EFFECT OF GLUTAMINE SUPPLEMENTED NUTRITION VIA DIFFERENT ROUTES ON MORTALITY AND MORBIDITY FOR CRITICALLY ILL PATIENTS

Hülya Sungurtekin[1], İbrahim Öztürk[2], Bayram Beder[1], Hale Daldal[1], Simay Serin[1]

1 Pamukkale Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon AD, Denizli
2 Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, Ankara

ABSTRACT

Objective: *We aimed to compare the effectiveness of enteral, parenteral and combined enteral-parenteral glutamine supplementations in nutrition of the critical care patients.*

Material and Method: *This is a single-center, prospective, randomized clinical trial. During the 5-day study period, all patients received standard enteral nutrition product and were divided into three groups, including parenteral glutamine (Group I), enteral glutamine (Group II) and enteral+parenteral glutamine (Group III) supplementations. Blood biochemistry, rates of infections, length of stay in intensive care unit and duration of mechanical ventilation were evaluated.*

Results: *Sixty patients were included in this study. There was no statistically significant difference for biochemical values between the different feeding groups. Frequency of infections were ranged as Group II>Group III>Group I and mortality as Group II=III>Group I. Length of stay in intensive care unit and duration of mechanical ventilation were significantly longer in Group II than the others.*

Conclusion: *Although mortality was not significantly different between groups, parenteral glutamine administration causes less stay of intensive care unit and mechanical ventilation days. Further studies are needed with larger randomized controlled groups.*

Keywords: *Nutrition therapy, glutamine, critically ill*
Nobel Med 2015; 11(2): 36-40

KRİTİK HASTALARDA FARKLI YOLLARLA GLUTAMİ Lİ BESLENMENİN MORTALİTE VE MORBİDİTEYE ETKİSİ

ÖZET

Amaç: Yoğun bakım hastalarının beslenmesinde enteral, parenteral ve kombine enteral/parenteral glutamin desteğinin etkinliğini karşılaştırmayı amaçladık.

Materyal ve Metot: Bu tek merkezli, prospektif, randomize çalışmadır. Beş günlük çalışma süresince, tüm hastalar standart enteral beslenme ürünü almış ve parenteral glutamine (I. Grup), enteral glutamine (II. Grup) ve enteral+parenteral glutamine (III. Grup) desteği içeren üç gruba ayrılmıştır. Kan biyokimyası, enfeksiyon oranları, yoğun bakımda yatış süresi ve mekanik ventilasyon süresi değerlendirildi.

Bulgular: 60 hasta çalışmaya dahil edildi. Farklı beslenme grupları arasında biyokimyasal değerler açısından anlamlı fark yoktu. Enfeksiyon sıklığı II. Grup >III. Grup >I. Grup şeklinde ve mortalite II. Grup= III. Grup >I. Grup şeklinde idi. Yoğun bakımda yatış ve mekanik ventilasyon süresi, Grup II'de diğerlerinden anlamlı olarak daha uzun idi.

Sonuç: Gruplar arasında mortalite açsından anlamlı fark olmamasına karşın parenteral glutamin uygulanması daha kısa yoğun bakımda yatış ve mekanik ventilasyon süresine neden olmuştur. Daha büyük randomize kontrollü gruplarla, daha büyük araştırmalara gereksinim vardır.

Anahtar kelimeler: Beslenme tedavisi, glutamin, kritik hasta **Nobel Med 2015; 11(2): 36-40**

INTRODUCTION

Nutrition is an important and fundamental part of the treatment of the patients in intensive care unit. Admission of immuncompromised patients, such as cancer, to intensive care units appreciated immunonutrition. Therefore, many substrates (arginine, glutamine and etc) were evaluated for this aim. Glutamine-based nutrition is rested on the decrease in the level of plasma glutamine for the patients in intensive care unit.[1] Importance of physiologic affects of glutamine and relation between decreased glutamine level and catabolic issues for critically ill patients support glutamine replacement in intensive care unit patients.[2]

Glutamine supplementation has been generally accepted especially in critically ill patients.[3-6] The arguments have lately increased on route of glutamine application, even if the idea of parenteral glutamine is superior to enteral administration has gained importance, a defined result has not been put on the record.[7]

We hypothesized that application route of glutamine except parenteral might be beneficial for critical ill patients. Therefore, we have aimed to search the effect on intensive care morbidity and mortality of glutamin-based nutrition applied from different ways (enteral, parenteral and combined) for the patients that taken into intensive care and need to mechanical ventilation because of these mentioned reasons.

MATERIAL AND METHOD

Study subjects: This prospective, randomized study was conducted at Pamukkale University Medical Center. Informed consent was obtained from all patients or the patient's relatives before inclusion and the study protocol was approved by the ethical committee of the Pamukkale University Medical Center. Patients were expected to require enteral nutrition support for ≥5 day in Intensive Care Unit. Exclusion criteria were as follows: insulin-dependent diabetes, renal disease (creatinine concentration >221 µmol.L^{-1}, or 2.5 mg.dL^{-1}), hepatic disease (total bilirubin concentration >51 µmol.L^{-1}, or 3 mg.dL^{-1}, AST and ALT>45 U.L^{-1}), autoimmune disease, conditions precluding use of enteral feeding (eg, bowel obstruction, gut dysfunction or pancreatitis), parenteral nutrition requirement, chronic steroid use, cardiac disease (class III or IV, New York State Heart Association), Glasgow Coma Scale score <5, chronic obstructive pulmonary disease, metastatic carcinoma and pregnancy.

Study procedures: Patients were randomized by sealed envelope (opaque) method and divided into three groups; intravenous glutamine group (Group I), enteral glutamine group (Group II) and intravenous – enteral combined glutamine group (Group III). During the 5-day study period, all patients received continuous infusion of standard enteral nutrition product (Nutrison Standard, Numit Food Products Industry, Levent, Istanbul) via nasogastric tube plus intravenous, enteral or intravenous–enteral combined glutamine supplementation. The contents of Nutrison Standard were as: energy (E) 500 kcal (1 kcal.mL^{-1}), protein 20 g (E 16%), carbohydrate 61.5 g (E 49%), fat 19.5 g (E 35%), carotenoids 1 mg and sodium 500 mg in per 500 mL. Energy requirements were calculated with Harris-Benedict formula. Nutrition support treatment was planned. Only difference between patients was application route of glutamine supplement. Subjects in the Group I recevied via central venous infusion of 20% L-Ala-L-Gln dipeptide (Dipeptiven, Fresenius-Kabi, Maslak, Istanbul) at 0,5 g.kg-1day-1. Subjects in the Group II recevied enteraly via nasogastric tube of L-Gln powder (Glutamine Resource, Nestle Food Industry, Maslak, Istanbul) at 0,5 g.kg^{-1}day^{-1} and subjects in the Group III combined intravenous infusion 20% L-Ala-L-Gln dipeptide and enteral L-Gln powder at 0,5 g.kg^{-1}day^{-1} (equal amounts of glutamine was applied in combination). Tube-feeding tolerance was monitored with daily recording of nausea, distention, or diarrhea. Subjects were also monitored for complications associated with central venous access (catheter infection, site infection, and venous occlusion).

Serial illness severity scoring: Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II and Sepsis-related Organ Failure Assessment (SOFA) scores of the patients were recorded at the admission to the intensive care unit.

Laboratory analysis: The measurement of serum albumin, total protein, total cholesterol, C-reactive protein (CRP), acetyl-transaminase (AST), alanine transaminase (ALT), erythrocyte sedimentation rate (ESR) and white blood counts (WBC) were taken twice for biochemical analysis at intensive care admission and fifth day. Antibiograms were made by getting the samples from tracheal aspirate, blood, urine and wound.

Primary outcomes: Infections were defined according to definitions from the Centers for Disease Control and Prevention. Five infection categories were defined: respiratory as pneumonia and other lower respiratory tract infections; bloodstream infection (laboratory-confirmed bloodstream infections and clinical sepsis); urogenital infection; abdominal infection (intra-abdominal infections); and other infection (ear, nose, and throat infections, skin, bone, and soft tissue infections and intrathoracic infections). Length of stay in intensive care unit and

Table 1. Characteristics of patients at admission.

		Group I n=20 Mean±SD		Group II n=20 Mean ±SD		Group III n=20 Mean±SD		p
Age (years)		56.9±17.5		53.5±18.9		59.3±20.7		NS
Weight (kg)		72.2±17.0		72.5±12.4		71.8±12.3		NS
Height (cm)		163.1±9.0		166.9±8.5		166.7±7.2		NS
BMI (kg.m^2)		27.1±6.2		26.0±4.0		25.8±4.4		NS
Gender (M/F)		13/7		14/6		12/8		NS
APAHCE II score		22.1±5.9		19.1±4.3		20.5±6.8		NS
SAPS II score		42.6±11.5		40.0±9.6		46.6±12.8		NS
GCS score		8.7±3.0		9.6±2.7		6.9±2.8		NS
SOFA score		7.0±2.6		7.2±1.9		8.0±2.8		NS
		n	%	n	%	n	%	
Diagnosis at admission	Cardiovascular	3	15	3	15	4	20	NS
	Respiratory	4	20	4	20	4	20	
	Cardiovascular and respiratory	9	45	7	35	6	30	
	Trauma	3	15	3	15	5	25	
	Burn	1	5	3	15	1	5	
Types of Patient	Medical	15	75	14	70	13	65	NS
	Surgical	5	25	6	30	7	35	

NS: Not significant

Table 2. Comparison of biochemical parameters between groups

	Group I n=20 Mean±SD		Group II n=20 Mean±SD		Group III n=20 Mean±SD		p
T. cholesterol day 1	130.967	30.914	138.867	36.682	137.400	44.700	NS
T. cholesterol day 5	128.387	39.521	138.300	38.922	134.733	35.880	NS
T. protein day 1	5.867	0.850	6.090	0.840	5.685	0.730	NS
T. protein day 5	5.990	0.676	5.850	0.666	5.613	0.633	NS
Albumin day 1	3.053	0.642	3.121	0.409	2.919	0.469	NS
Albumin day 5	2.972	0.342	3.022	0.386	2.800	0.418	NS
ALT day 1	96.467	179.270	164.933	482.075	212.200	643.431	NS
ALT day 5	41.327	40.845	42.800	36.908	89.200	158.565	NS
AST day 1	104.867	243.769	142.533	299.086	258.400	758.372	NS
AST day 5	50.133	68.453	45.333	24.153	52.600	43.035	NS
WBC day 1	16.463	9.462	15.900	9.078	17.593	8.032	NS
WBC day 5	11.885	5.376	13.260	6.225	14.340	5.228	NS
ESR day 1	46.067	35.684	35.600	28.397	46.267	40.047	NS
ESR day 5	42.267	38.902	39.933	21.117	53.333	36.976	NS
CRP day 1	13.74	8.36	13.77	10.92	12.22	11.85	NS
CRP day 5	6.95	4.76	11.75	9.41	6.71	5.38	NS

T. cholesterol: Total cholesterol, **T. protein:** Total Protein, **ALT:** alanine transaminase, **AST:** acetyl-transaminase, **WBC:** white blood cell, **ESR:** erythrocyte sedimentation rate, **CRP:** C-reactive protein, **NS:** Not significant between groups.

duration of mechanical ventilation and condition of discharge were noted. Weaning from mechanical ventilation was performed according to protocol (biochemical and hemodynamic stability, PaO_2>60 mmHg with FiO_2≤0.4 and PEEP <5 mbar, pH >7.3, respiratory rate <35/min, $PaCO_2$<55 mmHg, tidal volume >5 mL.kg^{-1}).

Secondary outcomes: Mortality in the ICU was accepted as secondary outcome.

Statistical analysis: Data are expressed as means and with their standard errors. SPSS for Windows 17.0 software (SPSS Inc, Chicago, IL, USA) was used to perform the statistical calculations. The distribution of normality was tested by the Kolmogorov-Smirnov Z test and the homogenity of the variances was tested both with the Levene and Welch test. Parametric data were analyzed by One way ANOVA test and non parametric data were analyzed by Kruskal-Wallis test. A Bonferroni correction was used for the within group comparisons on change for the hypothesis-generating secondary outcomes. Any p values <0.05 were considered significant.

RESULTS

This study was performed in Intensive Care Unit at Pamukkale University during 5 months period. 60 patients (20 patients in each groups) were included; 39 males (65%), 21 females (35%); age range, 18-80 years (56.45±18.81). Baseline characteristics of the 60 subjects are summarized in Table 1. There were no significant differences in demographic data, patient characteristics, diagnosis at admission, types of patients, APACHE II, SAPS II, SOFA and GCS scores (p>0.05) (Table 1). Patients were medical (70%) and surgical (30%) and their diagnosis were cardiovascular (16.6%), respiratory (20%), cardiovascular+respiratory (36.6%) disease, burn (18.3%) and trauma (8.3%).

In the first and fifth day total cholesterol and protein, albumin, WBC, ESR, ALT, AST, CRP values and changes were not statistically different between groups (Table 2).

The length of stay in intensive care unit was found significantly higher in Group II than in Group I and Group III (p<0.01, Table 3). Duration of mechanical ventilation was found significantly higher in Group II than in Group I (p<0.01, Table 3).

There was no statistically significant difference between the groups according to developing infections but frequency of infections was higher in Group II than Group III and I (Group II>Group III>Group I, Table 3). And also we could not find statistically significant difference between the groups, according to the patients who had none or any infection at least once (p>0.05, Table 3). Total numbers of infections between groups had not shown statistically significant difference. The most

isolated microorganisms were *P. aeruginosa* (20.2%), *S. aureus* (17.7%) and *A. baumannii* (14.8%). There was no statistically significant difference between the groups according to survival. Mortality in intensive care unit was 35% in Group I, 40% in Group II, 40% in Group III (Table 3).

Table 3. Comparison of outcomes between groups.

		Group I n=20		Group II n=20		Group III n=20		
		n	%	n	%	n	%	p
Types of Infections	Patients with no infection	14	70	11	55	13	65	NS
	Patients with at least one infection	6	30	9	45	7	35	
	Respiratory	4	20	7	35	5	25	NS
	Bloodstream	3	15	6	30	5	25	
	Urinary	0	0	2	10	2	10	
	Total number of infections	7	35	15	75	12	60	NS
		Mean±SD		Mean±SD		Mean±SD		
Length of stay in ICU (day)		9.8	4.3	18.0	9.9	12.0	4.7	0.001
Duration of MV (day)		8.3	4.1	16.2	8.2	11.0	5.2	0.001
Mortality		7	35	8	40	8	40	NS

NS: Not significant, **MV**: mechanical ventilation

DISCUSSION

Although glutamine as a non-essential amino acid is synthesized in high rate like 50-80 g.day^{-1}, protein catabolism occurs because of not satisfying the demand in case of catabolic stress, and glutamine becomes an essential amino acid.[3,4] There is no absolute contraindication or side effects of glutamine supplementation.[5,6] Jiang et al. have proved that 0.5 g.kg^{-1}.day^{-1} dose of glutamine is biochemically reliable.[6] For this reason, we applied in 0.5 g.kg^{-1}.day^{-1} dose for each group in this study.

Melis et al. have showed that glutamine which can be applied both enteral and parenteral caused an increase in the level of plasma glutamine.[7] When glutamine is applied as enteral, first pass elimination occurs in high level. It disperses different tissues of the body in relation to blood stream as opposed to parenteral glutamine.[3] Long-term oral glutamine supplementation has not improved the intestine permeability for the patients that have bowel disease.[8] Moreover, it has been stated that, in terms of mortality, infection rate and hospitalization period, it has no significant benefit for the patients of intensive care unit.[9,10]

Parenteral glutamine seems more positive than enteral glutamine. Singleton et al. have showed in an experimental study that intravenous glutamine in dosage of 0.75 g.kg^{-1} was applied to rats and it has increased survival rate after sepsis and has decreased the acute lung injury.[11] Estivariz et al. have indicated that parenteral glutamine decreases the infection rate in patients of cardiac, vascular, and colonic surgery in comparison with standard parenteral nutrition.[12]

Studies have indicated that there have possible benefits for elective surgery patients; parenteral administration is therapeutic for critical patients of intensive care but enteral administration is controversial; enteral glutamine is probably beneficial in patients suffering from burns or trauma.[10,13-15] Data is not sufficient for the patients with septic and acute lung injury.[16] In contrary to these specific populations, Goeters et al. supported that intravenous glutamine supplementation was beneficial for heterogenic population.[2]

In an experimental study, with different supplementations (enteral and parenteral glutamine, enteral saline and enteral glycine), Matheson et al. concluded that enteral glutamine has damaged the intestinal blood stream due to decreasing the absorptive metabolic stimulus of hyperemia of rats.[17]

Although the debates on enteral, combined enteral-parenteral glutamine have continued in American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines, parenteral glutamine is recommended in the level of A.[18] Dock-Nascimento et al. demonstrated preoperative intake of a glutamine-enriched carbohydrate beverage appeared to improve insulin resistance and antioxidant defenses and decreased the inflammatory response after cholecystectomy.[19] Parenteral glutamine administration in critically ill postoperative or ventilator dependent patients is beneficial in terms of decreasing infectious complications, length of stay in hospital and mortality.[20] ASPEN also recommends parenteral glutamine supplementation in doses >0.2 g.kg.day^{-1} to be effective.[20] On the other hand, guidelines recommend that glutamine should be added to a standard enteral formula in burn and trauma patients but there are not sufficient data to support enteral glutamine supplementation in surgical or heterogenous critically ill patients.[21] However, while parenteral glutamine is mostly supported, there are studies advocated that it does not support biochemical and clinical results.[22] Gianotti et al. have indicated that perioperative intravenous glutamine has not affected the results in well-nourished abdominal surgery patients.[23] Ong et al. have concluded that adding parenteral glutamine to paranteral nutrition has not decreased the sepsis rate in infants that have had gastrointestinal disease and have undergone surgery.[24]

However, our study has deduced that parenteral glutamine would be more beneficial than enteral glutamine in terms of the application period of

mechanical ventilation and length of intensive care unit stay. We have thought that this result is depended on experiencing the first pass elimination when enteral glutamine is applied. However a large study requires to correct those statistically significant differences.

Glutamine supported nutrition has not reduce mortality and infectious complications in a recent randomised controlled trial.[25] Those results were supported with Chen et al.'s meta-analysis.[26] However, in a recent another meta-analysis, Wischmeyer et al. showed that nutrition supported with parenteral glutamine had reduced in-hospital mortality and lenght of stay in hospital.[27]

Our study have some limitations: First, the sample size was relatively small because of the range of exclusion criteria. Because we aimed to examine the homogenous population and also to exclude the possible affects of co-existing diseases on glutamine metabolism. Second, diagnosises of patients at admission were various due to mixed intensive care unit.

In conclusion, enteral glutamine supplementation of standard enteral nutrition is not superior to parenteral or combined supplementations despite the limitations of study. Therefore, well-designed larger prospective randomized-controlled trials are necessary to evaluate the effectiveness of application route of glutamine supplementation in intensive care units.

* The authors declare that there are no conflicts of interest.

C **CORRESPONDING AUTHOR:** İbrahim Öztürk Bahçelievler mahallesi Muammer Aksoy caddesi Amaç apt. no:25/12 Çankaya, Ankara drozturk28@gmail.com

✔ **DELIVERING DATE:** 31 / 03 / 2014 • **ACCEPTED DATE:** 02 / 10 / 2014

REFERENCES

1. Newsholme P. Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? J Nut 2001; 131: 2515-2522.
2. Goeters C, Wenn A, Metes N, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med 2002; 30: 2032-2037.
3 Wernerman J. Role of glutamine supplementation in critically ill patients. Curr Opin Anaesthesiol 2008; 21: 155-159.
4. Ali S, Roberts PR. Nutrients with immune-modulating effects: what role should they play in the intensive care unit? Curr Opin Anaesthesiol 2006; 19: 132-139.
5. Wernerman J. Clinical use of glutamine supplementation. J Nutr 2008; 138: 2040-2044.
6. Jiang ZM, Cao JD, Zhu XG, et al. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double blind, controlled study of 120 patients. JPEN J Parenter Enteral Nutr. 1999; 23: 62-66.
7. Melis GC, Boelens PG, van der Sijp JRM, et al. The feeding route (enteral or parenteral) affects the plasma response of the dipetide Ala-Gln and the amino acids glutamine, citrulline and arginine, with the administration of Ala-Gln in preoperative patients. Br J Nutr 2005; 94: 19-26.
8. Hond ED, Hiele M, Peeters M, et al. Effetcs of long-term oral glutamine supplements on small intestinal permeability in patients with Crohn's disease. JPEN J Parenter Enteral Nutr 1999; 23: 7-11.
9. Schulman AS, Willcutts KF, Claridge JA, et al. Does the addition of glutamine to enteral feeds affect patient mortality? Crit Care Med 2009; 33: 2501-2506.
10. Hall JC, Dobb G, Hall J, et al. A prospective randomized trial of enteral glutamine in critical illness. Intensive Care Med 2003; 29: 1710-1716.
11. Singleton KD, Serkova N, Beckey VE, et al. Glutamine attenuates lung injury and improves survival after sepsis: role of enhanced heat shock protein expression. Crit Care Med 2005; 33: 1206-1213.
12. Estívariz CF, Griffith DP, Luo M, et al. Efficacy of Parenteral Nutrition Supplemented with Glutamine Dipeptide to Decrease Hospital Infections in Critically ill Surgical Patients. JPEN J Parenter Enteral Nutr 2008; 32: 389-402.
13. Morlion BJ, Stehle P, Wachtler P, et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg 1998; 227: 302-308.
14. Wernerman J, Kirketeig T, Andersson B, et al. Scandinavian glutamine trial: a pragmatic multi-centre randomised clinical trial of intensive care unit patients. Acta Anaesthesiol Scand 2011; 55: 812-818.
15. Pattanshetti VM, Powar RS, Godhi AS, et al. Enteral glutamine supplementation reducing infectious morbidity in burns patients: a randomised controlled trial. Indian J Surg 2009; 71: 193-197.
16. Ortiz Leyba C, Montejo González JC, Vaquerizo Alonso C, et al. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus SEMICYUC-SENPE: septic patient. Nutr Hosp 2011; 26: 67-71.
17. Matheson PJ, Harris BT, Hurt RT, et al. Enteral glutamine supplementation impairs intestinal blood flow in rats. Am J Surg 2008; 196: 293-299.
18. Wernerman J. Glutamine supplementation. Ann Int Care 2011; 1: 25.
19. Dock-Nascimento DB, de Aguilar-Nascimento JE, Faria MSM, et al. Evaluation of the effects of a preoperative 2-hour fast with maltodextrine and glutamine on insulin resistance, acute-phase response, nitrogen balance, and serum glutathione after laparoscopic cholecystectomy: a controlled randomized trial. JPEN J Parenter Enteral Nutr 2012; 36: 43-52.
20. Vanek VW, Matarese LE, Robinson M, et al. A.S.P.E.N. Position Paper: Parenteral Nutrition Glutamine Supplementation. Nutr Clin Pract 2011; 26: 479-494.
21. Kreymanna KG, Bergerb MM, Deutzc NEP, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr 2006; 25: 210-223.
22. Ockenga J, Borchert K, Stüber E, et al. Glutamine-enriched total parenteral nutrition in patients with inflamatory bowel disease. Eur J Clin Nutr 2005; 59: 1302-1309.
23. Gianotti L, Braga M, Biffi R, et al. Perioperative intravenous glutamine supplemetation in major abdominal surgery for cancer: a randomized multicenter trial. Ann Surg 2009; 250: 684-690.
24. Ong EG, Eaton S, Wade AM, et al. Randomized clinical trial of glutamine-supplemented versus standard parenteral nutrition in infants with surgical gastrointestinal disease. Br J Surg 2012; 99: 929-938.
25. Chen QH, Yang Y, He HL, et al. The effect of glutamine therapy on outcomes in critically ill patients: a meta-analysis of randomized controlled trials. Crit Care 2014: 18: 436.
26. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013: 368: 1489-1497.
27. Wischmeyer PE, Dhaliwal R, McCall M, Ziegler TR, Heyland DK. Parenteral glutamine supplementation in critical illness: a systematic review. Crit Care 2014: 18: 76.