Original Article

Nutrition program selection in acute ischemic stroke patients with GI hemorrhage

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Background and Objectives: The severity of neurologic impairment is significantly associated with gastrointestinal (GI) hemorrhage. Therefore, the aim of this study was to compare the effect of two nutritional interventions in acute ischemic stroke patients with GI hemorrhage. **Methods and Study Design:** We retrospectively studied consecutive ischemic stroke patients with GI hemorrhage from January 2014 to December 2018. They were stratified into two programs of nutritional therapy after GI hemorrhage: moderate feeding (more than 70% optimal caloric uptake, 50-100 mL/h) and trophic feeding (16-25% of the target energy expenditure, 25 kcal/kg per day, 10-30 mL/h) with supplemental parenteral nutrition. **Results:** The group receiving moderate feeding included 30 patients, and the group receiving trophic feeding and supplemental parenteral nutrition included 32 patients. There was no statistically significant difference between the two groups in the baseline characteristics of the patients. Mortality, Glasgow Coma Scale (GCS) score at discharge, and Glasgow Outcome Scale (GOS) score 3 months after discharge were compared between the two groups. In the moderate feeding group, the overall mortality was significantly lower than in the trophic feeding and supplemental parenteral nutrition group ($p<0.05$). Conscious state and neurological severity were assessed by the GCS score before discharge, and the score was higher in the moderate feeding group than in the other group ($p<0.05$). The GOS score 3 months after discharge was higher in the moderate feeding group than in the trophic feeding and supplemental parenteral nutrition group ($p<0.05$). These three items showed that moderate feeding led to a better prognosis: lower occurrence of mortality, higher GCS score at discharge, and higher GOS score 3 months after discharge. **Conclusions:** This study showed that moderate feeding had a much more profound effect on the outcomes than trophic feeding and supplemental parenteral nutrition, as it was associated with lower mortality, higher GCS score at discharge, and higher GOS score 3 months after discharge.

Key Words: gastrointestinal hemorrhage, nutrition therapy, stroke

INTRODUCTION

Gastrointestinal (GI) hemorrhage is a common complication of the acute and chronic stages of ischemic stroke.[1] One study regarding the association between acute ischemic stroke (AIS) and GI hemorrhage found that the incidence of GI hemorrhage is 1.24% in the United States.[2] Hospitalized AIS patients are at a high risk for various medical complications, which increase morbidity and mortality.[3] The severity of neurologic impairment is significantly associated with GI hemorrhage, which is associated with poor clinical outcomes, including neurologic deterioration, in-hospital mortality, and poor functional outcome.[4,5] All of the above events occur in the early stages of the disease. Furthermore, Yu fang Chou's report showed an association of certain long-term outcomes, such as an increased risk of 3-year mortality, in patients with acute, first-ever ischemic stroke.[6]

GI hemorrhage is a serious problem, especially in elderly and/or multimorbid patients, and it presents the physician with a dilemma, especially neurology clinicians.[7] Additionally, it may interfere with the treatment for ischemic stroke, such as antiplatelet or anticoagulant therapies, and discontinuing this type of therapy can significantly increase the risk for cerebrovascular complications.[6,7] Therefore, neurology clinicians need to actively prevent and cope with GI hemorrhage to improve the clinical prognosis.

In patients hospitalized in the intensive care unit (ICU), except for pharmacological agents (proton pump inhibitors (PPIs) and histamine type-2 receptor blockers (H2RBs)), enteral nutrition is the best prophylaxis against stress ulcer. Early enteral nutrition repairs and retains mucosal integrity throughout the GI tract.[8,9] Pharmacological agents routinely used for stress ulcer prophylaxis do not have any direct effect on mucosal integrity or defensive barriers.[10] Treatment of GI hemorrhage should follow guidelines, the guidelines suggest starting enteral nutrition after the hemorrhage has stopped and no signs

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of rehemorrhage are observed.[2,11] As soon as food can be tolerated, enteral nutrition should be administered. GI hemorrhage and repetitive fasting periods, enteral tube complications, and GI intolerance are the most frequently reported problems.[12]

Considering that the GI-hemorrhage patient receiving enteral nutrition alone often presents GI complications and undernutrition, it is important to know whether the patient needs to add parenteral nutrition and whether moderate feeding or trophic feeding (16-25% of the target energy expenditure, 25 kcal/kg per day, 10-30 mL/h) plus parenteral nutrition is the most effective nutritional program. The purpose of this retrospective study is to differentiate the effect of the two nutritional plans and find the preferred plan for ischemic stroke patients with GI hemorrhage.

METHODS

Study design

A retrospective cohort study was conducted at a tertiary hospital from January 2014 to December 2018. The project was approved by the Research Ethics Committee of the hospital. All consecutive patients aged more than 18 years were eligible. The clinical diagnosis of acute ischemic stroke was performed according to the World Health Organization criteria. The diagnosis was further confirmed by brain computed tomography or magnetic resonance imaging (MRI) scan.[13] A GI hemorrhage event was defined according to Davenport et al as any episode of fresh blood or coffee ground–like material in nasogastric aspirate, hematemesis, melena or bloody stool.[14] Exclusion criteria were as follows: a) specialized nutrition therapy for less than seven days after GI hemorrhage, b) unstable vital signs (excluding short-term unstable vital signs, and c) patients with cancer or other diseases whose life expectancy was less than 3 months.

Nutrition support protocol

The patients were stratified according to the program of nutritional therapy after GI hemorrhage, and the optimal caloric uptake was assumed to be 25 kcal/kg per day. As the daily energy target, one group received a moderate feeding allotment (more than 70% optimal caloric uptake).[2,6] The other group received trophic feeding (16-25% of the target energy expenditure, 25 kcal/kg per day, 10-30 mL/h) and supplemental parenteral nutrition, with a total caloric uptake above 70% of the optimal caloric uptake.[15] Both groups' enteral nutrition was implemented according to the consensus of enteral nutrition in patients with neurological diseases published in 2011.[16] The enteral nutrient solutions included homogenized meals made by our hospital's nutritionist and an enteral nutritional suspension. The parenteral nutrient solution was composed of fat emulsion, amino acids (17) and glucose (11%). Enteral nutrition was started within 24-48 h through a nasogastric tube when the hemorrhage stopped and no signs of rehemorrhage were observed. The total amount gradually reached approximately 70% of the daily energy target in 3-5 days. GI intolerances were monitored each day, especially GI hemorrhage. Parenteral nutrient solution was administered on the day after GI hemorrhage; trophic feeding represented 16-25% of the daily energy target, and the remaining energy intake was administered by parenteral nutrition, for a total amount gradually reaching approximately 70% of the daily energy target. The nutritional therapy was performed for 7-10 days.

Data collection

Patients' age, sex, weight, diagnosis, GCS score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were collected after admission. GI hemorrhage or clinically significant GI hemorrhage, nutritional strategy and actual distributed calories after GI hemorrhage were also monitored, and the corresponding data were collected. Furthermore, recurrent GI hemorrhage after nutritional therapy, complications such as hospital-acquired pneumonia (HAP), mortality, GCS score at discharge, and follow-up index GOS score were collected 3 months after discharge. Moreover, biochemical indexes related to nutrition were collected, such as hemoglobin and albumin.

Statistical analysis

SPSS statistical software, version 22.0 (SPSS Institute, Inc., Chicago, IL, USA) was used for all statistical analyses. We performed two-tailed t tests for normally distributed continuous variables, and Mann-Whitney U tests were performed in cases where the variable was not normally distributed. Chi-squared tests were used for confirmatory variables. p values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Over 5 years, 144 patients had GI hemorrhage. We enrolled 62 patients for analysis, including 39 males and 23 females. Thirty patients were included in the moderate feeding group, with a mean age of 68.4±10.3 years (range 34–85 years), and 32 patients were included in the trophic feeding and supplemental parenteral nutrition group, with a mean age of 68.1±12.9 years (range 41–93 years). Nutrition state, hemoglobin and albumin before GI hemorrhage were compared between the two groups (p>0.05). Age, gender, weight, GCS score and APACHE II score after admission were similar in the two groups (Table 1).

Table 1. Baseline characteristics

	Group 1 (n=30)	Group 2 (n=32)	p
Gender (Male/Female)	12/18	11/21	0.65
Age	68.4±10.3	68.1±12.9	0.92
Weight	70.2±10.8	72.7±10.5	0.35
APACHE II	11.2±4.4	11.7±3.8	0.62
GCS	12.4±3.3	11.4±3.7	0.26
Hemoglobin†	128.9±21.8	119.6±27.8	0.17
Albumin†	36.9±5.3	35.5±5.2	0.34

Group 1: moderate feeding group; group 2: trophic feeding and supplemental parenteral nutrition group. APACHE II: Acute Physiology and Chronic Health Evaluation II; GCS: Glasgow Coma Scale.

†Before GI haemorrhage.

Table 2. Caloric intake

	Group	Number	AVG (E)	SD	SE	*p*
Target energy (kcal)	1	30	1404.0	215.3	39.3	0.35
	2	32	1455.0	209.8	37.1	
Actual energy (kcal)	1	30	1072.0	300.7	54.9	0.08
	2	32	1268.4	533.0	94.2	

Group 1: moderate feeding group; group 2: trophic feeding and supplemental parenteral nutrition group; AVG: average; SD: standard deviation; SE: standard error.

Table 3. Clinical outcomes and prognosis

	Group 1 (n=30)	Group 2 (n=32)	Chi-square	*p*
Main prognostic indicators				
Mortality	0% (0/30)	15.6% (5/32)	4.936	0.03
Improvement (GOS 4-5)	40% (12/30)	15.6% (5/32)	4.623	0.03
GCS score at discharge	13.4±2.5	10.0±4.8	3.505	0.001
Secondary outcomes				
Recurrent GI hemorrhage	16.7% (5/30)	15.6% (5/32)	0.012	0.91
HAP	36.7% (11/30)	48.4% (19/32)	3.197	0.07

Group 1: moderate feeding group; group 2: trophic feeding and supplemental parenteral nutrition group; GOS: Glasgow Outcome Scale; GCS: Glasgow Coma Scale; HAP: hospital-acquired pneumonia.

Caloric intake comparison during the hemorrhage phase

On the basis of the weight, the moderate feeding group required a target energy of 1404±215 kcal, while the trophic feeding and supplemental parenteral nutrition group required a target energy of 1455±210 kcal. The target energy was similar between the two groups. However, the actual energy supply of the two groups fluctuated within a certain range that was different from the target energy. Indeed, the moderate feeding group received an energy of 1072±300.7 kcal, while the trophic feeding and supplemental parenteral nutrition group received an energy of 1268±533 kcal. These values were similar, thus showing no difference in the actual energy supply of the two groups (Table 2).

Clinical outcomes

This study enabled us to assess the effects of two different feeding strategies on clinical outcomes. The two groups were compared to evaluate the main prognostic indicators, i.e., mortality, GCS score at discharge, and GOS score 3 months after discharge. In the moderate feeding group, the overall mortality was significantly lower than in the trophic feeding and supplemental parenteral nutrition group ($p<0.05$). Conscious state and neurological severity were assessed by the GCS score before discharge, resulting in higher scores in the moderate feeding group than in the other group ($p<0.05$). GOS score 3 months after discharge was higher in the moderate feeding group than in the trophic feeding and supplemental parenteral nutrition group ($p<0.05$). The differences in these three items between the two groups were statistically significant, suggesting that the neurological symptoms recovered better in the moderate feeding group. However, no difference was observed in the secondary outcome recurrent GI hemorrhage or HAP between the two groups, suggesting that the moderate feeding dose and daily velocity to the GI hemorrhage patient did not increase the occurrence rate of recurrent GI hemorrhage or HAP (Table 3).

Biochemical parameters

The two groups were compared in terms of hemoglobin and albumin values before GI hemorrhage, and the results were not significant. After receiving the two different nutritional supports, hemoglobin and albumin were compared after one week, after two weeks and before discharge, and at these three different time points, the biochemical parameters were not significantly different between groups (Table 4).

DISCUSSION

GI complications can contribute to increased hospital length of stay, dependence, poor neurological outcome and even death.[1,2,4] The pathophysiological mechanism underlying poststroke GI hemorrhage remains controversial. Camara-Lemarroy et al found that stress, antiplatelet drug use, systemic inflammation, and oxidative stress can all lead to ulcer and result in poststroke GI hemorrhage.[17,18] Hemorrhage can result in hemodynamic insufficiency, but also, importantly, acute episodes of GI hemorrhage in case of discontinuation of antithrombotic treatment lead to a prothrombotic state or a hypercoagulable state. GI hemorrhage may result in abnormal platelet activation or coagulation cascades at many different levels. When cessation of antithrombotic therapy leads to the deterioration of neurological symptoms and poor functional outcome.[17,19,20] these symptoms are associated with poor outcome.

Early enteral nutrition plays an important role not only in the prevention of but also in the therapy against GI hemorrhage. In patients hospitalized in the ICU, enteral nutrition is the best stress ulcer prophylaxis. It has been suggested that the use of PPIs is imperative for curing GI-hemorrhage patients. However, Bonten et al demonstrated that continuous enteral nutrition was more likely to raise

Table 4. Changes in biochemical parameters

	Group 1 (n=30)	Group 2 (n=32)	*p*
Hemoglobin at admission	134.3±17.4	124.0±30.2	0.11
Albumin at admission	39.6±4.9	37.6±4.7	0.11
Hemoglobin before GI hemorrhage	128.9±21.8	119.6±27.8	0.17
Albumin before GI hemorrhage	36.9±5.3	35.5±5.2	0.34
Hemoglobin one week later	123.3±26.4	119.6±24.1	0.63
Albumin one week later	34.5±3.3	34.2±4.1	0.76
Hemoglobin two weeks later	115.9±26.6	117.1±22.7	0.90
Albumin two weeks later	35.7±3.3	32.6±5.0	0.05
Hemoglobin before discharge	119.1±22.1	113.9±22.9	0.41
Albumin before discharge	36.5±5.3	34.9±4.2	0.24

Group 1: moderate feeding group; group 2: trophic feeding and supplemental parenteral nutrition group; GI: gastrointestinal.

gastric pH to 3.5 than H2RBs or PPIs.[21] According to Hernandez et al, enteral fasting for four days in medical ICU patients caused mucosal atrophy.[22] However, in animal models, enteral nutrition may protect the gastric mucosa from stress-related gastric mucosal damage,[23] and patients receiving enteral nutrition have a lower incidence of stress ulceration than unfed patients.[24] Another study reported that a lack of enteral feeding results in GI mucosal atrophy, bacterial overgrowth, increased intestinal permeability, depletion of the liver's antioxidant enzymes, and possible translocation of bacteria and/or bacterial products.[25] Enteral nutrients buffer acid, may act as a direct source of mucosal energy, and induce the secretion of cytoprotective prostaglandins and mucus.[26] Furthermore, nutrition support attenuates the metabolic response to stress, limits oxidative cellular injury, and favorably modulates the immune response.[25,27] In case of hemorrhage due to gastric erosions, enteral nutrition can be resumed as soon as the patient tolerates it.[24] One post hoc analysis showed that continuous enteral nutrition was associated with a 70% reduction in the rate of ulcer GI hemorrhage.[28] Furthermore, the guidelines suggest administering more than 70% of goal calories (25–30 kcal/kg/day) to achieve the clinical benefit of enteral nutrition over the first week of hospitalization.[15]

The program of early enteral nutrition in patients with GI hemorrhage is a challenge to neurology clinicians. Early enteral nutrition can be poorly tolerated, with gastric repletion, regurgitation, vomiting, and a risk of aspiration pneumonia, especially during the first few days of treatment. However, the gradual introduction of early enteral nutrition can also result in patients not receiving their theoretical calorie requirements,[29] thus increasing the risk of HAP.[25] The guidelines suggest delaying enteral nutrition in patients with active upper GI hemorrhage.[2] Repetitive fasting periods, enteral tube complications, and GI intolerance are the most frequently reported problems.[30] Furthermore, it should be noted that nasogastric tubes can cause fluid aspiration and pneumonia.[31] In critical care, moderate feeding (lower than target) is supported by observational and prospective studies and is considered beneficial or at least as effective as full-feeding. Trophic feeding has been proposed as a strategy to maintain gut integrity and function due to reduced feeding complications and GI intolerances.[32] Trophic feeding tends to cause caloric and protein deficits for a longer time, and caloric and protein deficits are significant factors that increase the ICU stay and enhance mortality. These findings are relevant and suggest that more attention needs to be paid to the nutrition of this population of patients.[30]

However, relying solely on enteral nutrition often results in not achieving caloric targets. Indeed, even in stable ICU patients, early initiation of enteral nutrition is associated with a high incidence of GI intolerance and serious adverse events, requiring the suspension of enteral nutrition.[33] The selection of enteral versus parenteral nutrition should depend on the availability of the GI tract for feeding and the patient's tolerance levels.[31] The guidelines suggest delaying enteral nutrition in patients with active upper GI hemorrhage and starting enteral nutrition when the hemorrhage has stopped, and no signs of rehemorrhage are observed.[2] We do not know how long the hemorrhage will stop with no signs of rehemorrhage; the time depends on the patient's conditions. If we wait as long as possible, the more prolonged the duration of GI hemorrhage, the more likely the patient is to develop underfeeding. Underfeeding has been associated with an increased incidence of infection and with other complications, such as prolonged ventilation, prolonged hospital length of stay and pressure ulcers.[33,34] Only if enteral nutrition does not meet the energy targets does supplemental parenteral nutrition play a pivotal role in the optimization of feeding of critically ill patients with incomplete tolerance to enteral nutrition, and supplemental parenteral nutrition does not cause any harm if overfeeding is avoided by careful prescription.[35]

To avoid caloric and protein deficits from solely trophic feeding, this study adopted trophic feeding and supplemental parenteral nutrition to reach the nutritional support target. Trophic feeding maintains gut integrity due to the reduced feeding complications and GI intolerances. Parenteral nutrition supplements the caloric and protein deficit as much as possible. We compared trophic and parenteral nutrition to the moderate feeding (lower than target) of enteral nutrition in terms of mortality, GCS score at discharge, GOS score 3 months after discharge. This study showed that moderate feeding by enteral nutrition had a much more profound effect on the outcomes than trophic feeding and supplemental parenteral nutrition, since moderate feeding by enteral nutrition was associated with a low occurrence of mortality and better prognosis. The two strategies evaluated in this study were not associated with a difference in recurrent GI hemorrhage or HAP. Thus, this study demonstrated that solely moderate feeding is superior to supplemental parenteral nutrition. This study has some limitations. As a retrospective study, the findings may be misleading. First, all patients did not undergo endoscopy to provide evidence of GI bleeding or its causality. Second, biased nutritional interpretations might have arisen on account of nutritional treatment protocol selection and inconsistent enteral nutrition. Third, we cannot accurately obtain the patients' actual energy demand by indirect calorimetry. Fourth, a second stroke may affect one nutritional treatment more or less. Therefore, further prospective studies will be needed to investigate the best therapy in patients with GI hemorrhage.

Conclusions

This study showed that moderate feeding had a much more profound effect on the outcomes than trophic feeding and supplemental parenteral nutrition, since the former was associated with lower mortality, higher GCS score at discharge, and higher GOS score 3 months after discharge, suggesting a better prognosis after moderate feeding. The two evaluated strategies were not associated with a difference in recurrent GI hemorrhage or HAP. Our study also has some limitations. Principally, the study design was retrospective, with a relatively small sample size, and our study populations were too small to perform sensitivity analysis.

AUHTOR DISCLOSURES

The authors declare no conflict of interest.

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