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Effect of ligustrazine hydrochloride injection combined with hyperbaric oxygen therapy on postoperative complications, cerebral blood flow, and serum levels of sFKN and HMGB1 in patients with severe traumatic brain injury

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Abstract

Objective: To investigate the effects of ligustrazine hydrochloride injection combined with hyperbaric oxygen therapy on postoperative complication rates, cerebral blood flow, and serum levels of soluble fractalkine (sFKN) and high mobility group box protein 1 (HMGB1) in patients with severe traumatic brain injury (STBI). *Methods:* A total of 102 patients with severe TBI, treated at our hospital from February 2020 to February 2023, were randomly assigned into two groups using a sealed envelope method. Each group consisted of 51 patients. Both groups underwent decompressive craniectomy. The control group received hyperbaric oxygen therapy, while the observation group received ligustrazine hydrochloride injection combined with hyperbaric oxygen therapy, with treatment lasting for 1 month. The degree of National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), Mini-Mental State Examination (MMSE), cerebral blood flow parameters (vertebral artery [VA], basilar artery [BA], middle cerebral artery [MCA], anterior cerebral artery [ACA], posterior cerebral artery [PCA] blood flow velocities), serum brain injury markers (S100β protein, neuron-specific enolase [NSE], glial fibrillary acidic protein [GFAP]), and serum levels of sFKN and HMGB1 were compared before and 1 month after treatment. The incidence of postoperative complications and the 6-month prognosis were also recorded. *Results:* One month after treatment, the observation group showed significantly lower NIHSS scores and higher GCS and MMSE scores compared to the control group ($P < 0.05$). Blood flow velocities in the VA, BA, MCA, ACA, and PCA were significantly lower in the observation group than in the control group ($P < 0.05$). Additionally, serum levels of S100β, NSE, and GFAP were significantly lower in the observation group ($P < 0.05$). Serum levels of sFKN and HMGB1 were also significantly lower in the observation group ($P < 0.05$). The incidence of hydrocephalus, postoperative seizures, brain herniation, and cerebral vasospasm was significantly lower in the observation group ($P < 0.05$). At 6 months post-treatment, the observation group had a better overall prognosis than the control group ($P < 0.05$).
Conclusion: Ligustrazine hydrochloride injection combined with hyperbaric oxygen therapy significantly improves cerebral blood flow, reduces serum levels of sFKN and HMGB1, alleviates brain injury, enhances neurological recovery, and effectively reduces postoperative complications, leading to improved long-term prognosis in patients with STBI.

Keywords: Severe traumatic brain injury, ligustrazine hydrochloride, hyperbaric oxygen therapy, postoperative complications, cerebral blood flow, soluble fractalkine, high mobility group box protein 1

INTRODUCTION

Severe traumatic brain injury (STBI) is a common and critical condition in neurosurgery, which can cause mechanical deformation of the skull, meninges, and brain tissue, leading to neurological blockages, vascular changes, and a series of other pathological alterations, severely threatening the patient's life and health.[1,2] Decompressive surgery is the primary treatment measure for STBI, and the use of hyperbaric oxygen

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therapy (HBOT) postoperatively helps improve cerebral oxygen supply and promote neurological recovery.[3,4] Recent studies have indicated that ligustrazine hydrochloride injection can improve cerebral blood flow velocity in traumatic brain injury patients, effectively reducing the incidence of vasospasm and improving patient outcomes.[5] Additionally, soluble fractalkine (sFKN) has been identified as one of the earliest inflammatory markers following brain injury, with elevated levels contributing to enhanced inflammation and exacerbating neurological damage.[6] High mobility group box protein 1 (HMGB1) is another inflammatory marker related to brain injury, and studies have confirmed that elevated HMGB1 levels are associated with poor prognosis.[7,8] Based on these findings, the current study investigates the effects of ligustrazine hydrochloride injection combined with hyperbaric oxygen therapy on postoperative complications, cerebral blood flow, and serum levels of sFKN and HMGB1 in patients with STBI, aiming to provide clinical insights for the management of this condition. The results are reported as follows.

METHODS

General information

A total of 102 patients with STBI treated at our hospital from February 2020 to February 2023 were included in this study. Patients were randomly assigned into two groups using a computer-generated sequence concealed in opaque, sequentially numbered sealed envelopes. An independent statistician generated the allocation sequence with block randomization (block size=4), and a research nurse implemented enrollment and group assignment to ensure concealment. There were 51 patients in each group. The baseline characteristics, including sex, age, time from injury to admission, body mass index (BMI), injury causes, and trauma location, were comparable between the two groups ($P > 0.05$). The details are shown in Table 1

Sample size justification

An *a priori* power analysis was conducted using G*Power 3.1. Based on preliminary data (mean NIHSS difference = 4.5, SD = 3.2), we estimated that 48 patients per group would provide 90% power ($\alpha = 0.05$, two-tailed t-test). Accounting for a 10% dropout rate, the final sample size was set at 102 (51 per group). This aligns with similar TBI trials.

Inclusion and exclusion criteria

Inclusion criteria: 1) Diagnosis of STBI according to established criteria[9]; 2) Time from injury to hospital admission < 3 hours; 3) No history of previous TBI, neurological diseases, or head surgery; 4) Glasgow Coma Scale (GCS) score ≤ 8[10]; 5) Age between 18 and 60 years; 6) Informed consent obtained from the patient's family.

Exclusion criteria: 1) Patients with hematological diseases; 2) Patients with concurrent severe organ dysfunction; 3) Patients with malignant tumors; 4) History of infectious diseases within the past

Table 1: Comparison of general information between the two groups [($\bar{x}$ ±s)/n(%)]

Project	Observation group (n=51)	Control group (n=51)	t/χ^2	*P*
Gender (female / male)	22/29	20/31	0.162	0.687
Age (years)	18～60（40.57±9.71）	19～60（41.34±9.32）	0.409	0.684
Time from onset to admission (h)	0.5～2.9（1.35±0.42）	0.7～2.9（1.42±0.45）	0.812	0.419
BMI（kg/m^2）	18.9～27.6（23.89±1.85）	19.3～27.5（24.12±1.68）	0.657	0.513
Cause of injury			0.891	0.828
Traffic accident	32（62.75）	29（56.86）		
Heavy objects	10（19.61）	14（27.45）		
Fall from height	7（13.73）	6（11.76）		
Other	2（3.92）	2（3.92）		
Wound site			1.339	0.512
Left	23（45.10）	21（41.18）		
Right	20（39.22）	25（49.02）		
Bilateral	8（15.69）	5（9.80）		

3 weeks prior to admission; 5) Patients with autoimmune diseases; 6) Patients with chronic conditions such as hypertension, diabetes, or hyperlipidemia; 7) Patients with iron metabolism disorders or severe anemia; 8) Patients with intracerebral hemorrhage or a tendency for bleeding.

Methods

Both groups underwent decompressive craniectomy, performed by the same surgical team. Postoperatively, patients received standard care, including correction of electrolyte imbalances, infection prevention, and nutritional support. On this basis, the control group was administered HBOT. HBOT was initiated within 48±6 hours after decompressive craniectomy, based on clinical stability criteria (GCS ≥5, hemodynamic stability with MAP >65 mmHg, and no active intracranial bleeding on CT scan). Sessions were administered once daily for 30 consecutive days, with a standardized protocol (2.2 ATA for 60 minutes + 10-minute air breaks). The hyperbaric chamber (FLY-2895, Guizhou Fenglei Aviation Armament Co., Ltd.) was set to a pressure of 0.22 MPa (2.2 ATA), with an oxygen inhalation duration of 60 minutes, followed by a 10-minute break. The total duration of the HBOT session was 105 minutes, administered once daily.

The observation group received a combination of ligustrazine hydrochloride injection (20 mL, Pingguang Pharmaceutical Co., Ltd., National Drug Approval No. H20031302) and hyperbaric oxygen therapy. The HBOT regimen was the same as for the control group. Additionally, 20 mL of ligustrazine hydrochloride was mixed with 250 mL of normal saline for intravenous infusion, once daily. Both groups received treatment for one month.

Postoperative complications (hydrocephalus, seizures, brain herniation, vasospasm) were assessed daily by blinded neurologists and radiologists during the 1-month intervention period, with confirmatory imaging (CT/TCD) as needed.

Observational indicators

1) Neurological deficit, level of consciousness, and cognitive function were assessed before and 1 month after treatment in both groups using the National Institute of Health Stroke Scale (NIHSS)[11], GCS, and Mini-Mental State Examination (MMSE).[12]
2) Cerebral blood flow parameters, including the flow velocity of the vertebroarterial artery (VA), basilar artery (BA), middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA), were measured before and 1 month after treatment in both groups. These parameters were assessed using a color Doppler transcranial flow analyzer (JH model, Jiangsu Jiahua Electronic Equipment Co., Ltd.).
3) Serum biomarkers of brain injury, including S100β protein, neuronal-specific enolase (NSE), and glial fibrillary acidic protein (GFAP), were measured before and 1 month after treatment in both groups. Peripheral venous blood (5 mL) was collected at each time point, processed by centrifugation (radius 8 cm, 3500 rpm, 5 minutes), and the serum was stored at -70°C. S100β and GFAP levels were measured using enzyme-linked immunosorbent assay (ELISA) kits from Nanjing Jietan Biotechnology Co., Ltd., while NSE levels were detected using magnetic microparticle chemiluminescence assay kits from Jiangsu Zecheng Biotechnology Co., Ltd.
4) Serum levels of sFKN and high mobility group box protein 1 (HMGB1) were measured before and 1 month after treatment in both groups using ELISA. The kits were purchased from Shanghai Lanji Biological Technology Co., Ltd.
5) The incidence of postoperative complications, including hydrocephalus, post-surgical epilepsy, brain protrusion, and cerebral vasospasm, was recorded during the treatment period.
6) After a 6-month follow-up, prognosis was evaluated using the Glasgow Outcome Scale (GOS)[13], with five levels: death, vegetative state, severe disability, mild disability, and good recovery. Three patients withdrew (observation=1, control=2) due to relocation/family decisions. All received standard care until withdrawal; none discontinued treatment. Intention-to-treat analysis was applied. Attrition rate (2.9%) caused no significant bias (P>0.05).

To minimize bias, outcome assessors were blinded to group allocation. Neurological scales (NIHSS, GCS, MMSE) were evaluated by two independent neurologists unaware of treatment assignments. Cerebral blood flow measurements and laboratory analyses (S100β, NSE, GFAP, sFKN, HMGB1) were conducted using anonymized samples and imaging data. Discrepancies in assessments were resolved by a third blinded adjudicator.

Statistical methods

Data were analyzed using SPSS 22.0, with continuous normally distributed variables (e.g.,

NIHSS, biomarkers) compared via independent/paired t-tests, non-normal data via Mann-Whitney U/Wilcoxon tests, and categorical variables (e.g., complications) via χ^2/Fisher's exact tests. Ordinal outcomes (Glasgow Outcome Scale) were analyzed using Mann-Whitney U and trend tests. Effect sizes (Cohen's d, Cramér's V) and Bonferroni correction for multiple comparisons were applied, with sensitivity analyses confirming no bias from dropouts ($P = 0.60$).

RESULTS

NIHSS, GCS, and MMSE Scores

Compared with the control group, the observation group showed a significantly lower NIHSS score and higher GCS and MMSE scores after 1 month of treatment ($P < 0.05$). See Table 2.

Cerebral blood flow indicators

After 1 month of treatment, the observation group exhibited lower blood flow velocities in the VA, BA, MCA, ACA, and PCA compared to the control group ($P < 0.05$). See Table 3. Reduced flow velocities in the observation group (ligustrazine + HBOT) suggest improved cerebrovascular autoregulation and mitigated vasospasm, which is beneficial in severe TBI.

Serum brain injury markers

Compared with the control group, the observation group showed significantly lower levels of serum S100β, NSE, and GFAP after 1 month of treatment ($P < 0.05$). See Table 4 and Figure 1.

Serum sFKN and HMGB1

Compared with the control group, the observation group showed significantly lower levels of serum sFKN and HMGB1 after 1 month of treatment ($P < 0.05$). See Table 5. Furthermore, Post-hoc analysis showed that the reduction in sFKN levels was significantly correlated with MMSE score improvement ($r = 0.68$, $P < 0.01$), suggesting a link between inflammatory mitigation and cognitive recovery. Post-treatment reductions in sFKN levels showed strong positive correlation with neurological recovery (NIHSS improvement: $r=0.71$, $p<0.001$), while HMGB1 reduction moderately correlated with cognitive gains (MMSE: $r=0.53$, $p=0.003$).

Incidence of postoperative complications

The observation group had a significantly lower incidence of hydrocephalus, postoperative seizures, brain herniation, and cerebral vascular spasm compared to the control group ($P < 0.05$). See Table 6.

Prognosis

After 6 months of follow-up post-treatment, one patient in the observation group dropped out, compared to two patients in the control group. The observation group demonstrated a significantly better prognosis than the control group ($P < 0.05$). See Table 7.

DISCUSSION

STBI is characterized by its severity, rapid progression, and high mortality rate. Timely and effective treatment is crucial for improving patient prognosis.[14] With advances in modern medicine, treatment strategies for STBI have improved significantly, making it possible to save patients' lives. However, the recovery of neurological function and the overall prognosis remain suboptimal. Reducing neurological damage and improving patient outcomes have been key focuses in clinical practice.

HBOT is a newly developed adjunctive therapy that improves oxygen supply to brain tissue and increases oxygen reserves. It is currently widely used in the clinical treatment of various types of brain injuries and has shown certain efficacy in improving outcomes.[15,16] International studies[17] have suggested that HBOT can effectively reduce oxidative stress, correct the oxidative-antioxidative imbalance, and alleviate brain tissue damage, while also exerting anti-inflammatory effects. A domestic study on acute intracerebral hemorrhage[18] found that HBOT could further improve patients' daily living abilities and promote recovery. In the present study, after routine symptomatic treatment following STBI, HBOT was applied, leading to significant improvements in neurological deficits, coma status, and cognitive function. However, some patients still showed insufficient symptom improvement.

Previous reports[19] indicate that ligustrazine hydrochloride is primarily used in the clinical setting for neurological recovery in ischemic stroke with good efficacy. In recent years, Ligustrazine has also been applied to brain injury, but studies on its combination with HBOT in treating STBI are limited. The present study found that the combination of Ligustrazine hydrochloride

Table 2: Comparison of NIHSS, GCS, MMSE scores between the two groups

Time	Group	Number	NIHSS	Change%	GCS	Change%	MMSE	Change%
Before therapy	Observation group	51	25.86±4.21	——	6.75±1.34	——	12.29±3.28	——
	Control group	51	27.02±3.59	——	6.32±1.63	——	11.42±3.84	——
	t		1.497		1.455		1.230	
	P		0.138		0.149		0.222	
After 1 month of treatment	Observation group	51	11.70±1.93[a]	-54.7%	14.36±0.62[a]	+112.7%	28.09±1.74[a]	+128.6%
	Control group	51	16.19±2.84[a]	-40.1%	13.07±1.14[a]	+106.8%	26.25±2.36[a]	+129.9%
	t		9.338		7.099		4.482	
	P		<0.001		<0.001		<0.001	

Note: Compared with this group before treatment, [a]$P<0.05$. Change% = (post−pre)/pre×100. NIHSS: National Institutes of Health Stroke Scale, GCS: Glasgow Coma Scale, MMSE: Mini-Mental State Examination.

Table 3: Comparison of cerebral blood flow indexes between the two groups ($\bar{x}\pm s$, cm/s)

Time	Group	Number of cases	VA	BA	MCA	ACA	PCA
Before therapy	Observation group	51	69.42±6.59	67.38±4.67	125.19±24.52	97.68±8.57	90.06±8.40
	Control group	51	70.26±5.47	68.71±5.28	127.06±26.47	99.45±7.49	91.57±9.18
	t		0.700	1.348	0.370	1.111	0.867
	P		0.485	0.181	0.712	0.269	0.388
After 1 month of treatment	Observation group	51	60.35±3.72[a]	59.41±2.58[a]	101.58±14.70[a]	84.35±3.74[a]	72.84±4.26[a]
	Control group	51	65.08±4.61[a]	63.50±3.74[a]	112.81±17.61[a]	91.29±4.65[a]	78.96±5.52[a]
	t		5.702	6.429	3.496	8.305	6.268
	P		<0.001	<0.001	0.001	<0.001	<0.001

Note: Compared with this group before treatment, [a]$P<0.05$. VA: vertebral artery, BA: basilar artery, MCA: middle cerebral artery, ACA: anterior cerebral artery, PCA: posterior cerebral artery.

Table 4: Comparison of serum brain injury markers between groups ($\bar{x}\pm s$)

Time	Group	Number of cases	S100β（ng/mL）	NSE（ng/mL）	GFAP（pg/mL）
Before therapy	Observation group	51	0.59±0.15	36.48±6.15	5.62±0.57
	Control group	51	0.62±0.12	37.92±5.69	5.78±0.64
	t		1.115	1.227	1.333
	P		0.267	0.223	0.186
After 1 month of treatment	Observation group	51	0.23±0.04[a]	20.94±3.24[a]	2.70±0.25[a]
	Control group	51	0.37±0.07[a]	29.25±4.16[a]	3.49±0.37[a]
	t		12.401	11.255	12.634
	P		＜0.001	＜0.001	＜0.001

Note: Compared with this group before treatment, [a]$P<0.05$. S100β: S100 calcium-binding protein beta, NSE: neuron-specific enolase, GFAP: glial fibrillary acidic protein.

injection and HBOT significantly improved neurological deficits, coma status, and cognitive function in patients with STBI, suggesting that Ligustrazine plays an important role in promoting neurological recovery and improving prognosis in these patients. Ligustrazine, an alkaloid isolated from the traditional Chinese medicine "Chuanxiong" (川芎), can protect vascular endothelial cells by lowering cyclic adenosine monophosphate phosphodiesterase activity, increasing cyclic adenosine monophosphate levels, and reducing serotonin-induced arterial spasms.[20] An animal study[21] confirmed the protective effect of Ligustrazine in traumatic brain injury rats, suggesting its mechanism involves inhibition of neuronal apoptosis and protection of neuronal cells.

In this study, the combination of Ligustrazine hydrochloride injection and HBOT was found to significantly reduce the cerebral blood flow velocity in the VA, BA, MCA, ACA, and PCA in STBI patients. The observed reduction in cerebral blood flow velocities in the ligustrazine group likely reflects successful attenuation of post-traumatic vasospasm and restoration of normal vascular tone. This aligns with prior evidence that ligustrazine inhibits endothelial dysfunction and reduces oxidative stress, thereby improving microcirculation. Lower velocities correlate with decreased intracranial pressure and better perfusion, as evidenced by improved neurological scores. This, in turn, effectively reduced the incidence of cerebral vasospasm, alleviated brain tissue damage, and decreased the occurrence of postoperative seizures. Additionally, this treatment combination helped prevent the development of hydrocephalus, reduced intracranial pressure, and decreased the risk of brain herniation. Ultimately, this approach achieved the goal of protecting neurons, repairing damaged neurons, and improving neurological and cognitive functions in patients.

This study also found that the combination of Ligustrazine hydrochloride injection and HBOT effectively downregulated the serum levels of S100β, NSE, and GFAP in patients with STBI. These markers are closely related to brain tissue damage, with higher serum levels indicating more severe brain injury. This further supports the idea that the addition of Ligustrazine hydrochloride can improve the condition of STBI patients. Secondary brain injury factors following traumatic brain injury, such as brain ischemia, accumulation of oxygen free radicals, blood-brain barrier disruption, and brain edema, are all closely associated with the excessive release of inflammatory factors.[22,23]

sFKN plays a key role in regulating the inflammatory process of brain injury. It promotes the synthesis and secretion of various inflammatory factors, such as interleukin-6 and tumor necrosis factor-α. An elevated level of sFKN can exacerbate inflammation and worsen brain tissue damage.[24] High mobility group box protein 1 (HMGB1) is an inflammatory cytokine that promotes macrophage migration and increases arterial injury.[25] In this study, the combination of Ligustrazine hydrochloride and HBOT showed a significant advantage in downregulating serum levels of sFKN and

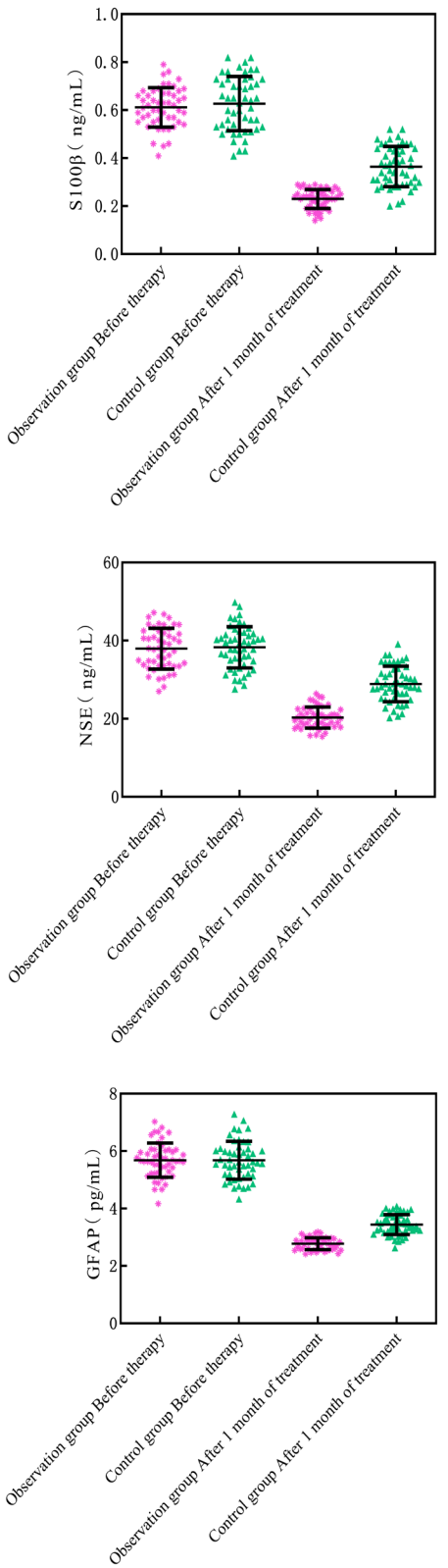

Figure 1. Comparison of serum brain injury indexes between the two groups. S100β and GFAP levels

HMGB1 in patients with STBI. This effect is likely related to the anti-inflammatory properties of Ligustrazine, which helps reduce neurological deficits and improve patient prognosis. Notably, the observed reductions in sFKN and HMGB1 levels correlated with clinical improvements, suggesting these inflammatory markers may serve as potential biomarkers for monitoring therapeutic response. The anti-inflammatory effects of ligustrazine combined with HBOT likely contributed to both the biochemical and clinical improvements observed, although the exact causal relationships warrant further investigation.

While this study focused on therapeutic outcomes, the safety profile of ligustrazine warrants mention. Although no significant adverse events (e.g., hypotension or bleeding) were observed in our cohort—likely due to strict exclusion criteria excluding patients with bleeding tendencies — prior studies report these as potential risks at higher doses. Our protocol used a standardized dose (20 mg/day) that aligns with Chinese guidelines for ischemic stroke, which has demonstrated safety in registry data. Future trials should include systematic monitoring of blood pressure and coagulation parameters. This study highlights ligustrazine's unique benefits, future multi-center collaborations could directly compare our protocol with international standards.

In conclusion, the combination of ligustrazine hydrochloride injection and HBOT significantly improved cerebral blood flow, reduced brain injury, enhanced neurological function, and decreased the incidence of postoperative complications. This therapeutic approach demonstrates high potential for clinical application. However, the study has limitations due to the small sample size, and the findings need to be validated through multi-center research.

DISCLOSURE

Ethics: The study was approved by the Ethics Committee of Zhangjiajie People's Hospital of Hunan Province (No.LL-2025-0019). Informed consent was obtained from all individual participants included in the study.

Data availability: The data generated in the present study may be requested from the corresponding author.

Financial support：None

Table 5: Comparison of serum sFKN and HMGB1 between the two groups ($\bar{x}$±s，ng/mL)

Time	Group	Number of cases	sFKN	HMGB1
Before therapy	Observation group	51	48.24±16.51	8.60±1.72
	Control group	51	51.83±17.27	8.94±2.03
	t		1.073	0.913
	P		0.286	0.364
After 1 month of treatment	group	51	15.29±5.95[a]	3.65±1.26[a]
	Control group	51	21.57±7.34[a]	5.17±1.58[a]
	t		4.747	5.371
	P		＜0.001	＜0.001

Note: Compared with this group before treatment, [a]*P*＜0.05

Table 6: Comparison of the incidence of complications between the two groups n (%)

Group	Number of cases	Hydrocephalus	Postoperative epilepsy	Cerebral bulge	Cerebral vasospasm
Observation group	51	3（5.88）	3（5.88）	7（13.73）	5（9.80）
Control group	51	11（21.57）	10（19.61）	16（31.37）	13（25.49）
χ^2		5.299	4.320	4.547	4.318
P		0.021	0.038	0.033	0.038

Table 7: Comparison of the prognosis of the two groups n (%)

Group	Number of cases	Death	Vegetative state	Severe disability	Mild disability	Good
Observation group	50	1（2.00）	2（4.00）	6（12.00）	13（26.00）	28（56.00）
Control group	49	4（8.16）	7（14.29）	10（20.41）	10（20.41）	18（36.73）
u				2.434		
P				0.015		

Note: Cases lost to follow-up (observation group: n=1; control group: n=2) have been excluded from the prognosis analysis.

Conflict of interests：The authors declare that they have no competing interests.

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