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Original Article

Treatment effects of monosialotetrahexosylganglioside on severe traumatic brain injury in adults

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Abstract: Objective: To determine the effects of monosialotetrahexosylganglioside (GM-1) on the curative effect on severe traumatic brain injury (TBI) in adults and assess the changes of serum inflammatory factors. Methods: Retrospective analysis was used in this study. A total of 130 adult patients with severe TBI treated in our hospital from April 2019 to July 2021 were enrolled. Among them, 63 patients treated with conventional therapy were grouped as the control group (Con group), and 67 patients given GM-1 based on conventional therapy were grouped as the observation group (Obs group). The therapeutic efficacy and incidence of adverse reactions were compared between the two groups. The Mini-Mental State Examination (MMSE), Glasgow coma scale (GCS), serum neuron specific enolase (NSE), and Barthel index were adopted for evaluating the two groups after treatment, and the two groups were compared in inflammatory response and stress response. Results: After treatment, the Obs group showed a significantly higher total effective rate and a significantly lower total incidence of complications than the Con group ($P<0.05$), and also had significantly higher MMSE score, GCS score and Barthel index than the Con group ($P<0.05$). After treatment, the NSE level in the Obs group was significantly lower than that in the Con group. Additionally, after treatment, the Obs group showed significantly lower levels of IL-6, IL-8 and TNF-α, a significantly higher SOD level, and a significantly lower MDA level than the Con group ($P<0.05$). Conclusion: For patients with severe TBI, adjuvant therapy with GM-1 can significantly raise the therapeutic effect and improve the nerve function and inflammatory reaction, which is worthy of clinical application.

Keywords: Monosialotetrahexosylganglioside, severe traumatic brain injury in adults, serum inflammatory factors, neurological function

Introduction

Traumatic brain injury (TBI) is a common critical neurological disease, which is often triggered by external violent trauma, such as skull fracture, and soft tissue or brain injury [1, 2]. With the urbanization and economization, accidents such as traffic accidents and work-related injuries are gradually increasing, which is accompanied by the increase of the incidence of TBI [3, 4]. Patients with mild TBI have mild symptoms, and they usually not suffer sequelae after cure, but severe TBI may result in serious sequelae, even disability or death [5]. Patients with severe TBI may have symptoms such as dilated pupils, vomiting, nausea, pain, disturbance of vital signs, and disturbance of consciousness, and have serious and rapidly progressing conditions, so they often need to be admitted to the hospital immediately for surgery [6].

Nowadays, surgery is usually used to reduce intracranial pressure of patients with severe TBI to save their lives [7]. However, this kind of surgery often brings great trauma to patients and increases the risk of postoperative complications [8]. Moreover, nerve function with damage triggered by trauma are often difficult to rebuilt, so patients with such damage will suffer from different degrees of nerve disorders and changes in life abilities after treatment [9]. In addition, there are stem cells and neuron precursor cell transplantation therapies, which replace defective neurons with inhibited cells, but it is still technically difficult to transplant

target cells into the brain [10]. Mild hypothermia therapy has also been carried out in many clinical trials, and it has brought some adverse reactions while improving the patient's condition, such as coagulation disorders, increasing chances of infection, arrhythmia and insulin resistance [11]. According to a study [12], patients with severe TBI still have periods of unconsciousness and suffer complications after treatment.

Different degrees of oxidative stress and inflammatory reactions will occur in TBI patients, and severe inflammatory reactions will further result in tissue cell damage and even necrosis [13]. Monosialotetrahexosylganglioside (GM-1) is a compound that can nourish nerves and effectively slow down the process of nerve degeneration [14]. Sialuronic neurosphingolipid is a component of nerve cell membranes, which can help maintain the integrity of nerve cell membranes and promote the differentiation of nerve cells and axonal regeneration [15]. GM-1 can restore the damaged nerve function by promoting the growth of neurons, so that the damaged central nerve can be repaired, so it is also applied to the treatment of nerve injury diseases [16].

The present study observed the curative effect of GM-1 on severe TBI in adults, and studied the changes of neurological function and inflammatory level in these adults, with the goal of providing a research basis for clinical practice.

Materials and methods

Patient information

In this retrospective analysis, a total of 130 adults with severe TBI treated in our hospital from April 2019 to July 2021 were enrolled. Among them, 63 patients (33 males and 30 females with average age of (36.94±16.04) years) were treated with conventional therapy as the control group (Con group), and 67 patients (38 males and 29 females with average age of (37.84±14.18) years) were given GM-1 based on conventional therapy as the observation group (Obs group). Each patient or his/her immediate family members signed the informed consent form, and the study was approved by the Medical Ethics Committee of our hospital (Ethical approval number: IRB-20190425).

Inclusion and exclusion criteria

The inclusion criteria: Patients confirmed with TBI according to imaging CT or MRI; patients with Glasgow coma scale (GCS) score ≤8 points; patients whose time from injury to admission was <12 h; those with detailed medical records.

The exclusion criteria: Patients with malignant tumour; patients with comorbid systemic infection; patients with severe heart, lung or kidney dysfunction; patients with coagulation dysfunction; patients with mental disorders; or those with cranial nerve diseases.

Treatment mode

Patients in the Con group were treated with routine treatment after admission. After admission, each patient was given timely debridement and also given routine antibiotics and assisted to keep the respiratory tract unobstructed. Endotracheal intubation could be performed if necessary to achieve continuous inhalation of oxygen and correction of cerebral hypoxia. Patients with cerebral hernia were immediately given intravenous drip of dehydration drugs, and cerebral hematoma was treated by bone flap decompression. In the case of intracranial pressure increase, 20% mannitol was quickly injected before the meninges were opened. Patients in the Obs group were treated with GM-1 (Shandong Qilu pharmaceutical co., Ltd., Batch number: 3100523DT) on the basis of the routine and comprehensive treatment given to the Con group. Specifically, each patient was given intravenous drip of 100 mg/d GM-1 for 3 weeks, and then given intravenous drip of 40 mg/d GM-1 for 3 consecutive weeks, with a total course of 6 weeks [18].

Outcome measures

Therapeutic effect: The curative effect on all patients was evaluated using the NIHSS score and clinical symptoms after treatment, and it was classified into four kinds: cured, remarkably effective, effective and ineffective. Cured: The NIHSS score decreased by more than 90%, and clinical symptoms and signs disappeared

or were alleviated significantly; Remarkably effective: The NIHSS score decreased by 46% to 90%, and clinical symptoms and signs were alleviated; Effective: The NIHSS score decreased by 18% to 45%, and clinical symptoms and signs were alleviated. Ineffective: The NIHSS score decreased by ≤17%, and the clinical symptoms and signs were not alleviated or even aggravated. The total effective rate = (The number of cured patients + the number of patients with remarkably effective treatment + the number of patients with effective treatment)/the total number of patients × 100% [19].

Complications: The incidence of intracranial infection, pulmonary infection, hydrocephalus and epilepsy complications in the two groups were recorded.

Disease-related score: The Mini-Mental State Examination (MMSE), GCS and Barthel index were adopted to score the patients before and after treatment. MMSE covers time orientation, immediate memory, delayed memory, attention and calculation, visual space, language and place orientation, with a total score of 30 points. A score of 27-30 points indicates normal situation, and a score <27 indicates cognitive dysfunction [20]. GCS covers three aspects: Eyes opening, verbal response and motor response, with a score of 3-15 points. A lower GCS score indicates more severe consciousness disorder [21]. Barthel index evaluates the ability of living activities, with a total score of 100 points. A higher Barthel index suggests a stronger ability of living [22].

Inflammatory factors and stress indicators: Venous blood (6 mL) was sampled from each patient before and after therapy, followed by 10-min centrifugation (3,000 × g, 4°C) to separate serum. Then the levels of inflammatory factors (IL-6, IL-8, and TNF-α) and stress indicators (SOD and MDA), and neuron specific enolase (NSE) in the serum were determined by ELISA with kits from the British abcam company (ab178013, ab214030, ab181421, ab119520, ab287797, and ab217778) under instructions.

Statistical analyses

SPSS 21.0 was used for all statistical analyses. The counting data (utilization rate (%)) were analyzed using the chi-square test, and expressed as X^2. Measurement data in a normal distribution were expressed as Mean ± SD. The inter-group comparison was conducted using the independent t test, and intra-group comparison was conducted using the paired t test. P<0.05 suggested a significant difference.

Results

Patient information

According to comparison of baseline data between the two groups, the two groups were not significantly different in age, gender, cause of injury, type of injury, place of residence, ASA grade, GCS score, intracranial pressure, NIHSS score and past history of craniocerebral trauma (P>0.05), indicating the two groups were comparable (**Table 1**).

Comparison of curative effect between the two groups

Comparison of therapeutic effect between the two groups revealed no notable difference between cure rate, remarkably effective treatment rate, and effective treatment rate, but revealed a significantly higher total effective rate in the Obs group than that in the Con group (P<0.05, **Table 2**).

Incidence of complications

According to the comparison of the complications between the two groups, both groups suffered intracranial infection, pulmonary infection, hydrocephalus and epilepsy, and the Obs group showed a significantly lower total incidence of complications than that in the Con group (7.46% vs. 20.63%, P<0.05, **Table 3**).

Improvement of neurological function and living ability of patients

We evaluated the recovery of patients' consciousness and neurological function by MMSE score and GCS score, and evaluated the improvement of patients' living ability by Barthel index. According to the results, after treatment, MMSE score, GCS score and Barthel index of both groups increased significantly (all P< 0.05), with notably higher MMSE score, GCS score and Barthel index in the Obs group than those in the Con group and lower NSE in the

Table 1. Baseline data

	The observation group (n=67)	The control group (n=63)	X^2/t	P
Age (years)	37.84±14.18	36.94±16.04	0.339	0.735
Gender			0.246	0.620
Male	38 (56.72)	33 (52.38)		
Female	29 (43.28)	30 (47.62)		
Cause of injury			0.808	0.848
High-altitude falling	24 (35.82)	22 (34.92)		
Traffic accident	20 (29.85)	19 (30.16)		
Contusion	15 (22.39)	17 (26.98)		
Other	8 (11.94)	5 (7.94)		
Injury type			0.578	0.966
Cerebral contusion	25 (37.31)	26 (41.27)		
Epidural hematoma	18 (26.87)	16 (25.40)		
Intracranial injury	10 (14.93)	8 (12.70)		
Skull fracture	9 (13.43)	7 (11.11)		
Other	5 (7.46)	6 (9.52)		
Place of residence			0.974	0.324
Urban area	53 (79.10)	54 (85.71)		
Rural area	14 (20.90)	9 (14.29)		
ASA grading			0.393	0.531
Grade II	45 (67.16)	39 (61.90)		
Grade III	22 (32.84)	24 (38.10)		
GCS score	6.13±0.98	6.35±0.79	1.404	0.163
Intracranial pressure (mmHg)	32.39±4.33	32.05±4.30	0.449	0.654
NIHSS score	32.30±4.10	31.43±4.53	1.149	0.253
Past history of craniocerebral trauma			0.278	0.598
Yes	13 (19.40)	10 (15.87)		
No	54 (80.60)	53 (84.13)		

Note: ASA grading: American society of Aneshesiologists physical status classification system; GCS score: Glasgow coma scale-score; NIHSS score: National Institute of Health stroke scale score.

Table 2. Curative effect on patients

	The observation group (n=67)	The control group (n=63)	X^2	P
Cured	22 (32.84)	15 (23.81)	1.299	0.254
Remarkably effective	36 (53.73)	30 (47.62)	0.485	0.486
Effective	7 (10.45)	9 (14.29)	0.443	0.506
Ineffective	2 (2.99)	9 (14.29)	5.363	0.021
Total effective rate	65 (97.01)	54 (85.71)		

Obs group than that in the Con group (P<0.05, **Figure 1**).

Changes of inflammatory levels in patients

According to the observation results, after treatment, the inflammatory factors (IL-6, IL-8 and TNF-α) in the two groups decreased significantly (P<0.05), with significantly lower levels of IL-6, IL-8 and TNF-α in the Obs group than those in the Con group (P<0.05, **Figure 2**).

Changes of stress response level in patients

After therapy, the level of SOD in both groups increased significantly (P<0.05) and the level of MDA decreased significantly (P<0.05), with a significantly higher SOD level and a significantly lower MDA level in the Obs group than those in the Con group (P<0.05, **Figure 3**).

Discussion

TBI is highly common in traffic accidents and construction accidents. With the rapid development of transportation, construction and other

Table 3. Incidence of complications

	The observation group (n=67)	The control group (n=63)	X^2	P
Intracranial infection	1 (1.49)	4 (6.35)		
Lung infection	2 (2.99)	3 (4.76)		
Hydrocephalus	1 (1.49)	3 (4.76)		
Epilepsy	1 (1.49)	3 (4.76)		
Total complication rate	5 (7.46)	13 (20.63)	4.723	0.030

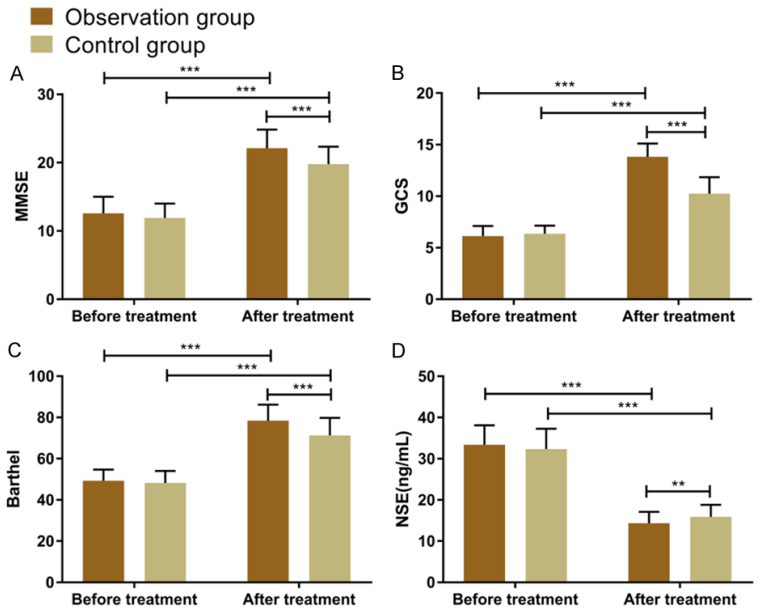

Figure 1. Improvement of neurological function and living ability of patients. A. After treatment, the MMSE scores of both groups increased significantly (P<0.001), with significantly higher MMSE scores in the observation group than that in the control group. B. After treatment, the GCS scores of both groups increased significantly (P<0.001), with significantly higher GCS scores in the observation group than that in the control group (P<0.001). C. After treatment, the Barthel index of both groups increased significantly (P<0.001), with a significantly higher Barthel index in observation group than that in the control group (P<0.001). D. After treatment, NSE of both groups decreased significantly (P<0.001), with a significantly lower NSE level in the observation group than that in the control group (P<0.001). Note: ***P<0.001.

industries, the incidence of craniocerebral trauma is gradually increasing [23]. Patients with severe TBI refer to severe patients who have been unconscious for more than 12 hours after trauma with a GCS score of 3-8 points. Because of the rapid progression of injury, the mortality and disability rate of severe TBI are extremely high [24]. Although even with the progress of medical technology, there are still different degrees of dysfunction after treatment, such as coma, aphasia and hemiplegia [25]. TBI is caused by the primary trauma, which will later result in secondary injury. The above-mentioned injury mechanisms will eventually give rise to the permanent loss of nerve cells in the injured area [26]. NSE exists in neurons and neuroendocrine cells. When neurons are damaged, NSE is rapidly released from the cytoplasm to the cerebrospinal fluid and then into the blood, resulting in the increase of serum NSE, which reflects the degree of neuronal damage. Therefore, NSE is considered to be a sign of nervous system injury [27]. After treatment, the NSE level in patients with GM-1 intervention decreased significantly, which also suggested that GM-1 could reduce neuronal apoptosis and improve brain injury.

At the current stage, medical treatment for severe TBI in clinical practice usually involves dehydration to reduce intracranial pressure and anti-infection, while surgical treatments involve hematoma removal and bone flap decompression, which can usually reduce the intracranial hypertension of patients and further alleviate the continuous damage of toxic and side metabolites to neurological function [27]. GM-1 is a substance extracted from the brains of pigs. It is a sugar sphingolipid containing sialic acid. As a component of the cell membrane, GM-1 has a strong affinity for nerve tissue. According to one study [28], GM-1 can protect the activities of various enzymes on the cell membrane, neutralize the toxicity of excitatory amino acids and eliminate free radicals, so as to alleviate the edema of nerve cells and the ischemia and hypoxia of brain tissue in the injured area of patients, and thus protect the nerve cells. Our study found that adjuvant therapy with GM-1 significantly improved the curative effect on patients, lowered the inci-

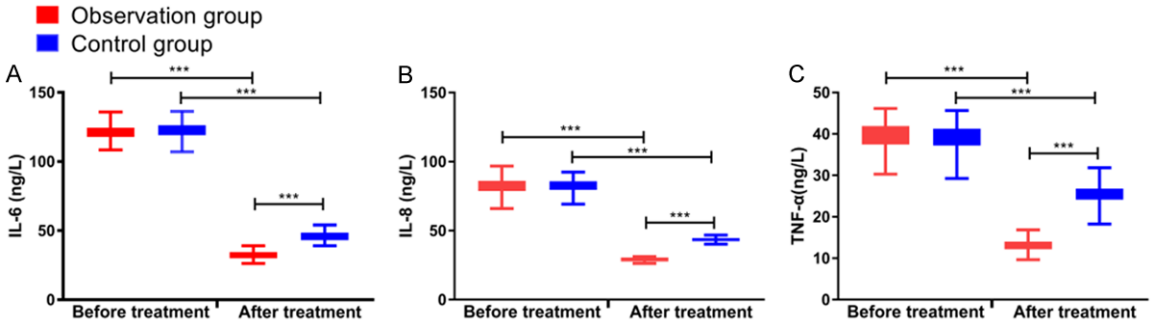

Figure 2. Changes of inflammatory levels in patients. A. After treatment, the IL-6 level in both groups decreased significantly (P<0.001), with a significantly lower IL-6 level in the observation group than that in the control group. B. After treatment, the IL-8 level in both groups decreased significantly (P<0.001), with a significantly lower IL-8 level in the observation group than that in the control group (P<0.001). C. After treatment, the TNF-α level in both groups decreased significantly (P<0.001), with a significantly lower TNF-α level in the observation group than that in the control group (P<0.001). Note: ***P<0.001.

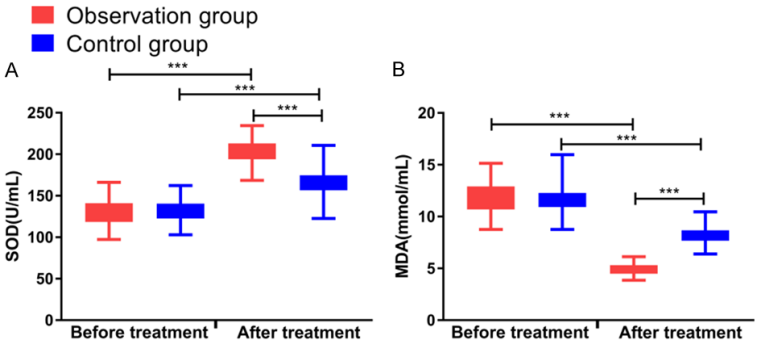

Figure 3. Changes of stress response levels in patients. A. After treatment, the SOD level in both groups increased significantly (P<0.001), with a significantly higher SOD level in the observation group than that in the control group. B. After treatment, the MDA level in both groups decreased significantly (P<0.001), with a significantly lower MDA level in the observation group than that in the control group (P<0.001). Note: ***P<0.001.

dence of related complications in patients, and contributed to significantly improved neurological function and living abilities to a great extent. The results may be attributed to the fact that GM-1 improved the curative effect on patients and their clinical signs by promoting the recovery of nerve cells and improving the nerve conduction of human body.

The main inducement of secondary nerve function injury of severe TBI includes inflammatory reactions. For patients with TBI, the cerebral vessels are compressed or stretched, resulting in vasospasm and insufficient local blood and oxygen supply, which gives rise to complications such as cerebral hernia, edema of peripheral organs and hypotension, and also ischemia and reperfusion [29]. Continuous activation of ischemia-reperfusion cusses the release of many inflammatory factors, resulting in inflammatory damage and further aggravation of TBI. In the process of inflammatory reaction, TNF-α is often activated first, which causes serious inflammatory damage of nerve function, and also results in the amplification of the inflammatory cascade, causing excessive inflammatory reactions in brain tissue. In this progress, the secretion of pro-inflammatory cytokines such as IL-6 is accelerated, which leads to the increase of permeability of vascular endothelial cells [30]. IL-8 is over-expressed in cases with hypoxia, ischemia-reperfusion or trauma. GM-1 can inhibit the secretion of related inflammatory factors and reduce the body's inflammatory response. The reason may be that GM-1 can directly enter the nerve centre, increase the local blood flow of brain tissue, repair damaged neurons, and reduce the inflammatory reaction, thus lowering the levels of inflammatory related factors. When there is craniocerebral trauma, the oxidative stress is intensified, with features of decreased SOD and increased MDA, which can affect the blood supply of organs, damage the kidney, lung and other important organs, or inhibit the immune function of the body and

increase the possibility of infection [31]. Finally, we also compared the stress response level of patients, and found a significantly better stress response level in patients treated with GM-1 than those not treated with GM-1. The release of inflammatory mediators will result in severe oxidative stress reaction. Excessive stress reactions will increase the risk of stress ulcers in patients, and is also likely to lead to secondary cerebral hemorrhage and aggravate the neurological impairment [32]. GM-1 can repair the damaged brain cells through the blood-brain barrier, thus alleviating the massive death of brain cells and tissues in the ischemic environment and reducing the stress reaction by alleviating the inflammatory reaction in the meantime. In the study of Chen et al. [33], lead-induced nerve damage in developing rats showed a significant decrease in learning and memory ability and severe oxidative stress, while GM-1 intervention reduced neuronal apoptosis and alleviated cognitive impairment by activating SIRT1/CREB/BDNF, which proved the protective effect of GM-1 on neurological function in animal experiments.

It can be seen that GM-1 has a satisfactory curative effect on severe TBI and can improve the injured neurological function of patients with it. However, the study still has some limitations. First of all, the research subjects of this study are patients with severe TBI, so whether the same effect can be acquired in patients with mild symptoms is still unclear. We hope that we can expand the research sample size in the future to support our research results. Secondly, this study only investigated the clinical data, so the mechanism of the specific influence of GM-1 needs further exploration by animal experiments. Finally, some studies have shown that GM-1 may cause some allergy in patients to develop Guillain-Barre syndrome. This is extremely rare [34], and we have not found any serious adverse reactions in the course of medication in this study. The innovation of this study is not only in the observation on the efficacy of GM-1 in the treatment of severe TBI patients, but also in the exploration in the changes of oxidative stress response in this process.

To sum up, for patients with severe TBI, adjuvant therapy with GM-1 can significantly promote the therapeutic effect and improve the nerve function and inflammatory reaction, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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