Effect of Early Enteral Nutrition on Traumatic Brain Injury and Complications

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Abstract **Background** Early and adequate nutrition plays a crucial role in the prognosis and occurrence of complications in patients with traumatic brain injury (TBI). We aimed to explore effect of early enteral nutrition (EN) on TBI and its complications. **Methods:** 200 eligible patients who were with TBI and received neurosurgery were recruited and randomly assigned to control group (n=100) or EN group (n=100). The controls were given conventionally intravenous nutrition, while, apart from conventional nutrition, patients in EN group were additionally given EN via nasal feeding 24 h post neurosurgery for 7-14 days. The clinical outcomes as reflected by Glasgow Coma Score (GCS), complications, and the level of inflammatory factors as well as blood beta-amyloid protein (Aβ) were analyzed. **Results:** Patients with TBI underwent EN had a higher GCSs than the controls (P<0.05). Higher total incidence of complications, including pulmonary infection and intracranial infection, in control group, was observed (P<0.05). EN exerted a striking improvement in nutritional status. Logistical regression analysis found EN treatment was a protective factor for the occurrence of complications. Dramatically, EN treatment significantly made a remarkable reduction in blood level of inflammatory factors as well as Aβ (P<0.05 for all). **Conclusion:** Our study concluded EN is conducive to improve the clinical outcomes and to decrease the incidence of complications.

Keywords: early enteral, traumatic brain injury, clinical outcomes, complication, glasgow coma score, inflammatory factors

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1. Introduction

Traumatic brain injury (TBI) is currently the leading cause for death and disability, particularly in adults under 40 years old [1]. It is estimated that over 800000 and 50 million individuals suffered from TBI, in China and worldwide, respectively [2], bringing a grave economic burden on both society and families. In addition, with a spurt of progress in society, the number of people with TBI resulting from traffic accidents and falling from height is raising [3]. Although surgical treatment has striking decreased the mortality rate of TBI, the fatality rate and disability rate are still high [4], thereby it is urgently needed to seek other strategies to improve the recovery.

Apart from early surgical treatment, other early strategies to minimize the complications are also the key to make a reduction in mortality rate, particularly in severe TBI patients. Recently, there is a spotlight on the intestine due to the discovery of brain-gut axis [5], implicating that the gut might hold the promise for regulating the brain functions. Indeed, several drugs, such as GV971, have shown the possibility that cognitive function and brain structure of patients with Alzheimer's disease can be improved by intervening gut [6]. Previous study revealed that patients suffered from TBI had a disrupted intestinal function as a result of none-food intake and acute stress response [7], indicating early and enough energy intake might be conducive to protect bowel from disruption. Patients with TBI usually are in a state of unconsciousness due to severe damage to the central nervous system [8], thereby resulting in difficulty in swallowing. However, TBI patients have an increased metabolism rate and are in a state of extreme energy consumption, making patients are vulnerable to bacterial infection, stressful ulcer, and other complications, which in turn deteriorate TBI symptoms [9,10]. Moreover, deficiency of energy could also decrease the clearance of metabolic waste and other toxic substance, such as β-amyloid protein (Aβ) that is known for causing dementia [11]. Therefore, it is highly imperative to deliver timely and quantitative energy to patients with TBI.

Enteral nutrition (EN) is widely utilized in clinic for delivering energy to those who are of difficulty in swallowing, particularly for unconscious subjects [12]. As mentioned above, time and quantitative energy intake is of

importance for rehabilitation of patients with TBI [13]. EN might be an acceptable choice to provide TBI patients with nutrition owing to its feasibility and simplicity. Although there are some evidences showing the positive effects of EN on the recovery of patients suffering from TBI [14,15], more researches are highly needed to furtherly verify the safety and efficacy of EN. Thus, our study analyzed a total of 200 patients with TBI who received enteral nutrition or not to explore its clinical outcomes, occurrence of complications, and biochemical indicators.

2. Methods

2.1. Subjects and Blood Samples

We consecutively recruited a total of 200 patients diagnosed with TBI who received neurosurgical treatment in Nantong Second People's Hospital from February, 2018 to February, 2022. TBI patients were segmented into two groups, the control group (n=100) who received intravenous nutritional support and the EN group (n=100) who were given EN. Blood samples were collected before and after the last EN treatment, centrifuged at 3000 rpm for 30 min and stored at -80°C until further analysis. We have obtained the consents for clinical information collection from families of patients, and this study was approved by the Institutional Review Board of Nantong Second People's Hospital.

2.2. Inclusion and Exclusion Criteria

Patients with TBI were included if they conformed to the following principles: (1) over 18 years old; (2) clinical symptoms and imaging evidence, including CT or MRI, showing craniocerebral injury; (3) patients undergo craniotomy after admission; (4) patient's family signed the informed consent. Conversely, patients were not eligible for the study if they meet either of the principles as followed: (1) age below 18 years old; (2) patients didn't meet the diagnosis of TBI; (3) patients have chronic disease history, such as diabetes, hypertension, and stroke.

2.3. Clinical Data Collection

General clinical information was obtained from the admission center, including age, sex, history of hypertension and diabetes etc. Complication occurrence during treatment was also recorded by nurses. The gastrointestinal intolerance is the major concerning, including diarrhea [16]. Intestinal stress ulcer was diagnosed by a positive stool blood test. The diagnostic standards for other complications, such as pulmonary infection, was according to previous study or guides [17,18].

2.4. Glasgow Coma Score (GCS)

GCS were performed to analyze the patient's level of consciousness after TBI according previous study [19]. GCS comprises three arms: eye response, verbal response, motor response, and three scales are combined into a single score that ranges from 3 to 15. All patients were evaluated by the scale by a professional neurosurgeon who was blind to the group information.

2.5. Nutritional Intervention

The controls were provided with intravenously nutritional support, including conventional amino acid, fat, glucose solutions, and other necessary elements. Apart from conventional parenteral nutrition like the controls, patients in EN group were additionally given EN via nasal feeding 24 h post neurosurgery for 7-14 days if they can't swallow or the oral nutrition intake can't meet the daily need of energy.

2.6. Measuring Level of Inflammatory Factors and Aβ in Blood

Inflammatory factors in blood, including TNF-α, IL-1β and IL-6 were detected by enzyme linked immunosorbent assay (ELISA) according to the manufacture and previous study [20]. Blood Aβ40 and Aβ42 were also measured by ELISA (Invitrogen, USA) according to previous research [20].

2.7. Statistical Analysis

All data were analyzed by SPSS 23.0 and were presented as mean±SD. All data were firstly examined by Kolmogorov–Smirnov test for normality detection. Independent t test was conducted to compare the two group if they complied with normal distribution. Comparisons between two categorical groups were performed by a chi-square test. Logistic regression model was performed to explore the contributing factors for the occurrence of complications. A P value <0.05 was considered as statistically significant.

3. Results

3.1. Patient Characteristics

As shown in Table 1, our study contains 200 patients with TBI, of which 100 subjects were given EN treatment, while other patients received conventionally intravenous nutrition. There was no significant difference in age, gender, and cause for TBI (P>0.05). Also, GCSs were not differed in two groups as well as biochemical indicators (P>0.05), such as albumin and hemoglobin. Additionally, all subjects enrolled had no obvious complications, including pulmonary infection, stressful ulcer, etc. (data were not shown).

3.2. Comparison for Occurrence of Complications and Clinical Outcomes When Discharged

After EN treatment, we found the occurrence rate of pulmonary infection in EN group was lower than that in control group (P<0.05), indicating that EN treatment could decrease the occurrence rate of complications in TBI patients during admission. Other occurrence of

complications, including intracranial infection, stressful ulcer, and diarrhea, didn't differ in two groups (P>0.05). In addition, EN treatment exerted a striking increase in GCSs in comparison with the control (P<0.05). Also, TBI patients with EN had a higher level of total protein than the controls (P<0.05), while the level of glucose seemed also higher, although the difference didn't reach statistical significance (P=0.07). There was no remarkable difference in the level of albumin and hemoglobin between EN group and control group (P>0.05).

3.3. The Impact of EN Treatment on the Occurrence of Complications

To address the contributing factors for the occurrence of complications, all subjects were subjected to logistical regression model. The dependent variable was defined by whether the patient had one of the above complications. As mentioned above, apart from EN treatment, other confounders, including age, sex, primary GCSs, durations etc., were treated as independent variables. Interestingly, we found EN treatment was a protective factor for the occurrence of complications, with the adjustment of age, sex, primary GCSs, durations etc.

3.4. The Effect of EN Treatment on the Level of Inflammatory Factors and Aβ in Blood

We furtherly measured the level of inflammatory factors, including TNF-α, IL-1β and IL-6, as well as Aβ40 and Aβ42 in blood. There was no remarkable difference in both level of inflammatory factors and Aβ between two groups at admission (Figure 1A, B, P>0.05). All patients with TBI underwent a dramatical decrease in the level of TNF-α, IL-1β and IL-6 (Figure 1A, B, P<0.05 for all). In addition, all levels of inflammatory factors in blood in control group were higher than that in EN group (Figure 1C, P<0.05 for all). Dramatically, EN treatment also exerted a striking decrease in both Aβ40 and Aβ42 level in blood in comparison with control group (Figure 1C, P<0.05 for all).

Table 1. Patient characteristics

Variable	Control group	EN group	Statistics	P value
No. of patients	100	100		
Age	42.13 ± 13.52	43.25 ± 12.82	t=0.601	0.548
Male (%)	49 (49)	51 (51)	χ^2=0.080	0.777
Cause for TBI			χ^2=0.357	0.550
Falling (%)	32 (32)	36 (36)		
Car accidents (%)	68 (68)	64 (64)		
Nasal feeding time (day)		15.7 ± 3.51		
GCSs	5.42 ± 4.53	5.02 ± 5.54	t=0.838	0.408
Total protein (g/L)	63.23 ± 6.23	62.89 ± 8.19	t=0.330	0.741
Albumin (g/L)	33.67 ± 5.29	32.26 ± 7.34	t=1.558	0.127
Hemoglobin (g/L)	129.07 ± 15.59	132.26 ± 12.12	t=1.615	0.108
Hypertension (%)	11 (11)	13 (13)	χ^2=0.189	0.663
Diabetes mellitus (%)	8 (8)	5 (5)	χ^2=0.740	0.390

Table 2. Occurrence of complications and clinical outcomes when discharged

Variable	Control group	EN group	Statistics	P value
Durations (days)	22.34 ± 8.22	24.25 ± 7.10	t=1.758	0.0802
Total complications (%)	38 (38)	24 (24)	χ^2=4.58	0.032
Pulmonary infection (%)	14 (14)	5 (5)	χ^2=4.71	0.030
Intracranial infection (%)	8 (8)	3 (3)	χ^2=1.54	0.215
Stressful ulcer (%)	12 (12)	10 (10)	χ^2=0.204	0.651
Diarrhea (%)	4 (4)	6 (6)	χ^2=0.105	0.746
GCSs	8.12 ± 5.13	9.82 ± 4.20	t=2.564	0.0111
Total protein (g/L)	64.23 ± 6.13	65.89 ± 4.63	t=2.161	0.0319
Albumin (g/L)	35.27 ± 5.23	36.26 ± 4.36	t=1.454	0.148
Hemoglobin (g/L)	130.37 ± 13.34	131.28 ± 11.38	t=0.519	0.604
glucose (mmol/L)	5.21 ± 3.14	5.91 ± 2.24	t=1.815	0.07

Table 3. Logistical regression analysis of factors contributing to occurrence of complications

Variable	β	SE	χ^2	P	OR	95%CI
Age	0.420	0.221	7.693	0.032	1.522	1.341-2.113
Gender	0.202	0.197	4.922	0.21	1.224	1.110-1.329
Hypertension	0.272	0.123	6.471	0.028	1.313	1.125-1.751
Diabetes mellitus	0.192	0.111	5.112	0.042	1.212	1.123-1.512
Primary GCSs	0.631	0.221	10.560	0.001	1.881	1.412-2.830
Total protein (g/L)	-0.238	0.215	5.210	0.041	0.788	0.604-0.830
Albumin (g/L)	-0.476	0.199	6.968	0.031	0.621	0.401-0.738
Hemoglobin (g/L)	0.0208	0.225	4.621	0.144	1.021	1.001-1.211
EN	-0.469	0.205	7.693	0.021	0.626	0.419-0.913
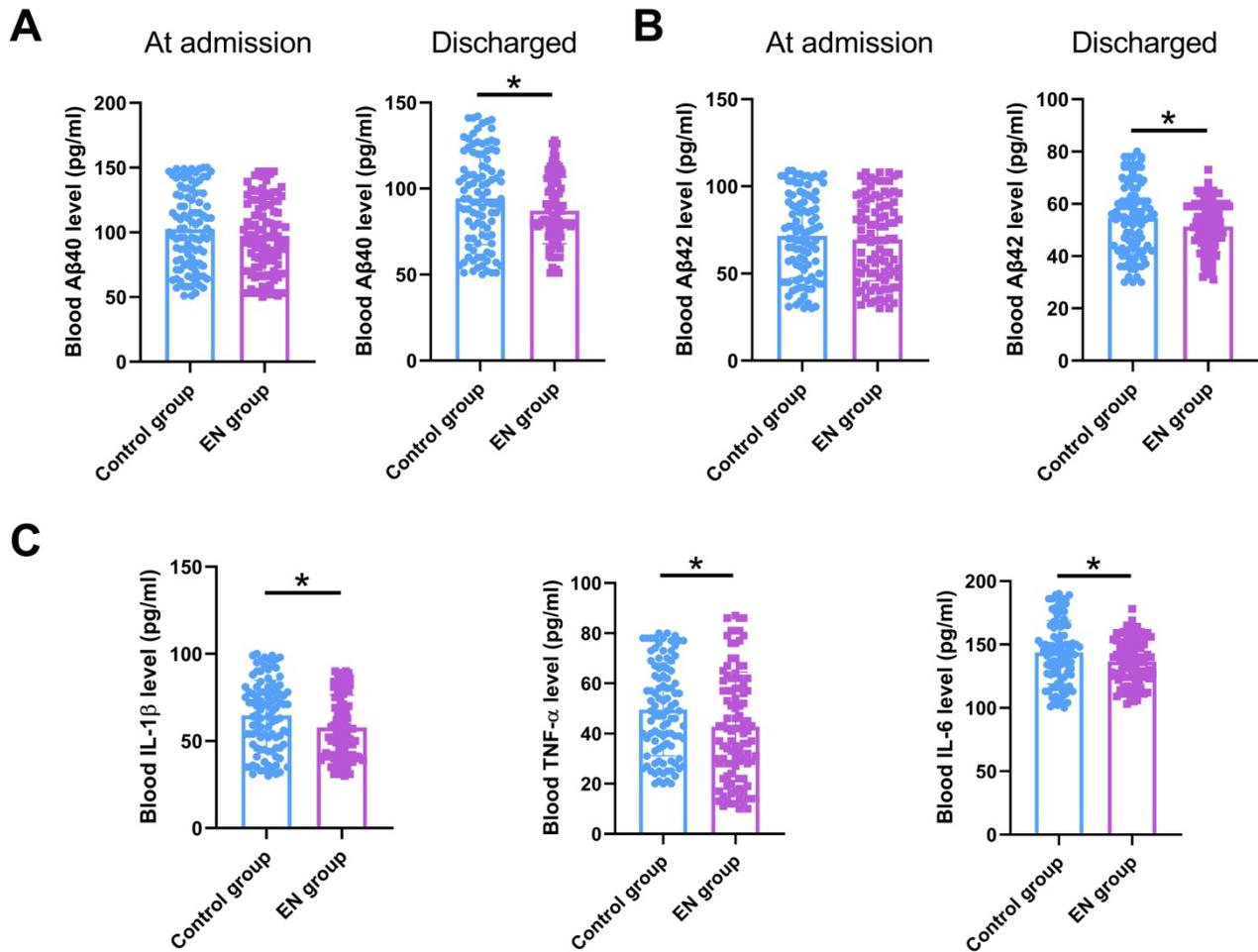
Figure 1. Effect of EN on the changes in blood inflammatory factors level and Aβ level. A, The comparison of blood Aβ40 level at admission and discharged between control group and EN group; B, The comparison of blood Aβ42 level at admission and discharged between control group and EN group; C, The comparison of blood IL-1β, IL-6, and TNF-α level between control group and EN group. N=100; The error bars are the SDs

4. Discussion

In the present study, we aimed to explore the effect of EN on the clinical outcomes, complications, and other biochemical indicators in patients with TBI. We found EN treatment had a positive effect on the GCSs, and decreasing the occurrence rate of complications. Logistical regression analysis revealed that EN treatment was an independently protective factor after adjusting confounders, including the age, sex etc. Dramatically, we also found EN treatment exerted a significant mitigation in both inflammatory factors level and Aβ level.

TBI is prevalent in China and worldwide due to a spurt of progress in society. TBI is responsible for approximately 13 death cases per 100 000 people and immense number of disabilities [2], bringing a grave burden on families and society. Apart from neurosurgery, other auxiliary treatments are also crucial to diminish the mortality rate and disability rate. Previous studies well demonstrated that patients with TBI were in a state of energy exhaustion and deficient in nutrition [9,10]. It is wildly accepted in clinic that adequate energy supplement is conducive for rehabilitation in injured patients, as indicated by those who received surgical treatment need timely and quantitative nutrition supplement [21]. Considering TBI is a kind of consumptive diseases [9,10], we aimed to verify whether timely and quantitative

nutrition supplement via EN could promote the recovery of TBI. Dramatically, we found patients with TBI underwent a striking increase in GCSs that is widely utilized to reflect disease severity, with no obvious adverse effects. Additionally, a critical concerning is whether EN would provoke the occurrence of server diarrhea due to the intolerance. Based on our findings, EN is not strong enough to evoke severe diarrhea. Previously several studies reported that EN availed to the recovery of TBI [14,22], which are consistent with our finds. Thus, combined with others' findings, we could draw a conclusion that timely and quantitative EN is help for the recovery of TBI.

It has aroused a heated discussion that whether EN could exert a protective effect on the occurrence of complications. In general, patients with TBI are in a state of unconsciousness or failing to swallow [23], resulting in a deficiency of energy, which impair the natural defense of patients against bacterial infection and others. Thus, we explored the effect of EN on the occurrence of bacteria-related complications [17,24], pulmonary infection, and intracranial infection. Dramatically, we found the occurrence rate of pulmonary infection, but not intracranial infection, in EN group was significantly lower than that in control group, indicating the EN might be a protective factor. Moreover, logistical regression analysis also revealed that EN was a protective factor in mitigating

the incidence of complications. Overall, EN is proven to be a protect patients from bacterial infection. As for the mechanism of the protective effect, we reason that might stem from the following explanations. It was previously demonstrated that there is a close interaction between brain and gut [25,26], such as the brain-gut axis. Indeed, TBI has been proven to disrupt the intestinal structure and functions, increasing the chance of bacterial infection [26,27]. In addition, due to the difficulty in food eating in TBI patients, impaired intestinal movement fails to flush out the toxic substance, which also disturb the balance of intestinal flora and provide the chance for bacteria infiltrating into blood circulation [28,29]. Therefore, timely, and quantitative EN is conducive for the recovery of intestinal structure and functions.

It has been previously demonstrated that stroke or TBI bears closely on the incidence of dementia [30], particularly for Alzheimer's disease (AD) [31]. Aβ has been proven to be the core pathological substance [11], which is mainly engendered in neurons in central nervous system [32]. TBI is a kind of severe damage to head, which makes the neurons impaired and incomplete. Thus, much intracellular Aβ is released into peripheral blood and adjacent regions, causing other neural damage and poor prognosis [33,34]. Therefore, decreasing Aβ level is also conducive for prognosis in TBI patients. Previous study revealed that metabolic disorder of energy could impede the clearance of Aβ, indicating the sufficient energy supplement promotes the decrease of Aβ. Given that EN has proven to provide timely, and quantitative energy, we wanted to uncover whether EN could strengthen the capacity for Aβ clearing. We firstly compared the primary level of Aβ40 and Aβ42 at admission, and found there was no difference in that. However, there was a significant decrease in both Aβ40 and Aβ42 in two groups, whereas the level of Aβ in EN group was lower than control group, denoting that EN could hasten the process of Aβ clearing. Over all, our study finds adequate energy supplement avails to clear Aβ in blood and improve short-term prognosis. Additionally, our study also found EN could lessen the level of pro-inflammatory factors, including TNF-α, IL-1β and IL-6. Inflammatory cytokine storm has been demonstrated to exacerbate the symptoms and prognosis of TBI [35]. In this regard, we speculate that EN might be also acceptable in the treatment of TBI. Notably, we reason the decreased level of pro-inflammatory factors might stem from that EN improves both intestinal function and capacity of body in clearing toxic substances.

5. Conclusion

Conclusively, our study found EN is conducive to improve the clinical outcomes and to decrease the incidence of complications.

List of Abbreviations

Traumatic brain injury (TBI);
Enteral nutrition (EN);
enzyme linked immunosorbent assay (ELISA);
Alzheimer's disease (AD);
beta-amyloid protein (Aβ)

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Consent for Publication

None.

Ethics Approval and Consent to Participate

All animal procedures were approved by Ethics Committee of Nantong Second People's Hospital.

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Competing Interests

The authors declare that they have no competing interests.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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