—**Original**—

Too Early Initiation of Enteral Nutrition is Not Nutritionally Advantageous for Comatose Acute Stroke Patients

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Background: Comatose acute stroke patients are at high risk of malnutrition, especially hypoproteinemia. However, when to start and how to provide nutrition to these patients are unclear. The purpose of this study was to determine the optimum timing and methods of nutritional supplementation to comatose acute stroke patients.

Methods: A total of 273 comatose acute stoke patients who were unable to eat were enrolled. They received peripheral intravenous low-calorie solutions for the first 4 days after admission (days 0–3), and serum protein concentrations were measured on days 2, 3, and 4. From day 4, 5 different nutritional regimens were administered (25 kcal/kg/day), (including enteral nutrition [EN], total parenteral nutrition [TPN], tube feeding of 20% glucose solution, and combinations of these nutritional supplementations),. Serum concentrations of total protein and albumin were measured on days 10, 14, and 21. The patients who had EN until day 21 from day 4 were defined as EN group, and who had TPN were as TPN group.

Results: Serum protein concentrations decreased slightly on day 2 and decreased significantly on days 3 and 4. From day 4 to 14, the recovery of serum protein was better in the TPN group than in the EN group. Conversely, after day 14, recovery from hypoproteinemia was better in the EN group than in the TPN group. However, when diarrhea was caused by EN, further hypoproteinemia occurred and caused patients to require TPN. The recovery from hypoproteinemia was earliest in patients receiving TPN with 20% glucose fed through a nasogastric tube from day 4 to 13 followed by EN after day 14. Hospitalization was statistically shorter for patients with a nutritionally early recovery than for patients with a delayed recovery, but clinical outcome did not differ significantly between the groups.

Conclusion: It is nutritionally disadvantageous not to start nutritional support within 3 days after admission in comatose acute stroke patients. However, starting EN too early is not nutritionally beneficial, and TPN with 20% glucose fed through a tube is recommended as adequate nutrition for these patients. However, TPN should not be employed for longer than 10 days, because switching to EN after this period contributes to better nutritional recovery than continuing TPN.

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Key words: serum albumin, coma, enteral nutrition, stroke, total parenteral nutrition

Introduction

In patients with acute stroke, malnutrition causes high incidences of respiratory and urinary tract infections, a high mortality rate, worse outcomes, and long duration of hospitalization[1–4]. Poor nutritional conditions, particularly hypoalbuminemia, lead to unfavorable functional recovery[5–8], but intensive nutritional supplementation has recently been reported to improve rehabilitation outcomes[9,10]. However, the nutritional status of patients with acute stroke may steadily deteriorate during hospitalization regardless of adequate nutritional support[11,12], and half of the patients admitted to inpatient rehabilitation stroke centers are reportedly undernourished[13]. Therefore, nutritional management for patients with acute stroke

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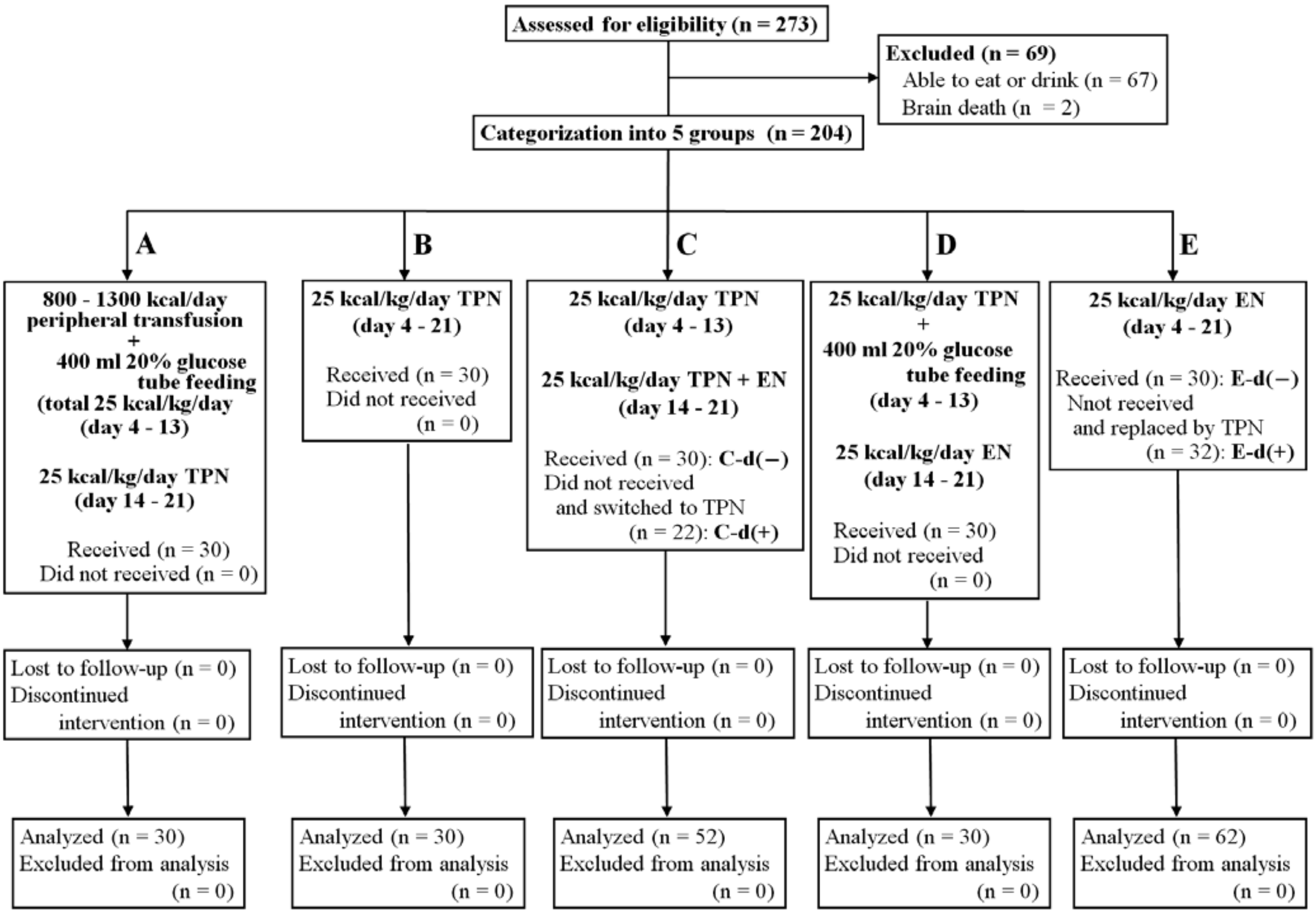

Fig. 1 Consort flow chart of the study

Total number of the nominated patients was 273; among them, 69 were exclueded because of recovery of eating function or deterioration to brain death within three days. The patients were categorized into 5 groups (from A to E) in hospitalization order. Neither missing follow-up nor discontinued intervention cases existed in any groups.

should be implemented at the time of admission. To achieve early recovery from hypoproteinemia, the present study focused on determining: (1) when nutritional intervention should be started in patients unable to swallow and (2) which type of intervention should be employed: total parenteral nutrition (TPN) or enteral nutrition (EN).

Materials and Methods

This prospective study was performed at Teikyo University Mizonokuchi Hospital from 2001 through 2003, Kochi University Kochi Medical School from 2004 through 2007, and at Risshou Koseikai Hospital from 2008 through 2010. Ethics committees in each institution approved the study and protocols. Study details were explained to each patient's family, and informed consent was obtained in written form with a signature.

A total of 273 patients with acute stroke were enrolled. The patients fulfilled the following criteria: (1) older than 40 years, (2) consciousness level less than 12 (E3V4M5) on the Glasgow Coma Scale, and (3) unable to eat or drink for at least 4 days. However, patients were excluded for the following criteria: (1) emergency operation under general anesthesia, (2) existing hypoproteinemia (<6.0 g/dL total protein or <3.0 g/dL albumin) on admission because of complications, (3) aspiration pneumonia on admission, and (4) death within three days.

1. Peripheral Venous Transfusion in Acute Period

The day of admission was defined as day 0. Until day 3 the patients received intravenous low-calorie solutions of 500 to 700 kcal/day in a total volume of 1,500 to 2,400 mL including glycerol (127 kcal/200 mL). The blood glucose level was maintained at less than 150 mg/dL using rapid-acting insulin. Serum concentrations of protein and albumin were measured on days 0, 2, 3, and 4.

2. TPN and EN Nutrition Groups (Fig. 1)

On day 4, nutritional support was begun. The patients were assigned to a group (from A to E) in order of hospitalization; first to A, second to B, and third to C. (**Fig. 1**). The total serum concentrations of protein and albumin were evaluated on days 10, 14, and 21. The total number

Table 1 Patient Characteristics

	N	Male : Female	Mean age (years) ±SD
Ischemia	171	92 : 79	76.8±9.4
Hemorrhage	102	63 : 39	69.4±13.8

of patients in this study decreased to 204 because 67 patients became able to eat or drink and 2 cases had died by day 21 (**Fig. 1**).

Group A: Peripheral intravenous low-calorie solutions and lipid solutions (20% Intralipid: Otsuka Pharmaceutical Co., Tokyo, Japan) were administered until day 13 with feeding via a nasogastric tube of 200 mL of a 20% glucose solution twice a day from day 4 to day 13 (25 kcal/kg/day), and EN (25 kcal/kg/day) was started from day 14 (n=30).

Group B: High-calorie TPN (25 kcal/kg/day containing vitamins and minerals) was started on day 4 and continued to day 21. Neither albumin nor globulin was administered intravenously during this period (n=30).

Group C: The TPN (25 kcal/kg/day with vitamins and minerals) was administered on days 4 through 13, and 400 kcal/day of EN was begun on day 14. The volume of EN was increased step-wise with concurrent tapering of the TPN, to maintain a total caloric intake of 25 kcal/kg/day. The EN was continued until day 21 in the absence of diarrhea (C-d(−): n=30), but EN was stopped and TPN was restarted if diarrhea was caused by EN (C-d(+): n=22).

Group D: Both TPN and feeding of 20% glucose with a nasogastric tube were started on day 4 and continued through day 13, and the feeding was changed to EN (25 kcal/kg/day) on day 14 (n=30).

Group E: The EN (25 kcal/kg/day) was started on day 4 and continued until day 21 if diarrhea did not occur (E-d(−): n=30). If diarrhea occurred, EN was replaced with TPN (E-d(+): n=32).

(The number of patient in each group was planned to be 30 evenly, but failed to unify the number in each group because diarrhea caused by EN forced a change from EN to TPN. However, the cases with diarrhea were evaluated in a separate nourishment state as a subgroup after the nutritional methods had been changed.)

For early feeding with an nasogastric tube, 20% glucose was used instead of EN in Groups A and D, because of the evidence from dogs that 20% glucose solution stimulates bowel movements and increases the blood flow of the superior mesenteric artery[14]. The EN, containing 1 kcal/mL, was diluted to 1.5 times with warm water to lowered osmotic pressure and administered in diluted form. In Groups A and D, the EN dosage was initially 150 mL/hr and was increased to 200 mL/hr if the patient remained diarrhea-free for at least 3 days. In Group C, the volume of EN was initially 400 mL (400 kcal)/day and was increased stepwise by 200 mL (200 kcal) each day. During the period, TPN was tapered and EN only was administered by day 18 to maintain a total caloric intake of 25 kcal/kg/day. In Group C, the EN dosage was initially 100 mL/hr and was gradually increased to 200 mL/hr, unless diarrhea occurred. In Group E, the EN dosage was initially 150 mL/hr and was increased to 200 mL/hr as in Groups A and D.

For tube feeding, a 14- or 16-French nasogastric tube (Terumo Corp., Tokyo, Japan) was inserted into patients' stomachs up to a length of 55 to 65 cm from the nostril at the time of admission. Correct placement of the tube was verified with x-ray examination. The patients were placed in a 45°-to-60° head-up position during EN feedings and kept in this position for 1 hour after the feeding was completed.

3. Definition and Management of Diarrhea

Diarrhea is generally defined according to 3 characteristics: fecal frequency, consistency, and quantity[15]. On the basis of the consistency, diarrhea was considered as follows: (1) mild diarrhea: paste feces; (2) moderate diarrhea: loose feces; and (3) severe diarrhea: watery feces. The EN was stopped and TPN was restarted when more than 200 g of severe diarrhea occurred or when more than 200 g of moderate diarrhea continued for more than 2 days.

4. Statistical Analysis

Statistical analysis was performed with computer program Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, WA, USA). To evaluate the serum protein and albumin concentrations, the χ^2-test and Student's *t*-test were used to determine any statistically significant differences between 2 groups. To determine statistically significant differences between more than 2 variables, the Kruskal-Wallis and Tukey tests were used. For all tests, results with P values<0.05 were considered statistically significant.

Results

1. Patients

Of the 273 patients, 171 had ischemic disease and 102 had hemorrhagic disease (**Table 1**). In the male-to-female ratios for ischemic and hemorrhagic strokes, the number

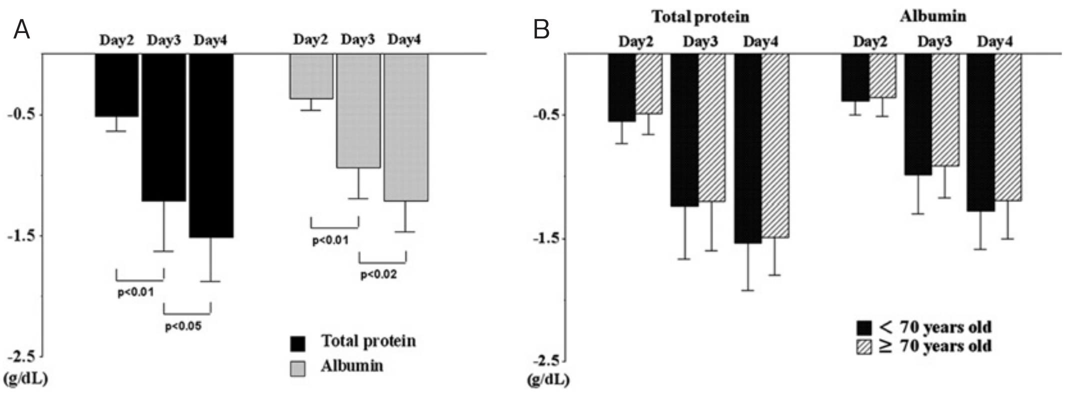

Fig. 2 (A) Decreases in serum total protein and albumin concentrations during peripheral intravenous low-calorie supplementation.
On day 2, the concentrations of total protein and albumin were reduced by less than 0.5 g/dL. The reduction became greater on day 3, and total protein decreased further by 1.5 g/dL and albumin by 1.2 g/dL on day 4, leading to high risk of malnutrition. The reductions of both total protein and albumin concentrations were significant between days 2 and 3, and between days 3 and 4.
(B) Relationship of age to the reduction in serum total protein and albumin concentrations. The reduction in total protein and albumin concentrations in acute stroke patients during administration period of peripheral low-calorie solutions did not differ significantly between patients who were 70 years or older and those who were younger than 70 years.

Table 2 Differences in total serum protein and albumin concentrations on admission between patients younger than 70 years and patients 70 years or older

Age (years)	N	Total protein (g/dL) ±SD	Albumin (g/dL) ±SD
<70	113	7.23±0.78	3.94±0.58
≥70	160	6.67±0.54	3.57±0.60

of male patients was bigger but was not statisitically significant (P>0.05). The mean age of patients with ischema was slightly greater than that of patients with hemorrhage, but the difference was not significant (P>0.05).

2. Decreases in the Concentrations of Total Serum Proteins and Albumin, and the Relationship to Age

Decreases in the concentrations of total serum proteins and albumin were not significant on day 2, but both concentrations decreased rapidly on day 3 (reduction of total protein was 1.2 g/dL and that of albumin was 0.9 g/dL) and decreased further on day 4 (reduction of total protein reached 1.5 g/dL and that of albumin reached 1.2 g/dL) (**Fig. 2A**). Reductions in both total serum protein and albumin concentrations were significant (P<0.05) between both days 2 and 3 and between days 3 and 4. Approximately 80% of the reduction of the total serum protein concentration was a result of a loss of serum albumin. Age was not a risk factor for protein-energy reduction because no significant differences between the 2 age groups were identified in the reduction of total serum protein and albumin concentrations (**Fig. 2B**). However, the absolute values of total serum protein and albumin levels on admission were lower in patients 70 years or older (**Table 2**) and suggested that such were more prone to hypoproteinemia and hypoalbuminemia.

Table 3 Statistics in Group A, B, C-d (+), C-d (–), D, E-d (+), and E-d (–)

Group	N	Male : Female	Mean age (years) ±SD
A	30	16 : 14	70.9±9.8
B	30	18 : 12	74.6±13.6
C-d (+)	22	13 : 9	76.3±10.3
C-d (–)	30	17 : 13	75.3±12.7
D	30	17 : 13	74.8±14.1
E-d (+)	30	19 : 11	73.1±12.8
E-d (–)	32	18 : 14	75.5±9.6

3. Recovery from Hypoproteinemia and Hypoalbuminemia in Each Group

The number of patients, the male-to-female ratios, and the mean age with standard deviations for each patient group are shown in **Table 3**. The mean ages did not differ significantly among the 7 groups.

Day 10

Total protein: The most rapid recovery from hypoproteinemia was identified in Group D (TPN plus feeding of 20% glucose with a nasogastric tube), but statistical differences were not identified among Groups A, B, C, and

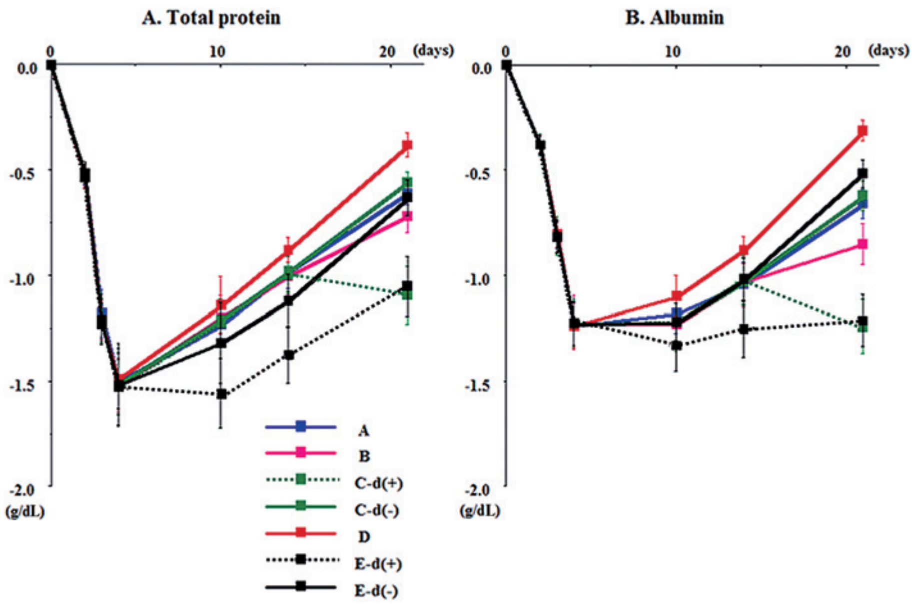

Fig. 3 Recovery from hypoproteinemia and hypoalbuminemia after nutritional supplementation with TPN or EN
(A) Total protein
On day 10, there were no significant differences in recovery of total serum protein among Groups A, B, C, and D, but Group E showed poorer recovery. On day 14, Group E-d (–) still demonstrated lower protein levels than Groups A, B, C, and D. However, by day 21, Group E-d (–) caught up with Group A and C-d (–), although Group B showed poor recovery of total protein after day 14. Diarrhea caused further reductions in total protein in Groups C-d (+) and E-d (+).
(B) Albumin
On days 10 and 14, concentration of serum albumin demonstrated the same pattern of change as total protein, exhibiting the highest recovery in Group D. On day 21, Group D also showed the highest recovery, and Group E-d (–) also revealed the second highest recovery, whereas Group B demonstrated very poor recovery of albumin after day 14. As seen for total protein analysis, diarrhea caused further decrease in albumin in both Groups C-d (+) and E-d (+).

D (**Fig. 3A**). Patients with TPN or peripheral nutrition plus feeding of 20% glucose with a tube from day 4 (Groups A, B, C, and D) showed more rapid recovery from hypoproteinemia than those with only EN from day 4 (Group E-d(−)). However, only Group D demonstrated significantly better recovery than Group E-d(−) (P<0.05). In the EN group, diarrhea further reduced total protein compared with day 4 (E-d(+)).

Albumin: Group D had the earliest serum albumin recovery than did all other groups (P<0.05) (**Fig. 3B**). Among Groups A, B, C, and E-d(−) there were no significant differences in serum albumin recovery, and hypoalbuminemia definitely worsened with diarrhea (E-d(+)).

Day 14

Total protein: Group D had the earliest total serum protein recovery compared with any other group (P<0.05) (**Fig. 3A**). Groups A, B, and C showed significantly better recovery than Group E-d(−) (P<0.05). Group E-d(+) exhibited gradual recovery in total serum protein concentration after the change to TPN with the same degree of recovery as Group B (TPN only).

Albumin: Group D displayed the highest serum albumin level on days 10, 14, and 21 of all groups (P<0.05) (**Fig. 3B**). Among Groups A, B, C-d(−), and E-d(−), there were no statistically significant differences in albumin concentration. Group E-d(+) showed the poorest serum albumin recovery even after switching to TPN from EN.

Day 21

Total protein: Serum total protein concentrations were significantly higher in the EN Groups (Groups A, C, D, and E-d(−)) than in the TPN Group (Group B) on day 21 (P<0.05) (**Fig. 3A**). Group D demonstrated the highest total serum protein recovery of any group (P<0.01), although the level of serum total protein did not reach the admission level. When diarrhea was induced by EN, the serum total protein decreased rapidly in Group C-d(+).

Albumin: The concentration of serum albumin was markedly lower in groups that had continued TPN from day 14 to day 21 (Group B and E-d(+)) than in the EN groups (Groups A, C, D, and E-d(−)) ($P<0.01$) (**Fig. 3B**). Group D had the highest level of serum albumin among all groups ($P<0.01$), whereas Group E-d(−) showed better recovery of serum albumin than did Group D from day 14 to 21. Diarrhea caused further reduction of serum albumin levels after day 14 (Group C-d(+)).

Most patients in Groups A and D, who were fed 20% glucose through a nasogastric tube, had mild diarrhea that resolved naturally within several days, and no moderate-to-severe diarrhea was observed when 20% glucose was replaced with EN. In contrast, 42.3% of patients (22 of 52 patients) of Group C, who underwent a 2-week fasting period, had diarrhea after EN was started, and 51.6% of patients (32 of 62 patients) of Group E, who received EN starting on day 4, had diarrhea. For most patients in C-d(+) and E-d(+) groups, diarrhea occurred during the second or third day after EN was started.

Clinical outcomes did not differ significantly among the nutrition groups, and most of patients transferred to a special nursing home where active rehabilitation is not performed.

Discussion

Clinicians must reduce the risk of hypoproteinemia in comatose acute stroke patients considering their increased energy demands in the recovery period[8,16]. In the present study, about 80% of the decrease of the total serum protein concentration was due to a loss of albumin (**Fig. 1**), and nutrition is considered the single most important factor in the regulation of albumin synthesis[17,18]. Albumin is important for its antioxidant effects, maintenance of normal microvascular permeability by binding to the endothelial glycocalyx, antiedema effects, and neuroprotection[7]. In patients with hypoalbuminemia due to stroke the risk of infectious complications is greater than in patients with normal albumin concentrations[2,3]. The serum albumin concentration is reportedly related to nutritional risk as follows: >3.5 g/dL, no risk; 3.0 to 3.5 g/dL, low risk, if 2.5 to 3.0 g/dL, moderate risk; and <2.5 g/dL, high risk[16]. In the present study, more than 50% of patients receiving only peripheral low-calorie supplementation were at a moderate nutritional risk by day 3, and more than 50% of these patients were at a high nutritional risk by day 4. If the nutritional intake of a patient who has had an acute stroke is inadequate for a prolonged period of time the risk of malnutrition is reportedly increased[8,19]. However, a "prolonged period" has not been defined. The present data resolved this question and proved that adequate caloric supplementation should be provided to patients within 3 days of admission, although the prevalence of malnutrition and the risk of malnutrition in patients with acute stroke are reported to increase remarkably during the first 10 days of admission[20].

The next subject examined in the present study was what constitutes adequate nutrition for comatose acute stroke patients. In general, EN is considered physiologically superior to TPN. Long-term TPN might cause deterioration of gut barrier function, which generates intestinal bacterial overgrowth, bacterial translocation, reduced intestinal mucosal immunity because of decreased production of immunoglobulin A, and atrophy of the intestinal mucosal villi[21–23], although the definition of "long-term" has not been clarified.

However, those results do not lead to a conclusion that an early start of EN supplementation is nutritionally more beneficial than TPN for patients with a severe acute stroke. The present study suggests that for comatose acute stroke patients the early start of EN is not more nutritionally beneficial than early TPN administration. From days 4 to 14, the concentrations of both serum total protein and albumin recovered more rapidly in TPN groups rather than EN groups (**Fig. 3**). Hypercatabolism is common in patients who have had a severe stroke[24,25], and aggressive nutritional support does not prevent substantial total protein loss during this hypercatabolic state[26]. Under these conditions, a simple glucose solution is more acceptable than EN, because active administration of amino acids and protein may adversely affect nitrogen balance and increase the concentration of blood urea nitrogen[25]. Another disadvantage of an early start of EN administration in comatose acute stroke patients was the high incidence of diarrhea. Even with adequate EN supplementation, diarrhea can occur. Diarrhea causes hypovolemia, which may cause ischemia to increase or recur in stoke patients. In addition, EN malabsorption resulting from diarrhea also leads to severe hypoproteinemia and hypoalbuminemia. Immobilization in patients receiving EN decreases both bowel peristalsis and the absorption of nutrition and may also lead to diarrhea. However, bowel movements seem to be largely influenced by autonomic nervous conditions, and the present study found no significant difference in nutritional conditions among the 7 nutritional groups in terms of consciousness levels.

Another important result of the present study was to clarify that TPN should not be provided for longer than 10 days. Between days 14 and 21, EN (Groups A, C-d(−), D, and E-d(−)) contributed to a greater rise in the serum concentrations of total protein and albumin than did TPN (Group B and C-d(+)) (**Fig. 3**). In particular, the concentration of serum albumin in the TPN groups did not recover well during the study period.

The early start of EN has been thought to improve the functional outcome after stroke[27], but the Feed Or Ordinary Diet trial found no significant differences in outcome between an early and late start of EN[5,28]. As the present study has found, an early start of TPN plus tube feeding of 20% glucose is more nutritionally beneficial than an early start of EN in patients after an acute stroke.

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