Original Article

Outcomes after Postoperative Amino Acid Supplementation in Patients Undergoing Elective Upper and Lower Gastrointestinal Tract Surgery: Randomized Controlled Trial

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Background: Surgical patients in a catabolic phase will affect vital functions such as the respiratory mechanism. Peripheral parenteral nutrition with amino acids can reduce fat and protein breakdown and preserve the protein sparing effect resulting in better outcomes. Due to financial limitations, most Thai surgical patients receive only peripheral venous feeding with glucose alone, without amino acids.

Objective: To investigate the postoperative nitrogen balance among Thai surgical patients receiving elective gastrointestinal surgery with different peripheral intravenous feeding.

Materials and Methods: Thirty-six post-elective gastrointestinal surgery patients were enrolled in an open labeled, prospective, randomized controlled trial. Patients received 3% amino acid with 7.5% dextrose (n = 12), 5% dextrose (n = 12), or 10% dextrose (n = 12). From the first postoperative day, the peripheral venous solutions were infused into the three groups for 72 hours. The nitrogen balance was assessed by collecting 24 hours urine on the first and third post-operative day. Markers for protein metabolism were investigated (viz., pre-albumin, transferrin, and blood urea nitrogen).

Results: The nitrogen balance on the first and third post-operative day were observed in all groups. There was significantly improvement after 3% amino acid plus 7.5% dextrose infusion (-1.37, -2.47), compared with either 10% dextrose (-8.53, -7.04), or 5% dextrose (-8.76, -7.90) infusion. Length of stay, serum transferrin, and serum pre-albumin made no significant difference among the three groups.

Conclusion: Three percent amino acids plus 7.5% dextrose reduced post-operative negative nitrogen balance in gastrointestinal tract surgical patients without any serious complications.

Keywords: Randomized controlled trial, RCT, Amino acid, Peripheral parenteral nutrition

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In general, surgical procedures interrupt normal body functions. All surgical patients are in a catabolic phase associated with a negative nitrogen balance, muscle protein breakdown, and weight loss[1-3]. If catabolism continued with no nutritional support, vital functions would be compromised such as respiratory and myocardial function, resulting in an increased rate of morbidity and mortality[4].

After surgery, most patients receive peripheral parenteral infusion for fluid and energy supplementation. During starvation, the energy used come from glucose stored as glycogen. When the glycogen reserves are depleted, glucose can be obtained from the breakdown of fat and protein. During the peri- and post-operative periods, surgical patients may not be allowed to eat or cannot eat enough. Glucose solution can preserve or reduce fat and protein breakdown, resulting in a protein sparing effect. Intake of 50 g/day of glucose can reduce production of ketones that result from the breakdown of fat.

Surgical patients who received intravenous fluid post-operative with amino acid plus glucose had better nitrogen balance than surgical patients who received glucose alone. Better nitrogen balance can also reduce plasma glucose and plasma insulin levels[5-8].

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Although peripheral intravenous feeding with amino acid plus glucose is known to benefit the nitrogen balance, there is lack of evidence in Thai people. Most surgical patients are still receiving peripheral intravenous feeding with glucose alone if they were predicted to start oral intake within seven days. Study risk and benefit of intravenous feeding amino acid plus glucose may help surgeons to consider postoperative peripheral intravenous feeding regimen.

The authors aimed to investigate post-operative nitrogen balance among Thai surgical patients undergoing elective gastrointestinal surgery with different peripheral intravenous feeding regimen of (a) amino acid plus glucose or (b) glucose alone.

Materials and Methods

Study objectives

The aim of the present study was to compare peripheral intravenous amino acid plus glucose with glucose alone, in terms of negative nitrogen balance (primary outcome), complications, and length of hospital stay.

Design

The present was a single center, open label, randomized controlled trial. Patients were randomized into three arms, namely, 3% amino acid plus 7.5% dextrose, 5% dextrose, and 10% dextrose, using block randomization. The randomization was started after the surgery.

Ethics

The project was approved by the Khon Kaen University Ethics Committee for Human Research (registration number: HE571063) and the Thai Clinical Trials Registry (registration number: TCTR20140929001).

Study settings

The trial was conducted at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand.

Study population

Inclusion criteria: Undergone elective gastro-intestinal surgery, at least 18 years of age but a maximum of 70, and mild to moderate malnutrition.

Exclusion criteria: Liver surgery, serum creatinine greater than 2, diabetes mellitus, severe cardiovascular disease, blood loss of more than 1,000 ml, postoperative ICU requirement and/or complication(s) requiring repeat surgery within three days.

Procedure

After their respective gastrointestinal surgery, patients were given peripheral feeding with 5% dextrose in normal saline solution/2 or normal saline with adjust volume according to the Holliday-Segar nomogram. In the morning, patients were randomized (using a computer-generated sequence with a varying block size 2, 4, 6) distributed in a sealed opaque envelope. Each envelope contained a card marked with three different peripheral feeding methods, 1) 3% amino acids plus 7.5% dextrose, 2) 10% dextrose in normal saline solution/2, or 3) 5% dextrose in normal saline solution/2. All patients received different peripheral feeding but at most 2,000 ml/day for postoperative day 1 to day 3. According to Holliday-Segar, if extra peripheral fluid was needed, they received 5% dextrose in normal saline solution/2. Patients were allowed to drink only water during immediate postoperative period to postoperative day 3. After day 3, they were started on a diet, liquid diet, soft diet, and regular diet, respectively.

Measurements

Before surgery, blood test was taken to determine pre-albumin, total iron binding capacity [TIBC], and blood urea nitrogen [BUN]. On post-operative day 1 and 3, the same blood tests were performed again. In addition, 24-hour urine for urea nitrogen was done on post-operative days 1 and 3.

Outcome measures

- Nitrogen balance was calculated as the difference between nitrogen intake and nitrogen loss
- Nitrogen intake = protein intake (g/day)/6.25
- Nitrogen loss = urinary urea nitrogen (g/day) + 4 g*
- *4 g is a fudge factor to account for miscellaneous nitrogen losses

Serum transferrin (mg/dl) = 0.8 × TIBC (mg/dl)

Sample size calculation

The sample size was calculated using a 2-tailed test criterion for analysis. The aim of the study was to identify whether or not different treatments would achieve a different post-operative nitrogen balance[8]. The sample size was calculated for a statistical significance of 95% (a = 0.05) and for the study to have a differentiating power of 90% (b = 0.1). Analysis of the data was performed on an intention to treat basis. The present study, thus, required 20 samples in each group (1:1:1).

Statistical analysis

The demographic characteristics of the participants (categorical data) were described using frequencies and percentages, while means and standard deviations were used for the continuous data.

The treatment strategies were compared on an intention to treat basis. Continuous variables were tested by using the ANOVA test with Bonferroni correction. All analyses were performed using Stata version 10.0 (StataCorp, College Station, TX). All test statistics were two-sided and a *p*-value of 0.05 or less was considered statistically significant.

Results

Between June 10, 2014 and August 12, 2015, 45 consecutive patients were enrolled in the present study. Thirteen patients were excluded from the study while a total number of 36 patients were available for the analysis. The patients were randomized into three treatment regimens (Figure 1). The baseline characteristics (Table 1) indicated the patients in the three groups were similar except that the number of females and pre-operative serum TIBC were prevalent in the group receiving 3% amino acid plus 7.5% dextrose. Most of the case were stage III and IV colorectal cancer.

Complete follow-up was achieved in all patients but some of the data were lost during the post-operative data collection process.

Length of hospital stay

There was no significant difference in length of hospital stay among the groups (Table 2, 3).

Nitrogen balance

The respective nitrogen balance on the first and third post-operative day was significantly improved after 3% amino acid plus 7.5% dextrose infusion, compared to 5% dextrose infusion and 10% dextrose infusion (Table 2, 3).

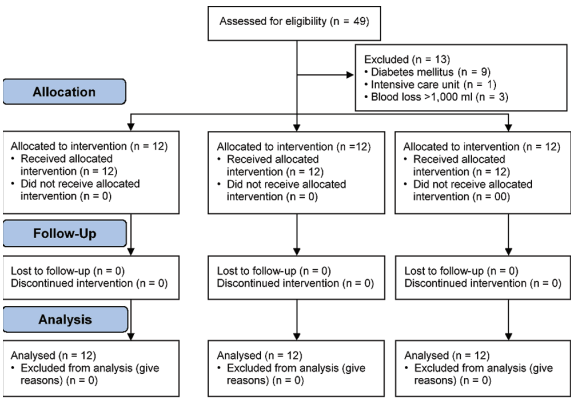

Figure 1. Consort diagram.

Table 1. Demographic characteristics

	3% amino acid + 7.5% dextrose	10% dextrose	5% dextrose
No. of patients	12	12	12
Gender			
Male	2	9	8
Female	10	3	4
Type of cancer [CA]			
CA stomach	2	3	2
CA colon	6	6	5
CA rectum	4	2	4
Other	0	1	1
Staging			
Stage I	2	1	2
Stage II	2	2	4
Stage III	4	4	3
Stage IV	4	4	2
Other	0	1	1
Age, mean ± SD	52.75±9.64	58.92±10.20	55.41±7.57
TIBC pre-op, mean ± SD	292.91±79.72	246.08±92.55	261.17±80.13
Transferrin pre-op, mean ± SD	234.32±63.77	196.87±74.04	208.93±64.10
Prealbumin pre-op, mean ± SD	14.75±5.93	11.53±8.10	12.01±7.85
BUN pre-op, mean ± SD	12.05±5.21	9.52±2.69	10.80±3.17

TIBC = total iron binding capacity; BUN = blood urea nitrogen

Nitrogen loss

The respective nitrogen loss was observed on the first and third post-operative day in all groups. Nitrogen loss on the third post-operative day was significantly improved after 10% or 5% dextrose infusion, compared to 3% amino acid plus 7.5% dextrose infusion. Notwithstanding, the respective nitrogen loss on the first and third post-operative day was not significantly different among other groups (Table 2, 3).

Transferrin and pre-albumin

The respective serum transferrin and pre-albumin on the first and third post-operative day was not significantly different among the groups (Table 2, 3).

Discussion

The injury caused by elective gastrointestinal surgery may interrupt normal body function, including hyper-metabolism and increased catabolism, leading to a negative nitrogen balance, muscle protein breakdown,

Table 2. Postoperative parameter comparing between 3 groups

	3% amino acid + 7.5% dextrose	10% dextrose	5% dextrose	*p*-value
Length of stay (days)	10.33±2.10	11.08±3.14	10.83±2.28	0.766
Transferrin post-op day 1	218.84±60.93	179.53±63.78	202.93±64.35	0.334
Transferrin post-op day 3	207.87±50.22	176.40±61.10	169.20±78.45	0.313
Prealbumin post-op day 1	9.45±6.30	11.36±6.30	9.87±6.52	0.750
Prealbumin post-op day 3	8.08±6.06	10.41±4.32	10.97±8.14	0.513
BUN post-op day 1	8.28±3.63	7.89±2.82	7.86±3.73	0.954
BUN post-op day 3	9.13±3.52	4.38±1.84	5.48±2.96	0.002
Nitrogen loss post-op day 1	10.77±1.99	8.53±2.11	8.76±3.63	0.160
Nitrogen loss post-op day 3	11.87±1.51	7.04±2.87	7.90±4.12	0.001
Nitrogen balance post-op day 1	-1.37±1.99	-8.53±2.11	-8.76±3.63	<0.001
Nitrogen balance post-op day 3	-2.47±1.51	-7.04±2.87	10.83±4.12	<0.001

Oneway analysis of variance [ANOVA] test with Bonferroni correction

Data are presented as mean ± SD

Table 3. Mean and mean difference comparing between 3 groups

	n	Mean	Mean diff.	95% CI	*p*-value
BUN post-op day 3					
3% amino acid + 7.5% DN/2	11	9.12			
10% DN/2	9	4.37	-4.74	-7.44 to -2.05	0.004
5% DN/2	10	5.48	-3.64	-6.26 to -1.02	0.025
Nitrogen loss post-op day 3					
3% Amino acid + 7.5% DN/2	12	11.87			
10% DN/2	10	7.03	-4.83	-7.45 to -2.21	0.002
5% DN/2	11	7.89	-3.97	-6.53 to -1.41	0.010
Nitrogen balance post-op day 1					
3% Amino acid + 7.5% DN/2	9	-1.37			
10% DN/2	11	-8.53	-7.16	-9.67 to -4.65	<0.001
5% DN/2	11	-8.76	-7.39	-9.90 to -4.88	<0.001
Nitrogen balance post-op day 3					
3% Amino acid + 7.5% DN/2	12	-2.47			
10% DN/2	10	-7.03	-4.56	-7.18 to -1.94	0.004
5% DN/2	11	-7.89	-5.42	-7.98 to -2.86	<0.001

Oneway analysis of variance [ANOVA] test with Bonferroni correction

weight loss, decline of immunological function, and/or dysfunction of multiple organs. If catabolism continues without nutritional emendation, vital functions will be affected with an increase in morbidity and risk of mortality[1-4]. The supplementation of branched chain amino acids can improve recovery of patients better than glucose solution alone[5-16]. Our present study observed the effects of amino acid on patients after gastrointestinal surgery.

In the present study, the authors began to supplement a formula containing amino acid on day 1 after surgery to (a) normalize the pattern of plasma amino acid concentration and (b) improve recovery of the patients. Amino acid supplementation can significantly improve nitrogen balance compared to either 5% dextrose or 10% dextrose formula alone, even if nitrogen loss, serum transferrin, and serum pre-albumin showed no improvement after this amino acid supplementation.

Only one of the patients who received amino acid supplementation developed complication, namely, complete small bowel obstruction within two weeks after colonic resection. Exploratory laparotomy revealed the cause of the obstruction was due to internal herniation due to surgical technique. The other complication such as respiratory complication was limited in the present study because the authors excluded postoperative ICU requirement that might need different intravenous fluid therapy.

Szpetnar et al[17] studied plasma branched chain amino acid concentration among post-operative gastrointestinal surgery for cancer patients and found a decrease in branched chain amino acids concentration.

Amino acid supplementation can improve nitrogen balance, normalize serum amino acid levels, reduce proteolysis, and increase proteolysis albeit no improvement in the clinical outcomes has been seen[18-20]. In traumatic, septic, and critically-ill patients, amino acid requirements are much higher to enable increased activity of the immune system[21-26].

Our target population included postoperative gastrointestinal surgical patients who were only mildly or moderately malnourished, perhaps explaining why amino acid supplementation did not improve outcomes dramatically. Nevertheless, amino acid

supplementation did improve nitrogen balance without any serious complications. To demonstrate a difference in clinical outcomes, a larger sample size would be needed.

The limitation of the present study was its' open label design, which could result in a selection bias and distorted findings. The study was terminated early before complete recruitment of 60 patients because statistical significance was already confirmed.

In conclusion, the nitrogen balance, nitrogen loss, serum transferrin, and pre-albumin were measured and compared three days after gastrointestinal surgery. Our results demonstrated that a formula including amino acids can improve nitrogen balance.

What is already known on this topic?

For surgical patients, during surgery there are many physiologic and metabolic disturbances. In gastrointestinal surgery, some patients are unable to eat. However, these patients also need a lot of energy for recovery. If they do not get that energy, they might have infection that prolong recovery time.

Parenteral nutrition by intravenous glucose with amino acid had better nitrogen balance than intravenous glucose alone. Anyway, there is limited study in Thai patients, especially in gastrointestinal cancer patients who underwent elective gastrointestinal cancer surgery.

What this study adds?

Parenteral nutrition by intravenous glucose with amino acid had better nitrogen balance than intravenous glucose alone in Thai surgical patients without serious complication. Although there are no clinically significant benefits, parenteral nutrition by intravenous glucose with amino acid should be administered for Thai surgical patients who are unable to have enteral nutrition.

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Potential conflicts of interest

The authors declare no conflict of interest.

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