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Original Research Article

Co-administration of oxiracetam and monosialotetrahexosylganglioside for the treatment of patients with craniocerebral injury, and their effect on serum S100 proteins and neuron-specific enolase

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Abstract

Purpose: *To determine the efficacy of oxiracetam plus monosialotetrahexosylganglioside (GM1) in the treatment of craniocerebral injury, and its effect on serum S100 proteins and neuron-specific enolase (NSE).*
Methods: *A total of eighty patients with severe craniocerebral injury admitted to Shengli Oilfield Central Hospital between January 2020 and December 2021 were selected for the study, and assigned 1:1 to control group (GM1 only, 2 mL daily through intravenous drip) and study group (GM1, 2 mL daily through intravenous drip, in combination with oxiracetam, and 4 g dissolved in 100ml of saline daily through intravenous drip). The treatment duration was two months.*
Results: *Baseline patient characteristics were comparable between the two groups ($p > 0.05$). GM1 plus oxiracetam produced better restoration of cranial functions of patients after craniocerebral injury when compared with GM1 alone, as evidenced by the significantly lower S100 proteins and NSE levels of the study group than the corresponding parameters of the control group after 1, 2, 3, and 7 days of treatment ($p < 0.05$). More significant mitigation of inflammatory reactions was observed in patients co-administered GM1 and oxiracetam than in those who received GM1 only, as shown by the lower serum concentrations of inflammatory factors {(c-reactive protein (CRP), tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and neuropeptide Y (NPY)} in the study group as compared with the control group ($p < 0.05$). A few patients experienced minor adverse reactions such as gastrointestinal discomfort, nausea and vomiting, dizziness and headache, and rash during treatment ($p > 0.05$).*
Conclusion: *Co-administration of oxiracetam and GM1 is a viable strategy for the treatment of patients with craniocerebral injury, as it significantly lowers the levels of serum S100 proteins and NSE, mitigates inflammatory reactions, and ameliorates cerebral hemodynamics in patients. The combined therapy also has a good safety profile.*

Keywords: *Oxiracetam, Monosialotetrahexosylganglioside, Craniocerebral injury, Cerebral hemodynamics, inflammatory factors*

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INTRODUCTION

Craniocerebral injuries are one of the common diseases in neurosurgery and are the result of sudden accidents, such as traffic, falls and mining accidents, as well as natural disasters. It features high disability and mortality, and constitutes a worldwide public health and socioeconomic concern [1]. Studies have shown that serum S100 proteins and neuron-specific enolase (NSE) are specific serum markers of craniocerebral injuries, and they reflect the degree of craniocerebral injury in patients, demonstrating immense potential for clinical treatment and prognostic assessment of craniocerebral injury [2,3]. Currently, craniofacial injuries are managed by conventional therapeutic measures such as haemostasis, fluid replacement, and dehydration; however, the treatment outcomes are unsatisfactory. With the in-depth research on monosialotetrahexosylganglioside (GM1), it has been extensively recognized as a brain injury repair agent in the clinical treatment of severe craniocerebral injury [4].

Oxiracetam is a pro-intellectual drug used for mild-to-moderate vascular dementia, Alzheimer's disease, and memory and intellectual impairment due to traumatic brain injury. Nonetheless, oxiracetam plus GM1 has been sporadically studied in the treatment of severe craniocerebral injury. To this end, the present study investigates the efficacy of oxiracetam plus GM1 in the treatment of craniocerebral injuries.

METHODS

Patients and grouping

Eighty patients with severe craniocerebral injury admitted to Shengli Oilfield Central Hospital in the time frame of January 2020 to December 2021 were recruited and assigned to control group (treated with GM1), and study group (given GM1 plus oxiracetam) (with 40 patients in each group). The study procedures were reviewed and approved by the Ethics Committee of Shengli Oilfield Central Hospital (approval no. SO20190098), and was conducted as per the guidelines of Declaration of Helsinki [5].

Inclusion criteria

Individuals who were admitted to the hospital within 6 h after injury and underwent head CT examination, aged 15 - 80 years, had a clear history of head trauma and no other serious systemic comorbid injuries, and provided signed consent forms were included in the study.

Exclusion criteria

Individuals who had a history of tumor, heart, liver, lung, kidney, and other substantive pathologies and other neurological diseases, hematologic diseases and coagulation disorders, hypotension and shock, and extremely serious and unstable conditions were excluded from the study.

Treatments

All patients received conventional therapeutic measures. Symptomatic treatment measures such as the maintenance of ventilation, dehydration to lower intracranial pressure, nutrition of brain cells, protection of gastric mucosa, and maintenance of electrolyte balance were performed. Subsequently, blood gas analysis was performed and biochemical indices, coagulation, cardiac enzymes, and liver and kidney functions of the patients were determined [6,7].

Control group

On top of conventional treatment, the patients received 2mL of GM1 (Qilu Pharmaceutical Co. Ltd) through intravenous drip daily.

Study group

In the addition to the treatment administered to control group, the patients in the study group were treated with 4g of oxiracetam (1g, Shiyang Ouyi Pharmaceutical Co. Ltd, NMPA approval no. H20100040), which was dissolved in 100 mL of saline, via intravenous drip daily. The duration of treatment was 2 months.

Evaluation of parameters/outcomes

Patients' baseline information was promptly collected after admission. It comprised age, gender, Glasgow Coma Scale (GCS) score, time of onset, body mass index (BMI), disease type, and treatment modality. Four mL fasting peripheral venous blood was obtained before treatment and after 1, 2, 3, and 7 days of treatment, stored using additive-free vacuum blood collection tubes (red cap tubes), and centrifuged at 3000 rpm for 10 min to obtain the serum, which was then stored at -20 ^{o}C. Serum S100 proteins and NSE concentrations were determined using electrochemiluminescence (Roche), and the NSE and S100 kits were also provided by Roche. C-reactive protein (CRP) and neuropeptide Y (NPY) levels were determined using radioimmunoassay, while tumor necrosis

factor-α (TNF-α), and interleukin-6 (IL-6) levels were determined using enzyme-linked immunosorbent assay.

Efficacy

Patients were cured if their clinical symptoms disappeared, and could take care of themselves completely. Treatment was regarded as *markedly effective* if their clinical symptoms were mitigated significantly, and the patients could basically take care of themselves; *effective* if their clinical symptoms were attenuated, and the patients could partially take care of themselves; and *ineffective* if their clinical symptoms and all signs showed no improvement or worsened.

Total effectiveness of treatment was computed as in Eq 1.

$$T_e = \{(N_c+N_m+N_e)/T_n\}100 \quad \ldots\ldots\ldots (1)$$

where T_e represents the total effectiveness of treatment, N_c represents the number of cured cases, N_m represents the number of markedly effective cases, N_e represents the number of effective cases, and T_n represents the total number of cases.

Cerebral hemodynamic indices

The cerebral hemodynamic indices of the patients were measured using the cerebral circulation dynamics test, including pulse index (PI), systolic peak flow velocity (Vs), and mean velocity (Vm).

Incidence of adverse drug reactions

The adverse drug reactions that occurred during the treatment were recorded in detail and the incidence of adverse reactions calculated.

Statistical analysis

The data analysis was done using SPSS22.0, while graphics rendering was plotted by using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Counting data are expressed as n (%), and were examined using the chi-square test, while measurement data are expressed as mean ± standard deviation (SD), and were compared using t-test. $P < 0.05$ was set as the cut-off value for statistically significant difference.

RESULTS

Patient baseline information

The baseline characteristics were generally balanced between the two groups in terms of age, gender, GCS scores, disease type, and BMI ($p > 0.05$; Table 1).

Levels of S100 proteins

The levels of S100 proteins in the study group were significantly lower than corresponding parameters in the control group after 1, 2, 3, and 7 days of treatment ($p < 0.05$; Figure 1).

Table 1: Comparison of general information between the two groups of patients (n = 40)

Indicators	Control group	Study group	χ^2/t	*P*-value
Age (years)	39.47 ± 4.05	40.22 ± 4.18	0.815	0.418
Gender			0.251	0.617
Male	28 (70)	30 (75)		
Female	12 (30)	10 (25)		
GCS scores	6.52 ± 2.03	6.45 ± 2.11	0.151	0.880
Time of onset (h)	4.59 ± 1.16	4.65 ± 1.13	0.234	0.815
BMI (kg/m^2)	23.30 ± 1.92	23.54 ± 1.87	0.566	0.573
Disease type				
Cerebral contusion	35 (87.5)	37 (92.5)	0.556	0.456
Intracranial hematoma	15 (37.5)	12 (30)	0.503	0.478
Epidural hematoma	11 (27.5)	10 (25)	0.065	0.799
Subdural hematoma	6 (15)	8 (20)	0.346	0.556
Treatment methods			0.052	0.820
Craniotomy	24 (60)	23 (57.5)		
Non-surgery	16 (40)	17 (42.5)		

The S100 proteins levels before treatment, after 1, 2, 3, and 7 days of treatment in the control group were: 7.95 ± 0.16, 8.74 ± 3.28, 8.51 ± 4.04, 6.63 ± 3.12, and 3.58 ± 2.09, respectively.

S100 proteins levels before treatment, after 1, 2, 3, and 7 days of treatment in the study group were 7.91 ± 0.13, 6.18 ± 2.27, 4.95 ± 1.57, 3.11 ± 0.80, and 2.01 ± 0.77, respectively.

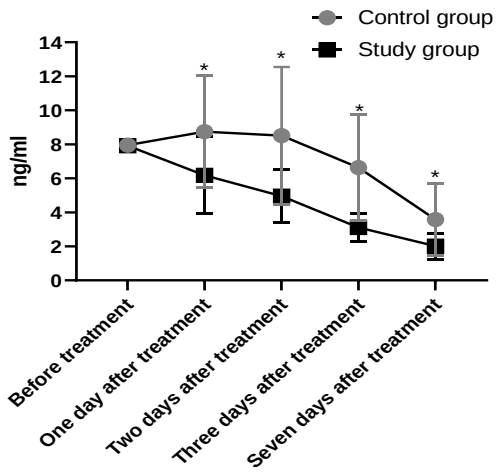

Figure 1: Comparison of changes in S100 protein levels between the two groups ($\bar{x}$±s). *From left to right indicates significant differences in S100 proteins levels between the two groups of patients after 1, 2, 3, and 7 days of treatment (t=4.538, 5.808, 7.728, and 4.984, respectively; all $p < 0.001$)

NSE levels

Significantly lower NSE levels were observed in the study group compared to the control group after 1, 2, 3, and 7 days of treatment ($p < 0.05$; Figure 2).

The NSE levels before treatment, after 1, 2, 3, and 7 days of treatment in the control group were 24.13 ± 6.33, 28.74 ± 6.25, 25.80 ± 5.21, 20.66 ± 3.81 and 19.05 ± 3.52, respectively. The NSE levels before treatment, after 1, 2, 3, and 7 days of treatment in the study group were 23.82 ± 6.26, 24.94 ± 4.67, 20.03 ± 4.06, 15.21 ± 2.49, 12.83 ± 2.75, respectively.

Levels of inflammatory factors

More significant mitigation of the inflammatory reactions was observed in the patients with co-administration of GM1 and oxiracetam than in those with GM1 only, evinced by the lower serum concentrations of CRP, TNF-α, IL-6, and NPY in the study group as compared with the control group ($p < 0.05$) (Table 2).

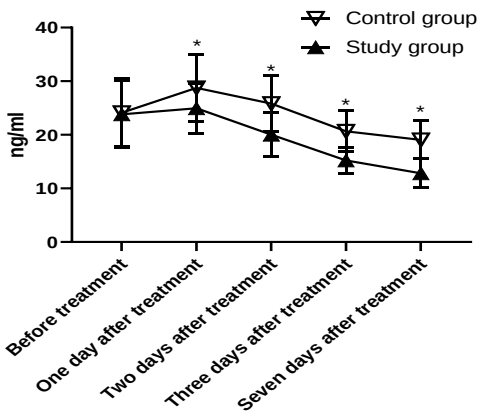

Figure 2: Comparison of NSE levels between the two groups (mean ± SD). *From left to right indicates significant differences in NSE levels between the two groups after 1d, 2d, 3d, and 7 days of treatment (t = 3.444, 6.177, 8.467, and 9.846, respectively; all $p < 0.001$)

Clinical efficacy/effectiveness

The study group exhibited significantly higher efficacy as compared to the control group ($p < 0.05$; Figure 3).

The control group had 10 cases of cured, 10 cases of markedly effective, 9 cases of effective, and 11 cases of ineffective, with a total of 29 cases of effective.

The study group had 19 cases of cured, 10 cases of markedly effective, 8 cases of effective, and 3 cases of ineffective, with a total of 37 cases of effective.

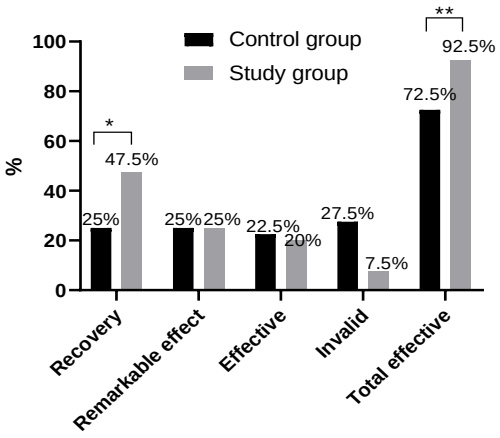

Figure 3: Comparison of the clinical efficacy between the two groups (%). *Significant difference in the cured rate between the two groups ($X^2 = 4.381$, $p = 0.036$); **significant difference in the total effectiveness between the two groups ($X^2 = 5.541$, $p = 0.019$)

Table 2: Comparison of levels of inflammatory factors between the two groups (mean ± SD)

Inflammatory factors		Control group (n=40)	Study group (n=40)	t/P
CRP (mg/L)	Before treatment	35.46 ± 2.41	35.71 ± 2.39	
	After treatment	15.03 ± 2.15	9.82 ± 2.11	10.938/<0.001
TNF-α (ng/L)	Before treatment	4.01 ± 0.20	4.04 ± 0.22	
	After treatment	1.68 ± 0.14	1.37 ± 0.12	10.633/<0.001
IL-6 (ng/L)	Before treatment	50.16 ± 3.74	50.04 ± 3.68	
	After treatment	30.64 ± 7.86	20.23 ± 7.19	6.181/<0.001
NPY (ng/L)	Before treatment	156.85 ± 11.02	156.93 ± 11.10	
	After treatment	75.62 ± 5.37	63.71 ± 5.76	9.565/<0.001

Table 3: Comparison of cerebral hemodynamic indices in the two groups (mean ± SD)

Cerebral hemodynamic index		Control group (n=40)	Study group (n=40)	t/P
PI	Before treatment	0.87 ± 0.28	0.86 ± 0.31	
	After treatment	0.83 ± 0.27	0.68 ± 0.25	2.578/0.012
Vs (cm/s)	Before treatment	82.94 ± 4.16	83.12 ± 4.23	
	After treatment	85.02 ± 3.05	88.03 ± 5.36	3.087/0.003
Vm (cm/s)	Before treatment	44.75 ± 2.33	44.86 ± 2.41	
	After treatment	46.61 ± 4.74	49.52 ± 5.01	2.668/0.009

Table 4: Comparison of the incidence of adverse reactions between the two groups {n (%)}

Group (n = 50)	Gastrointestinal discomfort	Nausea and vomiting	Dizziness and headache	Rash
Control	1 (2)	2 (4)	2 (4)	0 (0)
Study	2 (4)	2 (4)	3 (6)	1 (2)
χ^2	0.346	0.000	0.213	1.013
***P*-value**	0.556	1.000	0.644	0.314

Cerebral hemodynamics

After treatment, both groups had marked improvement in terms of PI, Vs, and Vm, in which the study group had a significantly lower PI and higher Vs and Vm than the control group ($p < 0.05$; Table 3).

Incidence of adverse reactions

A few patients experienced minor adverse responses such as gastrointestinal discomfort, nausea and vomiting, dizziness and headache, and rash during treatment, but the difference did not reach the statistical standard ($p > 0.05$) (Table 4).

DISCUSSION

Cranio-cerebral injuries are extremely common in neurosurgery, second only to limb fractures, and account for 10-15% of systemic injuries [8-10]. In recent years, frequent road traffic accidents in construction and mining, coupled with natural disasters such as earthquakes and mudslides, lead to an increasing incidence of cranio-cerebral injuries in China. In particular, the high disability and mortality from severe craniocerebral injury pose a heavy medical burden to society and families.

GM1 is a common clinical brain cell repair and protection agent. It easily enters the central nervous system via the damaged blood-brain barrier, integrates into brain cell membranes, and increases local brain tissue blood flow, thus accelerating the repair of brain cell damage, inhibiting the production of oxygen free radicals, and reducing lipid peroxidation reactions. Moreover, it enhances brain cell membrane activity, promotes nitric oxide synthesis, alleviates vascular endothelial cell injury, and suppresses brain cell apoptosis [11,12].

Oxiracetam reduces cerebral vascular resistance, improves microcirculation, increases blood flow, and alleviates ischemia-reperfusion injury by inhibiting platelet aggregation, thereby ameliorating neurotrophic metabolism and restoring damaged cerebral cortex function [13]. It has been reported that an effective synergistic effect can be achieved by combining the two drugs in the treatment of severe craniocerebral injury [14,15]. In the present study, significantly lower S100 proteins and NSE levels were seen in the study group versus the control group after

1, 2, 3, and 7 days of treatment. S100 protein is mainly distributed in the central and peripheral nervous systems, accounting for 95% of brain tissue, and is metabolized by the kidneys with a half-life of 2 h. Usually, the level of S100 proteins rises rapidly within 6 h after craniocerebral injury and decreases to normal range within 12 h after injury in most patients.

In craniocerebral injury, damage to neural tissue and disruption of the glial cells and blood-brain barrier substantially elevate the concentration of S100 proteins in serum and cerebrospinal fluid. As NSE levels in serum increased due to neuronal cell damage and increased blood-brain barrier permeability secondary to craniocerebral injury, NSE was positively correlated with the degree of neuronal injury, thereby confirming that co-administration of GM1 and oxiracetam was more effective in regulating the levels of S100 proteins and NSE in severe craniocerebral injury than monotherapy. After treatment, both groups witnessed a significant decline in the inflammatory response, with lower levels of CRP, TNF-α, IL-6, and NPY in the study group. The lower levels of inflammatory factors in the control group when compared with those before treatment indicated excellent inhibition of the inflammatory response in patients with severe craniocerebral injury by GM1, which was significantly enhanced by the combination of oxiracetam.

Additionally, the higher effectiveness of the study group is corroborated by previous evidence [16,17]. Oxiracetam penetrates the blood-brain barrier, excites cholinergic neurons distributed in the brainstem, and induces translocation of acetylcholine in the cerebral cortex and hippocampus. It further promotes the synthesis of phosphatidylcholine and phosphatidylethanolamine and enhances brain phosphodiesterase A1 activity, thereby inhibiting the breakdown of brain phospholipids and subsequently increasing energy storage in the brain and promoting RNA and protein synthesis. In addition, oxiracetam activates neurotrophic factors, promotes nerve axon regeneration, and alleviates clinical symptoms such as memory loss, consciousness, and mental impairment in patients with craniocerebral injury. After treatment, both groups showed significant improvements in PI, Vs, and Vm, with the study group displaying significantly lower PI and higher Vs and Vm than the control group, thus suggesting that both drugs can regulate cerebral hemodynamics in patients with severe craniocerebral injury, with better effects when the combination therapy was applied. The safety profiles in the two groups were similar, indicating that the conjunct therapy was safe and effective [18].

Limitations of the study

This study has the following limitations. First, given the time frame of the trial, a small size of participants was included. Second, few indices were observed, an issue that could limit generalizability. Third, the follow-up time in this trial was short.

CONCLUSION

Oxiracetam, when combined with GM1 is a promising approach to the treatment of patients with craniocerebral injury. It lowers the levels of serum S100 proteins, NSE, and inflammatory factors, and improves cerebral hemodynamics in patients. Moreover, it has a good safety profile. However, further clinical trials are recommended to validate these findings.

DECLARATIONS

Acknowledgements

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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

The authors 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 them.

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