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Original Article

Effect of enteral nutrition nursing combined with parenteral nutrition nursing intervention on nutritional status and immune function in patients with severe craniocerebral injury

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Abstract: Objective: To explore the effect of enteral nutrition nursing combined with parenteral nutrition nursing intervention on nutritional status and immune function in patients with severe craniocerebral injury. Methods: A prospective study was conducted on 82 patients with severe craniocerebral injury, and they were divided into the observation group and control group according to a random number table, with 41 cases in each group. Patients in the observation group were treated with enteral nutrition (EN) combined with parenteral nutrition (PN) nursing plan, while those in the control group received EN nursing intervention alone. The indicators of nutritional status and peripheral blood regulatory T (Treg) cells were detected before treatment and 14 days after treatment. The complications during treatment and Glasgow outcome scale (GOS) 30 days after treatment were recorded. Results: After treatment, the hemoglobin (Hb), serum total protein (TP), serum albumin (Alb) and serum prealbumin (Prealb) in the observation group were significantly higher than those in the control group ($P<0.01$ or $P<0.001$). The CD3+, CD4+ and CD4+/CD8+ ratio after treatment increased in both groups compared with those before treatment, while CD8+ decreased in both groups (all $P<0.001$). The CD3+, CD4+ and CD4+/CD8+ ratio in the observation group were higher than those in the control group, but CD8+ in the observation group was lower than that in the control group (all $P<0.001$). The differences of CD3+, CD4+, CD8+ and CD4+/CD8+ ratio before and after treatment in the observation group were higher than those in the control group (all $P<0.001$). This indicated that during treatment, the incidence of adverse reactions in the observation group was lower than that in the control group ($P=0.046$). After treatment, GOS in the observation group was higher than that in the control group ($P=0.027$). Conclusion: Enteral nutrition nursing combined with parenteral nutrition nursing intervention in patients with severe craniocerebral injury can improve the nutritional status of patients, contribute to the recovery of cellular immune function, reduce complications and promote the repair of neurological function.

Keywords: Enteral nutrition, parenteral nutrition, severe craniocerebral injury, nutritional status, immune function

Introduction

Craniocerebral injury is mainly caused by direct or indirect trauma on the head. Patients who remain in a coma for 6 hours after the injury or slip back into a coma are clinically referred to as having severe craniocer ebral injury [1, 2]. Clinical studies have indicated that with the high incidence of traffic accidents, construction site accidents and falling object injuries, the incidence of craniocerebral injury has also increased [3, 4]. Further studies have found that the disability rate and fatality rate of patients with severe craniocerebral injury are higher than other types of craniocerebral injury [5]. A study found that due to the systemic stress response in critically ill patients, the body is often in a negative nitrogen balance, resulting in malnutrition in more than 80% of critically ill patients [6]. Studies have shown that the nutritional status of the patients is an important factor affecting the treatment plan and prognosis of the disease [7]. Therefore, early application of nutritional support therapy

in patients with severe craniocerebral injury has a positive impact on the improvement of patients' prognosis [8]. The persistence of malnutrition in patients with severe craniocerebral injury is not conducive to the recovery of patients' immune function, and can easily lead to the damage to the immune function [9].

In clinical practice, EN and PN are commonly used in nutrition support. EN is a nutritional support method that provides nutrients required by metabolism through the gastrointestinal tract, and PN is intravenous nutrition serving as nutritional support before and after surgery, as well as in critically ill patients. Although the use of EN alone in critically ill patients can guarantee the nutritional supply and protect the gastrointestinal immune function [10], there can be intolerance of enteral nutrition [11]. PN supplementation for critically ill patients can help the intestinal tract rest and promote the recovery of intestinal function [12], but nutritional support by PN alone cannot meet the requirement of nutritional supplementation [13]. Studies have found that EN combined with PN in the treatment of critically ill patients with cancer can improve their electrolyte disturbance, reduce intestinal nutrition intolerance, maintain the balance of potential of hydrogen (pH) and osmotic pressure, and promote the recovery of immune function [14]. Previous studies have shown that EN combined with PN can significantly improve the nutritional status in patients with severe craniocerebral injury. In recent years, studies have indicated that the intestinal tract is also an immune organ in addition to the absorption of nutrients, which may play a positive role in the immune adjustment of human body [11]. At present, there has still been no clear conclusion on whether the application of EN combined with PN has an effect on the regulation of immune function in patients with severe craniocerebral injury [10]. Based on this, this study investigated the effect of EN combined with PN on nutritional status and immune function in patients with severe craniocerebral injury. The report is as follows.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of The Second Hospital of Jilin University. This study recruited 82 patients with severe craniocerebral injury who were treated in the intensive care unit (ICU) of The Second Hospital of Jilin University from March 2017 to December 2019. They were divided into the observation group and control group in accordance with a random number table method, with 41 cases in each group. Patients in the observation group were treated with EN combined with PN nursing, while those in the control group received EN nursing alone. All patients were 18-75 years old, with an average age of 64.5±6.0 years old. The family members of the patients included in this study signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria: Patients met the diagnostic criteria of the Neurological Injury and Repair Branch of the Chinese Neuroscience Society in 2016 for patients with severe craniocerebral injury [15]; computerized tomography examination was performed within 6 hours after the craniocerebral injury to confirm the diagnosis; the Glasgow coma scale (GCS) was within 8 points; patients were required to be hospitalized for nutrition support for more than 2 weeks.

Exclusion criteria: Patients with severe heart and lung disease, hepatic and renal insufficiency, previous history of brain injury or trauma, or other system damage were excluded from the study; female patients in pregnancy or lactation period were excluded from the study.

Methods

Patients in both groups were routinely treated for anti-infection, dehydration, hemostasis and sobriety according to the severity of their condition. Patients in the control group were given EN on the basis of routine treatment: Enteral nutritional suspension (TPF, Nutricia pharmaceutical Co., Ltd., China) was infused through a nasogastric feeding tube and power pump. The basal energy expenditure (BEE) was calculated by the Harris-Benedict (HB) Equation, and the resting energy expenditure (REE) was calculated by the Clifton Equation. The EN was infused with 50% of REE on the first day, and there was no adverse reaction after the infusion. On the second day, EN was administered with 100% of REE and the infusion lasted for 20 hours. The nutrition was stopped for a rest period of 4 hours to rest the gastrointestinal tract.

Patients in the observation group were given EN combined with PN nutrition support nursing intervention: PN was applied within 72 hours upon admission by routine intravenous injection. Amino acid-fat emulsion (17%) and glucose (11%) injection (Kabiven, Huarui pharmaceutical Co., LTD., China) was pumped through the central venous catheter with an infusion pump. The pump speed was 120 mL/h, and the daily intake of calories was about 8 kJ. There were no feeding contraindications after 72 hours. Then the EN nutrition support intervention was conducted in the observation group, which was the same as the control group. The duration of nutrition support in the two groups was 18.9±4.7 days.

Outcome measures

Nutrition indicators: Three tubes of venous blood were extracted from the patients on the early morning of admission and 14 days after treatment, with 5 mL blood in each tube. The Hb, TP, Alb and Prealb were detected by a full-automatic biochemical analyzer (Beckman Coulter, USA).

Detection of peripheral blood Treg cells: 5 mL venous blood was extracted from all patients on the early morning of admission and 14 days after treatment. After anticoagulating with heparin, peripheral blood mononuclear cells were isolated by lymphocyte separation medium (Axis-shield, Norway). The cells were diluted with RPMI-1640 medium containing 10% fetal bovine serum (Guangzhou Dingguo Biotechnology Co., Ltd., China) at a cell concentration of 1×10^6/mL. Then, 200 μL of cell suspension was drawn into an EP tube, 20 μL of anti-CD3-FITC, anti-CD4-PE-A and anti-CD8-PC5.5A monoclonal antibodies (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., China) were added into the tube, respectively. The isotype control antibody was IgG1-FITC. The suspension was mixed and incubated in the dark for about 25-30 mins. Then the suspension was washed twice with phosphate buffer solution (PBS) and resuspended with 0.5 mL of PBS. After mixing, the peripheral blood Treg cells were detected by FACSCanto II flow cytometry (BD, USA).

The incidence of adverse reactions during nutritional support therapy: The adverse reactions included vomiting, diarrhea, abdominal distension, constipation, gastrointestinal bleeding, lung infections, etc. If multiple complications occurred in the same patient, the corresponding types of complications were counted.

Thirty days after treatment, GOS of the patients was assessed to evaluate the neurological function with a total of 5 points, of which 1 indicated death, 2 indicated in a vegetative state, 3 indicated severe disability, 4 indicated mild disability and 5 indicated good recovery and returning to a normal life. Patients were discharged after treatment and GOS was assessed by outpatient services or telephone follow-up.

Statistical analysis

All data were analyzed by SPSS 17.0 statistical software. The continuous variables were expressed as mean ± standard deviation ($\bar{x}$ ± sd), independent sample t-test was used for the data conforming to normal distribution and homogeneity of variance, and paired t-test was used for the comparison before and after treatment. The count data were described as percentage (%), and Pearson chi-square test was applied. Rank-sum test was applied to the ranked data. $P<0.05$ was considered statistically significant.

Results

Comparison of the general information and baseline data

There was no significant difference between the two groups in gender, age, GCS, cause of injury, type of craniocerebral injury or BMI (all $P>0.05$). See **Table 1**.

Comparison of the nutritional status

Before treatment, there was no significant difference in Hb, TP, Alb and Prealb between the two groups. After treatment, the Hb, TP, Alb and Prealb in the observation group were significantly higher than those in the control group ($P<0.01$ or $P<0.001$). See **Table 2**.

Comparison of peripheral blood Treg cell subsets before and after treatment

There was no significant difference between the two groups before treatment in CD3+,

Table 1. Comparison of general information and baseline data ($\bar{x}$ ± sd, n)

Items	Observation group (n=41)	Control group (n=41)	χ^2/t	P
Gender (Male:Female)	24:17	26:15	0.205	0.651
Age (year)	64.7±6.6	64.3±5.4	0.291	0.772
GCS on admission	5.67±2.21	5.42±2.39	0.582	0.599
Causes of injury			0.218	0.897
Traffic accident injury	28	26		
Blow injury	7	8		
Fall injury	6	7		
Types of craniocerebral injury			0.049	0.825
Open type	20	19		
Closed type	21	22		
BMI (kg/m^2)	25.21±3.62	24.82±3.54	0.412	0.684

Note: GCS: Glasgow coma scale; BMI: body mass index.

Table 2. Comparison of nutritional status ($\bar{x}$ ± sd)

	Observation group	Control group	t	P
Hb (g/L)				
Before treatment	114.28±12.05	115.28±11.97	0.666	0.508
After treatment	127.38±12.28	119.23±11.23	11.230	<0.001
T	4.293	3.892		
P	<0.001	<0.001		
TP (g/L)				
Before treatment	59.63±5.76	59.22±5.29	0.170	0.866
After treatment	64.58±6.12	61.23±5.89	2.579	0.008
T	3.656	2.783		
P	<0.001	0.012		
Alb (g/L)				
Before treatment	32.87±4.12	33.01±4.21	0.471	0.640
After treatment	36.87±4.78	34.91±3.48	3.221	0.003
T	3.682	2.923		
P	<0.001	0.002		
Prealb (g/L)				
Before treatment	0.24±0.05	0.23±0.06	0.589	0.573
After treatment	0.27±0.05	0.24±0.05	3.452	0.001
T	3.201	0.589		
P	0.008	0.592		

Note: Hb: hemoglobin; TP: total protein; Alb: albumin; Prealb: prealbumin.

CD4+, CD8+ and CD4+/CD8+ ratio (all P> 0.05). The CD3+, CD4+ and CD4+/CD8+ ratio 14 days after treatment increased in both groups compared with those before treatment, but CD8+ level decreased in both groups (all P<0.001). After treatment, the CD3+, CD4+ and CD4+/CD8+ ratio in the observation group were higher than those in the control group, but CD8+ level in the observation group was lower than that in the control group (all P<0.001). The difference in CD3+, CD4+, CD8+ and CD4+/CD8+ ratio before and after treatment in the observation group were higher than those in the control group (all P<0.001). See **Table 3** and **Figure 1**.

Comparison of incidence of adverse reactions during treatment

The incidence of adverse reactions such as vomiting, diarrhea, abdominal distension, constipation, gastrointestinal bleeding and lung infection in the observation group was lower than that in the control group (P<0.05). See **Table 4**.

Comparison of GOS 30 days after treatment between the two groups

After treatment, the average score of GOS in the observation group was 3.42±1.71, which was higher than the result of 2.43±1.52 in the control group (P<0.05). See **Table 5**.

Discussion

With the increasing incidence of severe craniocerebral injury, as well as its high disability rate and fatality rate, how to actively and effectively treat the disease and improve the prognosis has become a new research interest. Studies have found that 80% of critically ill patients suffer from malnutrition [6]. Patients with craniocerebral injury present with unconsciousness and cannot resume normal eating, meanwhile, their

Table 3. Comparison of peripheral blood Treg cell subsets before and after the treatment ($\bar{x} \pm sd$)

	Observation group	Control group	t	P
CD3+ (%)				
Before treatment	65.32±3.86	65.48±3.92	0.196	0.845
After treatment	73.34±4.61	69.07±4.23	4.361	<0.001
T	8.541	3.986		
P	<0.001	<0.001		
Difference before and after treatment	8.02±0.75	3.59±0.31	68.460	<0.001
CD4+ (%)				
Before treatment	32.84±3.16	32.86±3.12	0.028	0.978
After treatment	42.56±3.84	38.42±3.34	5.203	<0.001
T	12.521	7.789		
P	<0.001	<0.001		
Difference before and after treatment	9.72±0.68	5.57±0.22	37.079	<0.001
CD8+ (%)				
Before treatment	28.15±2.74	27.86±2.58	0.498	0.620
After treatment	21.51±1.86	24.35±2.31	6.118	<0.001
T	12.840	6.480		
P	<0.001	<0.001		
Difference before and after treatment	6.64±0.88	3.50±0.26	21.797	<0.001
CD4+/CD8+ ratio (%)				
Before treatment	0.18±0.01	0.19±0.01	0.575	0.567
After treatment	1.98±0.01	1.58±0.01	165.821	<0.001
T	122.203	653.421		
P	<0.001	<0.001		
Difference before and after treatment	0.81±0.01	0.40±0.02	139.103	<0.001

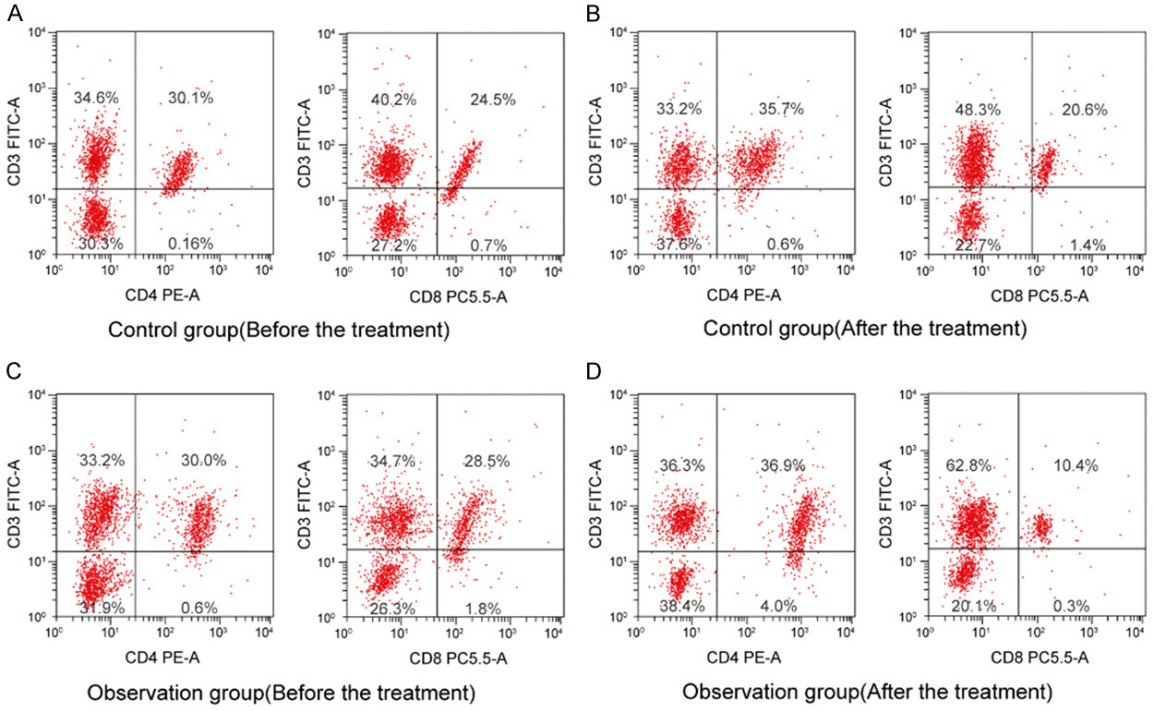

Figure 1. Comparison of flow cytometry scatter plot of CD3, CD4 and CD8 before and after treatment. A. The distribution of peripheral blood Treg cell subsets before treatment in the control group; B. The distribution of peripheral blood Treg cell subsets after treatment in the control group; C. The distribution of peripheral blood Treg cell subsets before treatment in the observation group; D. The distribution of peripheral blood Treg cell subsets after treatment in the observation group.

Table 4. Comparison of incidence of adverse reactions between two groups (n, %)

Adverse reactions	Observation group (n=41)	Control group (n=41)	X^2	P
Diarrhea	1 (2.44%)	3 (7.32%)	0.263	0.608
Vomiting	0 (0.00%)	1 (2.44%)	0.000	1.000
Abdominal distension	3 (7.32%)	3 (7.32%)	0.000	1.000
Constipation	1 (2.44%)	3 (7.32%)	0.263	0.608
Gastrointestinal bleeding	1 (2.44%)	2 (2.44%)	0.000	1.000
Lung infection	1 (2.44%)	3 (7.32%)	0.263	0.608
Total	7 (17.07%)	15 (36.58%)	3.976	0.046

Table 5. Comparison of GOS after the treatment between the two groups

Items	Observation group (n, %)	Control group (n, %)	Z/t	P
GOS (score)			2.207	0.027
1	9	13		
2	3	10		
3	9	5		
4	6	8		
5	14	5		
Average score	3.42±1.71	2.43±1.52	2.344	0.027

Note: GOS: Glasgow outcome scale.

bodies are in a stress state manifesting as high consumption. Therefore, the disease may progress to hypoproteinemia and immune function decline, which makes the patients susceptible to infection and increased fatality rate [16]. In 2017, the European Society of Intensive Care Medicine pointed out in the guidelines that critically ill patients should receive nutritional support within 24 hours [8]. Hence, nutritional support is particularly important for patients with severe craniocerebral injury, and the detection of nutritional indicators in critically ill patients is important for observation of the disease severity and prognosis. Clinical studies have also shown that early application of EN nutrition support can significantly improve the prognosis of critically ill patients with cancer and craniocerebral injury [17, 18]. In this study, the EN and PN were combined together to treat patients with severe craniocerebral injury. The combined use can improve the nutritional status of the patients, the improvement of hemoglobin, serum albumin, total protein and serum prealbumin by combination therapy was higher than that with EN alone. In recent years, studies have indicated that patients treated with the EN often suffer from diarrhea symptoms, which are related to intestinal intolerance after nutritional support [19]. Therefore, some studies have combined the use of EN and PN, which not only meets the nutritional requirements of the body, but also enables the maintenance of the function and structure of the gastrointestinal tract. In addition, it is conducive to self-repair of the nervous system [8]. In this study, the combined use of EN and PN lead to a lower incidence of complications, which might be related to the fact that the rational use of EN and PN contributed to the recovery of intestinal function and immune function.

Previous studies have found that Treg cells are important in the immune system and play an important role in the body's immunity. The number and function of Treg cells are abnormally expressed when the immune system is impaired [20, 21]. Studies have found that the expression of CD4+ Treg cells in the peripheral blood of healthy people can reach 5-15% [22, 23]. CD4+ can assist B cells to produce antibodies and is the most important cell in the regulation of the immune system [24]. Due to the dysfunction of autonomic nerve regulation, the systemic stress response and the increment of nutrient consumption and metabolic rate in patients with severe craniocerebral injury, the immune functions can be rapidly suppressed. Among them, the cellular immune ex-

pression is the most affected, mainly centering on the decrease of CD4+ and the imbalance of CD4+/CD8+ ratio [25]. In this study, the expression of CD3+ and CD4+ decreased, but the expression of CD8+ increased in patients with severe craniocerebral injury before treatment. After treatment, the expression of CD3+ and CD4+ increased, but the expression of CD8+ decreased in both groups, and the improvement was more obvious in the observation group. The reason may be that the combined use of EN and PN nutritional support can improve nutritional status, reduce complications and effectively restore immune function.

GOS can be used to evaluate the neurological function in patients with severe craniocerebral injury, and it has been widely used in clinical practice because of its simple and practical characteristics [26]. Early rational use of nutritional support therapy can improve patients' immune function, reduce the inflammatory response and promote nerve repair [27]. It was found in this study that the combined use of EN and PN in the observation group could improve the nutritional status and immune function. The GOS in the observation group was higher than that in the control group, which was consistent with the above study results, indicating that the application of EN combined with PN could improve the prognosis in patients with severe craniocerebral injury.

The sample size of this study was small and it was only conducted in a single center. It is necessary to further expand the study sample size with multi-center cooperation and conduct an in-depth study on the relevant mechanisms. Moreover, the observation time was relatively short in this study, so it is necessary to increase the observation time to explore the long-term recovery in the two groups after treatment.

To sum up, enteral nutrition combined with parenteral nutrition nursing intervention in patients with severe craniocerebral injury can improve the nutritional status of patients, contribute to the recovery of cellular immune function, reduce complications and promote the repair of neurological function.

Disclosure of conflict of interest

None.

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