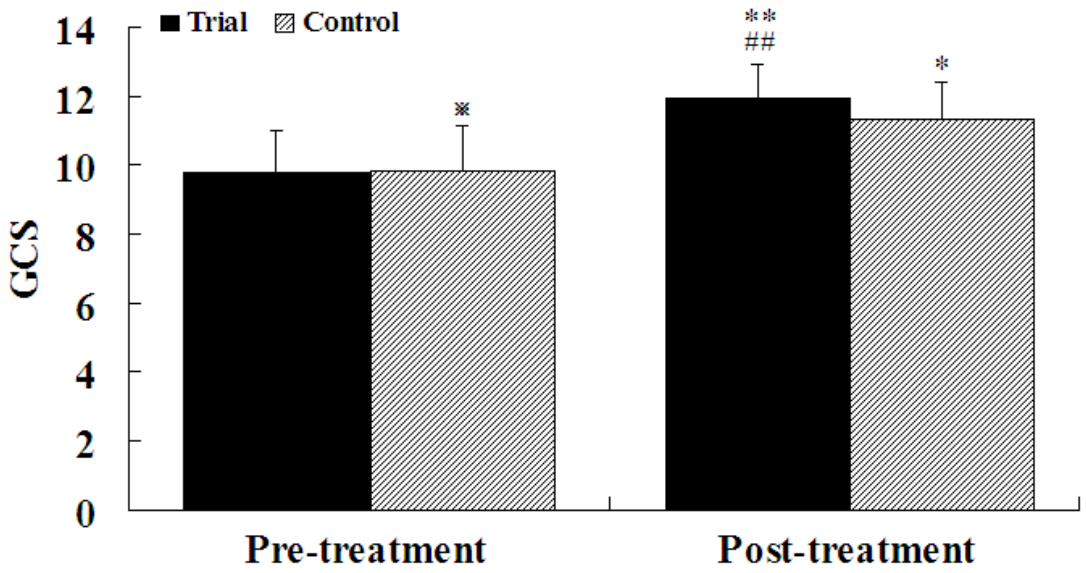

Figure 1. Comparison of GCS score in the control and trial groups (Score). ※P>0.05, trial group vs. control group of pre-treatment; **P<0.01, pre-treatment vs. post-treatment; ##p<0.01, trial group vs. control group of post-treatment; *p<0.05, pre-treatment vs. post-treatment.

Table 2. Comparison of coagulation functions in the two groups pre- and post-treatment. #p<0.05, pre-treatment vs. post-treatment. ▲p<0.01, the trial post-treatment vs. the control group post-treatment. (PT: prothrombin time; INR: international normalized ratio; APTT: activated partial thromboplatin time; TT: thrombin time; Fbg: fibrinogen; DD: D-dimer.)

Group	PT (s)	INR	APTT (s)	TT (s)	Fbg (g)	DD (μg/L)
Trial						
Pre-treatment	12.05±0.48	1.04±0.47	27.59±6.72	15.79±2.96	4.52±0.45	246.49±175.06
Post-treatment	12.11±0.53	1.09±0.54	28.46±7.26	16.73±4.58	3.71±0.38#,▲	182.73±113.21#,▲
Control						
Pre-treatment	12.08±0.74	1.06±0.38	27.61±7.83	15.46±5.87	4.43±0.54	241.05±146.32
Post-treatment	12.13±0.49	1.05±0.42	27.75±8.19	16.12±4.67	4.36±0.49	234.69±142.86

increased (to 11.97±0.95, p<0.01; 11.35±1.02, p<0.05, respectively).

However, the post-treatment score of the trial group was clearly higher than that of the control group, with significant difference (p<0.01).

Comparison of coagulation indexes in the two groups pre- and post-treatment

As shown in Table 2, there was no significant difference in PT, INR, APTT, TT between the two groups pre- and post-treatment (p>0.05). Fibrinogen (Fbg) and D-dimer (DD) of post-treatment in the trial group significantly reduced compared with that of pre-treatment (p<0.05). There was also a significant difference in the two indexes between the two groups post-treatment (p<0.01).

Comparison of intracranial hematoma absorption in the two groups pre- and post-treatment

Compared with pre-treatment volume (28.12±7.96 ml), intracranial hematoma volume after 1 week and 2 weeks of treatment significantly reduced (to 18.47±5.62 and 13.58±4.12 ml, respectively, p<0.01) as shown in Figure 2. There was also a significant difference between the two groups post-treatment (p<0.05).

Comparison of GOS in the two groups pre- and post-treatment

The post-treatment GOS was (4.58±1.23) in the trial group while that in the control group was (4.07±0.87). Total effective rate of 100% in the trial group was clearly

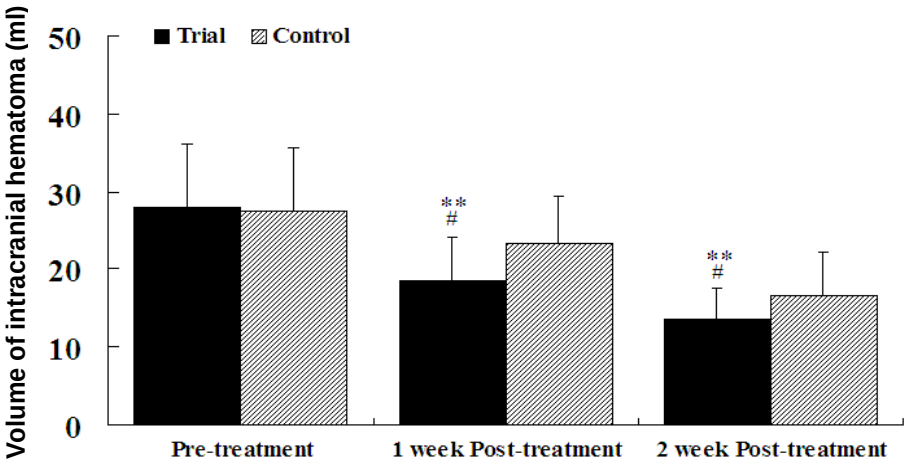

Figure 2. Comparison of intracranial hematoma volume after 1 week and 2 weeks of treatment. **p<0.01, 1 week and 2 weeks of trial treatment vs. trial pre-treatment. #p<0.05, 1 week and 2 weeks of trial treatment vs. control post-treatment.

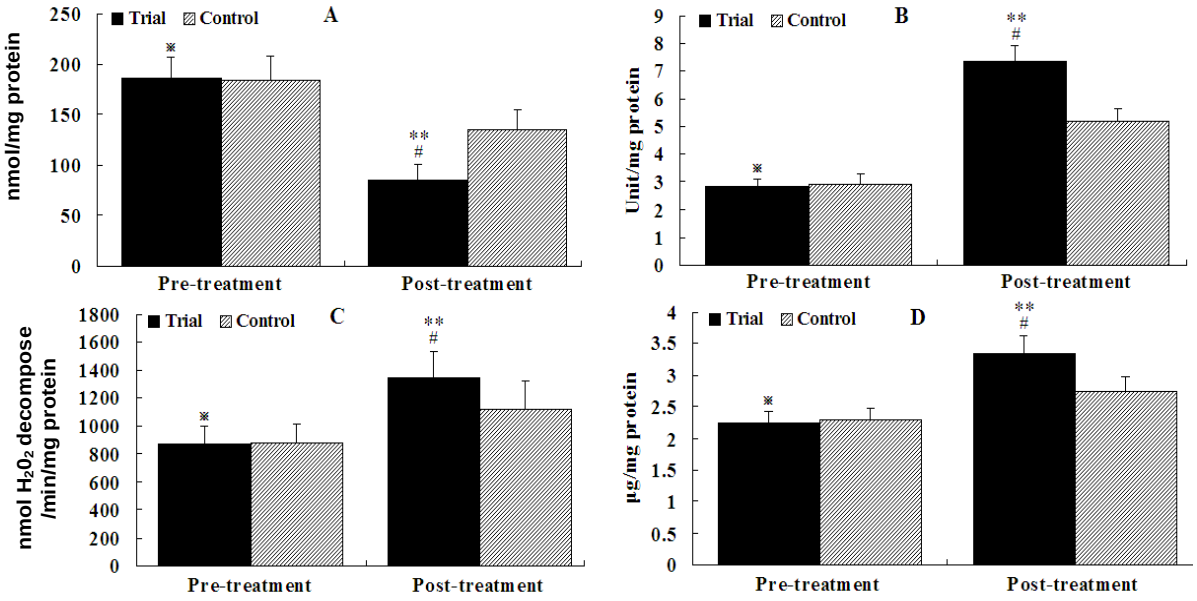

Figure 3. Effect of biochemical estimation: (A) malondialdehyde (MDA); (B) superoxide dismutase (SOD); (C) catalase (CAT); (D) glutathione (GSH). ※P>0.05, trial group vs. control group of pre-treatment; **P<0.01, pre-treatment vs. post-treatment; #p<0.05, trial group vs. control group of post-treatment.

higher than that (78.6%) in the control group. There was also significant difference in GOS between the two groups (p<0.05).

Effect of biochemical estimation

Figure 3 showed there was no significant difference in the serum levels of MDA, SOD, CAT, GSH between the two groups pre-treatment (p>0.05). The trial post-treatment serum level of MDA level was significantly decreased compared with trial pre-treatment (p<0.01) and control post-treatment (p<0.05), while the trial post-treatment serum levels of SOD, CAT and GSH obviously increased compared with trial pre-treatment (p<0.01) and control post-treatment (p<0.05).

Adverse reaction

No abnormal changes in blood routine examination,

alanine transferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, electrocardiogram tests were seen in all patients. Only one patient reported a mild fever which resolved without symptomatic therapy. Apart from this, no other obvious adverse reaction occurred.

DISCUSSION

TICH belongs to the category of "blood stasis" in traditional Chinese medicine (TCM) (Ma et al., 2008). Traditional Chinese medicine (TCM) thought that "blood circulating out of vessels was known as blood stasis" and blood stasis is an important underlying pathology of many disease processes according to traditional Chinese medicine. Described in TCM theory as a slowing or pooling of the blood due to injury or disruption of heart Qi, it is often understood in biomedical terms in terms of hematological disorders such as hemorrhage, congestion, thrombosis, local ischemia (microclots) and tissue changes (Zhao et al., 2008). The strategy of activating blood circulation and resolving stasis has been extensively in clinical application of Chinese materia medica. Numerous studies reported that it can improve microcirculation, eliminate toxic products, and attenuate cerebral edema, thus promoting the absorption of intracranial hematoma and improving the functions of the nervous system (Ma et al., 2008).

The Chinese material medica, such as *S. miltiorrhiza* Bge, *C. tinctorius* L, *P. lactiflora* Pall, *L. chuanxiong* Hort. and *A. sinensis*, which are consisted in XBJ, all have the function of activating blood circulation and resolving stasis in accordance with the principals of TCM. Safflor yellow A, the main component of XBJ, mainly has the same function according to TCM principals and modern pharmacological studies. Some research also reported XBJ protect brain (Wei et al., 2005), lung tissue (Qiu et al., 2009), pancreas (Sun et al., 2007) through anti-oxidative effect. Moreover, Safflor yellow A could protect HUVECs from hypoxia induced injuries by inhibiting cell apoptosis and cell cycle arrest (Ji et al., 2009), inhibit thrombosis and platelet aggregation (Tian et al., 2003). It provided neuroprotection against cerebral ischemia/reperfusion injury through its antioxidant action (Wei et al., 2005) and exhibited neuroprotective effects after permanent middle cerebral artery occlusion (MCAO) in rats (Zhu et al., 2003). But there was no report on the effects of XBY on TICH, and the mechanisms of its neuroprotective effect are remains poorly understood.

In the study, we observed the clinical therapeutic efficacy of XBJ on the treatment of traumatic intracranial hematoma. Trial group treatment in combination with XBJ could obviously improve the prognosis (promote the scores of GCS in Figure 1 and GOS) and make intracranial hematomas absorbed (Figure 2), compared with control group treatment. As expected, XBJ exhibited neuroprotective effects on patients with TICH. Its mechanism of action may be achieved by lowering fibrinogen content, promoting fibrolysis, and improving microcirculation (Table 2). Except XBJ, some other studies (Yuan et al., 2009a; Chen et al., 2007; Deng et al., 2009) showed that traditional Chinese herbs could significantly improve clinical effect, improve nerve impairment, and accelerate hematoma absorption. Interestingly, Shuxuetong injection (Jin et al., 2008) and Danhong injection (Sun et al., 2009) (Chinese materia medica injection) also demonstrated the similar effects to XBJ on clinical neuroprotective effects just as reported in the study. However, the mechanism of oxidative stress was studied in our research, which was not seen in these reports.

Oxidative stress is the result of an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant system in favour of the former (Santanu et al., 2008). So, intensity of oxidative stress is determined not only by the free radicals production but also by antioxidants (enzymatic and non-enzymatic) defense (Beltowski et al., 2000). Oxidative stress is increased in brain injury, playing significant roles in neuronal apoptosis (Yu et al., 2002).

Malondialdehyde (MDA), the degradation product of the oxygen-derived free radicals and lipid oxidation, can interfere with the metabolism of protein, glucose, and nucleic acid, which results in the decrease in activity of enzyme, template dysfunction of nucleic acid, and injury of tissues and cells (Zheng et al., 2008). Antioxidant defense system protects our body from the deleterious effect of reactive oxygen metabolites. Catalase (CAT) act as preventive antioxidants and superoxide dismutase (SOD), a chain breaking antioxidant, play an important role in protection against the deleterious effect of lipid peroxidation (Dinkovo-Kostova, 2002). Depletion of GSH is one of the primary factors that permit lipid peroxidation (Konukoglu et al., 1998). Figure 3 showed that trial and control treatment both could reduce the serum level of MDA, increased the activities of SOD and the serum level of GSH. To our surprise, the indexes in the trial group was superior to that of the control group ($p<0.05$), that is to say XBJ can further promote the clinical effects compared with the routine therapy. These also indicate that XBJ can scavenge various free radicals effectively through enhancing the activities of the antioxidant enzymes in trial group. Furthermore, the antioxidant enzymes in trial groups were found to be enhanced by XBJ.

Brain injury is a complicated syndrome and requires comprehensive treatment. In addition to routine medicinal treatment, traditional Chinese medicine has been paid more and more attention in treating complex diseases worldwide. Polypharmacology may provide a solution in this field (Frantz, 2005). Traditional Chinese medicines (TCMs) consist of several types of medicinal herb or mineral, and multiple components can hit multiple targets

and exert synergistic therapeutic effects. The study provides evidence for the first time to elucidate the integrated protective effects of XBJ for improve the prognosis of TICH mainly through anti-oxidation and anti-coagulation. The studies on its more and precise mechanism of action are underway. Therefore, XBJ may be safely used as an effective and promising agent for both TICH and other complex diseases.

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