

# A randomized pilot study of parenteral glutamine supplementation in severe sepsis

Vijo Poulouse, Jansen Koh, Tay Tunn Ren, Wong Hang Siang, Ian Wee, Hannah Hsien Hwei, Kam Jia Wen

## Abstract

**Purpose:** Glutamine depletion can occur in critically ill patients and parenteral glutamine supplementation can have beneficial effects on critically ill patients by preserving gut barrier and improving immune function. We wanted to examine the effect of glutamine supplementation in a cohort of severe sepsis patients admitted to a hospital in South East Asia.

**Design:** A single center, randomized, double-blinded, placebo-controlled, pilot study. The primary outcome was 28-day mortality. Secondary outcomes were ICU length of stay (LOS), hospital LOS, duration of mechanical ventilation and occurrence of new infections. Disease severity on admission was assessed by Sequential Organ Failure Assessment (SOFA) score.

**Setting:** Medical intensive care unit (MICU) of Changi General Hospital, which is a 1000-bedded teaching hospital in Singapore.

**Patients and participants:** Patients admitted to the MICU for severe sepsis with  $\geq 2$ -organ dys-

function.

**Interventions:** In the intervention arm, intravenous glutamine was given for 5 days at a dose of 0.5 g/kg body weight/day. The placebo was normal saline.

**Measurements and results:** Thirty-nine patients were randomized to receive glutamine (n=19) or placebo (n=20). The glutamine group exhibited milder disease severity than placebo (median SOFA score 8 vs 11, p=0.038). There was no overall difference in 28-day mortality between the glutamine and placebo (42% vs 15%, p=0.06). When adjusted for disease severity, the glutamine arm had 5.6 times higher death rates (95% CI 1.1-30.2, p=0.044). The glutamine group had lower incidence of new infections (0% vs 30%, p=0.02). There was no difference in ICU LOS, hospital LOS and the duration of mechanical ventilation.

**Conclusions:** Parenteral glutamine may increase mortality risk in ICU patients with severe sepsis while reducing the risk of new infections.

**Key words:** Glutamine, severe sepsis, parenteral, mortality, ICU.

## Introduction

Glutamine is one of the most abundant amino acids in the human body and has many physiologic functions including acting as a fuel substrate for the gut epithelial cells and the cells of the immune system. In the catabolic state of critical illness, glutamine can become deficient and this has been associated with increased mortality and depressed immune

function. (1,2) A few, small randomized control trials (RCTs) conducted on critically ill patients receiving parenteral nutrition showed that parenteral glutamine reduced infection rates with no effect on mortality. (3,4) A meta-analysis done in 2002 on surgical and critically ill patients showed that glutamine given in enteral or parenteral forms reduced infections and resulted in a trend towards lower mortality. (5). The authors also concluded that maximum benefit was seen when glutamine was used in parenteral form in doses  $>0.2$  g/kg body weight/day.

The 2009 ASPEN (American Society for Parenteral and Enteral Nutrition), ESPEN (European Society for Clinical Nutrition and Metabolism) and Canadian Clinical Practice Guidelines recommended supplementing parenteral glutamine in all critically ill patients who were on parenteral nutrition because of the benefits in survival, infectious complications and hospital length of stay (LOS).

The optimal dose of glutamine was unknown, al-

---

From Department of Respiratory and Critical Care Medicine, Changi General Hospital, Singapore (Vijo Poulouse, Jansen Koh, Tay Tunn Ren, Wong Hang Siang), Department of Pharmacy, Changi General Hospital, Singapore (Ian Wee, Hannah Hsien Hwei), and Clinical Trials & Research Unit, Changi General Hospital, Singapore (Kam Jia Wen).

## Address for correspondence:

Vijo Poulouse, FCCP  
 Department of Respiratory and Critical Care Medicine  
 Changi General Hospital, Singapore  
 Tel: (65) 81258236  
 Email: vijo\_poulouse@cgh.com.sg

though doses up to 0.5 g/kg body weight/day were shown to be safe. (6) Severe sepsis has been shown to produce marked glutamine depletion (7,8) and we postulated that parenteral glutamine supplementation would have positive clinical outcomes in this group of patients. We targeted severe sepsis patients with multi-organ failure ( $\geq 2$ -organ dysfunction). Also, to our knowledge, this is the first RCT conducted on a South East Asian population involving parenteral glutamine supplementation to the critically ill.

## Materials and methods

### *Design and Setting*

This was a single center, randomized, placebo-controlled, double-blinded, pilot study conducted in the medical intensive care unit (MICU) of Changi General Hospital. This is a 1000-bedded teaching hospital in the eastern part of Singapore. Ethics approval for the study was granted by the SingHealth Centralized Institutional Review Board and the study was funded by a SingHealth Foundation Research Grant. The trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) on September 24th, 2012.

### *Randomization and blinding*

A randomization table that was generated by an independent statistician was used and study subjects were randomized in a 1:1 ratio. Allocation was random and concealed and was blinded to everyone except the study pharmacist who was responsible for the preparation and delivery of the products to the MICU. Patients were randomly assigned to receive intravenous glutamine (0.5 g/kg body weight/day, Dipeptiven\*, Fresenius-Kabi) for 5 days vs placebo (normal saline). To maintain blinding, glutamine and placebo were prepared by an unblinded local study pharmacist and delivered as masked solutions to the MICU.

The data were collected by blinded study staff (investigators, dietician, nurses and Clinical Research Co-ordinators). All serious adverse events related to the study drug were reported to the SingHealth Centralized Institutional Review Board and the Singapore Health Sciences Authority.

### *Study population*

All patients admitted to the MICU during the period February 2011 to March 2013 were screened for eligibility. Inclusion criteria were 1) Adults ( $\geq 18$  years) 2) meeting criteria for severe sepsis with  $\geq 2$ -organ dysfunction as per the 2001 International Sepsis Definitions Conference. (9) The exclusion criteria were 1)  $>48$  hours from admission to ICU

2) not expected to survive  $>48$  hours as decided by the primary team 3) allergy to glutamine or its constituents 4) absolute contraindication to enteral nutrition 5) patients with a primary admission diagnosis of burns 6) body weight  $<40$  kg or  $>200$  kg 7) previous randomization to this study or enrolled in a related ICU interventional nutrition study 8) pregnant or lactating mothers with the intent to breastfeed 9) prisoners.

Sequential Organ Failure Assessment (SOFA) score within first 24 hours of MICU admission was used for assessing disease severity. All patients were followed up until hospital death or discharge. Patients who were discharged before the 28-day period were followed up via telephone call to check on the outcomes.

### *Outcome measures*

The primary outcome was 28-day mortality. Secondary outcomes were ICU LOS, hospital LOS, duration of mechanical ventilation and occurrence of new infections. New infections were defined as nosocomial infections (as per CDC criteria) occurring within the hospital stay after enrollment into the trial.

### *Statistical analysis*

Analyses were performed on an intention to treat basis. Categorical data was presented as frequency (percentage). Continuous data was presented as mean (standard deviation) for parametric distribution and median interquartile range (IQR) for non-parametric distribution. The differences in characteristics were examined using Chi-Square test or Fisher's Exact test for categorical variables, and 2-sample t-test or Mann Whitney U-test for continuous variables, where appropriate. Patients' baseline demographics (such as gender, age, races, and SOFA) were compared between glutamine and placebo groups. The null hypotheses being tested that there were no significant differences between these two groups. Logistics regression analysis was then performed to determine the significant association between glutamine and placebo groups with the primary outcome, i.e. 28-day mortality status with adjustment for SOFA score. Relative risk (RR) was presented, associated with its 95% confidence interval (CI). Secondary outcomes such as duration of mechanical ventilation, ICU and hospital LOS and the occurrence of new infections were compared between glutamine and placebo groups using non-parametric Mann Whitney U-test with median and IQR presented. A two tailed, p-value of  $<0.05$  was considered statistically significant for all comparisons. Statistical analysis

was performed with SPSS statistical software, version 19.0 (IBM Corp. Armonk, NY).

## Results

The recruitment procedure is shown in **Figure 1**. Thirty-nine patients were recruited during the study period. The baseline characteristics are shown in **Table 1**. The mean ages of the glutamine and placebo arms were  $62.2 \pm 14$  and  $66.9 \pm 16$  years respectively. There were no differences in age, gender and race between the 2 groups. There were no withdrawals or dropouts. A total of 13 subjects did not complete the 5-day duration of the glutamine/placebo (5 patients died, 2 were discharged from the hospital and 6 patients developed fluid overload from oliguric acute kidney injury). **Table 2** shows the effect of glutamine on clinical outcomes. The glutamine group had less disease severity than placebo (median SOFA score 8 vs 11,  $p=0.038$ ). There was no overall difference in 28-day mortality (42% vs 15%,  $p=0.06$ ), but when corrected for SOFA scores, the mortality was 5.6 times higher in the glutamine group (95% CI 1.05-30.2,  $p=0.044$ ). Hospital mortality was also higher in the glutamine group, but did not reach statistical significance (OR 3.1, 95% CI 0.69-14.2). For the secondary outcomes, there was lesser occurrence of new infections in the glutamine group compared to placebo (0% vs 6%,  $p=0.02$ ). There were no differences in the ICU LOS, hospital LOS and duration of mechanical ventilation.

## Discussion

To the best of our knowledge, this was the first randomized trial of parenteral glutamine conducted exclusively in patients with severe sepsis. Our study showed that in sepsis patients with  $\geq 2$ -organ dysfunction, intravenous glutamine reduced the development of new infections, while conferring a higher risk of death. Although previous evidence from small RCTs supported the use of parenteral glutamine in the critically ill, there has been some recent evidence that suggests otherwise. The Scandinavian and SIGNET trials were large, multi-centre trials using parenteral glutamine. (10,11) The former showed no improvement in organ function scores (primary outcome), but a reduction in ICU mortality (secondary outcome). The SIGNET trial showed no benefit in reducing mortality or infections (both were primary outcomes). The REDOX study published in 2013 has been the largest RCT to date. The study was done in ICU patients with multi-organ failure and the findings showed that glutamine supplementation (given as combined enteral and parenteral

forms; total dose of 0.6 g/kg body weight/day) was associated with increased mortality. (12) However, the mechanism by which glutamine caused harm was not known.

To address the contrasting results of REDOX and the previous smaller RCTs, a large meta-analysis was conducted on RCTs that used only parenteral glutamine. (13) This showed that in the critically ill, glutamine supplementation reduced hospital mortality, but had no effect on overall mortality or infections. The most recent international guidelines discourage the routine use of any form of glutamine in the critically ill. (14) So, is intravenous glutamine harmful or beneficial? It seems pretty clear that glutamine supplementation does not benefit all critically ill patients. Recent data has shown that only 25-35% of patients are glutamine depleted on admission to the ICU and high plasma glutamine levels are actually associated with increased mortality. (12,15) Perhaps intravenous glutamine is harmful in patients who are not glutamine depleted, especially when given in high doses ( $>0.5$  g/kg body weight/day)? One should also be cognizant of the fact that all standard enteral feeds contain some glutamine, which usually accounts for 7-8% of the amino acid content. (16) Our study has a few limitations. It was a small, pilot study which was not powered for outcomes. Hence an association between glutamine and mortality cannot be made conclusively. The small sample size probably resulted in the difference in illness severity between the intervention and control arms. We did not measure admission plasma glutamine levels to determine glutamine status of our patients. While reduced infections and increased mortality has been reported in previous studies, both these positive and negative outcomes have never been observed within a single study. We can only postulate why this happened in our patients. Is the glutamine response in severe sepsis with multi-organ failure different from other critically ill patients? Do South East Asians behave differently from other populations? Were our patients glutamine replete and hence the combined intravenous and enteral feed glutamine caused harm? Hence in conclusion, parenteral glutamine appeared to increase risk of mortality in this cohort of ICU patients from South East Asia with severe sepsis, while reducing the occurrence of new infections. These findings add support to recent international guidelines that state glutamine supplementation not be given routinely to critically ill patients.

**Declarations**

The authors declare that they have no competing interests.

The trial was registered at Clinicaltrials.gov on September 24th, 2012 (NCT 03048994), and was approved by the SingHealth Centralized Institutional Review Board (CIRB number 2010/740/C) and has been performed in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all patients or their surrogates. The study was

funded by a SingHealth Foundation Research Grant (grant number SHF/FG420S/2009). The funding body had no role in the design of the study and collection, analysis and interpretation of data and writing the manuscript.

**Acknowledgements**

We are grateful for the help provided by Yeh Lay Hwa and Geraldine Lim from the Clinical Trials & Research Unit.

**Table 1.** Baseline characteristics

Baseline	Placebo (n=20)	Glutamine (n=19)	p value
Demographics			
- Mean age (SD)	66.9 (16.3)	62.2 (14.3)	0.347
- Male (n, %)	13 (65.0%)	15 (78.9%)	0.333
Race (n, %)			0.128
- Chinese	7 (35.0%)	14 (73.7%)	
- Malay	11 (55.0%)	3 (15.8%)	
- Others	2 (10.0%)	2 (10.5%)	
Source of sepsis			>0.999
- Respiratory tract	14 (70.0%)	9 (64.3%)	
- Others	6 (30.0%)	5 (35.7%)	
* Urinary tract	1	1	
* Hepatobiliary	1	1	
* Skin/soft tissue	2	0	
* Endovascular	0	2	
* Multiple sites	2	1	
* Unknown	0	5	
Severity of illness			
- Median SOFA on admission (IQR)	11.0 (8.5-13.8)	8.0 (4.0-11.0)	0.038
Daily nutrition intake (over the 5-day treatment period)			
- Mean calories (SD)	697.2 (484.9)	700.3 (502.1)	0.984
- Mean protein in grams (SD)	25.4 (20.2)	36.2 (30.7)	0.210

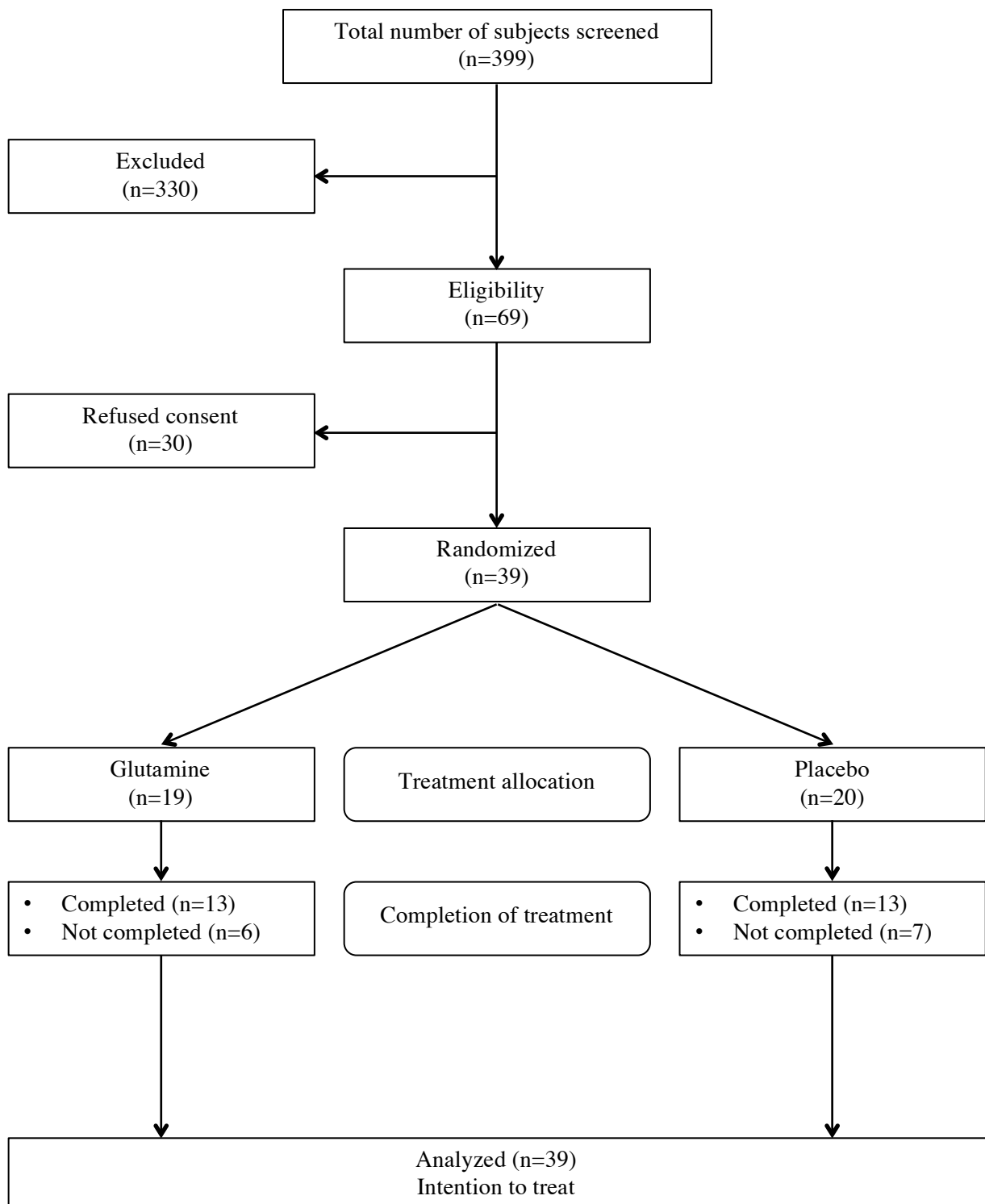
Legend: SOFA=Sequential Organ Failure Assessment score; IQR=interquartile range; SD=standard deviation.

**Table 2.** Clinical outcomes

Clinical outcomes	Placebo (n=20)	Glutamine (n=19)	p value
Occurrence of new infections (%)	6 (30.0%)	0 (0%)	0.020
Median duration of mechanical ventilation (IQR)	1.0 (0.3-3.8)	2.0 (0.0-2.0)	0.771
Median ICU LOS (IQR)	1.5 (1.0-4.8)	2.0 (1.0-2.0)	0.531
Hospital LOS	14.5 (5.3-32.5)	10.0 (5.0-15.0)	0.296
28-day mortality	3 (15.0%)	8 (42.1%)	0.060
28-day mortality*	Reference	5.6 (1.05-30.2)	0.044
Hospital mortality	5 (25.0%)	8 (42.1%)	0.257
Hospital mortality*	Reference	3.1 (0.69-14.2)	0.141

Legend: IQR=interquartile range; ICU=Intensive Care Unit; LOS=length of stay; \*=logistics regression analysis was performed for the clinical outcome of 28-day mortality and hospital mortality by adjusting to SOFA score. Relative risk with 95% CI was presented.

**Figure 1.** Flow diagram



## References

1. Parry-Billings M, Baigrie RJ, Lamont PM, Morris PJ, Newsholme EA. Effects of major and minor surgery on plasma glutamine and cytokine levels. *Arch Surg* 1992;127:1237-40.
2. Oudemans-van Straaten HM, Bosman RJ, Treskes M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med* 2001;27:84-90.
3. Grau T, Bonet A, Minambres E, Pineiro L, Irlles JA, Robles A. The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. *Crit Care Med* 2011;39:1263-8.
4. Estívariz CF, Griffith DP, Luo M, Szeszycki EE, Bazargan N, Dave N, 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.
5. Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: A systematic review of the evidence. *Crit Care Med* 2002;30:2022-9.
6. Sacks GS: Glutamine supplementation in catabolic patients. *Ann Pharmacother* 1999;33:348-54.
7. Karin AM, Pan M, Lin CM, Strange R, Souba WW. Glutamine Metabolism in Sepsis and Infection. *J Nutr* 2001;131:2535S-8S.
8. Roth E, Funovics J, Muhlbacher R, Schemper M, Mauritz W, Sporn P, et al. Metabolic disorders in severe abdominal sepsis: glutamine deficiency in skeletal muscle. *Clin Nutr* 1982;1:25-41.
9. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250-6.
10. Wernerman J, Kirketeig T, Andersson B, Berthelson H, Ersson A, Friberg H, et al. Scandinavian glutamine trial: a pragmatic multicenter randomized clinical trial of intensive care unit patients. *Acta Anaesthesiol Scand* 2011;55:812-8.
11. Andrews PJ, Avenell A, Noble DW, Campbell MK, Croal BL, Simpson WG, et al. Randomized trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. *BMJ* 2011;342:d1542.
12. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med* 2013;368:1489-97.
13. Wischmeyer PE, Dhaliwal R, McCall M, Ziegler TR, Heyland DK. Parenteral glutamine supplementation in critical illness: a systematic review. *Crit Care* 2014;18:R76.
14. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016;40:159-211.
15. Rodas PC, Rooyackers O, Hebert C, Norberg A, Wernerman J. Glutamine and glutathione at ICU admission in relation to outcome. *Clin Sci (London)* 2012;122:591-7.
16. Smedberg M, Wernerman J. Is the glutamine story over? *Crit Care* 2016;20:361.