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Original Article

The effect of early enteral nutrition combined with anti-infection intervention on gut bacteria translocation-related infections in patients with severe traumatic brain injury

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Abstract: Objective: To investigate the effect of early enteral nutrition combined with anti-infection intervention on gut bacteria translocation-related infections in patients with severe traumatic brain injury (sTBI). Methods: One hundred and two patients with sTBI were randomly divided into two groups: the patients in one group received routine care after their operations (the control group, n=51) and the other group received enteral nutrition support combined with anti-infection strategies from the first day after their operations (the observation group, n=51). Then the patients' infected tissues were collected, and the pathogenic strains were isolated, inoculated, and cultured. The bacterial strains were identified, and the patterns of the infected strains were recorded. The incidence and site of the infections, the proportion of T-lymphocyte subsets changed, the patients' nutrition level changes after the intervention, the concentrations of the serum inflammatory factors, and the complications were compared between the two groups. Results: The infection rate in the observation group was significantly lower than the rate in the control group (P=0.013). For both groups, gram-negative bacilli (48.78%) were the main infection strain, followed by gram-positive cocci (39.02%), and fungi (12.20%). Compared with the data from the first day after the operation, the ratios of CD_4^+ and CD_4^+/CD_8^+ in the two groups increased significantly on the 15th day after treatment (P<0.001), and the ratios in the observation group increased even more (P<0.001; P=0.017). The total protein (TP), albumin (Alb), and transferrin (TRF) serum levels in the observation group significantly increased (all P<0.01) and were significantly higher than the levels in the control group (all P<0.001) after treatment for 15 days. The TNF-α and IL-6 serum levels in both groups decreased significantly (P<0.05 or P<0.01) after the treatment for 15 days and even more in the observation group (P<0.001). The incidence of complications in the observation group was significantly lower than it was in the control group (P=0.009), but there was no significant difference in mortality (P=1). Conclusion: The infection rate of patients with sTBI is very high, and the main pathogen is gram-negative bacilli. Early postoperative enteral nutrition support combined with anti-infection therapy can improve the immune function, balance the nutritional status, reduce the inflammatory reaction, lower the risk of complications, and help to improve patient prognosis.

Keywords: Early enteral nutrition, anti-infection, severe traumatic brain injury, infection, immunity, nutritional status

Introduction

Severe traumatic brain injury (sTBI), a kind of central nervous system dysfunction, is one of the most common neurosurgical diseases. According to clinical statistics, the incidence of brain injury - of which sTBI make up about 20% of the total cases - is increasing gradually year by year in China [1, 2]. Patients with sTBI are in a state of severe hypermetabolism [3], which leads to immune dysfunction [4, 5]. Combined with the influence of invasive procedures such as catheterization, the patients are prone to severe postoperative complications such as severe infection, sepsis, and other conditions, which tend to cause death in patients with sTBI.

The mortality of sTBI patients is as high as 60% [6, 7]. The exclusive use of broad-spectrum antibiotics and the resistance of pathogenic bacteria can easily lead to intestinal flora disorders, which can significantly increase the severity of the infections and can even increase the risk of death. Therefore, seeking new effective measures to reduce the risk of infections and improve the prognosis of patients with sTBI is becoming a research hotspot.

After a brain injury, one cannot eat. The nutrients stored in the body are gradually consumed and the metabolism is blocked, which can indirectly lead to an insufficient energy supply in the brain tissues, which then causes ischemia and anoxia of the brain tissues with the combined effect of brain edema [8]. Early and reasonable nutrition support can alleviate the brain metabolic disorder caused by postoperative nutrients deficiency, and it's important to promote the postoperative recovery of patients [9]. Total parenteral nutrition (TPN) support was applied initially, and this kind of nutrition support worked fast. However, the long-term resting state of the intestines under TPN support easily decreases the gastrointestinal blood perfusion and peristalsis, which leads to intestinal tract flora disorder and affects intestinal tract digestion and absorption. It is disadvantageous to the recovery of patients. In recent years, enteral nutrition support has been widely applied in surgery, but there are few reports about whether early enteral nutrition support can reduce the risk of postoperative infection in patients with sTBI. The prospective study method was adopted in our study to investigate the effect of early enteral nutrition support combined with anti-infection intervention after operations in patients with sTBI. The results showed that this therapy can effectively reduce the risk of gut bacteria translocation-related infection after operations on sTBI patients.

Materials and methods

General materials

From December 2017 to May 2019, a total of 102 patients with sTBI were recruited for the study and were randomly divided into the observation group (n=51) and the control group (n=51). All the patients were diagnosed using CT or MRI.

Enrolment criteria: Patients with a clear history of head trauma, patients with Glasgow Coma Scores (GCS) from 3 to 8, patients with multiple cerebral contusions and lacerations, intracranial hematoma, epidural or subdural hematoma, obvious lateral ventricle compression, or midline displacement on head CT scans, patients who agreed to the surgery, patients with complete clinical data, patients who had no contraindications to the treatment methods adopted in this study, and patients who signed the informed consent.

Exclusion criteria: Patients with extremely severe brain injuries, patients with primary brain stem injuries, patients with gastrointestinal complex injuries, patients with compromised immune systems resulting from other causes such as malignancy, patients already infected, patients with hypoproteinemia clinically diagnosed as the primary disease, and patients who were pregnant or lactating. This study was approved by the Medical Ethics Committee of the School of Public Health of Nanchang University.

Methods

All the patients in the two groups were given adequate hemostasis, routine fluid replacement, intracranial pressure reduction, brain cell nutrition, and other treatment measures.

The patients in the control group received routine treatment and care after their operations. The nursing staff monitored their vital signs closely and informed the patients and their families of the possible complications and matters needing attention after the operation. For patients with septic shock, a timely replenishment of the blood volume was performed.

The patients in the observation group were given enteral nutrition support combined with anti-infection strategies from the first day after the operations. The early enteral nutrition support method was as follows: The nasointestinal tube was implanted under x-ray guidance, and the enteral nutrition suspension (TPF-FOS) was pumped into the intestine at a constant speed (manufacturer: Abbott Laboratories B.V., registration number: H20150255, specification: 1.07 kcal/mL). The infusion rate and amount of the nutrient solution were adjusted according to the patients' tolerance. The temperature of

Table 1. General baseline data (n, ($\bar{x}$ ± sd))

Group	Observation (n=51)	Control (n=51)	χ^2/t	P
Male/female (n)	27/24	23/28	0.628	0.428
Age (year)	48.6±5.5	49.7±6.1	0.956	0.341
Time from injury to admission (h)	1.87±0.70	2.05±0.82	1.192	0.236
GCS on admission (score)	5.48±1.53	5.12±1.85	1.071	0.287
APACHE Π on admission (score)	50.27±8.31	52.51±6.60	1.507	0.135
SOFA on admission (score)	30.34±2.46	29.48±2.29	1.827	0.071

Note: GCS: Glasgow coma score; Apache II: acute physiology and chronic health evaluation; SOFA: sepsis-related organ failure assessment.

the enteral nutrition suspension was kept between 37°C and 42°C, and the feeding speed started from slow to fast. The feeding speed of the enteral nutrition suspension was 25 mL/h on the first day after the operation, and it increased to 80-100 mL/h after 3-5 days. For the patients with severe disease, a small amount of pure water and probiotics were dripped into their gastric tubes first. The enteral nutrition solution was fed through a nasointestinal tube when there were no adverse reactions within 6 hours. The special "Nasointestinal Tube" label was put on the nasointestinal tube, and the patients were reminded not to touch the nasointestinal tube to ensure it was not twisted and folded when they turned over or moved. The nasointestinal tubes were flushed with 25 mL warm water every 2-4 hours to prevent blockage. The anti-infection care method was as follows: (1) The nursing staff or family members cleaned the patient's body when the patient returned to the ICU or ward after the operation. The environment of the ward was strictly disinfected according to the established requirements; (2) Disposable oxygen tubes were used (purchased from Foshan Nanhai Fenghua Medical Equipment Co., Ltd.). The oxygen tube, humidification bottle, and sterile distilled water were replaced daily to prevent lung infections caused by bacteria; (3) Chymotrypsin for injection (Shanghai No. 1 Biochemical & Pharmaceutical Co., Ltd., Specification: 4000 U) and terbutaline sulfate injection (Chengdu Huayu Pharmaceutical Co., Ltd., specification: 2 mL: 0.5 mg) were added to 2 mL of 0.9% sodium chloride injection. The mixture was uniformly mixed and prepared into an atomizing liquid medicine for the patient to inhale; (4) After having a tracheotomy for 7 days, the patients' airways were humidified with a humidifying liquid daily, and the humidifying liquid was continuously pumped into the airway at a rate of 2-5 mL/h.

Outcome measures

(1) The sites and incidences of infection were recorded and compared between the two groups. (2) The patterns of the infection strains in the infected patients were recorded. The infected tissues were collected and the pathogen was isolated and inoculated on an agar medium. The bacteria were identified using the paper disc diffusion method with a Siemens automatic microorganism analyzer. (3) About 5 mL of venous blood was collected on the first day after the operation and on the 15th day after the treatment. The blood was centrifuged and stored. The T-lymphocytes (CD_4^+, CD_8^+) in the whole blood were measured using a flow cytometer [10] and the proportion of CD_4^+/CD_8^+ was calculated. The mouse anti-human CD3-PreCP, mouse anti-human CD4-FITC, mouse anti human CD8-PE as well as their isotype controls, the mouse IgG-PreC, mouse IgG-FITC, mouse IgG-PE, were all purchased from Becton, Dickinson and Company, commodity codes: NY3876, NY6498, NY9475, and BT3625, BT2745, BT2277, Origin: USA. (4) The TP, Alb and TRF serum levels were measured using an Enzyme-Linked ImmunoSorbent Assay (ELISA) [11]. The ELISA Kits were purchased from the Sigma-Aldrich Company, item numbers: A096773, A056738, and T190989, origin: Germany. (5) The serum levels of the inflammatory factors such as TNF-α and IL-6 were measured using a Radioimmunoassay [12]. (6) The incidences of postoperative complications was calculated and compared between the two groups.

Statistical analysis

SPSS 20.0 was used to analyze the data. The enumeration data were expressed as the number of cases/percentage (n/%) and analyzed using χ^2 tests. The complications data were analyzed using adjusted χ^2 tests except for the total complication rate. The measurement data were expressed as the mean ± standard deviation ($\bar{x}$ ± sd). Paired t tests were adopted to

Table 2. Infections in the two groups (n, %)

Group	Incision	Intracranial	Lung	Urinary	Digestive system	Incidence
Observation (n=51)	1 (1.96)	3 (5.88)	2 (3.92)	2 (3.92)	4 (7.84)	12 (23.53)
Control (n=51)	4 (7.84)	4 (7.84)	6 (11.76)	4 (7.84)	6 (11.76)	24 (47.06)
χ^2	0.841	0	1.221	0.177	0.111	6.182
P	0.359	1	0.269	0.674	0.739	0.013

Table 3. Patterns of the infection strains in the infected patients (n=41)

Pathogenic bacteria	Number (n)	Percentage (%)
Gram-positive cocci	16	39.02
Staphylococcus aureus	7	17.07
Streptococcus pneumoniae	5	12.20
Enterococcus faecalis	2	4.88
Others	2	4.88
Gram-negative bacilli	20	48.78
Pseudomonas aeruginosa	9	21.95
Escherichia coli	5	12.20
Klebsiella pneumoniae	2	4.88
Acinetobacter baumannii	2	4.88
Others	2	4.88
Fungi	5	12.20

compare the results before and after treatment within the same group, and independent t tests were used to compare the results between the two groups. P<0.05 was considered statistically significant.

Results

Comparison of the general baseline data

There was no significant differences in the baseline data between the two groups (P>0.05). See **Table 1**.

Infections of patients in the two groups

Comparison of the sites and rates of infection of the patients in the two groups: Infections occurred in the incisions, the intracranial area, the lungs, the urinary tract and digestive system in the two groups, but the infection rate in the observation group was lower than the rate in the control group (23.53% vs 47.06%, P<0.05). See **Table 2**.

Patterns of the infection strains in the infected patients: A total of 41 strains were isolated from the infected sites in 36 patients, among which 16 strains (39.02%) were gram-positive cocci, 20 strains (48.78%) were gram-negative bacilli, and 5 strains (12.20%) were fungi. The patterns of the infected strains in the infected patients are shown in **Table 3**.

The cellular immune function before and after the treatment

Compared with the first day after the operation, the ratio of CD_4^+ in the two groups (P<0.01) and the ratio of CD_4^+/CD_8^+ in the observation group (P<0.01) on the 15th day after treatment were significantly increased, and the degree of increase was greater in the observation group (P<0.05 or P<0.001). See **Table 4**.

The nutritional status before and after the treatment

Compared with the first day after operation, the TP, Alb, and TRF serum levels in the observation group on the 15th day after the treatment were significantly increased (all P<0.01), and the degree of increase was greater in the observation group (P<0.001). See **Table 5**.

Comparison of the concentrations of the serum inflammatory factors before and after the treatment

Compared with the first day after the operation, the TNF-α and IL-6 serum levels in the two groups on the 15th day after the operation decreased significantly (P<0.05 or P<0.01), and the degree of decrease was greater in the observation group (P<0.001). See **Table 6**; **Figure 1**.

Complications

In the observation group, there were 2 cases of upper gastrointestinal bleeding and 12 cases of infection, so the incidence of complications was 27.45%. There were 2 deaths, so the mortality rate was 3.92%. In the control group, there were 2 cases of upper gastrointestinal

Table 4. Cellular immune function before and after treatment ($\bar{x}$ ± sd)

Indicator	Observation (n=51)	Control (n=51)	t	P
CD_4^+ (%)				
1 d after operation	30.38±3.28	29.70±3.75	0.975	0.332
15 d after treatment	37.98±4.10**	33.57±3.70**	5.703	<0.001
CD_8^+ (%)				
1 d after operation	25.40±2.57	26.11±3.29	1.215	0.227
15 d after treatment	25.63±3.17	26.87±3.20	1.966	0.052
CD_4^+/CD_8^+				
1 d after operation	1.21±0.33	1.19±0.38	0.284	0.777
15 d after treatment	1.40±0.34**	1.25±0.28	2.432	0.017

Note: CD_4^+: CD_4^+ T-lymphocytes; CD_8^+: CD_8^+ T-lymphocytes. Compared with the 1st day after the operation, **P<0.01.

Table 5. Comparison of the nutrition-related outcome measures before and after the treatment ($\bar{x}$ ± sd)

Indicator	Observation (n=51)	Control (n=51)	t	P
TP (g/L)				
1 d after operation	50.46±4.38	51.28±4.22	0.963	0.338
15 d after treatment	56.60±5.59**	51.40±5.33	4.808	<0.001
Alb (g/L)				
1 d after operation	1.67±0.32	1.71±0.41	0.549	0.584
15 d after treatment	2.23±0.40**	1.78±0.49	5.081	<0.001
TRF (g/L)				
1 d after operation	1.84±0.26	1.78±0.30	1.079	0.283
15 d after treatment	2.33±0.45**	1.85±0.42	5.569	<0.001

Note: TP: total protein; Alb: albumin; TRF: transferrin. Compared with the first day after the operation, **P<0.01.

bleeding, 24 cases of infection, and 1 case of acute renal failure, so the incidence of complications was 52.94%. There were 3 deaths, so the mortality rate was 5.88%. The incidence of complications in the observation group was significantly lower than it was in the control group (P<0.01), and there was no significant difference in mortality (P<0.05). See **Table 7**.

Discussion

Patients with brain injuries are prone to organ function damage after surgery, and gastrointestinal failure is the most common to occur. Because the defense function of the gastrointestinal barrier is significantly weakened, the invasion of pathogenic microorganisms easily occurs, and this can induce a variety of infections and lead to sepsis [13], multiple organ dysfunction syndrome (MODS) [14], septic shock, and even death. It has a serious impact on patient prognosis [15]. In our study, 36 of 102 patients were infected, for an infection rate of 35.29%. And 41 strains were isolated, of which the main infection strain was gram-negative bacilli (48.78%), followed by gram-positive cocci (39.02%). In addition, 5 strains (12.20%) of fungi were isolated. The causes of the high infection rate may be related to gastrointestinal mucosal dysfunction after the operations, a decrease in the ability of the bronchial mucosa to block the invasion of bacteria caused by long-term bedrest, urinary retention, and hospital cross infection.

For patients with sTBI, it is very important to take appropriate intervention measures to promote the recovery of intestinal function, maintain the intestinal flora balance, prevent and cure postoperative infections, and promote postoperative rehabilitation. Enteral nutrition support, which means various nutrients are provided to the body in the form of nutrient solution in the early stage of pathology, can weaken the body's hypermetabolism and ensure the functions of the body's organs and tissues [16]. It is an advanced nutritional support method at present. Studies have shown that early enteral nutrition support can improve the prognosis and shorten the length of ICU stays of patients with brain injury [17]. Patients with sTBI who have a long hospital stay, severe gastrointestinal dysfunction, and a weakened gastrointestinal defense function can easily be invaded by pathogenic microorganisms and subjected to various infections. Therefore, attention should be paid to hospital cleaning and sanitation, infection management, and other systems as well as taking appropriate anti-infective measures to minimize the risk of infection [18]. The incidence of postoperative infection was 35.29% in our study, and the major sites of the infections were the incisions, the

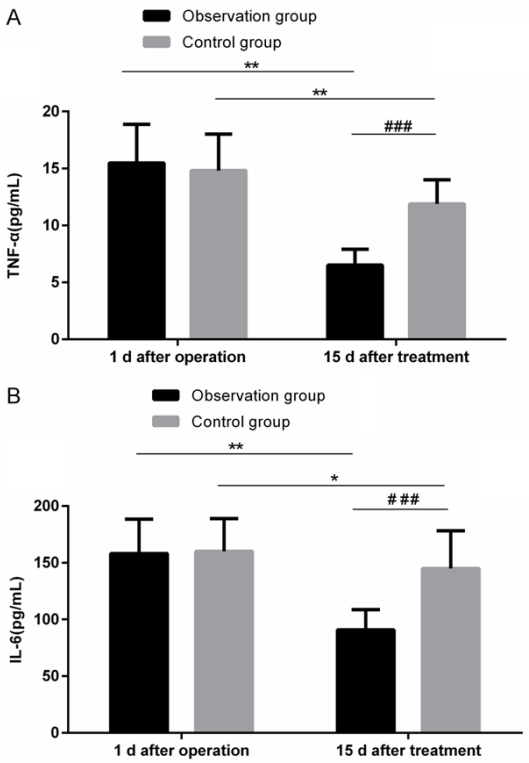

Figure 1. A comparison of the concentrations of the serum inflammatory factors before and after the treatment. A: A comparison of the serum levels of TNF-α in the two groups before and after the treatment; B: A comparison of the serum levels of IL-6 in the two groups before and after the treatment. TNF-α: tumor necrosis factor α; IL-6: interleukin-6. Compared with the first day after the operation, $^{*}P<0.05$, $^{**}P<0.01$; compared with the control group on the 15 d after the treatment, $^{\#\#\#}P<0.001$.

intracranial area, the lungs, the urinary tract, and the digestive system. There were no significant differences in the infection sites between the two groups. The infection rate was lower in the observation group, suggesting that early enteral nutrition support combined with anti-infection intervention can help to prevent or reduce postoperative infections in patients. This finding is consistent with the results of other studies on this topic [19].

In patients with sTBI, under the stimulation of surgery and trauma, the autonomic regulation of the hypothalamus-pituitary-adrenal cortex axis is disordered. The body enters a hypermetabolic state, in addition to not eating normally, so there is a severe consumption of protein. The patients are in a state of negative nitrogen balance, which is unfavorable to postoperative recovery [20]. Compared with normal people, patients with sTBI consume about 30% more energy and increase their protein consumption. If the protein is not supplemented in time and effectively, it can lead to severe complications such as low immune function, being infected easily, malnutrition, and organ function damage, conditions which have a serious effect on patient rehabilitation [21]. In this study, the ratio of CD_4^+ in the two groups and CD_4^+/CD_8^+ in the observation group on the 15th day after treatment were significantly higher than they were on the 1st day after the operations. The TP, Alb, and TRF serum levels in the observation group were significantly increased and were higher than the levels in the control group, showing that early postoperative enteral nutrition support combined with anti-infection intervention can significantly improve the immune function and nutritional status of patients with sTBI. This is crucial for promoting the patient's recovery after surgery.

The study showed that the concentrations of the serum inflammatory factors such as TNF-α and IL-6 in patients with sTBI were positively correlated with the severity of brain injury. More severe brain injuries cause higher concentrations of serum inflammatory factors and a more severe inflammatory response. Inflammatory reactions can further aggravate brain injuries [22, 23]. Therefore, reducing the excessive production of the inflammatory factors can improve the prognoses of patients with sTBI. Rosenthal et al. reported that early postoperative nutritional support can reduce the serum levels of TNF-α and IL-6 in patients with severe trauma [24]. Similar results were found in our study. The serum TNF-α and IL-6 levels in the observation group on the 15th day after the treatment were significantly lower than the levels on the first day after the operation and lower than the levels in the control group. We found that the observation group had a lower incidence of complications. The results showed that early postoperative enteral nutrition support combined with the anti-infection intervention mode can significantly correct the nutritional disorders of patients with sTBI, reduce the concentrations of the inflammatory factors, and weaken the inflammatory reaction state, which are important in reducing the risk of postoperative complications and improving the prognosis of patients with sTBI. However, there are some shortcomings to this study, such as only com-

Table 6. Comparison of the concentrations of the serum inflammatory factors before and after the treatment ($\bar{x} \pm sd$)

Indicator	TNF-α (pg/mL)		IL-6 (pg/mL)	
	1 d after operation	15 d after treatment	1 d after operation	15 d after treatment
Observation (n=51)	15.48±3.40	6.50±1.40**	158.09±30.27	90.70±18.06**
Control (n=51)	14.80±3.22	11.89±2.11**	160.09±28.89	144.98±33.27*
T	1.037	15.201	0.341	10.240
P	0.302	<0.001	0.734	<0.001

Note: TNF-α: Tumor necrosis factor α; IL-6: interleukin-6. Compared with the 1st day after operation, *P<0.05, **P<0.01.

Table 7. Complications (n, %)

Group	Upper gastrointestinal bleeding	Infection	Acute renal failure	Incidence of complication	Morality
Observation (n=51)	2 (3.92)	12 (23.53)	0 (0.00)	14 (27.45)	2 (3.92)
Control (n=51)	2 (3.92)	24 (47.06)	1 (1.96)	27 (52.94)	3 (5.88)
χ^2	0.260	6.182	0	6.892	0
P	0.610	0.013	1	0.009	1

paring the data from the 15th day after the surgery with the data from the first day after the operation, and not comparing the data of other time points during the treatment with that of after the operation. We can't predict the trend of change, and more detailed research is still needed to improve the verifiability of our results.

In conclusion, the infection risk of patients with sTBI is high after the operation, and the infections are caused by gram-negative bacilli. Early postoperative enteral nutrition support combined with anti-infection intervention can insignificantly improve the immune function and nutritional status of patients with sTBI. In addition, this therapy can also reduce the inflammatory response and the risk of complications. It helps improve patient prognosis.

Disclosure of conflict of interest

None.

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