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Clinical Article

Impact of Early Enteral Nutrition on In-Hospital Mortality in Patients with Hypertensive Intracerebral Hemorrhage

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Objective : We conducted this study to evaluate the clinical impact of early enteral nutrition (EN) on in-hospital mortality and outcome in patients with critical hypertensive intracerebral hemorrhage (ICH).
Methods : We retrospectively analyzed 123 ICH patients with Glasgow Coma Scale (GCS) score of 3-12. We divided the subjects into two groups : early EN group (< 48 hours, n = 89) and delayed EN group (≥ 48 hours, n = 34). Body weight, total intake and output, serum albumin, C-reactive protein, infectious complications, morbidity at discharge and in-hospital mortality were compared with statistical analysis.
Results : The incidence of nosocomial pneumonia and length of intensive care unit stay were significantly lower in the early EN group than in the delayed EN group ($p < 0.05$). In-hospital mortality was less in the early EN group than in the delayed EN group (10.1% vs. 35.3%, respectively; $p = 0.001$). By multivariate analysis, early EN [odds ratio (OR) 0.229, 95% CI : 0.066-0.793], nosocomial pneumonia (OR = 5.381, 95% CI : 1.621-17.865) and initial GCS score (OR = 1.482 95% CI : 1.160-1.893) were independent predictors of in-hospital mortality in patients with critical hypertensive ICH.
Conclusion : These findings indicate that early EN is an important predictor of outcome in patients with critical hypertensive ICH.

KEY WORDS : Enteral nutrition · Intracerebral hemorrhage · Mortality.

INTRODUCTION

Nutritional support of critically ill patients is very important and should be considered a conerstone in critical care. Patients with brain injury commonly suffer from metabolic alterations that trigger increased energy and protein expenditure than patients without brain injury. Enteral nutrition (EN) decreases the catabolic response to injuries[17] and reduces infection rate and hospital stay in patients with such injuries[11,13,23,27,28]. However, there are only a few studies specifically addressing the influence of early EN on outcome of hypertensive intracerebral hemorrhage (ICH). We investigated the clinical implication of early EN in critical patients with ICH.

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MATERIALS AND METHODS

We retrospectively analyzed on 123 consecutive patients harboring critical hypertensive ICH with Glasgow Coma Scale (GCS) score of 3-12. All these patients had been admitted to our institution during the recent 6 years between January 2004 and December 2009. ICH was initially diagnosed by brain computed tomography (CT) scans in the emergency setting, and all of them were admitted to the intensive care unit (ICU). Parental fluids were supplied in traditional manners, and after vital signs became stabilized, enteral nutritional support was provided as soon as possible.

The subjects were classified as early EN group (< 48 hours) and delayed EN group (≥ 48 hours). We reviewed medical records and radiological data, and collected baseline characteristics including age, sex, locations of ICH, hematoma volume, initial GCS score, length of ICU stay, modified Rankin scale[37] at discharge, 30-day mortality, in-hospital mortality. Additionally, possible confounding variables including current smoking, alcohol consumption, previous stroke, diabetes, heart diseases were retrieved. We also reviewed

data regarding enteral nutritional including the time interval to EN after admission, body weight, total intake and output, feeding method, aspiration episodes during enteral feeding, serum albumin, C-reactive protein (CRP), calories and diet volume on day 4, because similar amount and calories have been provided in 2 groups after about 4 days[23]. We compared morbidity at discharge, in-hospital mortality and infectious complications including nosocomial pneumonia, urinary tract infection and sepsis between two groups.

For the purpose of this study, each parameters were defined as follows : Critical hypertensive ICH was defined as hypertensive ICH with GCS score of 3-12; early EN was defined as enteral feeding within 48 hours of admission; diabetes, a previous medical history of diabetes or fasting glucose value > 7.78 mmol/L at admission; previous strokes, history of cerebral infarction except for transient ischemic attack; heart diseases, only coronary artery diseases; current smoking, daily use of > 10 cigarettes during previous 6 months; alcohol consumption, ingestion of > 700 g/week of alcohol during previous 2 months or a history of chronic alcoholism; noscocomial pneumonia was defined as a compatible chest X-ray seen interpreted by chest radiologist, as well as fever and yellow sputum from the tracheal tube with positive culture; urinary tract infection was defined as a positive urine culture (more than 100,000 colony forming units/mL); sepsis was defined as systemic inflammatory response syndrome with bacteriological evidence of infection[2]. Infectious complications were defined as nosocomial pneumonia, urinary tract infection and sepsis. Aspiration episodes during feeding was defined as a coughing episodes during feeding or coughing episodes by vomiting during or after feeding.

Statistical analysis

All variables were expressed as mean ± standard deviation (SD). Pearson χ^2 or Fisher's exact test was used to assess proportions in nominal variables for bivariate analyses. To compare continuous variables between two groups, independent-samples t-test or Mann-Whitney U test were performed in distributions of parametric variables. Confounding variables with a value of $p < 0.1$ were included in the multivariate analysis model, and were categorized as quartiles for multivariate analysis. To identify the correlations between continuous variables, the Spearman correlation coefficient was used. To determine independent predictors of in-hospital mortality, multiple logistic regression analysis models (backward method) were constructed. Adjusted odds ratio (OR) with the respective 95% CI are provided. All p values are two-sided and considered as having significant difference when $p < 0.05$. All statistical analyses were conducted with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics of 123 patients with ICH according to the time interval to EN were summarized in Table 1. Mean age was 61.9 (SD = 14.1) years old, and men outnumbered women by 75 (61.0%) to 48 (39.0%). The mean duration of in-hospital stay was 26.5 days (SD = 20.1). The early EN group was more predominating, in 89 patients (72.4%).

There were no statistically significant differences in initial GCS score, hematoma volume and intraventricular hemorrhages on initial CT (all $p > 0.05$) scans between two groups. The incidence of both nosocomial pneumonia (21.3% vs. 41.2%; $p = 0.026$) and sepsis (0% vs. 14.7%; $p < 0.001$) were significantly lower in the early EN group than in the delayed EN group. Infectious complications occurred in 50 patients (40.7%), and were lower in the early EN group than in the delayed EN group (36.0% vs. 52.9%, respectively), but was not statistically significant ($p = 0.086$). Morbidity at discharge estimated by modified Rankin scale was significantly lower in the early EN group than in the delayed EN group ($p = 0.011$). In-hospital mortality was found in 21 patients (17.1%) and were significantly lower in the early EN group than in the delayed EN group (10.1% vs. 35.3%, respectively; $p = 0.001$). In addition, length of ICU stay was significantly shorter in the early EN group than in the delayed EN group ($p < 0.001$).

All patients were initially fed by nasogastric tube in the ICU. About 100-330 mL of formula was continuously administrated over 30 to 60 minutes q 3-6 hours. The mean time to enteral feeding after admission was 1.0 day (SD = 0.8) and 5.5 days (SD = 3.2) in the early and delayed EN groups, respectively. There were no statistically significant differences in body weight, total intake and output, total calories of intake and diet volume on 4th day between both groups ($p > 0.05$). Aspiration episodes during enteral feeding were not significantly different between two groups ($p = 0.176$). C-reactive protein checked at 14 days after admission was significantly higher in the delayed EN group (61.0 mg/L, SD = 55.7) than in the early EN group (33.5 mg/L, SD = 41.4) ($p = 0.004$). Table 2 shows data with reference to the enteral nutritional in 123 ICH subjects.

The results of univariate analysis of 123 patients according to the in-hospital mortality are presented in Table 3. Hematoma volume, initial GCS score, intraventricular hemorrhage and nosocomial pneumonia were significantly different between survival and death groups.

There was a correlation between the time interval to EN and length of ICU stay (r = 0.570, $p < 0.001$) and C-reactive protein 14 days after admission (r = 0.229, $p = 0.004$). But, there was no correlation between the time interval of EN and

Table 1. Baseline characteristics of 123 patients with critical intracerebral hemorrhage

Variables	Total (n = 123)	Enteral nutrition		*p**
		< 48 h (n = 89)	≥ 48 h (n = 34)	
Age (SD)	61.9 (14.1)	63.0 (14.4)	58.9 (13.3)	0.151
Male (%)	75 (61.0)	51 (57.3)	24 (70.6)	0.177
Current smoking (%)	42 (31.1)	32 (36.0)	10 (29.4)	0.494
Alcohol consumption (%)	49 (39.8)	37 (41.6)	12 (35.3)	0.525
Diabetes (%)	18 (14.6)	14 (15.7)	4 (11.8)	0.578
Previous strokes (%)	19 (15.4)	13 (14.6)	6 (17.6)	0.676
Heart diseases (%)	14 (11.4)	8 (9.0)	6 (17.6)	0.176
Location of hemorrhage				0.673
Basal ganglia (%)	57 (46.3)	40 (44.9)	17 (50.0)	
Thalamus (%)	24 (19.5)	20 (22.5)	4 (11.8)	
Pons (%)	5 (4.1)	3 (3.4)	2 (5.9)	
Cerebellum (%)	12 (9.8)	9 (10.1)	3 (8.8)	
Lobar (%)	25 (20.3)	17 (19.1)	8 (23.5)	
Hematoma volume, mL (SD)	36.7 (21.7)	34.9 (20.8)	41.5 (21.5)	0.124
Intraventricular hemorrhage (%)	52 (42.3)	35 (39.3)	17 (50.0)	0.284
Initial GCS score, median (Q1, Q3)	9 (7, 11)	9 (8, 11)	9 (6, 10)	0.207
Infectious complications (%)†	50 (40.7)	32 (36.0)	18 (52.9)	0.086
Nosocomial pneumonia (%)	33 (26.8)	19 (21.3)	14 (41.2)	0.026
Urinary tract infection (%)	22 (17.9)	16 (18.0)	6 (17.6)	0.966
Sepsis (%)	5 (4.1)	0 (0)	5 (14.7)	< 0.001
Length of ICU stay, day (SD)	9.4 (16)	6.1 (8.9)	18.6 (26.3)	< 0.001
modified Rankin scale at discharge, median (Q1, Q3)	2 (1, 3)	2 (1, 3)	2 (2, 4)	0.011
30-day mortality (%)	16 (13.0)	7 (7.9)	9 (26.5)	0.006
In-hospital mortality (%)	21 (17.1)	9 (10.1)	12 (35.3)	0.001

**p* value for differences between early enteral nutrition and delayed enteral nutrition after intracerebral hemorrahge; Pearson χ^2 or Fisher's exact test, Student t-test, Mann-Whitney test as appropriate. †Infectious complications include nosocomial pneumonia, urinary tract infection and sepsis. GCS : Glasgow coma scale, ICU : intensive care unit, SD : standard deviation

Table 2. Comparison of data regarding nutrition according to the time interval to enteral nutrition

Variables	Total (n = 123)	Enteral nutrition		*p*
		< 48 h (n = 89)	≥ 48 h (n = 34)	
Time interval to EN, days (SD)	2.2 (2.8)	1 (0.8)	5.5 (3.2)	< 0.001
Calories, 4th day, cal (SD)	619 (147)	626 (154)	600 (125)	0.386
Aspiration episodes (%)	14 (11.4)	9 (17.6)	6 (17.6)	0.176
Body weight, kg (SD)				
1 day	63.4 (6.8)	63.4 (6.9)	63.5 (6.4)	0.964
14 days	61.9 (6.7)	62.2 (6.9)	61.2 (6.0)	0.495
Total intake and output, mL (SD)				
1 day				
Intake	3,630 (354)	3,604 (341)	3,698 (382)	0.186
Output	2,913 (345)	2,915 (336)	2,910 (372)	0.953
14 days				
Intake	2,893 (309)	2,873 (294)	2,944 (346)	0.255
Output	2,404 (294)	2,378 (281)	2,474 (322)	0.106
Serum albumin, g/dL (SD)				
1 day	3.4 (0.6)	3.5 (0.6)	3.4 (0.64)	0.355
14 days	3.2 (0.59)	3.2 (0.64)	3.2 (0.45)	0.307
CRP, mg/L (SD)				
1 day	20.2 (32.9)	18.4 (30.6)	25.2 (38.3)	0.307
14 days	41 (47.2)	33.5 (41.4)	61.0 (55.7)	0.004

CRP : C-reactive protein, EN : enteral nutrition, SD : standard deviation

Table 3. The univariate analysis of 123 patients according to in-hospital mortality after intracerebral hemorrhage

Variables	In-hospital mortality		p^*
	Survival (n = 102)	Death (n = 21)	
Age (SD)	60.8 (13.5)	67.1 (16.1)	0.062
Male (%)	63 (61.8)	12 (57.1)	0.693
Current smoking (%)	35 (34.3)	7 (33.3)	0.931
Alcohol consumption (%)	42 (41.2)	7 (33.3)	0.504
Diabetes (%)	11 (10.8)	7 (33.3)	0.008
Previous strokes (%)	17 (16.7)	2 (9.5)	0.524
Heart diseases (%)	11 (10.8)	3 (14.3)	0.706
Early EN (< 48 hours) (%)	80 (78.4)	9 (42.9)	0.001
Hematoma volumes, mL (SD)	32.7 (17.7)	56.1 (25.9)	< 0.001
Initial GCS score, median (Q1, Q3)	9 (8, 12)	6 (5, 8)	< 0.001
Intraventricular hemorrhage (%)	38 (37.3)	14 (66.7)	0.013
Nosocomial pneumonia (%)	21 (20.6)	15 (71.4)	< 0.001
Operation (%)	23 (22.8)	4 (19.0)	0.708

*p value for differences between survival and death group after intracerebral hemorrahge; Pearson χ^2 or Fisher's exact test, Student t-test, Mann-Whitney test as appropriate.
EN : enteral nutrition, GCS: Glasgow coma scale, SD : standard deviation

Table 4. Multivariate logistic regression analysis for in-hospital mortality

Variables	Odds ratio (95% CI)*	p
Age, years	0.962 (0.919-1.006)	0.093
Initial GCS Score	1.482 (1.160-1.893)	0.002
Nosocomial pneumonia	5.381 (1.621-17.865)	0.006
Early EN (< 48 hours)	0.229 (0.066-0.793)	0.020

*Adjusted odds ratio was obtained for in-hospital mortality using binary logistic regression analysis (backward method). CI : confidence interval, EN : enteral nutrition, GCS : Glasgow coma scale

serum albumin 14 days after admission (r = -0.060, p = 0.510).

Multivariate analysis

Multivariate logistic regression analysis was performed for the following variables : age (continuous variable), diabetes, early EN (< 48 hours), initial GCS score, intraventricular hemorrhage and nosocomial pneumonia. We excluded hematoma volume in multivariate logistic regression analysis because of strong correlation (r = -0.710, p < 0.001).

In multivariate analysis, early EN (OR = 0.229, 95% CI : 0.066-0.793), nosocomial pneumonia (OR = 5.381, 95% CI : 1.621-17.865) and initial GCS score (OR = 1.482, 95% CI : 1.160-1.893) were proved as independent predictors of in-hospital mortality in patients with critical hypertensive ICH (Table 4).

DISCUSSION

There were few studies showing the relation between early EN and subsequent neurological outcomes in patients with hypertensive ICH, although the effect of traumatic brain injury on metabolism and nitrogen wasting have been thoroughly studied[37]. EN is one of the crucial outcome predictors of patients with severe traumatic brain injury[13]. Many well-designed clinical trials conducted in critically ill patients revealed a statistically significant reduction both in mortality and nosocomial pneumonia attributable to early EN within 24 hours of injury[7,8,22,23,29,33]. At present, benefits of early EN have been commonly accepted by most clinicians. In the current study, early EN (< 48 hours) and nosocomial pneumonia were independent predictors of in-hospital mortality in critical hypertensive ICH patients of GCS score 3-12. Our findings are consistent with a previous clinical trial of postoperative patients with critical hypertensive ICH that early EN improves 3-month neurological outcome[38].

Hypercatabolism is a common finding in most critical illness such as surgery, trauma and stroke. Patients with acute critical illness lose on average 5-10% of skeletal muscle mass per week during their ICU stay[14]. Even in paralyzed patients, energy expenditure remained elevated by 20-30% in some trauma patients[10]. Weight reduction, negative nitrogen balance and immune dysfunction constitute a characteristic response in patients with most critical illness. This condition facilitates the onset of acute inflammation and infectious complications, and consequently results in an increased incidence of morbidity and mortality[12].

The gastrointestinal tract is known to play an important role in the immune response aside digesting and absorbing functions. The gut is another intricate immune system that consists of three main components : the epithelium, the mucosal immune system and the commensal normal flora[9]. In the early stages of critical illness, immune function of the gut is compromised through increased intestinal permeability, a reduction of lymphoid tissue and immunoglobulin A secretion and mucosal atrophy[24,25]. The normal florae of the gut

decreases, whereas pathogenic bacteria increase[9]. Translocation of indigenous bacteria or their products from the gut into the circulation, due to increased permeability of the intestinal mucosa, is a well-known feature of the metabolic response in trauma patients. This translocation of pathogenic bacteria from the gut leads to stimulation of systemic cytokine release, and resulting in an increase in infectious susceptibility. The resultant cytokine storm drives the critically ill patients towards uncontrollable multiple organ dysfunction syndrome, thus increasing the risk of mortality[6,9]. Two recent studies highlights the role of EN in ameliorating these changes[24,25]. Intestinal alkaline phosphatase (iAP) is an important brush-border protein expressed exclusively in villus-associated enterocytes, and is thought to actively remove bacterial lipopolysaccharide (LPS) and decrease bacterial translocation[15,36]. The expression and function of iAP is decreased in the presence of starvation in patients with critical illness, but is maintained with the provision of EN[15]. It is likely that the iAP dysfunction during fasting is an important component of the gut mucosal immune compromise seen in critically ill patients[15].

EN is one of preferred modes of nutritional support, as it is more physiologic, less invasive and less expensive than total parenteral nutrition[19,21]. An ideal EN has not yet been developed, but it is generally believed that formulas containing trophic effects for the intestinal mucosa, immune-enhancing nutrients or ingredients to decrease the inflammatory acute phase reaction would be valuable[30]. However, decreased incidence of nosocomial pneumonia in injured patients is probably not a consequence of formula composition but rather a result of early initiation of EN[5,22]. Early EN has also been reported as an infection-reducing factor even when administered below the daily requirements[4,30].

Nasogastric tube feeding is the preferred, universal method for early feeding of injured patients, because it is easy and therefore not time consuming to institute. However, gastric EN is blamed for inducing silent pulmonary aspiration and the resulting pneumonia in ventilated patients suffering from upper digestive intolerance[16,18,32]. A main factor implicated in aspiration associated with enteral feeding in critically ill patients is the size and location of the feeding tube[3]. Continuous postpyloric feeding has been recommended to avoid upper digestive intolerance, but in a review of delivery of enteral feed, only two of 193 patients were fed jejunally[1,20]. The reason may be that transpyloric tube passage is time-consuming and does not necessarily protect from pulmonary aspiration[26]. However, recent clinical trials revealed that early EN can lead to a decreased risk of nosocomial pneumonia[5,22]. In the present study, aspiration episodes in early EN group were not more frequent than in delayed EN group, and incidence of nosocomial pneumonia was significantly decreased in early EN group. It is likely that early EN may promote gut motility, decreases gastric residuals and reduces microaspiration and vomiting, thus reducing the incidence of nosocomial pneumonia.

Some limitations of our retrospective case-control study may have been existed. First, some possibilities of selection bias may exist in this study because of small number of subjects of study group. Second, EN may also be a useful prophylaxis against stress ulceration[31,34,35]. But, it was not analyzed in our present study. Last, the reason for not instituting early EN in some patients was not commented although this proportion was not significant. Ultimate patient's outcome would have been influenced by delayed EN, irrespective of their causes.

CONCLUSION

Our findings suggest that early EN may be an important predictor of outcome of patients with critical hypertensive ICH. Early EN is not likely to increase occurrence of respiratory complications, and may be an useful method of nutritional support in patients with critical hypertensive ICH. Further prospective study is needed to determine the impact of early EN in patients with hypertensive ICH.

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