Tropical Journal of Pharmaceutical Research August 2022; 21 (8): 1799-1805
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i8.30

Original Research Article

Clinical efficacy of combined use of Xuebijing and mild hypothermia therapy for the treatment of severe traumatic brain injury, and its effect on patient mortality and complications

Yadong Zheng, Peng Chen, Qingtao Zhang, Chao Sun, Yi Xiang, Weiduo Zhou, Yi Xu*

Department of Neurosurgery, Chongqing Emergency Medical Center, The Fourth People's Hospital of Chongqing, Chongqing University Central Hospital, Chongqing, China

For correspondence:* ***Email:* *xuyi_doctor1981@126.com*

Sent for review: 31 January 2022 *Revised accepted: 17 July 2022*

Abstract

Purpose: *To investigate the clinical efficacy of combined use of Xuebijing and mild hypothermia therapy in severe traumatic brain injury (TBI), and its effect on mortality and incidence of complications.*
Methods: *Eighty-six severe TBI patients admitted to The Fourth People's Hospital of Chongqing were selected. Patients were randomly and equally assigned to control group (COG) who received conventional treatment, and study group (EXG) given a combination of Xuebijing and mild hypothermia therapy. Relevant clinical indicators and therapeutic effects were compared.*
Results: *Post-treatment levels of inflammatory indices, including procalcitonin (PCT), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were significantly reduced, with lower levels in EXG ($p < 0.05$). Between-group differences were seen in human leukocyte antigen-DR isotype (HLA-DR), $CD3^+$, $CD4^+$, $CD8^+$, and C3 indicators ($p < 0.05$). EXG had significantly lower protein expression levels of neuron-specific enolase (NSE) and S100 beta than COG ($p < 0.05$). After treatment, plasma protein levels of coagulation indices, viz, prothrombin time (PT) and activated partial thromboplastin time (APTT) were lower than pre-treatment levels, with even much lower levels in EXG ($p < 0.05$). There were reduced incidence of lung infection, acute gastrointestinal injury, acute respiratory distress syndrome (ARDS) and hypernatremia ($p < 0.05$). More patients had better recovery in EXG ($p < 0.05$) than in control group.*
Conclusion: *The combined therapy improves the prognosis of severe TBI, lowers the levels of inflammatory factors, ameliorates plasma coagulation, and enhances immunity with a high degree of safety. However, further clinical trials should be undertaken prior to application in clinical practice.*

Keywords: *Severe traumatic brain injury (TBI), Mild hypothermia therapy, Xuebijing, Clinical efficacy*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Statistics have revealed that the incidence of severe traumatic brain injury (TBI), which is second only to that of limb fractures, accounts for 15 - 20 % of injuries in all parts of the body [1,2]. In recent years, with increased incidence of events such as traffic accidents, falls, and

trauma, severe TBI has become an emergency and a critical illness in neurosurgery, and a source of increased morbidity and mortality [3,4]. At present, the clinical treatment of TBI patients is mostly limited to arresting bleeding, lowering intracranial pressure, protecting neurological function, and preventing secondary organ injury. However, these strategies produce unsatisfactory clinical efficacy. Currently, mild hypothermia treatment is used in neurology to reduce intracranial pressure and protect nerve function in the brain. However, this treatment often induces a complication of coagulation disorder in hypothermia state, resulting in some therapeutic limitations. Clinical studies have found that most cases of severe TBI are accompanied by multiple organ dysfunction involving a variety of pathological mechanisms such as inflammatory response and disturbance in coagulation function [5-8].

Xuebijing suppresses inflammation in patients through multi-pathway and multi-target mechanisms. It is used mostly for the clinical treatment of acute and critical diseases e.g., sepsis. Therefore, it is likely that combination of *Xuebijing* and mild hypothermia therapy may result in enhanced clinical treatment efficacy. Currently, not much is known about the clinical effect of this combination treatment on severe TBI, as well as the underlying mechanism. Therefore, this research was aimed to investigate the clinical effect of the combination of *Xuebijing* and mild hypothermia therapy on severe TBI, as well as the underlying mechanism.

METHODS

Patients

A total of 86 patients with severe TBI and admitted to *The Fourth People's Hospital of Chongqing* (January 2019 - January 2020) were selected for this prospective study. Based on their order of admission, they were assigned to control group (COG) which was given basic treatment + mild hypothermia therapy (n = 43), and study group (EXG) given basic treatment + *Xuebijing* + mild hypothermia therapy (n = 43). This study got the approval of the ethics committee of *The Fourth People's Hospital of Chongqing* (approval no. 20181172), and complied with the guidelines of Declaration of Helsinki [9]. Written and signed informed consent was obtained from the patients and/or guardians.

Inclusion criteria

The patients enrolled were those who were meeting the diagnostic criteria in the Guidelines for the Management of Severe TBI (2016 version), patients who were diagnosed with severe TBI after cranial CT examination, and patients with GCS scores of 5 - 8 points, with coma time duration more than 6 h.

Exclusion criteria

Patients in the following categories were excluded: Those with TBI complicated with severe organ dysfunction or acute infectious diseases, patients with other cardiovascular and cerebrovascular diseases, and those with previous limb motor dysfunction. Moreover, patients with poor treatment compliance, and those who were pregnant or lactating, were excluded.

Treatments

On admission, patients in both groups received conventional treatments according to their conditions. The conventional treatments comprised surgery, reduction of intracranial pressure using dehydration therapy, *nourishment* of cranial nerves, oxygen inhalation, use of antibiotics, hyperbaric oxygenation, supportive care, acid suppression, and maintenance of homeostasis. During the treatments, the patients' respiratory tracts were kept clear, and low blood oxygen status was actively corrected [10-13].

In addition to conventional treatment, patients in EXG received combination of *Xuebijing* and mild hypothermia therapy. With respect to mild hypothermia therapy, within 24 h of injury, HGT-200 double-blanket mild hypothermia therapeutic instrument was used to cool the body of the patient, with rectal and brain temperatures maintained at 32.0 - 35.0 °C and 32.5 - 35.0 °C, respectively. At the same time, a hibernation and muscle-relaxing mixture (100 mg of chlorpromazine + 100 mg of promethazine + 400 mg of atracurium + 500 mL of normal saline) was administered via intravenous drip at a flow rate of 13 - 20 drops/min. The volume and flow rate were adjusted in line with changes in vital signs of patients.

The treatment lasted for 4 - 7 days. Slow re-warming of the patients was conducted after cessation of mild hypothermia therapy, with temperature increased at the rate of 1 °C every 4 h, and the administration of hibernation mixture was stopped gradually over a period of 24 h. *Xuebijing* (50 mL; Tianjin Chase Sun Pharmaceutical Co. Ltd., specification: 10 mL; NMPA approval no. Z20040033) was administered with intravenous micro-dosage

pump thrice daily continuously for 5 - 7 days. The other treatments were same as in COG [14,15].

Evaluation of indicators/parameters

Levels of inflammatory factors

Before and after treatment, the serum PCT levels in both groups were determined with fluorescence enzyme immunoassay, while the TNF-α and IL-6 levels were determined with enzyme-linked immunosorbent assay (ELISA).

Cellular and humoral immunity levels

Before and after treatment, 3 mL of peripheral vein blood was drawn from each patient for determination of the levels of human leukocyte antigen-DR isotype (HLA-DR), $CD3^+$, $CD4^+$, $CD8^+$, immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement-3 (C3), complement-4 (C4) and other humoral immune indicators, using immunoturbidimetry.

Serum protein levels of neuron-specific enolase (NSE) and S100 beta

The protein levels of NSE and S100 beta in patients of both groups were determined with ELISA before and after treatment.

Plasma coagulation

Plasma activated partial thromboplastin time (APTT) and prothrombin time (PT) were measured in patients in both groups before and after treatment, using wet chemical method.

Complications

Complications during the treatments were compared between the two groups. These complications comprised lung infection, acute gastrointestinal injury, ARDS, disseminated intravascular coagulation (DIC) and hypernatremia.

Treatment outcomes and mortality

All patients were followed up for six months, and the Glasgow Outcome Scale was used to assess the effect of treatment in each group. Patient's status was rated as *good recovery* (patient had minor defects but was able to live normally), *moderate disability* (patient was disabled, but was able to work under protection and carry out basic activities of daily living), *severe disability* (patient was conscious but unable to take care of themselves without help), or *persistent vegetative state.* Cases of death were also recorded.

Statistical analysis

Statistical analysis was done with SPSS 21.0 software, while graphics was done with GraphPad Prism 7 (GraphPad Software, San Diego, USA). Enumeration data are expressed as numbers and percentages (n (%)), while measurement data are expressed as mean ± standard deviation (SD). Enumeration data and measurement data were compared using χ^2 test and *t*-test, respectively. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Patients' profile

There were no statistical differences in general profile between the two groups ($p > 0.05$; Table 1).

Levels of inflammatory factors

After treatment, there were reduced levels of PCT, TNF-α, IL-6 and other indicator inflammatory factors in patients in both groups, with lower levels in EXG than in COG ($p < 0.05$), as presented in Table 2.

Cellular immunity and humoral immunity

After treatment, there were between-group differences in HLA-DR, $CD3^+$, $CD4^+$, $CD8^+$ and C3 indicators in patients ($p < 0.05$; Table 3).

Serum protein levels of NSE and S100 beta

The EXG had lower protein levels of NSE and S100 beta than COG ($p < 0.05$), as shown in Figure 1.

Plasma coagulation indices (PT and APTT)

As shown in Table 4, after treatment, plasma levels of PT and APTT in both groups were markedly reduced, with lower values in EXG than in COG ($p < 0.05$).

Incidence of complications

There were lower numbers of patients with lung infection, acute gastrointestinal injury, ARDS and hypernatremia in EXG than in COG ($p < 0.05$). Although the incidence of DIC in EXG was slightly lower than that in COG ($p > 0.05$). Details are demonstrated in Table 5.

Table 1: Comparison of general patient information

Parameter	COG	EXG	t/χ^2	*P*-value
Age (years)	45.29±6.25	43.88±6.17	1.0528	0.2955
GCS score	6.64±1.32	6.73±1.41	0.3056	0.7607
Disease course (h)	9.41±3.30	9.27±2.86	0.2102	0.8340
BMI (kg/m^2)	26.87±3.06	25.91±3.02	1.4642	0.1469
Gender			0.1911	0.662
Male	24 (55.81)	26 (60.47)		
Female	19 (44.19)	17 (39.53)		
Cause of injury			0.4223	0.516
Car accident	18 (41.86)	21 (48.84)		
Fall from height	12 (27.91)	10 (23.26)		
Strike	8 (18.60)	8 (18.60)		
Others	5 (11.63)	4 (9.30)		
Pathological feature			0.1946	0.659
Contusion and laceration of brain combined with intracranial hematoma	27 (62.79)	25 (58.14)		
Diffuse brain swelling	9 (20.93)	10 (23.26)		
Extensive contusion and laceration of brain	4 (9.30)	5 (11.63)		
Primary injured brain trunk	3 (6.98)	3 (6.97)		

Table 2: Comparison of levels of inflammatory factors

Indicator	COG (n = 43)		EXG (n = 43)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
PCT (pg/mL)	6.79±0.66	2.55±0.78	6.82±0.71	1.68±0.41*
TNF-α (μg/L)	42.85±8.47	25.36±6.22	42.39±8.33	16.45±6.56*
IL-6 (μg/L)	58.62±10.24	29.11±8.52	29.13±10.33	19.98±8.49*

*P < 0.05, versus COG post-treatment

Table 3: Comparison of levels of cellular immunity and humoral immunity

Indicator	COG (n = 43)		EXG (n = 43)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
HLA-DR (%)	69.47±4.58	52.16±7.54	68.94±4.39	57.46±7.21*
$CD3^+$ (%)	51.97±4.21	52.67±5.13	52.06±4.18	55.13±5.08*
$CD4^+$ (%)	28.85±3.64	27.33±4.14	29.11±3.58	29.88±4.01*
$CD8^+$ (%)	20.68±2.35	25.16±3.56	20.57±2.39	23.27±3.42*
IgA (g/L)	1.61±0.40	1.96±0.35	1.62±0.42	1.99±0.34
IgG (g/L)	8.81±1.16	9.33±1.54	8.79±1.22	9.46±1.55
IgM (g/L)	0.83±0.24	0.90±0.17	0.85±0.26	0.92±0.18
C3 (g/L)	1.03±0.19	1.62±0.17	1.05±0.21	1.39±0.15*
C4 (g/L)	0.24±0.06	0.23±0.04	0.25±0.04	0.24±0.05

*P < 0.05, versus COG post-treatment

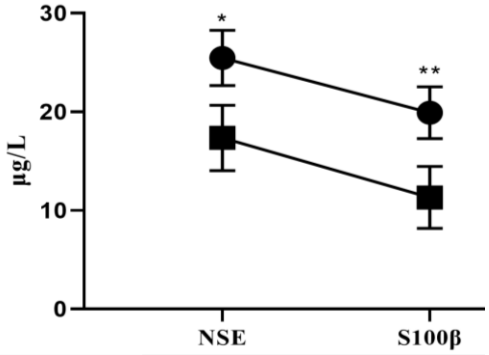

Figure 1: Serum protein levels of NSE and S100 beta. *P < 0.001, NSE level in EXG after treatment vs NSE level in COG after treatment; **p < 0.001, S100 beta protein level in EXG after treatment vs S100 beta protein level in COG after treatment

Treatment outcomes

No statistical differences were seen in cases of moderate disability, severe disability, persistent vegetative state and death between the two groups (p > 0.05). However, after treatment, more patients had good recovery in EXG than in COG (p < 0.05). Details are presented in Table 6.

DISCUSSION

Due to rapid deterioration of severe traumatic brain injury (TBI), patients often experience ischemia and hypoxia of brain tissue, and varying degrees of inflammatory reactions, leading to complications and secondary lesions [16].

Table 4: Comparison of plasma levels of coagulation indices (n = 43)

Group	PT (sec)		APTT (sec)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
COG	29.58±2.45	19.03±2.15	55.52±11.08	35.77±2.28
EXG	29.67±2.36	14.55±2.28	55.67±11.16	27.86±2.08
t		9.3743		16.8067
P-value		<0.001		<0.001

Table 5: Comparison of incidence of complications (n = 43)

Group	Lung infection	Acute gastrointestinal injury	ARDS	DIC	Hypernatremia
COG	24 (55.81)	10 (23.26)	7 (16.28)	3 (6.98)	8 (18.60)
EXG	14 (34.56)	3 (6.98)	1 (2.33)	1 (2.33)	2 (4.65)
χ^2	4.7149	4.4405	4.9615	1.0488	4.0737
P-value	0.030	0.035	0.026	0.306	0.044

Table 6: Comparison of treatment outcomes (n = 43)

Group	Good recovery	Moderate disability	Severe disability	Persistent vegetative state	Death
COG	12(27.91)	12(27.91)	15(34.88)	2(4.65)	2(4.65)
EXG	21(48.84)	12(27.91)	7(16.28)	1(2.33)	2(4.65)
χ^2	3.983	0.000	3.909	0.345	0.000
P-value	0.046	1.000	0.051	0.557	1.000

Mild hypothermia therapy is often applied for treating TBI. It relieves TBI-induced pathological damage by alleviating cerebral edema, improving cerebral oxygen metabolism and effectively lowering cerebrovascular endothelial cell metabolism. Moreover, mild hypothermia therapy mitigates Ca^{2+}-induced nerve cell damage by reducing Ca^{2+} influx, protecting brain tissue, and reducing ischemia-reperfusion injury. It achieves these by inhibiting excessive release of harmful substances such as acetylcholine, reactive oxygen species (ROS) and monoamines, and by suppressing lipid peroxidation [17].

Several studies in China have shown that *Xuebijing* injection significantly suppressed lipid peroxidation in cardiac muscle cells, alleviated myocardial injury, and reduced inflammatory reactions by enhancing activity of superoxide dismutase (SOD) [18]. Mild hypothermia therapy in combination with *Xuebijing* injection has been effective in the treatment of severe diseases. However, not much is known about the effect of the combined treatment on severe TBI.

Therefore, 86 severe TBI patients were chosen for this prospective study for the investigation on the clinical efficacy of combination of *Xuebijing* injection and mild hypothermia therapy on the disease. The results showed that after treatment, there were marked reductions in PCI, TNF-α and IL-6 in both groups, with lower levels in EXG than in COG. These are similar to those reported in a previous study [19]. In addition, after treatment, the plasma coagulation indices: PT and APTT were reduced in both groups, but with lower levels in EXG than in COG. Patients with severe TBI often experience brain tissue edema, aggravated cerebral swelling, rapid rise in intracranial pressure, as well as coagulation disorder (a complication). These changes lead to reduction in plasma fibrinogen level, prolongation of PT and APTT, and aggravation of TBI. In addition, traumatic stimulus and oxidative stress activate the immune system and up-regulate inflammatory factors, leading to a series of inflammatory reactions. Pro-inflammatory factors such as PCT, TNF-α and IL-6 reflect the degree of inflammation *in vivo*, while PT and APTT are reliable indices of fibrinolytic function. Thus, the combined use of *Xuebijing* injection and mild hypothermia therapy effectively inhibited inflammatory response and improved coagulation function in severe TBI patients.

Furthermore, this study showed that after treatment, levels of HLA-DR, $CD3^+$, $CD4^+$, $CD8^+$ and C3 indicators in patients in both groups differed significantly, implying that the combination treatment improved cellular immune function, enhanced neutralization of endotoxins, reduced secondary brain damage, and prevented infection. The proteins NSE and S100 beta are important serum indicators of the severity of TBI. These parameters reflect the degree of brain tissue damage and the degree of blood-brain barrier (BBB) injury through the permeability of brain capillaries. In this study, EXG had lower

protein expression levels of NSE and S100 beta than COG, indicating that the combined treatment inhibited brain tissue damage and protected the BBB, most likely due to reduction of *in vivo* inflammation.

Cases of lung infection, acute gastrointestinal injury, ARDS and hypernatremia in EXG were lower than those in COG, while the incidence of DIC was comparable in both groups. Moreover, more patients had good recovery in EXG than in COG. These results suggest that the incidence of complications associated with severe TBI may be reduced by combined use of *Xuebijing* injection and mild hypothermia therapy. The alleviation of inflammatory reactions and improvement of coagulation function reduced the incidence of complications, thereby confirming the effectiveness of the combined treatment.

The condition of patients who were treated with *Xuebijing* injection in combination with mild hypothermia therapy was better than that of those who received only conventional treatment, possibly due to the mitigating effect of the combined treatment on multiple organ dysfunction syndromes. This implies that *Xuebijin* and mild hypothermia therapy exerted synergistic effect on TBI by reducing excessive inflammatory response, improving coagulation function, inhibiting release of ROS, and protecting vascular endothelial cells. As a result, the combined treatment enhanced resistance to inflammatory response, cell apoptosis and ischemia-reperfusion injury, thereby decreasing damage to various body functions. Therefore, the combination treatment has a high clinical value in the prognosis of severe TBI in patients.

Limitations of the study

The recommended clinical dose of *Xuebijing* injection for patients with systemic inflammatory response syndrome is 50 mL twice a day, or 50 mL three times a day in severe cases; while the dose for patients with multiple organ dysfunction syndromes is 100 mL twice a day, or 100 mL three times a day in severe cases. However, in this study, there were no control groups given various doses via different administration methods. Therefore, there is need for large-scale prospective studies to determine the optimum dose and administration regimen for the combination treatment. Moreover, since mild hypothermia therapy is not suitable for patients with hemorrhagic shock or severe cardiopulmonary diseases, or those over 70 years, the contraindications and indications of patients should be considered before using the combination regimen.

CONCLUSION

The combination of *Xuebijing* injection and mild hypothermia therapy improves the prognosis of severe TBI in patients, lowers the levels of inflammatory factors, improves coagulation function, and enhances immunity. However, further clinical trials of the combined therapy on a larger scale is recommended prior to its introduction into clinical practice.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yadong Zheng and Yi Xu conceived and designed the study, and drafted the manuscript. Yadong Zheng, Peng Chen, Qingtao Zhang, Chao Sun, Yi Xiang and Weiduo Zhou collected, analyzed and interpreted the experimental data. Peng Chen and Yi Xu revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

REFERENCES

1. *Yang T, Li S. Efficacy of different treatment times of mild cerebral hypothermia on oxidative factors and neuroprotective effects in neonatal patients with moderate/severe hypoxic–ischemic encephalopathy. J Int Med Res 2020; 48(9): 300060520943770.*
2. *Dai HB, Xu MM, Lv J, Ji XJ, Zhu SH, Ma RM, Miao XL, Duan ML. Mild Hypothermia Combined with Hydrogen Sulfide Treatment During Resuscitation Reduces Hippocampal Neuron Apoptosis Via NR2A, NR2B, and PI3K-Akt Signaling in a Rat Model of Cerebral Ischemia-Reperfusion Injury. Mol Neurobiol 2016; 53(7): 4865-4873.*
3. *Liu LQ, Liu XR, Zhao JY, Yan F, Wang RL, Wen SH, Wang L, Luo YM, Ji XM. Brain-selective mild hypothermia promotes long-term white matter integrity after ischemic stroke in mice. CNS Neurosci Ther 2018; 24(12): 1275-1285.*
4. *Ji YB, Zhuang PP, Ji Z, Huang KB, Gu Y, Wu YM, Pan SY, Hu YF. TFP5 is comparable to mild hypothermia in improving neurological outcomes in early-stage ischemic stroke of adult rats. Neurosci 2017; 343: 337-345.*
5. *Wang CF, Zhao CC, He Y, Li ZY, Liu WL, Huang XJ, Deng YF, Li WP. Mild hypothermia reduces endoplasmic reticulum stress-induced apoptosis and improves neuronal functions after severe traumatic brain injury. Brain Behav 2019; 9(4): e01248.*
6. *Zhao CC, Wang CF, Li WP, Lin Y, Tang QL, Feng JF, Mao Q, Gao GY, Jiang JY. Mild Hypothermia Promotes Pericontusion Neuronal Sprouting via Suppressing Suppressor of Cytokine Signaling 3 Expression after Moderate Traumatic Brain Injury. J Neurotrauma 2017; 34(8): 1636-1644.*
7. *Zhao K, Li R, Bi S, Li Y, Liu L, Jia YL, Han P, Gu CC, Guo XZ, Zhang WP, et al. Combination of mild therapeutic hypothermia and adipose-derived stem cells for ischemic brain injury. Neural Regen Res 2018; 13(10): 1759-1770.*
8. *Luo SH, Zhang ZH. Effects of mild hypothermia combined EPO therapy on cerebral injury, myocardial injury and oxidative stress of neonatal hypoxic ischemic encephalopathy. J Hainan Medical Universit 2018; 24(16): 59-62.*
9. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
10. *Zhang HB, Cheng SX, Tu Y, Zhang S, Hou SK, Yang Z. Protective effect of mild-induced hypothermia against moderate traumatic brain injury in rats involved in necroptotic and apoptotic pathways. Brain Inj 2017; 31(3): 406-415.*
11. *Bagnato S, Boccagni C. Moderate/severe traumatic brain injury as a trigger of chronic neurodegeneration in humans. Neural Regen Res 2020; 15(7): 1247-1248.*
12. *Shankar JJS, Green R, Virani K, Wong H, Eddy K, Vandorpe R. Admission perfusion CT for classifying early in-hospital mortality of patients with severe traumatic brain injury: a pilot study. AJR Am J Roentgenol 2020; 214(4): 872-876.*
13. *Gómez PA, Castaño Leon AM, Lora D, Cepeda S, Lagares A. Final outcome trends in severe traumatic brain injury: a 25-year analysis of single center data. Acta Neurochir (Wien) 2018; 160(12): 2291-2302.*
14. *Brolliar SM, Moore M, Thompson HJ, Whiteside LK, Mink RB, Wainwright MS, Groner JI, Bell MJ, Giza CC, Zatzick DF, et al. A qualitative study exploring factors associated with provider adherence to severe pediatric traumatic brain injury guidelines. J Neurotrauma 2016; 33(16): 1554-1560.*
15. *Chesnel C, Jourdan C, Bayen E, Ghout I, Darnoux E, Azerad S, Charanton J, Aegerter P, Pradat-Diehl P, Ruet A, et al. Self-awareness four years after severe traumatic brain injury: discordance between the patient's and relative's complaints. Results from the PariS-TBI study. Clin Rehabil 2018; 32(5): 692-704.*
16. *Wang L, Liu Z, Dong Z, Pan J, Ma X. Effects of Xuebijing injection on microcirculation in septic shock. J Surg Res 2016; 202(1): 147-154.*
17. *Ma C, Han DF, Jin H, Cheng YY, Hu HX, Wang X. A combination of ulinastatin and Xuebijing amplifies neuroprotection after transient cerebral ischemia via attenuating apoptosis signal pathways in hippocampus. Curr Pharm Des 2018; 24(44): 5342-5347.*
18. *He F, Wang J, Liu Y, Wang X, Cai N, Wu C, Gao Q. Xuebijing injection induces anti-inflammatory-like effects and downregulates the expression of TLR4 and NF-kappa B in lung injury caused by dichlorvos poisoning. Biomed Pharmacother 2018; 106: 1404-1411.*
19. *Zuo L, Sun Z, Wang Z, Ding D, Xu T, Liu L, Gao L, Du S, Kang J, Zhang X. Tissue distribution profiles of multiple major bioactive components in rats after intravenous administration of Xuebijing injection by UHPLC–Q–Orbitrap HRMS. Biomed Chromatogr 2019; 33(2): e4400.*