Effects of decompressive craniectomy combined with edaravone on postoperative neurological functions and hemodynamics of patients with severe traumatic brain injury

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ABSTRACT

الأهداف: تقييم آثار استئصال القحف الخافض للضغط مع إيدارافون على كلاً من الوظائف العصبية بعد العملية الجراحية وديناميكا الدم للمرضى الذين يعانون من إصابات الدماغ المؤلمة الشديدة (STBI).

المنهجية: شملت الدراسة على 186 مريضًا من مرضى STBI الذين تم قبولهم خلال يناير 2018م ويناير 2021م. تم اعتماد طريقة جدول الأرقام العشوائية لتعيين مجموعة العمليات (العدد=82) ومجموعة الأدوية المشتركة (العدد=104) للمرضى. وقد لوحظت التغيرات في المؤشرات السريرية.

النتائج: بالمقارنة مع مجموعة العمليات الجراحية، حصلت مجموعة الأدوية المشتركة على درجة أعلى في فحص الحالة المعرفية السلوكية العصبية، ودرجة مؤشر بارثيل، ومعدل الاستجابة الإجمالي ومعدل ضربات القلب (p<0.05). علاوة على ذلك، وعلى النقيض من مجموعة العمليات الجراحية، انخفض متوسط الضغط الشرياني ومؤشرات مخطط عضلة القلب ومؤشرات الوظيفة العصبية بعد العملية الجراحية ومعدل حدوث المضاعفات الإجمالي لمجموعة الأدوية المشتركة (p<0.05). بالمقارنة مع مجموعة العمليات، أظهرت مجموعة الأدوية المشتركة ارتفاعًا في سرعة الدم في الجانب المقابل (p<0.05). علاوة على ذلك، كان لدى مجموعة الدواء المشترك تشخيص أفضل لمدة عام بعد العملية الجراحية مقارنة بمجموعة العمليات (p<0.05).

الخلاصة: اظهرت الدراسة أن إيدارافون مع استئصال القحف الخافض للضغط يفيد في تحسين الوظائف العصبية بعد العملية الجراحية لمرضى STBI، واستقرار ديناميكا الدم بشكل فعال، ويحدث مضاعفات قليلة ويحسن التشخيص.

Objectives: To assess the effects of decompressive craniectomy combined with edaravone on the postoperative neurological functions and hemodynamics of patients with severe traumatic brain injury (STBI).

Methods: The subjects included totally 186 STBI patients admitted during January 2018 and January 2021. The random number table method was adopted to set an operation group (n=82) and a combined medication group (n=104) for the subjects. The changes of the clinical indicators were observed.

Results: Compared with the operation group, the combined medication group had higher Neurobehavioral Cognitive Status Examination score, Barthel index score, total response rate and heart rate (p<0.05). Besides, by contrast to those of the operation group, the mean arterial pressure, myocardial zymogram indicators, postoperative neurological function indicators and total incidence rate of complications of the combined medication group were reduced (p<0.05). In comparison with the operation group, the combined medication group exhibited raised ipsilateral contralateral blood velocities (p<0.05). Furthermore, the combined medication group had a better postoperative 1-year prognosis than the operation group (p<0.05).

Conclusion: Edaravone in combination with decompressive craniectomy benefits the postoperative improvement of neurological functions of STBI patients, effectively stabilizes the hemodynamics, induces few complications and improves the prognosis.

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Traumatic brain injury, as a common form of injury in daily life, can be classified into different degrees according to clinical symptoms, one of which is severe traumatic brain injury (STBI). This disease is generally severe in patients and even leaves them in a moderate or deep coma.[1] Patients with STBI have a weak response to the outside, and those with severe skull fractures, brain lacerations, intracerebral hematomas, and brain stem injuries should be treated in time by operations.[2,3] The STBI tends to be complicated with cerebral laceration and increased intracranial pressure therein, as one of the leading causes of death, causing high rates of disability and mortality. As a traditional surgery, craniectomy often causes serious complications and has a poor therapeutic effect. Instead, craniectomy under stepwise decompression can modulate the intracranial pressure stepwise, thereby helping relieve ischemia-reperfusion injury and reduce the incidence rate of complications.[4,5]

Edaravone can scavenge free radicals in neurons and neuroendocrine cells. In addition, it is able to inhibit lipid peroxidation and mitigate endothelial damage.[6] Until now, decompressive craniectomy and edaravone have seldom been combined to treat STBI. Thus, the present study aims to evaluate decompressive craniectomy plus edaravone

Methods.

Subjects. The ethics committee of the hospital issued an approval for the present study, which was performed in accordance with the Helsinki Declaration principles. Strictly based on the ethical standards of the hospital, the subjects and their family members provided the consent form after being informed of the study. The subjects were selected from STBI patients (186 in total) who were hospitalized during January 2018 and January 2021. The random number table method was utilized to establish an operation group (n=82) together with a combined medication group (n=104) for the subjects. To be specific, the subjects were numbered one by one from 001 to 104. The starting point and order of sampling in the random number table were arbitrarily determined. Then all the numbers were selected by the subjects from the table in turn.

The operation group consisted of 43 females plus 39 males aged (52.69±5.92) years old on average. The duration from the injury to admission was 9 hours and (1.68±0.19) hours on average. The injuries included blow injury (9 cases), fall injury (20 cases), traffic accident injury (36 cases) and others (17 cases). The combined medication group had 53 males and 51 females aged (52.73±5.88) years old averagely. The duration from the injury to admission was 0.3-1.8 hours and the mean duration was (1.64±0.23) hour. The causes of injury included blow injury (11 cases), fall injury (25 cases), traffic accident injury (41 cases), and others (27 cases). The above data were comparable between the 2 groups (p>0.05).

The following inclusion criteria were adopted: 1) Patients diagnosed with STBI based on the Modern Craniocerebral Injury and confirmed by CT and MRI, 2) those undergoing an operation at 24 h after admission, and 3) those without multiple or recurrent injuries.

The exclusion criteria involved 1) patients suffering chest, abdominal, or limb trauma, 2) those complicated with severe central nervous system disease, cerebrovascular disease or systemic infections, or 3) those with vascular stenosis or spasm.

Treatment methods. Both groups were subjected to hemostasis, anti-inflammation, dehydration and nutritional support medications after admission. The operation group received craniectomy under stepwise decompression as follows. The whole scalp was first cut by making incisions at the frontal, temporal and parietal lobes, and hemostasis was performed in time. The periosteum was then peeled and the skin flap was separated. After bone drilling and sawing, the bone flap was removed, and the medial and lateral sphenoid ridge was taken out with a bone cutter, followed by decompression. Afterwards, the patients were given intravenously 40-80 mg of furosemide and 250 mL of 20% mannitol. The cerebrospinal fluid and intracranial hematoma were released in a controlled manner through a small hole in the blue dura. After the bone window pressure was released, a radial incision was made on the dura to fully remove the deactivated cerebral tissues and intracranial hematoma. In the case of insignificant or weak brain tissue pulsatility, it is necessary to reduce the brain herniation, with corresponding treatment depending on the particular situations.

The combined medication group was treated with craniectomy under stepwise decompression combined with edaravone (Nanjing Simcere Dongyuan Pharmaceutics Co., Ltd., Nanjing, China; 20 mL: 30 mg). The mixture of edaravone and 0.9% NaCl solution (30 mg evenly diluted in 100 mL) was infused intravenously within 30 min twice a day for 2 weeks. The treatment outcomes were observed after treatment.

Determination of neurobehavioral cognitive status examination (NCSE) score and Barthel index score. The NCSE was used to assess the cognitive status, and the score was in direct proportion to the cognitive status of the subjects. The subjects were also evaluated on the activities of daily living from 10 aspects, including

eating, bathing, dressing, walking on a level ground, going up and down stairs, and controlling urination and defecation with Barthel index. The total score was 100 points, and the score was directly proportional to the activities of daily living.

Detection of hemodynamics indicators. The number of pulse beats per min was measured by feeling the pulse when the subjects were in a calm state. The mean arterial pressure (MAP) was determined using direct manometry. A special catheter was percutaneously punctured and the arteries around the catheter were inserted into the aorta and connected to a monitoring manometer at the end of the catheter, and the blood pressure was recorded after being displayed. The ipsilateral and contralateral blood flow velocities in the middle cerebral artery were measured by Voluson E8 TruScanTM color Doppler flow imager (Shanghai Hanfei Medical Devices Co., Ltd., Shanghai, China). Transcranial Doppler ultrasound examination was conducted on all the subjects in a quiet state without abnormal conditions before and after treatment. A 2 MHz probe was placed in the temporal windows above the zygomatic arch and between the orbit and the ear, and the middle cerebral artery was selected as the target vessel with a detection depth of 40-65 mm.

Detection of myocardial zymogram indicators. The levels of aspartate aminotransferase (AST; 10-40 U/L as the reference value), creatine kinase (CK; reference value at 50-310 U/L and 40-200 U/L for male and female, respectively), as well as CK-MB (reference value: 0-25 U/L) were detected by a Libang i15 blood gas automatic biochemical analyzer (Shanghai Hanfei Medical Devices Co., Ltd., Shanghai, China) strictly according to the instructions.

Examination of postoperative neurological functions. Each subject underwent collection of fasting venous blood (5 mL) at 9:00 am before and after treatment. The supernatant was obtained by centrifuging the samples (radius: 15 cm, speed: 3,000 r/min, time: 10 min), followed by preservation using a refrigerator (-80°C) for subsequent assays. Enzyme-linked immunosorbent assay was conducted to determine ES (reference value: 12.7-38.4 pg/ml), neuropeptide Y (NPY; reference value: 101-189.2 pg/ml) and endothelin-1 (ET-1; reference value: 43.22-58.38 pg/ml). The serum samples were first taken out from the refrigerator and stored at room temperature for 30 seconds, and standard serum and solution were prepared. The plate was washed using 300 µL of plate-washing solution for 30 seconds. After the micro-wells were patted dry, the plate was added successively with 50 µL of buffer, standard solution, sample and detection antibody, sealed, shaken and incubated for 2 h at room temperature (37°C). Then the plate wells were added with enzyme marker (100 µL) after washing. The plate was also sealed, shaken and placed at room temperature for 45 min. Following plate washing, the micro-wells were added with substrate solution in a volume of 100 µL for 30 min of incubation in dark. Subsequently, the micro-wells were added with 100 µL of stop buffer and shaken. Finally, a microplate reader was employed to examine at 450 nm for the absorbance.

Evaluation of treatment outcomes. The treatment outcomes (marked response, moderate response and no

Table 1 - NCSE score and Barthel index score [($\bar{x} \pm s$), point].

Groups	n	NCSE score		Barthel index score	
		Before treatment	After treatment	Before treatment	After treatment
Operation	82	45.68±4.59	64.23±6.45	43.29±4.31	72.59±7.28
Combined medication	104	45.72±4.53	78.45±7.89	43.25±4.36	81.46±8.17
t		0.059	13.210	0.062	7.709
P		0.953	0.001	0.950	0.001

Table 2 - Hemodynamics indicators ($\bar{x} \pm s$).

Groups	n	HR (beat/min)		MAP (mmHg)		Ipsilateral blood flow velocity (cm/s)		Contralateral blood flow velocity (cm/s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Operation	82	102.39±10.25	64.29±6.45	94.25±9.43	63.12±6.34	52.39±5.26	81.06±8.11	52.36±5.28	69.54±6.97
Combined medication	104	102.44±10.19	73.45±7.38	94.29±9.38	75.46±7.58	52.43±5.21	95.48±9.57	52.33±5.34	78.69±7.93
t		0.033	8.879	0.029	11.830	0.052	10.900	0.038	8.236
P		0.974	0.001	0.977	0.001	0.959	0.001	0.970	0.001

Table 3 - Myocardial zymogram indicators [($\bar{x} \pm s$), U/L].

Group	n	CK		AST		CK-MB	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Operation	82	825.46±82.57	348.15±34.83	47.58±4.76	26.85±2.69	36.59±3.67	27.48±2.75
Combined medication	104	825.49±82.53	296.48±29.67	47.53±4.83	19.64±1.98	36.54±3.71	21.65±2.18
t		0.002	10.920	0.071	21.050	0.092	16.130
P		0.998	0.001	0.944	0.001	0.927	0.001

Table 4 - Postoperative neurological functions [($\bar{x} \pm s$), pg/mL].

Group	n	ES		NPY		ET-1	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Operation	82	50.68±5.09	42.38±4.27	325.49±32.57	219.67±22.08	83.46±8.37	65.49±6.58
Combined medication	104	50.65±5.12	34.19±3.44	325.44±32.62	178.25±17.86	83.44±8.42	57.23±5.74
t		0.040	14.490	0.010	14.140	0.016	9.133
P		0.968	0.001	0.992	0.001	0.987	0.001

Table 5 - Treatment outcomes [n (%)].

Groups	n	Marked response	Moderate response	No response	Total response rate
Operation	82	39	32	11	71 (86.59)
Combined medication	104	66	35	3	101 (97.12)
χ^2					7.304
P					0.007

Table 6 - Postoperative 1-year prognosis [n (%)].

Groups	n	Good recovery	Moderate disability	Severe disability	Vegetative survival	Death
Operation	82	26	24	19	6	7
Combined medication	104	64	28	9	1	2
χ^2		16.338	0.125	7.556	5.113	4.355
P		0.001	0.723	0.006	0.024	0.037

response) were evaluated based on the NCSE score and Barthel index score. The degree of improvement ≥21 points was marked response, the degree of improvement of 8-20 points represented moderate response, and those failing to meet the above criteria indicated no response. Total response rate=marked response rate+moderate response rate.

Observation of complications. The incidence rates of intraoperative and postoperative complications of patients, including acute intraoperative encephalocele, delayed intracranial hematoma, severe hyponatremia, and large-area cerebral infarction were compared between the 2 groups.

Observation of postoperative 1-year prognosis. The prognosis of the patients was followed up and recorded according to the criteria of death, vegetative survival, severe disability, moderate disability, and good recovery at 1 year after operation.

Statistical analysis. Statistical analysis was performed by means of SPSS 26.0 software provided by IBM Inc. (Armonk, New York, NY, USA). The format of ( ) was utilized to express measurement data. The comparisons between and within groups were accomplished through independent-samples t-test and paired t-test, respectively. The percentage (%) was selected for presenting count data. A $p<0.05$ indicated a statistically significant difference.

Results. The NCSE score and Barthel index score. Before treatment, the 2 groups had similar NCSE and Barthel index scores (t=0.059, 0.062, $p>0.05$). Both groups exhibited raised NCSE and Barthel index scores after treatment, while such scores were higher in the combined medication group than in the operation group (t=13.210, 7.709, $p<0.05$) (**Table 1**).

Hemodynamics indicators. Before treatment, the hemodynamics indicators heart rate (HR), MAP and

ipsilateral and contralateral blood flow velocities were comparable between the 2 groups (t=0.033, 0.029, 0.052, 0.038, p>0.05). After treatment, HR and ipsilateral and contralateral blood flow velocities increased, but MAP decreased in both groups. Compared with the operation group, the combined medication group had higher HR, lower MAP and higher ipsilateral and contralateral blood flow velocities (t=8879, 11.830, 10.900, 8.236, p<0.05) (**Table 2**).

Myocardial zymogram indicators. As shown in **Table 3**, the levels of myocardial zymogram indicators CK, AST and CK-MB were similar between the 2 groups before treatment (t=0.002, 0.071, 0.092, p>0.05). However, CK, AST and CK-MB levels declined in both groups after treatment, and the combined medication group had lower levels of CK, AST and CK-MB than those of the operation group (t=10.920, 21.050, 16.130, p<0.05).

Neurological functions following operation. The levels of postoperative neurological function indicators ES, NPY and ET-1 in the 2 groups were comparable before treatment (t=0.040, 0.010, 0.016, p>0.05). After treatment, the ES, NPY and ET-1 levels decreased, and the combined medication group presented elevated levels by contrast with the operation group (t=14.490, 14.140, 9.133, p<0.05) (**Table 4**).

Treatment outcomes. Compared to the operation group, the combined medication group displayed an increased total response rate (p<0.05) (**Table 5**).

Complication incidence rate. There were 3 cases of acute intraoperative encephalocele, 2 cases of delayed intracranial hematoma, 2 cases of severe hyponatremia, 4 cases of large-area cerebral infarction and 5 cases of other complications in the operation group. In the combined medication group, there were 1 case of acute intraoperative encephalocele, 1 case of severe hyponatremia, 1 case of large-area cerebral infarction and 2 cases of other complications. The combined medication group had a lower total incidence rate of complications (4.81%) than that of the operation group (19.51%) (χ^2=9.898, p=0.002).

Postoperative 1-year prognosis. According to **Table 6**, the combined medication group was superior to the operation group in terms of the postoperative 1-year prognosis (p<0.05).

Discussion. The STBI refers to a type of the head injury due to external force. Most patients with brain injury are in coma again or suffer from coma for more than 6 hour, seriously threatening their life and safety. At present, the principles of emergency treatment plus shock correction need to be adhered to, thereby improving the prognosis of patients as much as possible.[7,8]

Previously, patients with STBI were usually treated with traditional standard large craniectomy, but this method seriously affects the safety and health of patients due to the high incidence rates of severe complications, such as acute encephalocele and large-area cerebral infarction, and the increases in disability and mortality rates.[9,10] For patients with STBI, decompressive craniectomy can better control the postoperative intracranial pressure through stepwise regulation, and reduce the incidence rates of intraoperative and postoperative complications without increasing the operation time, thereby improving the prognosis.[11-13] Decompressive craniectomy has many advantages:[14-16] 1) The dura was cut open step by step, which helps to reduce or avoid brain tissue displacement due to rapid decompression, and to decrease the incidence rates of complications such as secondary cerebral infarction and acute intraoperative encephalocele, delayed intracranial hematoma, and local bulge, thereby protecting cerebral vessels, i.e. reducing or avoiding cerebral vascular distortion. 2) Stepwise decompression can relieve or avoid blood vessel injury and reduce the incidence rates of complications such as delayed traumatic brain injury. 3) The controlled reduction of the intracranial pressure during the operation helps to protect the blood vessels and vasomotor center, alleviate the ischemia-reperfusion injury and brain swelling, and lower vascular permeability.

After operation, the neurological functions fail to be improved in patients with traumatic brain injury and need to be repaired by medications. As a brain protective agent, edaravone can prolong the survival function of neurons, inhibit the lipid peroxidation reaction, alleviate the apoptosis of neurons and decrease the incidence rate of complications such as brain edema in patients with STBI, thus promoting their postoperative recovery.[17-19] In this study, patients with STBI receiving decompressive craniectomy combined with edaravone had a significantly lower incidence rate of intraoperative complications and a better postoperative 1-year prognosis than those of the patients treated with decompressive craniectomy alone. Therefore, with the adjunctive treatment of edaravone, the clinical symptoms and neurological functions were improved to some extent, with a positive effect on the prognosis of the patients.

The changes in hemodynamics parameters are closely related to intracranial blood pressure, and cerebral congestion and vasospasm have an impact on the prognosis of patients.[20] In this study, decompressive craniectomy combined with edaravone effectively

improved the hemodynamics, probably because the combination reduced the levels of some markers in the cerebrospinal fluid to normal levels. After surgery, acute ischemia-hypoxia or necrosis occurs in the myocardial cells of patients with traumatic brain injury due to coronary artery spasm, thereby releasing myocardial enzymes in large amounts and significantly increasing the serum levels. CK, AST and CK-MB are commonly used to assess the myocardial injury in patients.[21,22] In this study, the patients with STBI treated with decompressive craniectomy combined with edaravone had decreased levels of serum myocardial zymogram indicators, possibly because the combination relieved the neurogenic myocardial damage to a certain extent.

In the case of STBI, free radicals are released to cause different degrees of secondary damage to brain tissues. Besides, acute traumatic brain injury affects the hypothalamic function in an emergency state, resulting in the excitement of the sympathetic-adrenomedullary system. Clinically, ES, NPY and ET-1 are often used to assess the degree of neurological impairment after operation, with controlling of their levels as one of the key points in clinical treatment.[23,24] The ES, first discovered in the mouse vascular endothelioma cells, has been recognized as the most potent angiogenesis inhibitor and has an obvious inhibitory effect on angiogenesis by the mechanism that the basic regions compete with angiogenic factors to bind heparin. The ET-1 is a stress hormone and a vasoactive polypeptide, and its level significantly increases when the cerebral vessels are damaged or the peripheral vessels are strongly constricted and the peripheral tissues are in the ischemic and hypoxic states, showing a higher probability in predicting the death of patients.[25,26]

As a neurotransmitter generally in a precursor form, NPY not only exists in diversified tissues and organs surrounding the central nervous system as well as within the central nervous system with widespread expressions, but also binds other receptors to work, with a high predictive value for nerve injury. The mechanism of its elevation may be that traumatic brain injury causes local ischemia-hypoxia, enhanced sympathetic-catecholamine system reflex excitability, and exacerbated local inflammatory response.[27] Based on the results of this study, decompressive craniectomy combined with edaravone effectively reduced the levels of neurotransmitters in patients with STBI, probably because the combined treatment mitigated the cerebral vascular injury and improved the neurological functions and prognosis.

In conclusion, decompressive craniectomy combined with edaravone can significantly improve the neurological functions in patients with STBI, recover the hemodynamics to normal levels, improve the cognitive status and self-care abilities, and reduce the incidence rates of complications. Hence, this method is worthy of clinical application. However, limitations including small numbers of cases and case sources exist in the present study. Additionally, this study does not involve the results of adverse drug reactions, which needs to be explored in the future.

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