Administration of Yunnan Baiyao improved clinical prognosis of emergency craniotomy in patients with moderate-to-severe TBI: a randomized controlled trial

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Research

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Abstract

Background: Although emergency craniotomy has been performed to reduce the mortality of traumatic brain injury (TBI), it is associated with secondary injury and poor prognosis. The efficacy of a wound-healing medicine Yunnan Baiyao (YB) was compared with a TBI medicine Xingnaojing (XNJ) and orthodox therapy (OT).

Method: Eighty patients (39±7 yrs.) with moderate-to-severe TBI (Glasgow Coma Scale(GOS), 3-12) received craniotomy before randomly assigned to (n=20) 7 days treatment of: 1) OT; 2) OT+XNJ (20 ml i.v. drip/daily); 3) OT+low dose-YB (oral, 1,000 mg/day); 4) OT+high dose-YB, 2,000 mg/day). Serum S100B and superoxide dismutase (SOD), Glasgow Outcome Scale (GOS) and Karnofsky Performance Scale (KPS) were evaluated.

Results: GCS score was lowest on admission that improved more quickly and became significantly higher in XNJ, l-YB, h-YB groups than in OT group (P<0.01). S100B peaked higher but declined more slowly and became significantly higher in OT than in other groups (P<0.01). By Day 7, S100B declined to 20% below baseline in other groups but remained 19.4% above baseline in OT group. OT lost 38% SOD activity on Day 3 and regained 69% of SOD activity on Day 7 whereas other groups lost 16.7%~23.4% SOD on Day 3 but regained 91.8%~99.5% activity on Day 7 (P<0.01). GOS and KPS scores were significantly greater (~25%~30%) in the XNJ, l-YB, h-YB groups than in OT group 1-3 months post-surgery.

Conclusion: YB is significantly better than OT and non-inferior to XNJ in improving postoperative recovery and clinical prognosis after emergency craniotomy in patients with moderate-to-severe TBI.

Introduction

Traumatic brain injury (TBI) is a major cause of mortality and disability with more than 27 million new cases reported worldwide in 2016[1]. TBI is complicated with intracerebral hemorrhage, edema, hydrocephalus, elevated intracranial pressure (ICP), coagulopathy and stress. Although orthodox treatments (OT) such as hyperosmolar therapy, sedation, barbiturate coma, hypothermia therapy and ventricular drainage have been used in TBI management, they are often not effective.

Surgical removal of intracranial hematoma and fractured brain tissue (craniotomy/decompression craniectomy) can reduce the mortality of severe TBI, incidence of ICP, and length of hospital stay in TBI patients [2–4]. Surgery, however, could also worsen the clinical outcomes of TBI [5, 6], partly due to secondary injury, increased gastrointestinal bleeding and inflammatory complications [4, 7–11].

Timely appropriate drug treatment after craniotomy could potentially reduce the impact of secondary injuries and improve the prognosis [12]. So far, all experimental drugs for treatment of TBI failed in clinical trials [13]. According to the "Guidelines for the Management of Severe Traumatic Brain Injury" (2017, US): high doses of hormones, magnesium ions and albumin increase the risk of mortality in patients with acute TBI whereas calcium antagonists, glutamate receptor antagonists, free radical scavengers, bradykinin antagonists, peptide drugs and mitochondrial functional protective agents are ineffective in the treatment of acute TBI [14].

Herbal medicine, as a monotherapy or adjuvant therapy, has been reported to have improved clinical outcomes of TBI [15–17]. Yunnan Baiyao (YB) is a well-known wound healing medicine since World War II in Asia and it has recently been shown to be more effective for treating TBI-induced bleeding [18–20]. Administration of YB induced significantly greater anti-hemorrhage effect (92%) than pantoloc (71%) in TBI-induced gastrointestinal bleeding, brain edema and secondary brain injury [21–24]. Preoperative administration of YB significantly reduced blood loss and improved hemostasis and safety of bimaxillary orthognathic surgery [25].

Intravenous Xingnaojing (XNJ) is a modified intravenous injection of a traditional coma medicine Angong Niu Huang Pill (ANP) that has been used for detoxification, detumescence, recovery of cerebral microcirculation, coma and disturbance of consciousness, ischemic stroke and intracerebral hemorrhage in China [26–30]. XNJ differ from YB in major active ingredients (Moschus, Fructus Gardeniae, Curcuma Radix and Borneolum Syntheticum vs. Panax Notoginseng and Rhizoma Paridis) that could serve as a positive control for YB, with potential differences in mechanism of therapeutic action and efficacy for TBI.

S100β is a glial-specific calcium-binding protein that promote neuronal survival at low concentration but exacerbates neurovascular inflammatory responses and apoptosis at high concentration after TBI [31]. Serum S100B protein is a valid biomarker of TBI severity [32–40]. Extracellular SOD is the only extracellular scavenger of superoxide anion (O_2^-) and radicals which are major causes of oxidative damage and secondary injury of TBI [41–44].

So far, no study has examined the impact of YB on postoperative recovery and clinical prognosis after craniotomy. In this prospective randomized controlled trial, we tested the hypothesis that YB adjuvant therapy may have therapeutic effects on postoperative recovery and clinical prognosis after craniotomy in patients with moderate-to-severe TBI.

Methods

Participants and treatments

This randomized controlled trial included 80 age- and severity-matched TBI patients, admitted to the Emergency Department before transferred to the Neurosurgery Department for emergency craniotomy at Chinese PLA General Hospital between September 2010 and October 2011. The inclusion criteria include: 1) diagnosed with moderate-to-severe TBI (within 8 hours of TBI, Glasgow Coma Scale score, 3 ~ 12), without injury to other organs; 2) intracranial

contusion/laceration, intracranial/epidural/subdural hematoma and other organic lesions confirmed by computed tomography (CT); 3) between 15 and 65 years of age; 4) received emergency craniotomy within 12 hours of TBI. The exclusion criteria included: 1) severe multiple or combined injuries; 2) history of severe chronic illness; 3) participated in any drug trial one month prior to this trial; 4) had malignant tumor or other diseases in the nervous or immune systems; 5) pregnant and lactating women; 6) with more than 400 ml blood transfusion during treatment; 7) uncooperative; 8) automatic discharge or death; 9) had a second craniotomy; 10) history of allergy to YB or intravenous XNJ. All study procedures were conducted in accordance with the Helsinki Declaration of 1975, in adherence to CONSORT guidelines (<http://www.consort-statement.org/>), and were approved by the Ethics Committee of Chinese PLA General Hospital. The clinical trial is retro-registered (ChiCTR2000030280 and ChiMCTR2000003057, respectively). The primary outcomes include changes in postoperative scores of Glasgow Coma Scale (GCS) and post-discharge scores of Glasgow Outcome Scale (GOS) and Karnofsky Performance Scale (KPS). The secondary outcome is changes in serum S100B protein and serum superoxide dismutase (SOD) activity.

The sample size was calculated according to the hypothesis that the expected means $\pm$ standard deviation of GOS in three adjunct treatment groups would be 4.0 ± 0.8 after the intervention. The expected means $\pm$ standard deviation of GOS in the OT group would be about 3.0 ± 0.8 after the intervention. The α level was set as 0.05 and the power was set as 0.85 (β level as 15%). The calculated sample size is 17 per group, and the total sample size was 68. With an expected 15% dropout rate ($n = 10.88$), at least 80 patients would be required, with 20 participants per group.

At admission, TBI patients underwent complete medical history inquiry, physical examination, routine laboratory tests and cranial CT scan. The demographic and general clinical diagnosis at admission include scoring, degree of Glasgow Coma Scale (GCS), type and cause of injury, and type of craniotomy. Emergency craniotomy included intracranial hematoma evacuation, inactivated brain tissue resection, bone flap decompression and so on.

After surgery, patients were randomly assigned to one of the four following treatments for 7 days using a predetermined randomization code generated by a random number generator according to the order of admission: 1) orthodox treatment (OT); 2) OT plus Xingnaojing (XNJ) (intravenous drip of 20 ml Xingnaojing in 500 ml normal saline, daily, Wuxi Jimin Xinshanhe Pharmaceutical Co., Ltd., China); 3) OT plus low dose Yunnan Baiyao (l-YB) (1,000 mg, q.i.d) (Yunnan Baiyao Group Co., Ltd., China, oral or via stomach tube, q.i.d.); 4) OT plus high dose YB (h-YB) (2,000 mg, q.i.d). Orthodox treatments (OT) include dehydration, hemostasis, diuresis, prophylactic dose of antibiotics, hormone therapy, prevention of epilepsy and other necessary symptomatic treatments. Medical treatment was administered daily. Changes in clinical symptoms including vital signs, conscious state, pupil changes, etc. were scored daily.

The GCS was used to evaluate disturbance of consciousness with eye opening, speech condition and motor response (mild = 13–15, moderate = 8–12, severe = 3–7, Appendix 1). The Glasgow Outcome Scale (GOS) and Karnofsky Performance Scale (KPS, Appendix 2&3) were performed at 30 and 90 days after surgery to evaluate clinical prognosis. The outcome of GOS was classified as good (4–5), bad (2–3) and death (1). KPS reflects changes in physical strength, functional rehabilitation and the abilities of daily life and work. A score of > 80 points indicates independent, adequate capability of self-care in daily life; a score of 60 ~ 70 points indicate semi-dependent in daily life and a score of < 60 points indicates lack of self-care capability.

Five ml of venous blood was drawn on admission and on Days 1, 3, 5, and 7 after surgery. After 2000r/min centrifugation, the serum was stored at -80°C , and thawed at 4°C overnight before assaying. Serum S100B was determined by an enzyme-linked immunosorbent assay (Elisa) kit for human serum S100B protein (Randy D Company, USA) and serum superoxide dismutase (SOD) activity was determined by pyrogallol autoxidation method (PAM) using the SOD detection kit (Fujian Fuyuan Biotechnology Co., Ltd., China).

Statistical analysis

Normally distribution of GCS, S100B, SOD, GOS and KPS were confirmed and presented as mean $\pm$ SD. General linear model of repeated measures was performed to measure the effects of treatments, time and treatment*time interactions. Changes and change rate (%) at each postoperative observation time over the baseline (on admission) were also analyzed using independent t-tests, ANOVA or nonparametric tests (Mann–Whitney U-test) as appropriate (SPSS 24, USA). For categorical variables, χ^2 test was conducted. Pearson correlations between experimental variables were calculated. A two-tailed P value < 0.05 was considered statistically significant.

Result

Clinical characteristics of TBI patients

Traffic accident was the main cause of TBI and brain contusion was the primary damage type in this study (Table 1). There were no baseline differences in demographic and clinical characteristics including age, gender, GCS score, type and cause of TBI and type of craniotomy between the treatment groups: OT, OT + XNJ, OT + l-YB and OT + h-YB (Table 1).

Table 1
Clinical characteristics, GCS score, main causes and damage type of the participants.

Characteristics/ No. of cases	OT (n = 20)	XNJ (n = 20)	I-YB (n = 20)	h-YB (n = 20)	χ^2	P
Male: Female	12:8	11:9	13:7	12:8	0.417	0.937 ^a
Age, y, mean(min-max)	41.7 ± 10.54	43.1 ± 10.66	42.3 ± 14.05	42.3 ± 9.65	0.461	0.927 ^b
Degree of injury						
Severe: Moderate	10:10	8:12	8:12	12:8	2.020	0.568 ^a
Admission time (hours from injury) mean(min-max)	4.7(1.5–8)	5.3(2.5–12)	4.8(2–7.5)	5.1(2–8)	0.59	0.899 ^b
Causes of TBI (N/%)					3.628	0.989 ^a
Traffic accident	9(45)	7(35)	7(35)	8(40)		
Falling	4(20)	5(25)	4(20)	3(15)		
Blow	5(25)	3(15)	4(20)	4(20)		
tumble	2(10)	3(15)	3(15)	3(15)		
crush	0(0)	2(10)	2(10)	2(10)		
Damage type (N/%)					2.296	0.999 ^a
Epidural hematoma	2(10)	3(15)	2(10)	3(15)		
Subdural hematoma	5(25)	6(30)	6(30)	4(20)		
Brain contusion	10(50)	9(45)	9(50)	10(50)		
Intracerebral hematoma	2(10)	1(5)	1(5)	1(5)		
Multiple hematoma	1(5)	1(5)	2(10)	2(10)		
Operation method (N/%)						
Decompressive craniectomy	12(60)	8(40)	9(45)	11(55)	2.000	0.572 ^a
Intracranial hematoma evacuation	10(50)	11(55)	11(55)	10(50)	0.201	0.978 ^a
Inactivated brain tissue resection	10(50)	9(45)	9(45)	10(50)	0.201	0.978 ^a
^a Chi-square Test;						
^b K Independent Samples test.						
OT, Orthodox therapy; XNJ,OT + Xingnaojing; I-YB,OT + low-dose Yunnan Baiyao; h-YB, OT + high dose Yunnan Baiyao						

Repeated measure analysis and ANOVA showed significant Time effect ($P < 0.001$) and Time x Treatment interaction ($P < 0.001$) in GCS scores (Tables 2 & 3, Fig. 1A) that was lowest on admission in all groups but improved more quickly and became significantly greater in XNJ, I-YB, h-YB groups than in OT group since Day 3 ($P < 0.01$) (Table 2, Fig. 2A). Moreover, the improvement rate in GCS were significantly greater in h-YB than in I-YB and XNJ groups on Days 3, 5 and 7 ($P < 0.01$, all)(Figs. 2B&2C) which may also reflex a relatively lower baseline GCS value in the h-YB group (7.30 ± 2.43) than in OT, XNJ and I-YB groups (8.10 ± 2.38 , 8.60 ± 2.50 , 8.50 ± 2.48 , respectively).

Table 2
Repeated measure analysis of Glasgow Coma Scale, Serum S100B and SOD proteins, Glasgow Outcome Scale and Karnofsky Performance Scale after emergency craniotomy in patients with moderate-to severe TBI show significant treatment effects and time * treatment interaction of OT, XNJ, I-YB and h-YB therapies

No. of cases	Treatment	Time	Time * Treatment
	F, P	F, P	F, P
GCS (N, 80)	1.57, 0.20	250.8, 0.00	6.16, 0.00
S100B (N, 80)	40.4, 0.000	1482.8, 0.00	27.3, 0.00
SOD (N, 80)	19.1, 0.000	456.1, 0.00	22.8, 0.00
GOS (N,80)	4.60, 0.005	138.6, 0.00	0.839, 0.477
KPS (N, 80)	7.04, 0.000	378.0, 0.00	0.489, 0.691

Table 3
Evaluation of postoperative recovery and clinical prognosis after craniotomy and treatments of orthodox therapy, Xingnaojing, low and high doses of Yunnan Baiyao adjuvant therapies in patients with moderate-to severe TBI (means $\pm$ SD)

Daiyao adjuvant therapies in patients with moderate-to-severe TBI (means ± SD)									
OT (n = 20)				OT + XNJ (n = 20)		OT + l-YB (n = 20)		OT + h-YB (n = 20)	
	Days		P (a)		P (a),P (b)		P (a),P (b)		P (a),P (b)
GCS Score	Admission	8.10 ± 2.38	/	8.60 ± 2.50	/,0.52	8.50 ± 2.48	/,0.61	7.30 ± 2.43	/,0.31
	1	8.20 ± 2.29	0.063	8.80 ± 2.33	0.059, 0.40	8.70 ± 2.16	0.061,0.48	7.35 ± 2.16	0.057,0.23
	3	8.30 ± 1.95	0.056	9.90 ± 2.00	0.018, 0.01	9.90 ± 1.97	0.016,0.01	9.80 ± 1.77	0.022,0.02
	5	9.35 ± 2.06	0.029	10.90 ± 1.58	< 0.001, 0.01	10.65 ± 1.69	< 0.001,0.02	10.95 ± 1.43	< 0.001, < 0.001
	7	10.10 ± 1.80	0.021	11.85 ± 1.93	< 0.001, < 0.001	11.55 ± 1.70	< 0.001,0.01	11.30 ± 1.53	< 0.001,0.03
	Admission	2.08 ± 0.14	/	1.99 ± 0.18	0.07	2.00 ± 0.15	0.11	2.00 ± 0.16	0.09
S100B protein (µg/l)	1	2.74 ± 0.15		2.67 ± 0.13	0.13	2.81 ± 0.14	0.11	2.73 ± 0.14	0.89
	3	3.38 ± 0.23		2.99 ± 0.34	< 0.001	3.20 ± 0.32	0.05	3.12 ± 0.30	0.01
	5	2.84 ± 0.20		1.83 ± 0.23	< 0.001	1.93 ± 0.29	< 0.001	1.94 ± 0.18	< 0.001
	7	2.48 ± 0.23		1.57 ± 0.29	< 0.001	1.59 ± 0.23	< 0.001	1.51 ± 0.25	< 0.001
Serum SOD activity (U/ml)	Admission	114.80 ± 8.93	/	112.91 ± 8.61	0.47	115.44 ± 7.23	0.81	115.76 ± 7.77	0.71
	1	105.10 ± 7.95		105.65 ± 9.03	0.83	101.06 ± 6.15	0.12	103.05 ± 8.67	0.42
	3	74.75 ± 7.51		95.26 ± 6.00	< 0.001	91.79 ± 6.64	< 0.001	94.41 ± 6.07	< 0.001
	5	80.97 ± 5.85		104.60 ± 7.89	< 0.001	101.64 ± 7.92	< 0.001	101.74 ± 5.82	< 0.001
	7	83.47 ± 7.71		112.59 ± 9.83	< 0.001	107.24 ± 9.23	< 0.001	110.29 ± 6.05	< 0.001
	Months								
GOS Score	1	2.90 ± 1.07	/	3.80 ± 0.95	/,0.00	3.70 ± 0.57	/,0.01	3.70 ± 0.87	/,0.01
KPS Score	3	3.65 ± 0.99	/	4.35 ± 0.81	/,0.01	4.45 ± 0.61	/,<0.001	4.30 ± 0.80	/,0.01
	1	39.00 ± 21.25	/	62.50 ± 20.49	/,<0.001	59.50 ± 10.99	/,<0.001	58.50 ± 17.25	/,<0.001
	3	57.00 ± 20.80	/	78.00 ± 18.53	/,<0.001	77.50 ± 15.17	/,<0.001	76.50 ± 17.55	/,<0.001
Change in Score Score	Days								
GCS score	1	0.10 ± 0.85	0.063	0.20 ± 0.89	0.059,0.72	0.20 ± 0.89	0.061,0.72	0.05 ± 0.89	0.057,0.86
	3	0.20 ± 1.36	0.056	1.30 ± 0.73	0.018, < 0.001	1.40 ± 0.82	0.016, < 0.001	2.50 ± 1.32	0.022, < 0.001
	5	1.25 ± 0.79	0.029	2.30 ± 1.22	< 0.001, 0.003	2.15 ± 0.93	< 0.001,0.01	3.65 ± 1.35	< 0.001, < 0.001
	7	2.00 ± 0.86	0.021	3.25 ± 1.02	< 0.001, < 0.001	3.05 ± 1.00	< 0.001,0.002	4.00 ± 1.17	< 0.001, < 0.001
Change in	1	0.65 ± 0.17		0.68 ± 0.19	0.57	0.80 ± 0.10	0.002	0.73 ± 0.09	0.09
S100B (µg/l)	3	1.30 ± 0.18		0.99 ± 0.29	< 0.001	1.19 ± 0.26	0.17	1.12 ± 0.21	0.02
	5	0.75 ± 0.19		-0.16 ± 0.25	< 0.001	-0.07 ± 0.24	< 0.001	-0.06 ± 0.16	< 0.001
	7	0.40 ± 0.23		-0.42 ± 0.33	< 0.001	-0.42 ± 0.10	< 0.001	-0.49 ± 0.13	< 0.001

(a) Within group comparison vs. baseline at admission

(b) Compared with OT

OT = Orthodox therapy; XNJ = OT + Xingnaojing, l-YB = OT + low-dose Yunnan Baiyao, h-YB = OT + high dose Yunnan Baiyao

		OT (n = 20)		OT + XNJ (n = 20)		OT + l-YB (n = 20)		OT + h-YB (n = 20)	
Change in	1	-9.70 ± 9.24		-7.26 ± 5.54	0.17	-14.38 ± 1.38	0.009	-12.71 ± 12.63	0.09
SOD (U/ml)	3	-40.05 ± 9.22		-17.65 ± 4.72	< 0.001	-23.65 ± 3.97	< 0.001	-21.35 ± 2.56	< 0.001
	5	-33.83 ± 11.04		-8.31 ± 5.62	< 0.001	-13.80 ± 4.09	< 0.001	-14.02 ± 2.07	< 0.001
	7	-31.33 ± 11.44		-0.33 ± 5.42	< 0.001	-8.20 ± 3.56	< 0.001	-5.47 ± 2.07	< 0.001
Months									
Change in GOS	3	0.75 ± 0.44	/	0.55 ± 0.61	/,0.21	0.75 ± 0.44	/,1.00	0.60 ± 0.50	/,0.35
Change in KPS	3	18.00 ± 7.68	/	15.50 ± 8.26	/,0.33	18.00 ± 8.34	/,1.00	18.00 ± 7.68	/,1.00
Days									
(%) Change	1	1.98 ± 10.72	0.063	4.02 ± 12.20	0.059,0.60	4.48 ± 11.93	0.061,0.52	2.58 ± 13.73	0.057,0.88
in GCS	3	5.29 ± 16.70	0.056	18.76 ± 15.55	0.018,0.06	21.09 ± 20.46	0.016,0.03	42.67 ± 32.53	0.022, < 0.001
	5	18.31 ± 13.55	0.029	33.58 ± 27.70	< 0.001,0.09	31.62 ± 25.15	< 0.001,0.14	61.37 ± 39.55	< 0.001, < 0.001
	7	29.47 ± 20.63	0.021	44.36 ± 28.26	< 0.001,0.12	43.52 ± 30.33	< 0.001,0.14	65.83 ± 38.00	< 0.001, < 0.001
(%) Change	1	31.68 ± 9.41		34.94 ± 12.50	0.26	40.43 ± 6.75	0.003	36.94 ± 6.58	0.07
in S100B	3	62.49 ± 9.51		50.56 ± 15.97	0.004	59.71 ± 13.63	0.49	56.19 ± 9.98	0.12
	5	36.49 ± 9.82		-7.70 ± 13.02	< 0.001	-3.73 ± 12.23	< 0.001	-2.92 ± 7.97	< 0.001
	7	19.44 ± 11.29		-20.51 ± 16.17	< 0.001	-21.12 ± 6.33	< 0.001	-24.71 ± 8.24	< 0.001
(%) Change	1	-9.56 ± 8.93		-7.08 ± 5.49	0.15	-14.22 ± 0.92	0.008	-12.50 ± 2.58	0.09
in SOD	3	-38.30 ± 8.76		-16.73 ± 4.32	< 0.001	-23.40 ± 3.71	< 0.001	-20.71 ± 1.60	< 0.001
	5	-32.22 ± 10.00		-7.99 ± 5.45	< 0.001	-13.69 ± 4.10	< 0.001	-13.55 ± 1.08	< 0.001
	7	-29.81 ± 10.66		-0.52 ± 5.15	< 0.001	-8.22 ± 3.75	< 0.001	-5.20 ± 1.61	< 0.001
Months									
(%) Change	3	30.00 ± 19.76	/	17.50 ± 20.21	/,0.03	21.25 ± 13.10	/,0.12	18.33 ± 16.36	/,0.04
in GOS									
(%) Change	3	62.90 ± 43.30	/	29.93 ± 21.04	/,<0.001	30.58 ± 14.56	/,<0.001	34.65 ± 18.76	/,0.001
in KPS									
(a) Within group comparison vs. baseline at admission									
(b) Compared with OT									
OT = Orthodox therapy; XNJ = OT + Xingnaojing, l-YB = OT + low-dose Yunnan Baiyao, h-YB = OT + high dose Yunnan Baiyao									

Serum S100B and SOD

Significant effects of Treatment, Time and Time x Treatment interaction ($P < 0.001$) were found in serum S100B concentration that increased rapidly after surgery and peaked in all groups on Days 3 before fell more rapidly and became significantly lower ($P < 0.01$) in the XNJ, l-YB and h-YB groups than in the OT group on Days 3, 5 and 7 (Tables 2 & 3, Fig. 1B). The change and rate of change (%) in serum S100B was significantly greater ($P < 0.05$) in l-YB than in OT

group on Day 1 of the treatment, and significantly greater ($P < 0.01$) in the OT group than in XNJ and h-YB groups on Day 3 of the treatment whereas reduction and percentage reduction in serum S100B level was significantly greater in XNJ, l-YB and h-YB groups than in OT group since Day 5 of treatment (Figs. 3B&C). On Day 7, S100B declined to 20.5%, 20.1% and 24.7% below baselines in the XNJ, l-YB, h-YB groups, respectively whereas it remained 19.4% above baseline in OT group.

Significant effects of Treatment, Time and Time x Treatment interaction ($P < 0.001$) were found in SOD (Tables 2 & 3). Serum SOD activity declined rapidly after craniotomy and reached nadir on Days 3 day in all groups with a greater reduction found in the OT group (38.3%) than in XNJ, l-YB and h-YB groups (16.7%, 23.4% and 20.7%) (Table 3, Fig. 1C). Serum SOD then bounced back more rapidly and became significantly higher in the XNJ, l-YB and h-YB groups than in the OT group after Day 3 of surgery ($P < 0.01$). ANOVA show no significant difference in SOD activity between the XNJ, l-YB and h-YB groups except it was significantly lower in l-YB group than in XNJ group on Day 7 after surgery ($P > 0.05$) (Figs. 4B&C). Change and rate of change over the baseline showed the greatest SOD deficits on Day 3 in all groups (Figs. 4B&C). By Day 7, XNJ, l-YB and h-YB groups resumed most of the baseline SOD activities (99.5%, 91.8% and 94.8%, respectively) compared to OT group (69.2%) ($P < 0.01$).

GOS and KPS scores

The mean scores of GOS and KPS showed continued improvement in clinical prognosis in all patients after 1 and 3 Months of surgery, with the patients in the XNJ, l-YB and h-YB groups showing consistent better clinical prognosis than the OT group ($P < 0.01$, all). GOS and KPS scores, however, were similar between XNJ, l-YB and h-YB groups ($P > 0.05$) (Table 3, Figs. 5&6). One month after the surgery the scores of GOS (3.80 ± 0.95 , 3.70 ± 0.57 , 3.70 ± 0.87) and KPS (62.50 ± 20.49 , 59.50 ± 10.99 , 58.50 ± 17.25) in the XNJ, l-YB, h-YB groups were 27.5%~31% and 50%~60% significantly greater than that in OT group (2.90 ± 1.07 and 39.00 ± 21.25) ($P < 0.01$, all), respectively. Similar differences remained 3 months after surgery.

Correlations between experimental variables

GCS score was significantly correlated with GOS/KPS scores in pooled TBI patients and in each of the treatment groups ($P < 0.01$) (Table 4), indicating a critical impact of postoperative recovery during the acute phase of post-surgery on long-term clinical prognosis of TBI. It is noticed that the correlation between GOS/KPS and GCS scores improved progressively from Day 1 till Day 7 after surgery. However, the reduced level of correlation between most variables immediately after the surgery (Day 1) indicates a disruptive effect of craniotomy.

Table 4
Correlations of the variables in the pooled participants (N = 80)

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005
GCSa	Pearson Correlation	1	.936**	.835**	.835**	.875**	.689**	.685**	.688**	.694**	-.354**	-.399**	-.324**	-.324**
	Sig. (2-tailed)		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.003	0.003
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
GCS1	Pearson Correlation	.936**	1	.847**	.808**	.860**	.600**	.619**	.605**	.614**	-.281*	-.316**	-.289**	-.289**
	Sig. (2-tailed)	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.012	0.004	0.009	0.009
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
GCS3	Pearson Correlation	.835**	.847**	1	.935**	.925**	.711**	.675**	.720**	.713**	-.398**	-.382**	-.353**	-.353**
	Sig. (2-tailed)	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
GCS5	Pearson Correlation	.835**	.808**	.935**	1	.932**	.768**	.714**	.764**	.758**	-.433**	-.401**	-.380**	-.380**
	Sig. (2-tailed)	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
GCS7	Pearson Correlation	.875**	.860**	.925**	.932**	1	.788**	.738**	.799**	.781**	-.434**	-.431**	-.376**	-.376**
	Sig. (2-tailed)	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
GOS1	Pearson Correlation	.689**	.600**	.711**	.768**	.788**	1	.848**	.968**	.877**	-.438**	-.396**	-.414**	-.414**
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
GOS3	Pearson Correlation	.685**	.619**	.675**	.714**	.738**	.848**	1	.878**	.962**	-.412**	-.337**	-.387**	-.387**
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.002	0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
KPS1	Pearson Correlation	.688**	.605**	.720**	.764**	.799**	.968**	.878**	1	.921**	-.487**	-.402**	-.446**	-.446**
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
KPS3	Pearson Correlation	.694**	.614**	.713**	.758**	.781**	.877**	.962**	.921**	1	-.469**	-.355**	-.429**	-.429**
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.001	0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
S100a	Pearson Correlation	-.354**	-.281*	-.398**	-.433**	-.434**	-.438**	-.412**	-.487**	-.469**	1	.502**	.638**	.638**
	Sig. (2-tailed)	0.001	0.012	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
S1001	Pearson Correlation	-.399**	-.316**	-.382**	-.401**	-.431**	-.396**	-.337**	-.402**	-.355**	.502**	1	.405**	.405**
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005
	Sig. (2-tailed)	0.000	0.004	0.000	0.000	0.000	0.000	0.002	0.000	0.001	0.000		0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
S1003	Pearson Correlation	-.324**	-.289**	-.353**	-.380**	-.376**	-.414**	-.387**	-.446**	-.429**	.638**	.405**	1	
	Sig. (2-tailed)	0.003	0.009	0.001	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000		0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
S1005	Pearson Correlation	-0.146	-0.125	-.423**	-.419**	-.427**	-.456**	-.483**	-.544**	-.527**	.444**	0.200	.517**	1
	Sig. (2-tailed)	0.197	0.269	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.075	0.000	
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
S1007	Pearson Correlation	-.333**	-.283*	-.567**	-.627**	-.630**	-.606**	-.535**	-.655**	-.616**	.493**	.314**	.526**	1
	Sig. (2-tailed)	0.003	0.011	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
SODa	Pearson Correlation	.329**	.381**	.390**	.361**	.346**	.250*	.327**	.230*	.336**	-0.027	0.039	-0.037	0.000
	Sig. (2-tailed)	0.003	0.000	0.000	0.001	0.002	0.025	0.003	0.040	0.002	0.814	0.728	0.747	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
SOD1	Pearson Correlation	.335**	.347**	.324**	.288**	.313**	.270*	.249*	.249*	.296**	0.075	-0.087	0.026	0.000
	Sig. (2-tailed)	0.002	0.002	0.003	0.010	0.005	0.016	0.026	0.026	0.008	0.510	0.442	0.818	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
SOD3	Pearson Correlation	0.213	.244*	.495**	.523**	.507**	.492**	.485**	.532**	.561**	-.244*	-0.091	-.396**	0.000
	Sig. (2-tailed)	0.058	0.029	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.029	0.423	0.000	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
SOD5	Pearson Correlation	0.189	0.192	.436**	.455**	.478**	.477**	.418**	.527**	.519**	-0.158	-0.075	-.304**	0.000
	Sig. (2-tailed)	0.093	0.087	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.162	0.510	0.006	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80
SOD7	Pearson Correlation	.260*	.260*	.535**	.551**	.553**	.540**	.467**	.581**	.569**	-.224*	-0.154	-.363**	0.000
	Sig. (2-tailed)	0.020	0.020	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.046	0.172	0.001	0.000
	N	80	80	80	80	80	80	80	80	80	80	80	80	80

Table 5
Correlations of the variables of the orthodox treatment group (N = 20)

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005
GCSa	Pearson Correlation	1	.934**	.821**	.948**	.953**	.912**	.888**	.886**	.877**	-.513*	-.482*	-.587**	-.587**
	Sig. (2-tailed)		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.021	0.032	0.007	0.007
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS1	Pearson Correlation	.934**	1	.919**	.913**	.914**	.783**	.779**	.752**	.733**	-.454*	-0.302	-.613**	-.613**
	Sig. (2-tailed)	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.044	0.195	0.004	0.004
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS3	Pearson Correlation	.821**	.919**	1	.903**	.829**	.620**	.604**	.579**	.582**	-0.429	-0.295	-.488*	-.488*
	Sig. (2-tailed)	0.000	0.000		0.000	0.000	0.004	0.005	0.007	0.007	0.059	0.206	0.029	0.029
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS5	Pearson Correlation	.948**	.913**	.903**	1	.926**	.804**	.788**	.754**	.775**	-.498*	-0.418	-.492*	-.492*
	Sig. (2-tailed)	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.025	0.067	0.028	0.028
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS7	Pearson Correlation	.953**	.914**	.829**	.926**	1	.823**	.789**	.786**	.766**	-.453*	-.457*	-.555*	-.555*
	Sig. (2-tailed)	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.045	0.043	0.011	0.011
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GOS1	Pearson Correlation	.912**	.783**	.620**	.804**	.823**	1	.910**	.990**	.931**	-.552*	-.589**	-.631**	-.631**
	Sig. (2-tailed)	0.000	0.000	0.004	0.000	0.000		0.000	0.000	0.000	0.012	0.006	0.003	0.003
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GOS3	Pearson Correlation	.888**	.779**	.604**	.788**	.789**	.910**	1	.910**	.971**	-.530*	-0.418	-.614**	-.614**
	Sig. (2-tailed)	0.000	0.000	0.005	0.000	0.000	0.000		0.000	0.000	0.016	0.067	0.004	0.004
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
KPS1	Pearson Correlation	.886**	.752**	.579**	.754**	.786**	.990**	.910**	1	.934**	-.568**	-.590**	-.643**	-.643**
	Sig. (2-tailed)	0.000	0.000	0.007	0.000	0.000	0.000	0.000		0.000	0.009	0.006	0.002	0.002
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
KPS3	Pearson Correlation	.877**	.733**	.582**	.775**	.766**	.931**	.971**	.934**	1	-.613**	-.498*	-.602**	-.602**
	Sig. (2-tailed)	0.000	0.000	0.007	0.000	0.000	0.000	0.000	0.000		0.004	0.025	0.005	0.005
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S100a	Pearson Correlation	-.513*	-.454*	-0.429	-.498*	-.453*	-.552*	-.530*	-.568**	-.613**	1	0.401	.695**	.695**
	Sig. (2-tailed)	0.021	0.044	0.059	0.025	0.045	0.012	0.016	0.009	0.004		0.080	0.001	0.001
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1001	Pearson Correlation	-.482*	-0.302	-0.295	-0.418	-.457*	-.589**	-0.418	-.590**	-.498*	0.401	1	0.378	0.378
	Sig. (2-tailed)	0.032	0.195	0.206	0.067	0.043	0.006	0.067	0.006	0.025	0.080		0.037	0.037
	N	20	20	20	20	20	20	20	20	20	20	20	20	20

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S
	Sig. (2-tailed)	0.032	0.195	0.206	0.067	0.043	0.006	0.067	0.006	0.025	0.080		0.100	0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
S1003	Pearson Correlation	-.587**	-.613**	-.488*	-.492*	-.555*	-.631**	-.614**	-.643**	-.602**	.695**	0.378	1	.
	Sig. (2-tailed)	0.007	0.004	0.029	0.028	0.011	0.003	0.004	0.002	0.005	0.001	0.100		0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
S1005	Pearson Correlation	-.710**	-.737**	-.638**	-.654**	-.731**	-.554*	-.711**	-.570**	-.675**	.516*	0.207	.511*	1
	Sig. (2-tailed)	0.000	0.000	0.002	0.002	0.000	0.011	0.000	0.009	0.001	0.020	0.381	0.021	
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
S1007	Pearson Correlation	-.731**	-.528*	-0.380	-.632**	-.753**	-.759**	-.744**	-.735**	-.772**	0.421	.650**	.447*	.
	Sig. (2-tailed)	0.000	0.017	0.098	0.003	0.000	0.000	0.000	0.000	0.000	0.064	0.002	0.048	0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
SODa	Pearson Correlation	0.166	0.280	0.428	0.340	0.263	0.001	0.157	-0.048	0.126	0.007	0.229	0.032	-
	Sig. (2-tailed)	0.485	0.232	0.060	0.143	0.262	0.997	0.510	0.841	0.596	0.977	0.331	0.895	0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
SOD1	Pearson Correlation	0.021	-0.004	0.167	0.118	0.014	0.031	0.074	-0.013	0.133	0.017	0.154	0.170	0
	Sig. (2-tailed)	0.930	0.987	0.482	0.621	0.952	0.897	0.757	0.958	0.575	0.944	0.517	0.473	0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
SOD3	Pearson Correlation	0.317	0.347	.448*	.451*	0.350	0.167	0.285	0.113	0.266	-0.311	0.073	-0.400	-
	Sig. (2-tailed)	0.174	0.134	0.048	0.046	0.131	0.481	0.223	0.635	0.257	0.182	0.759	0.081	0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
SOD5	Pearson Correlation	-0.112	-0.236	-0.091	-0.008	-0.051	-0.060	-0.171	-0.091	-0.113	0.048	-0.243	0.062	0
	Sig. (2-tailed)	0.637	0.317	0.704	0.974	0.832	0.801	0.470	0.704	0.636	0.839	0.303	0.796	0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
SOD7	Pearson Correlation	0.236	0.176	0.339	0.363	0.316	0.164	-0.003	0.116	0.055	-0.149	-0.324	-0.133	0
	Sig. (2-tailed)	0.316	0.458	0.144	0.116	0.175	0.491	0.992	0.627	0.819	0.531	0.163	0.577	0
	N	20	20	20	20	20	20	20	20	20	20	20	20	2
**. Correlation is significant at the 0.01 level (2-tailed).														
*. Correlation is significant at the 0.05 level (2-tailed).														
a. group = 1														

Table 6
Correlations of the variables of the Xingnaojing (XNJ) treatment group (N = 20)

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005
GCSa	Pearson Correlation	1	.934**	.972**	.939**	.926**	.805**	.616**	.760**	.709**	-0.006	-0.420	-0.104	0.084
	Sig. (2-tailed)		0.000	0.000	0.000	0.000	0.000	0.004	0.000	0.000	0.981	0.065	0.664	0.726
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS1	Pearson Correlation	.934**	1	.968**	.953**	.942**	.741**	.511*	.694**	.600**	0.008	-0.434	-0.039	0.166
	Sig. (2-tailed)	0.000		0.000	0.000	0.000	0.000	0.021	0.001	0.005	0.972	0.056	0.869	0.484
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS3	Pearson Correlation	.972**	.968**	1	.974**	.967**	.792**	.574**	.740**	.663**	0.050	-0.416	-0.036	0.131
	Sig. (2-tailed)	0.000	0.000		0.000	0.000	0.000	0.008	0.000	0.001	0.833	0.068	0.882	0.581
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS5	Pearson Correlation	.939**	.953**	.974**	1	.970**	.768**	.511*	.701**	.605**	0.058	-0.382	0.076	0.248
	Sig. (2-tailed)	0.000	0.000	0.000		0.000	0.000	0.021	0.001	0.005	0.808	0.096	0.750	0.293
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS7	Pearson Correlation	.926**	.942**	.967**	.970**	1	.815**	.539*	.757**	.655**	-0.024	-0.379	0.048	0.229
	Sig. (2-tailed)	0.000	0.000	0.000	0.000		0.000	0.014	0.000	0.002	0.921	0.099	0.841	0.331
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GOS1	Pearson Correlation	.805**	.741**	.792**	.768**	.815**	1	.776**	.972**	.872**	-0.066	-0.383	-0.093	-0.036
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.782	0.096	0.696	0.881
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GOS3	Pearson Correlation	.616**	.511*	.574**	.511*	.539*	.776**	1	.830**	.958**	-0.134	-.538*	-0.349	-0.283
	Sig. (2-tailed)	0.004	0.021	0.008	0.021	0.014	0.000		0.000	0.000	0.574	0.014	0.132	0.226
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
KPS1	Pearson Correlation	.760**	.694**	.740**	.701**	.757**	.972**	.830**	1	.915**	-0.139	-0.337	-0.125	-0.078
	Sig. (2-tailed)	0.000	0.001	0.000	0.001	0.000	0.000	0.000		0.000	0.560	0.146	0.598	0.745
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
KPS3	Pearson Correlation	.709**	.600**	.663**	.605**	.655**	.872**	.958**	.915**	1	-0.210	-.489*	-0.302	-0.162
	Sig. (2-tailed)	0.000	0.005	0.001	0.005	0.002	0.000	0.000	0.000		0.374	0.029	0.195	0.496
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S100a	Pearson Correlation	-0.006	0.008	0.050	0.058	-0.024	-0.066	-0.134	-0.139	-0.210	1	0.242	.493*	0.246
	Sig. (2-tailed)	0.981	0.972	0.833	0.808	0.921	0.782	0.574	0.560	0.374		0.303	0.027	0.297
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1001	Pearson Correlation	-0.420	-0.434	-0.416	-0.382	-0.379	-0.383	-.538*	-0.337	-.489*	0.242	1	.472*	0.281

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005
	Sig. (2-tailed)	0.065	0.056	0.068	0.096	0.099	0.096	0.014	0.146	0.029	0.303		0.035	0.230
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1003	Pearson Correlation	-0.104	-0.039	-0.036	0.076	0.048	-0.093	-0.349	-0.125	-0.302	.493*	.472*	1	.649**
	Sig. (2-tailed)	0.664	0.869	0.882	0.750	0.841	0.696	0.132	0.598	0.195	0.027	0.035		0.002
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1005	Pearson Correlation	0.084	0.166	0.131	0.248	0.229	-0.036	-0.283	-0.078	-0.162	0.246	0.281	.649**	1
	Sig. (2-tailed)	0.726	0.484	0.581	0.293	0.331	0.881	0.226	0.745	0.496	0.297	0.230	0.002	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1007	Pearson Correlation	-.710**	-.689**	-.720**	-.780**	-.747**	-.547*	-0.359	-0.439	-0.419	0.075	.493*	0.046	-0.318
	Sig. (2-tailed)	0.000	0.001	0.000	0.000	0.000	0.012	0.120	0.053	0.066	0.755	0.027	0.849	0.172
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SODa	Pearson Correlation	0.362	0.345	0.348	0.371	0.357	0.433	.487*	0.437	.568**	-0.094	-0.214	-0.216	0.033
	Sig. (2-tailed)	0.117	0.136	0.133	0.107	0.123	0.057	0.030	0.054	0.009	0.693	0.365	0.359	0.891
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SOD1	Pearson Correlation	0.400	0.369	0.425	0.430	0.434	.530*	0.378	.489*	.483*	0.241	-0.090	0.042	0.033
	Sig. (2-tailed)	0.080	0.110	0.062	0.058	0.056	0.016	0.101	0.029	0.031	0.306	0.704	0.859	0.890
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SOD3	Pearson Correlation	.463*	0.440	.488*	.473*	.481*	.544*	.460*	.497*	.553*	0.149	-0.291	-0.100	-0.058
	Sig. (2-tailed)	0.040	0.052	0.029	0.035	0.032	0.013	0.041	0.026	0.011	0.530	0.213	0.676	0.807
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SOD5	Pearson Correlation	0.413	0.378	0.441	.449*	.449*	.535*	0.371	.480*	.471*	0.269	-0.115	0.060	0.024
	Sig. (2-tailed)	0.070	0.100	0.052	0.047	0.047	0.015	0.107	0.032	0.036	0.252	0.629	0.801	0.921
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SOD7	Pearson Correlation	0.518	.477*	.540*	.547*	.546*	.617**	.477*	.556*	.580**	0.178	-0.251	-0.028	0.033
	Sig. (2-tailed)	0.019	0.034	0.014	0.013	0.013	0.004	0.033	0.011	0.007	0.453	0.286	0.907	0.890
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
**. Correlation is significant at the 0.01 level (2-tailed).														
*. Correlation is significant at the 0.05 level (2-tailed).														
a. group = 2														

Table 7
Correlations of the variables of the low dose Yunnan Baiyao (I-YB) group (N = 20)

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005	
GCSa	Pearson Correlation	1	.935**	.958**	.970**	.954**	.705**	.754**	.839**	.804**	-.502*	-.479*	-0.256	-0.159	
	Sig. (2-tailed)		0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.024	0.033	0.275	0.504	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
GCS1	Pearson Correlation	.935**	1	.935**	.950**	.909**	.564**	.675**	.660**	.716**	-0.274	-0.317	-0.204	0.039	
	Sig. (2-tailed)	0.000		0.000	0.000	0.000	0.010	0.001	0.002	0.000	0.243	0.173	0.389	0.871	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
GCS3	Pearson Correlation	.958**	.935**	1	.966**	.944**	.673**	.702**	.775**	.730**	-.472*	-.485*	-0.242	-0.201	
	Sig. (2-tailed)	0.000	0.000		0.000	0.000	0.001	0.001	0.000	0.000	0.036	0.030	0.303	0.395	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
GCS5	Pearson Correlation	.970**	.950**	.966**	1	.965**	.647**	.727**	.781**	.783**	-.469*	-.462*	-0.209	-0.100	
	Sig. (2-tailed)	0.000	0.000	0.000		0.000	0.002	0.000	0.000	0.000	0.037	0.040	0.376	0.676	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
GCS7	Pearson Correlation	.954**	.909**	.944**	.965**	1	.721**	.770**	.832**	.811**	-.510*	-.518*	-0.259	-0.137	
	Sig. (2-tailed)	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.022	0.019	0.269	0.565	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
GOS1	Pearson Correlation	.705**	.564**	.673**	.647**	.721**	1	.716**	.897**	.698**	-0.421	-0.231	-0.174	-0.222	
	Sig. (2-tailed)	0.001	0.010	0.001	0.002	0.000		0.000	0.000	0.001	0.065	0.326	0.463	0.347	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
GOS3	Pearson Correlation	.754**	.675**	.702**	.727**	.770**	.716**	1	.827**	.932**	-0.287	-0.247	0.028	-0.080	
	Sig. (2-tailed)	0.000	0.001	0.001	0.000	0.000	0.000		0.000	0.000	0.220	0.293	0.906	0.737	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
KPS1	Pearson Correlation	.839**	.660**	.775**	.781**	.832**	.897**	.827**	1	.844**	-.597**	-0.412	-0.194	-0.328	
	Sig. (2-tailed)	0.000	0.002	0.000	0.000	0.000	0.000	0.000		0.000	0.005	0.071	0.413	0.158	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
KPS3	Pearson Correlation	.804**	.716**	.730**	.783**	.811**	.698**	.932**	.844**	1	-0.362	-0.263	-0.131	-0.079	
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000		0.116	0.264	0.583	0.742	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
S100a	Pearson Correlation	-.502*	-0.274	-.472*	-.469*	-.510*	-0.421	-0.287	-.597**	-0.362	1	.778**	.595**	.564**	
	Sig. (2-tailed)	0.024	0.243	0.036	0.037	0.022	0.065	0.220	0.005	0.116		0.000	0.006	0.010	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
S1001	Pearson Correlation	-.479*	-0.317	-.485*	-.462*	-.518*	-0.231	-0.247	-0.412	-0.263	.778**	1	0.418	.553*	
	Sig. (2-tailed)														
	N														

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005	
	Sig. (2-tailed)	0.033	0.173	0.030	0.040	0.019	0.326	0.293	0.071	0.264	0.000		0.066	0.012	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
S1003	Pearson Correlation	-0.256	-0.204	-0.242	-0.209	-0.259	-0.174	0.028	-0.194	-0.131	.595**	0.418	1	0.206	
	Sig. (2-tailed)	0.275	0.389	0.303	0.376	0.269	0.463	0.906	0.413	0.583	0.006	0.066		0.384	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
S1005	Pearson Correlation	-0.159	0.039	-0.201	-0.100	-0.137	-0.222	-0.080	-0.328	-0.079	.564**	.553*	0.206	1	
	Sig. (2-tailed)	0.504	0.871	0.395	0.676	0.565	0.347	0.737	0.158	0.742	0.010	0.012	0.384		
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
S1007	Pearson Correlation	-.542*	-0.342	-.520*	-.520*	-.528*	-0.422	-0.275	-.567**	-0.323	.926**	.844**	.565**	.504*	
	Sig. (2-tailed)	0.014	0.140	0.019	0.019	0.017	0.064	0.241	0.009	0.165	0.000	0.000	0.009	0.023	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
SODa	Pearson Correlation	0.281	0.402	0.235	0.228	0.309	0.404	0.310	0.235	0.297	0.295	0.291	0.087	0.405	
	Sig. (2-tailed)	0.231	0.079	0.318	0.334	0.185	0.077	0.184	0.318	0.203	0.206	0.214	0.715	0.076	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
SOD1	Pearson Correlation	0.285	0.407	0.244	0.244	0.327	0.379	0.299	0.225	0.298	0.275	0.239	0.085	0.381	
	Sig. (2-tailed)	0.223	0.075	0.300	0.301	0.159	0.100	0.200	0.340	0.202	0.241	0.310	0.721	0.097	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
SOD3	Pearson Correlation	0.083	0.195	0.041	0.052	0.176	0.237	0.237	0.097	0.217	0.376	0.152	0.156	0.320	
	Sig. (2-tailed)	0.729	0.411	0.864	0.828	0.459	0.314	0.314	0.685	0.359	0.103	0.521	0.512	0.168	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
SOD5	Pearson Correlation	0.251	0.338	0.156	0.197	0.313	0.341	0.281	0.222	0.301	0.292	0.210	0.162	0.378	
	Sig. (2-tailed)	0.285	0.145	0.512	0.404	0.179	0.141	0.230	0.347	0.197	0.211	0.373	0.496	0.100	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
SOD7	Pearson Correlation	.489*	.540*	0.425	0.415	.502*	.551*	.491*	.448*	.484*	0.114	0.018	0.039	0.243	
	Sig. (2-tailed)	0.029	0.014	0.062	0.069	0.024	0.012	0.028	0.047	0.031	0.633	0.940	0.869	0.301	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	
**. Correlation is significant at the 0.01 level (2-tailed).															
*. Correlation is significant at the 0.05 level (2-tailed).															
a. group = 3															

Serum S100B levels were negatively correlated with GCS/GOS/KPS scores in pooled patients and in each treatment group (Tables 4–8). This and other analysis suggest that a higher S100B level on admission day or on Day 7 are better predictors of poor TBI outcomes (low GCS/GOS/KPS scores). In contrast, serum SOD activity was positively correlated with GCS/GOS/KPS scores ($P < 0.01$) in the pooled and in the 3 co-treatment groups but not in the OT group (Table 4). Similarly, SOD level on postoperative Day 7 is a better predictor of GCS/GOS/KPS scores than SOD on other days in the pooled and 3 adjuvant treatment groups but not the OT group. Our data suggest that GCS and SOD are positive predictors and S100B is a negative predictor of clinical prognosis.

Discussion

Although emergency craniotomy has been performed to reduce the mortality rate of TBI, it is associated with secondary injury and unfavorable outcomes [5, 6]. Effective agents are needed to reduce these side effects. In this study, the wound-healing medicine YB were compared with a positive control medicine XNJ, and orthodox therapy in craniotomized patients with moderate-to-severe TBI. Repeated-measure analysis showed significantly better clinical prognosis of YB and XNJ adjuvant treatments than OT. The significant greater improvement rate in GCS after high dose YB than after low dose YB and XNJ treatment indicates a dose-dependent therapeutic effects of YB on postoperative recovery.

GCS is a scale to quantify disruption of consciousness (DOC) during acute phase of TBI. Although GCS score improved in all groups, the improvement was greater in YB and XNJ groups than in OT group three days after surgery. While GCS scores were similar between XNJ and YB groups, the rate of change were significantly greater in the high dose YB group than in low dose YB and in XNJ groups, respectively. Effective recovery from DOC has significant impact on the overall well-being, cognition recovery and clinical prognosis of TBI patients. In this study, the GCS score on Days 7 was highly correlated with the clinical outcome scores of GOS ($r = 0.79$, $P < 0.01$) and KPS ($r = 0.80$, $P < 0.01$) after 30 days of surgery, indicating a intrinsic relationship between acute postoperative recovery and long-term clinical prognosis of TBI.

The GOS scores at 3 months after surgery were significantly higher in the I-YB (4.45 ± 0.61), h-YB (4.3 ± 0.8) and XNJ (4.35 ± 0.81) groups than in the OT (3.65 ± 0.99) group. GOS is a prognostic criterion of TBI, with the score ≥ 4 classified as good outcome whereas KPS reflects the functional recovery and disability of TBI patients. The KPS scores at 3 months after surgery were significantly higher in the I-YB (76.50 ± 17.55), h-YB (77.50 ± 15.17) and XNJ (78.00 ± 18.53) groups than in the OT (57.00 ± 20.80) group, indicating an almost adequate recovery in the 3 co-treatment groups. A KPS score of more than 80 points indicates independent, adequate capability of self-care in daily life; a score of 60 to 70 points indicate semi-dependent in daily life and a score of below 60 points indicates dependent, lack of self-care capability in daily life.

The attenuated elevation in serum S100B levels after YB and XNJ treatments indicates attenuated brain injury after YB and XNJ adjuvant therapy. While no difference found on admission and on Day 1, serum S100B peaked three days after surgery in all groups before declined more rapidly in YB and XNJ groups that became significantly lower than in the OT group since Days 3 and became below baseline levels on Day 7. Increased serum s100b is a biomarker of astrocyte injury and an early predictor of high intracranial pressure and mortality in TBI patients. [35–40] Other studies show that serum S100b level outperforms clinical diagnosis for identification of intracranial injury after TBI [45]. In this study, serum S100b on admission and on Days 7 after DC were negatively correlated with GCS scores ($r = -0.35$, $P < 0.01$, $r = -0.63$, $P < 0.01$, respectively) and with 1&3 Months after discharge scores of GOS ($r = -0.44$, $P < 0.01$, $r = -0.61$, $P < 0.01$, respectively) and KPS ($r = -0.49$, $P < 0.01$, $r = -0.66$, $P < 0.01$ respectively), indicating that serum S100b is a negative predictor for both acute brain tissue damage and long-term clinical prognosis. Our results agree with the report that early postoperative serum s100B levels predict ongoing brain damage after meningioma surgery [46]. It has been reported that elevated serum S100B may have extracerebral origins including traumatized tissues and is a predictive index of overall injury and prognosis after trauma/surgery [35].

In contrast, serum SOD activity was positively correlated with GCS, GOS and KPS scores in pooled TBI patients and in h-YB and XNJ groups, and to a less extent, in I-YB group but not in the OT group. And the level of correlation increased from admission till postoperative Day 7. A significant negative correlation between serum SOD activity and serum S100B concentration was found on Day 7 only in pooled patients. Our results are in agreement with a recent clinical study of 56 patients with severe TBI whose blood SOD and total antioxidant capacity after 7 and 14 days of TBI were significant predictors of clinical outcomes (GOS score ≥ 4) three months later [47].

Serum superoxide dismutase (SOD) activity reflects the body's defense against free radicals-induced damage. Massive production and release of superoxide and radicals after TBI can cause artery dilation, edema and hemostasis [48, 49] whereas SOD can dose-dependently scavenge excess superoxide anion, reduce brain edema and attenuates acute brain injury after subarachnoid hemorrhage [42]. Other studies have shown that blood-brain barrier (BBB) permeability, anti-oxidative and anti-apoptotic capability, brain edema, cerebral blood flow, cognitive and behavioral function, and necrotic cavity volume are CuZn-SOD dose-dependently protected in heterozygous and homozygous transgenic mice with human CuZn-SOD gene [50] and in other SOD-upregulating TBI models [49, 51, 52].

In this study, both YB and XNJ treatments resulted in similar improvements in neuroprotection and clinical prognosis. However, some differences do exist. The h-YB resulted in significant (rate of) increases in GCS score than I-YB and XNJ three days after surgery, suggesting more effective intervention after high dose YB administration whereas XNJ therapy resulted in more consistent and significantly less (rate of) reduction in SOD activity than YB, indicating a greater antioxidative potential of XNJ than YB. The greater loss in SOD activity in I-YB group than in h-YB group on Day 1 and 3 and a great rate of increase in S100b in I-YB than XNJ on Day 3, indicating a dose-dependent neuroprotection of YB, possibly related to the multi anti-hemorrhage, anti-hemostasis and anti-inflammation properties of YB as discussed below.

Intracranial bleeding, edema and coagulopathy are major predictors of mortality and morbidity of TBI that still lacks of effective therapy[9, 53, 54]. YB and its major active ingredient Notoginseng saponins (PNS) have dual anti-hemorrhage and anti-hemostasis properties [19, 55]. YB showed significantly better anti-bleeding efficacy (92.30%) than pantoloc (71.20%) in severe TBI-induced stress gastrointestinal bleeding and ulcer [21, 22] and is more effective in controlling gastrointestinal tract inflammation in colitis model of inflammatory bowel disease (IBD), by suppressing pro-inflammatory cytokine expression (including TNF α , IL-12p40, and IL-17) and T- and B-lymphocytes, and but promoting intestinal epithelial wound-healing/repairing [56]. Gastrointestinal bleeding and dysfunction are common complications of TBI (developed in up to 80% of severe TBI) [7, 57–59]. Intracerebral hemorrhage destroys gut mucosa and intestinal barrier, increases plasma levels of malondialdehyde (MDA) and reactive oxygen species (ROS), endotoxin, inflammatory cytokines and oxidative stress, but decreases SOD activity in mice [8]. Although the mechanism is unknown, TBI-induced stress and intracranial bleeding-induced intracranial pressure may trigger massive increases in sympathetic activity responsible for gastrointestinal lesions [60–62].

This pilot study has limitations. Parameters including GI bleeding, systematic inflammation and mortality rate were not recorded nor the lesion size and hemorrhage volume after emergency craniotomy. The hemodynamics and anticoagulant properties of YB in TBI remains to be studied. A potential cause-

effect relationship may exist between S100b and SOD inductions and that needs to be further explored.

Conclusion

Yunnan Baiyao adjuvant therapy is non-inferior to the positive control medicine Xingnaojing but is more effective than orthodox mono-therapy in improving postoperative recovery and clinical outcomes after emergency craniotomy in patients with moderate-to-severe TBI. The therapeutic effects of YB appear to be dose-dependent and regulated partly through attenuated disruption in S100b- and SOD-pathways. If proved in different cohorts, YB could be used to control TBI-induced morbidity and mortality especially in situations of limited resources.

Abbreviations

ANP: Angong Niu Huang Pill

BBB: blood-brain barrier

CONSORT:

CT: computed tomography

DOC: disruption of consciousness

GI: gastrointestinal (tract)

GCS: Glasgow Coma Scale

GOS: Glasgow Outcome Scale

h-YB: high dose Yunnan Baiyao

IBD : inflammatory bowel disease

ICP: intracranial pressure

KPS: Karnofsky Performance Scale

l-YB: low dose Yunnan Baiyao

MDA: malondialdehyde

OT: orthodox therapy

PNS: Notoginseng saponins

ROS: reactive oxygen species

S100B

SOD: superoxide dismutase

TBI: traumatic brain injury

XNJ: Xingnaojing, a TBI medicine approved in China

YB: Yunnan Baiyao (a wound-healing medicine)

Declarations

Ethical Approval and Consent to participate

All study procedures were conducted in accordance with the Helsinki Declaration of 1975 and were approved by the Medical Ethics Committee of Chinese PLA General Hospital. Each participant signed legal consent forms. Informed consent was obtained from all subjects.

Consent for publication

All authors have approved the manuscript for submission.

Availability of Data and materials

The raw data could be available from the corresponding authors upon reasonable request and with permission of the study sponsor.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be a potential conflict of interest.

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Author Contributions

Project conception and organization (XM, GX, BG); clinical examinations and follow up evaluations, (HJ, LC); histological examinations (HJ); statistical analysis (GX, AA, YY), figures and tables (GX), literature and interpretation (GX), manuscript preparation (LC, YY, GX).

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Appendix 1

Glasgow Coma Scale

Table 8
Correlations of the variables of the high dose Yunnan Baiyao (h-YB) group (N = 20)

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1005
GCSa	Pearson Correlation	1	.932**	.849**	.882**	.926**	.621**	.735**	.727**	.766**	-.549*	-0.356	-.584**	-.584**
	Sig. (2-tailed)		0.000	0.000	0.000	0.000	0.003	0.000	0.000	0.000	0.012	0.124	0.007	0.007
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS1	Pearson Correlation	.932**	1	.848**	.823**	.925**	.510*	.727**	.651**	.742**	-.535*	-0.346	-.519*	-.519*
	Sig. (2-tailed)	0.000		0.000	0.000	0.000	0.021	0.000	0.002	0.000	0.015	0.135	0.019	0.019
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS3	Pearson Correlation	.849**	.848**	1	.912**	.942**	.648**	.714**	.733**	.741**	-.602**	-.569**	-0.395	-.395
	Sig. (2-tailed)	0.000	0.000		0.000	0.000	0.002	0.000	0.000	0.000	0.005	0.009	0.085	0.085
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS5	Pearson Correlation	.882**	.823**	.912**	1	.899**	.710**	.656**	.764**	.705**	-.637**	-.527*	-.575**	-0.575**
	Sig. (2-tailed)	0.000	0.000	0.000		0.000	0.000	0.002	0.000	0.001	0.003	0.017	0.008	0.008
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GCS7	Pearson Correlation	.926**	.925**	.942**	.899**	1	.671**	.784**	.778**	.808**	-.662**	-.574**	-.488*	-.488*
	Sig. (2-tailed)	0.000	0.000	0.000	0.000		0.001	0.000	0.000	0.000	0.001	0.008	0.029	0.029
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GOS1	Pearson Correlation	.621**	.510*	.648**	.710**	.671**	1	.821**	.956**	.829**	-.558*	-.501*	-0.427	-0.427
	Sig. (2-tailed)	0.003	0.021	0.002	0.000	0.001		0.000	0.000	0.000	0.011	0.024	0.060	0.060
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
GOS3	Pearson Correlation	.735**	.727**	.714**	.656**	.784**	.821**	1	.872**	.977**	-.468*	-0.399	-0.281	-.281
	Sig. (2-tailed)	0.000	0.000	0.000	0.002	0.000	0.000		0.000	0.000	0.037	0.081	0.230	0.230
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
KPS1	Pearson Correlation	.727**	.651**	.733**	.764**	.778**	.956**	.872**	1	.903**	-.572**	-.537*	-0.428	-0.428
	Sig. (2-tailed)	0.000	0.002	0.000	0.000	0.000	0.000	0.000		0.000	0.008	0.015	0.060	0.060
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
KPS3	Pearson Correlation	.766**	.742**	.741**	.705**	.808**	.829**	.977**	.903**	1	-.450*	-0.409	-0.285	-0.285
	Sig. (2-tailed)	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000		0.047	0.074	0.224	0.224
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S100a	Pearson Correlation	-.549*	-.535*	-.602**	-.637**	-.662**	-.558*	-.468*	-.572**	-.450*	1	.821**	.736**	.736**
	Sig. (2-tailed)	0.012	0.015	0.005	0.003	0.001	0.011	0.037	0.008	0.047		0.000	0.000	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1001	Pearson Correlation	-0.356	-0.346	-.569**	-.527*	-.574**	-.501*	-0.399	-.537*	-0.409	.821**	1	0.324	0.324
	Sig. (2-tailed)			0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20

		GCSa	GCS1	GCS3	GCS5	GCS7	GOS1	GOS3	KPS1	KPS3	S100a	S1001	S1003	S1004
	Sig. (2-tailed)	0.124	0.135	0.009	0.017	0.008	0.024	0.081	0.015	0.074	0.000		0.164	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1003	Pearson Correlation	-.584**	-.519*	-0.395	-.575**	-.488*	-0.427	-0.281	-0.428	-0.285	.736**	0.324	1	0.000
	Sig. (2-tailed)	0.007	0.019	0.085	0.008	0.029	0.060	0.230	0.060	0.224	0.000	0.164		0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1005	Pearson Correlation	-.471*	-.501*	-.550*	-0.390	-.609**	-0.281	-.462*	-0.403	-0.421	.538*	.621**	0.246	1
	Sig. (2-tailed)	0.036	0.024	0.012	0.090	0.004	0.231	0.040	0.078	0.065	0.014	0.004	0.296	
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
S1007	Pearson Correlation	-.718**	-.676**	-.645**	-.755**	-.769**	-.568**	-.471*	-.629**	-.507*	.871**	.672**	.800**	.500
	Sig. (2-tailed)	0.000	0.001	0.002	0.000	0.000	0.009	0.036	0.003	0.022	0.000	0.001	0.000	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SODa	Pearson Correlation	.652**	.705**	.712**	.723**	.707**	0.438	.536*	.566**	.597**	-0.300	-0.309	-0.162	-0.000
	Sig. (2-tailed)	0.002	0.001	0.000	0.000	0.000	0.054	0.015	0.009	0.005	0.200	0.184	0.495	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SOD1	Pearson Correlation	.637**	.690**	.715**	.692**	.717**	.446*	.574**	.579**	.627**	-0.280	-0.304	-0.094	-0.000
	Sig. (2-tailed)	0.003	0.001	0.000	0.001	0.000	0.049	0.008	0.008	0.003	0.232	0.192	0.693	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SOD3	Pearson Correlation	.624**	.680**	.684**	.727**	.693**	.448*	.514*	.557*	.566**	-0.424	-0.416	-0.258	-0.000
	Sig. (2-tailed)	0.003	0.001	0.001	0.000	0.001	0.048	0.020	0.011	0.009	0.063	0.068	0.271	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
SOD5	Pearson Correlation	.645**	.694**	.719**	.717**	.711**	0.437	.539*	.563**	.597**	-0.308	-0.324	-0.138	-0.000
	Sig. (2-tailed)	0.002	0.001	0.000	0.000	0.000	0.054	0.014	0.010	0.005	0.186	0.163	0.561	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
	Pearson Correlation	.616**	.658**	.712**	.719**	.689**	.469*	.531*	.580**	.588**	-0.339	-0.379	-0.148	-0.000
	Sig. (2-tailed)	0.004	SOD7	0.000	0.000	0.001	0.037	0.016	0.007	0.006	0.144	0.100	0.533	0.000
	N	20	20	20	20	20	20	20	20	20	20	20	20	20
**. Correlation is significant at the 0.01 level (2-tailed).														
*. Correlation is significant at the 0.05 level (2-tailed).														
a. group = 4														

Score	Eye opening	Score	Verbal response	Score	Motor response
4	Spontaneous opening	5	Oriented responses with the patient being coherent and answering appropriately	6	Conscious obeying of the motor commands given
3	Eye opening to auditive stimulus	4	Confused answering with the patient disoriented	5	Movement towards pressure/ pain stimulus
2	Eye opening to pain stimulus	3	Inappropriate words with the patient saying words but not sentences	4	Withdrawal from pain/ pressure stimulus
1	No eye opening	2	Incomprehensible sounds	3	Flexor reaction
		1	No verbal response	2	Extensor reaction
				1	No motor response

GCS is an established method to quantify the conscious state of TBI patients. The score was used to evaluate the degree of disturbance of consciousness with eye opening, speech condition and motor response (mild =13 to 15, moderate = 8 to 12, severe= 3 to 7 points)

Appendix 2

Glasgow Outcome Scale

Score	State	Description
1	Dead	Dead
2	Persistent vegetative state	Patient exhibits no obvious cortical function.
3	Severe disability	Patient depends upon others for daily support due to mental or physical disability or both.
4	Moderate disability	Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	Recover	Resumption of normal activities even though there may be minor neurological or psychological deficits.

GOS is the commonly used prognostic criterion for evaluating TBI prognosis with five grades: dead, persistent vegetative state, severe disability (conscious but disabled), moderate disability (disabled but independent) and recovery. The outcome was classified as good (GOS 4 to 5), bad (GOS 2 to 3) and death (GOS =1)

Appendix 3

Karnofsky Performance Scale

Score	Description
100	Normal no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

KPS is an index to evaluate the ability of daily life and work. It includes 10 items with the range of score from normal (100) to dead (0). A score of more than 80 points indicates independent, adequate capability of self-care in daily life; a score of 60 to 70 points indicate semi-dependent in daily life and a score of

below 60 points indicates dependent, lack of self-care capability in daily life. KPS reflects the recovery of functional activity and disability in patients with craniocerebral injury

Figures

Figure 1

Repeated measure analysis show significant differences and patterns of change in Glasgow Coma Scale (GCS) (A); serum S100B concentration (B); serum superoxide dismutase (SOD) activity (C); Glasgow Outcome Scale (GOS) (D); and Karnofsky Performance Scale (KPS) (E), after treatment of orthodox therapy (OT), Xingnaojing (XNJ) adjuvant treatment, low-dose Yunnan Baiyao (l-YB) and high-dose Yunnan Baiyao adjuvant treatments in craniotomized patients with moderate-to-severe TBI,

Figure 2

Differences in GSC, change and rate of change in GCS score between the treatment groups. A) GCS score was lowest on admission in all groups but improved more quickly and became significantly greater in XNJ, I-YB, h-YB groups than in OT group on Days 3, 5 and 7 ($P<0.01$); B) the improvement in GCS and; C) rate of improvement (%) in GCS were significantly greater in XNJ, I-YB, h-YB groups than in OT group after 3, 5 and 7 days of emergency craniotomy ($P<0.01$) and greater in h-YB than in I-YB and XNJ groups after 3, 5 and 7 days of emergency craniotomy ($P<0.05$, all). *, $P<0.05$, ** $P<0.01$ vs. OT; a, $P<0.05$, aa, $P<0.01$ vs. XNJ; b, $P<0.05$, bb, $P<0.01$ vs. I-YB

Figure 3

Differences in serum S100b protein concentration A), change B) and rate of change C) of serum S100b in craniotomized TBI patients. A) S100B concentration increased sharply after admission and peaked in all groups on Days 3 before it fell more rapidly and became significantly lower ($P<0.01$) in the XNJ, I-YB and h-YB groups than in the OT group after 3, 5 and 7 days of emergency craniotomy; B) & C) Increases and percentage increase in serum S100B was significantly

greater ($P<0.01$) in OT than in XNJ and h-YB groups on Day 3 whereas reduction and reduction rate was significantly greater in XNJ, l-YB and h-YB groups than in OT group after 5 and 7 days of emergency craniotomy. *, $P<0.05$, ** $P<0.01$ vs. OT; a, $P<0.05$, aa, $P<0.01$ vs. XNJ

Figure 4

Differences in serum superoxide dismutase (SOD) activity A), change B) and rate of change C) in SOD activity. A) Serum SOD activity declined rapidly after craniotomy and reached nadir on Days 3 day in all groups with a greater reduction in the OT group (38.3%) than in XNJ, l-YB and h-YB groups (16.7%, 23.4% and 20.7%) before increased more rapidly and became significantly higher in the XNJ, l-YB and h-YB groups than in the OT group after 3, 5 and 7 days of emergency craniotomy ($P<0.01$). By Days 7, XNJ, l-YB and h-YB groups resumed more of the baseline SOD activities (99.5%, 91.8% and 94.8%, respectively) than OT group (69.2%) ($P<0.01$). *, $P<0.05$, ** $P<0.01$ vs. OT; a, $P<0.05$, aa, $P<0.01$ vs. XNJ

Figure 5

Glasgow Outcome Scale (GOS) score shows continued improvement in clinical prognosis in all patients after 30 and 90 days of emergency craniotomy, with the XNJ, l-YB and h-YB groups showing consistent better clinical prognosis than the OT group ($P<0.01$). A GOS score of 4-5 is classified as good outcome. *, $P<0.05$, **, $P<0.01$ vs. OT

Figure 6

Karnofsky Performance Scale (KPS) score show continued improvement in functional rehabilitation and the ability of daily life and work in all patients after 30 and 90 days of emergency craniotomy, with the XNJ, l-YB and h-YB groups showing better clinical prognosis than the OT group ($P<0.01$). A score of more than 80 points indicates independent, adequate capability of self-care in daily life; a score of 60 to 70 points indicate semi-dependent in daily life. *, $P<0.05$, **, $P<0.01$ vs. OT