



REVIEW ARTICLE

Glutamine in Critically ill Patients – When and How?

Khaled Sewify

Critical Care Department, King Fahd Military Medical Complex, Saudi Arabia

Abstract

EN contains little glutamine that inadequate to normalize the plasma level and PN doesn't contain glutamine because, it is unstable in aqueous solutions that is why IV Glutamine supplementation stayed for decades, a standard of care whenever TPN is prescribed. Recent practices focus on pharmaco-nutrition especially when feeding critically ill patients, that why many meta-analysis tried to figure out whether glutamine works or not? Although glutamine is generally well tolerated and adverse events are very rare, better identification of the ideal characteristics of effective glutamine coupled with improved understanding of mechanisms of action will help to delineate the true beneficial effects of glutamine in various disorders. This review highlights current practice and areas of concern and establishes our current knowledge in this field.

Keywords: Glutamine; Enteral Nutrition (EN); Parenteral Nutrition (PN); Critically ill Patient.

Introduction

Glutamine is considered as a precursor for nucleotide synthesis and an important fuel for fast dividing cells that is rapidly depleted in hypercatabolic patients.

Ornithine ketoglutarate — Ornithine Ketoglutarate (OKG) is a glutamine precursor that efficiently restores pools of glutamine in hypercatabolic patients.

There is an insufficient evidence to recommend using glutamine in critically ill patients on enteral feeding, despite enteral nutrition formulas contain very few glutamine: 2-4 g/L which is inadequate to normalize the plasma concentration of glutamine. Also, parenteral nutrition formulas do not have glutamine because glutamine is unstable in aqueous an solution that is why IV Glutamine supplementation remained a state of art in total parenteral nutrition.

Why is Glutamine thought to be needed in critically ill patients? [1]

Simply because plasma glutamine concentration is very low in patients with critical illness and a low level of glutamine is an independent risk factor for mortality. Also, a low level of glutamine in plasma is an excellent indicator of glutamine depletion.

We know that skeletal muscle is the major glutamine producer and deep depletion of skeletal muscle seen in critical illnesses is a reflection of the need for glutamine production.

Glutamine is consumed in rapidly dividing cells in the area of viscera.

The majority of glutamine is oxidized, but the presence of excess glutamine is important for de novo nucleotide synthesis and is crucial for cell division and protein synthesis.

Scientists have long been shown in animal studies that glutamine can prevent bacterial translocation in patients with the critical illness, especially acute pancreatitis, and this was the basis behind the use of glutamine in human trials.

How to give IV glutamine supplementation?

Glutamine is available in ampoules with 100 ml (Glutamine 13.4 gm and Alanine 8.2 gm).

Glutamine IV should be given to patients with critical illness at a dose of 0.35-0.5 mg/kg/day (1.5-2.5 ml/kg/day) by continuous infusion via a central venous catheter.

Still, glutamine can be administered via a peripheral catheter but with a 1: 1 dilution in physiological saline to achieve an osmolality of less than 800.

It should not be given concomitantly with enteral glutamine or in shock / MODS, particularly severe renal and hepatic insufficiency.

Also, administration of midazolam to the same lumen is completely discouraged due to incompatibility.

IV Glutamine before Redox Trial Era

The Canadian Guidelines for 2013 have indicated that based on 9 Level 1 studies and 19 Level 2 studies when prescribing PN, glutamine IV should be taken into account [2].

IV glutamine 0.3-0.5 g / kg / day correlates with an improved effect for patients with TPN. This is equivalent to an exogenous

Correspondence to: Khaled Sewify, Critical Care Department, King Fahd Military Medical Complex, Saudi Arabia, Tel: +966544802229; E-Mail: drsewafie[AT]Hotmail[DOT]com

Received: Mar 16, 2018; **Accepted:** Mar 19, 2018; **Published:** Mar 24, 2018

IV glutamine of 20-30 g / day, which normalizes the plasma concentration in most patients with the critical illness.

An endogenous production of glutamine 50-80 g / day usually occurs in health issues. The glutamine synthesis usually takes place in the skeletal muscle and then is exported to the area of the visceral space for use primarily in enterocytes and immune cells.

Finally, glutamine production is not lower with a critical illness, but this is usually insufficient to maintain adequate plasma concentration.

IV Glutamine after Redox Trial Era

A randomized control trial of glutamine and antioxidants in critically ill patients (REDOX) [3].

1223 suddenly adults from 40 intensive care units who had multiple organ failures and received mechanical ventilation were randomly assigned to receive glutamine, antioxidants and both or placebo. Glutamine started within 24 hours after admission into the ICU and was administered both intravenously and intestinal. The primary endpoint was 28-day mortality.

The conclusion from the study was that timely administration of glutamine or antioxidants did not improve clinical outcomes and even glutamine was associated with increased mortality in patients with critical illness with multiple organ failures.

Thus, most of the guidelines have a step back from glutamine that is afraid of increased mortality.

Also Van Zanten also reported, following the publication of Metaplus's study, that we do not need these fancy things to take care of critically ill patients, we just need to stick to aggressive standard nutrition with high protein diet [4].

REDOX Trial Critique

Feeding the patient with severe shock and multiple organ dysfunction syndromes, especially in the glutamine arm, is absolutely not recommended (more than 95% is presented with shock).

The administration of high-dose glutamine in both enteral and parenteral has not been tested before and sounds very strange.

The time frame for the primary endpoint was a 28-day mortality that did not differ between the groups.

The new primary endpoint was generated during the study, which was 6-month hospital mortality and entered into the database. This endpoint has not been reported in the study protocol, so it is considered exploratory and not worthwhile.

Also, these endpoints were not corrected for the interim analysis.

The P-value for the primary endpoint was multiplied by 0.05 / 044 for the two intermediate assays.

The groups were not comparable, which was a major concern in the study: The number of patients with baseline multi-organ failure in the glutamine group was much higher than the glutamine-free group (n = 187 vs. n = 148, respectively). This may explain the observed higher mortality in the glutamine group. Thus, mortality can be explained by adding to an unbalanced group (39 patients more with 3-4 instrumentalities). Also, more patients with hepatic impairment are included in the glutamine group.

In conclusion, patients with a more severe disease were on the glutamine side due to a randomized and inadequate feeding error, and I believe the correct conclusion from the REDOX test, such as Professor Dr. Paul van Leeuwen of Amsterdam said: Timely administration of glutamine and/or antioxidants in patients with severe shock conditions and MODS did not improve the clinical outcome.

IV Glutamine in Trauma Patients

The result of a randomized trial of IV Glutamine supplementations in trauma patients: [5]

142 patients with polytrauma were randomly assigned to double-blind polycentric RCT to receive 0.5mg/kg Ala-Gln dipeptide for 5 days versus placebo (pharmacovigilance).

There was no effect on infectious complications, length of stay or mortality. Also, the subgroup of patients with severe trauma (ISS > 24) did not show any difference. 39% of patients treated had low end-of-treatment rates and were associated with worse results.

Glutamine Administration in Renal Failure Patients Undergoing Renal Replacement Therapy

Small molecules are significantly lost during hemodialysis or ultrafiltration as compared to a loss of urine in a healthy kidney.

Thus, the question arises as to whether IV glutamine should be administered during intermittent hemodialysis and especially during CRRT or not.

A recent study revealed that all amino acids including glutamine are lost during CRRT.

Thus, it makes sense that when CRRT is necessary, glutamine should be supplemented slightly more than usual: 0.5 g/kg/day and not 0.3 g/kg/day.

Glutamine in the Latest Two Meta-Analyses

The effect of glutamine therapy on outcomes in critically ill patients: a meta-analysis of randomized controlled trials [6]

The meta-analysis includes 18 RCTs, the mortality was reported in 1x7 RCTs.

There was no significant difference in mortality between the glutamine group and the control group. In the high-dose glutamine subgroup (> 0.5g/kg/d), the mortality rate in the

glutamine group was significantly higher than that of the control group.

In 15 studies, involving a total of 2,862 patients, the administration of glutamine significantly affected the onset of hospital infections in patients with the critical illness. The incidence of hospital infections in the glutamine arm was significantly lower than that of the control.

In both subgroups of ICU surgery and parenteral nutrition, glutamine supplementation statistically reduced the rate of hospital infections. The length of hospitalization was not affected by the addition of glutamine.

Conclusions of the meta-analysis

Despite glutamine administration did not affect overall mortality or length of hospitalization in patients with the critical illness, however, this treatment was associated with reduced hospital acquired infections, which varied according to patient populations, modes of nutrition and doses of glutamine.

Parenteral Glutamine Supplementation in critical illness: Meta-analysis of RCT: [7]

In total, 2 484 patients participated in 26 RCTs who only looked at parenteral supplemental GLN administration in ICU patients.

Parenteral supplementation of GLN was associated with a tendency to reduce overall mortality and a significant reduction in mortality in the hospital. Also, parenteral GLN has been associated with a strong tendency to reduce infectious complications and length of stay in ICU and a significant reduction in hospital LOS. In the subset of studies that looked at patients receiving parenteral nutrition, parenteral supplementation of GLN was associated with a tendency to reduce overall mortality.

Conclusions of the meta-analysis

Because parenteral GLN administered in combination with nutrition support continues to be associated with a significant reduction in hospital morbidity and mortality, it should continue to be considered to improve the outcome in patients with critical illness.

Glutamine in the latest guidelines

Canadian Guidelines 2015

When parenteral nutrition is prescribed in patients with the critical illness, they recommend that parenteral glutamine NOT to be used. They also recommend that intravenous glutamine should not be used in EN fed patients with the critical illness [8].

ASPEN Guidelines 2016

They recommend that parenteral glutamine should NOT be used in a routine way in critically ill patients. [Quality of evidence: Moderate] [9]

ESPEN Guidelines 2017

They recommend that in patients who cannot be adequately enterally fed and require exclusive PN, the parenteral glutamine supplement may be suggested (grade B) [10]

Summary of How and When to use IV Glutamine?

The difference in the results between REDOXs study and old published trials that was suggesting that glutamine should be a standard of care in the TPN emphasizes the need for large multicenter randomized control trial to answer the question clearly, how and when to use glutamine?

Until we have such trial, the most evidence based practices to consider using glutamine with the following precautions:

1. Use with TPN and hypercatabolic states without shock or MODS.
2. Never use in shock and MODS particularly severe hepatic and renal insufficiency.
3. Never give without adequate feeding.
4. Do not administer more than 0.35 - 0.5gm / kg / day in total (1.5 - 2ml / kg / 24hrs.).
5. Never mix enteral and parenteral glutamine.
6. Never exceed 3 weeks of treatment.

References

1. Jan Werneman (2011) Glutamine supplementation to critically ill patients? *Crit Care* 18: 214. [[View Article](#)]
2. Dhaliwal R, Cahill N, Lemieux M, Heyland DK (2014) The Canadian Critical Diet Guidelines in 2013: A briefing on current recommendations and implementation strategies. *Nutr Clin Pract* 29: 29-43. [[View Article](#)]
3. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, et al. (2013) A randomized trial of glutamine and antioxidants in critical patients. Additional files. *N Engl J Med* 368: 1489-1497. [[View Article](#)]
4. van Zanten ARH, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, et al. High-protein intestinal nutrition enriched with nutrients that alter the immunosuppressive action against typical high-protein intestinal diet and hospital infections in the ICU. *JAMA* 312: 514. [[View Article](#)]
5. Pérez-Bárcena J, Marsé P, Zabalegui-Pérez A, Corral E, Herran-Monge R, et al. (2014) A randomized trial of intravenous glutamine supplementation in trauma ICU patients. *Intensive Care Med* 40: 539-547. [[View Article](#)]
6. Chen QH, Yang Y, He HI, Xie JF, Cai SX, et al. (2014) The effect of glutamine treatment on results in patients with critical disease: a meta-analysis of randomized controlled trials. *Crit Care*: 18: 1-8. [[View Article](#)]
7. Wischmeyer PE, Dhaliwal R, McCall M, Ziegler TR, Heyland DK (2014) Parenteral glutamine supplementation in critical illness: a systematic review. *Crit Care* 18: 1-76. [[View Article](#)]
8. Rahman A, Hassan RM, Agarwala R, Martin C, Day AG, Heyland DK (2015) Canadian food guidelines for critical reasons. *Clin Nutr* May 25. [[View Article](#)]

9. Warren M, McCarthy MS, Roberts PR (2016) Practical Implementation of the Revised Guidelines for Providing and Evaluating Nutritional Support Treatment to the Patient Patient Adult Patient: A Case Study Approach. *Nutr Clin Pract* 31: 334-341. [[View Article](#)]
10. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, et al. (2017) ESPEN Directive: Clinical nutrition in Surgery. *Clin Nutr* 36: 623-650. [[View Article](#)]

Citation: Sewify K (2018) Glutamine in Critically ill Patients – When and How?. *J Nutr Diet Pract* 2: 001-004.

Copyright: © 2018 Sewify K. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.