Commentary

Crit Care Shock (2017) 20:21-23

Three years after the REDOXS study: What we have learned in the use of glutamine in ICU patients?

Alberto Leguina-Ruzzi, Marcial Cariqueo, Ricardo Gálvez

Abstract

Critical illness has been associated with glutamine (Gln) plasma levels depletion and its supplementation is related with better outcomes. In 2013 the Reducing Deaths due to Oxidative Stress (REDOXS) study, showed that the supplementation of Gln to total parenteral nutrition was associated with higher mortality without conferring beneficial effects. These conclusions had a high impact in the clinical field: two of the main guidelines downgraded its recommendation. However, recent studies are answering questions regarding the safety use of this amino acid use and even suggesting new potential beneficial effects.

It is important to understand the main lessons learned of the REDOXS study related to the correct use of Gln intra venous and do not rule out its use for the intensive care unit patients. The scientific community is actively working in the field and we expect to have more evidence to guide the correct of this amino acid in parenteral nutrition.

Key words: Glutamine, parenteral nutrition, REDOXS.

Gln (glutamine) is a conditionally essential amino acid (AA) (1) that has been widely used for decades as supplement to total parenteral nutrition (TPN) in the critical care patients. (2) In them, it has been described a considerable plasmatic levels depletion related to the hypercatabolic conditions. (3) Several molecular targets explain its beneficial effects, improving the outcome of these patients. (4)

During critical illness Gln plasma levels decrease and this deficiency has been associated with increased mortality in several trials. Therefore, the rational to supplement critical care patients with Gln has been emphasized. In 2002 Goether et al. showed improve the six-month survival in patients with at least 9 days of parenteral Gln supplementation. (5)

In 2013 the Reducing Deaths due to Oxidative Stress (REDOXS) study, the largest trial to date, showed that the supplementation of Gln was associated with higher mortality and no beneficial effects were seen. The study used a combined enteral and intravenous (IV) Gln supplementation in higher doses than the recommended by the clinical guidelines, also the heterogeneous enrollment included patients that fulfilled contraindication criteria for its supplementation.

In the interventional set they supplemented Gln enteral 30 g/day plus parenteral 15 g/day giving around 1 g/kg/day, doses way higher than the classically recommended by the clinical guidelines of the date. (6)

The REDOXS study was an investigation into the clinical effects of alanyl-glutamine dipeptide, as a synthetic drug. Nevertheless, the study did not make it clear that at these pharmacological/supraphysiological dosages there are no published toxicity or safety data in animals or humans, that international regulatory authorities would have reviewed and approved for clinical use.

Interestingly, one year later the authors reported a post hoc analysis of this study concluding that an early provision of high-dose was not beneficial and may be associated with increased mortality in critically ill patients with multiorgan failure that included renal dysfunction upon study enrollment. (7) Attention needs to be drawn to this very important point: a possible explanation of the incorporation of these patients might be based on early studies that showed improvement in outcomes for renal failure patients that received Gln. (8-10)

These conclusions had a high impact not only in the pharmaceutical industry but also in the clinical

From Czech Academy of Science, Praha, Czech Republic (Alberto Leguina-Ruzzi), Hospital Clínico Universidad de Chile, Santiago, Chile (Marcial Cariqueo and Ricardo Gálvez).

Address for correspondence:
Alberto Leguina-Ruzzi, PhD
Senior Researcher
Institute of Physiology, Dept. of Mitochondrial Physiology
Czech Academy of Science
Vídeňská 1083, Praha 4 142 00, Czech Republic
Email: albertoandres.leguinaruzzi@fgu.cas.cz

practice: two of the most important guidelines changed dramatically the recommendation of use of Gln. First, in 2015 the Canadian Clinical Practice Guidelines downgraded the Gln supplementation based on the REDOXS results and a series of studies that do not justify this change. (11) In 2016, following the same trend, the American Society for Parenteral and Enteral Nutrition (ASPEN) also downgraded its IV use, primarily based on the controversial conclusion published two years before. (12)

Even when these important guidelines almost eliminated the use of this AA as a supplement for TPN, the research in the Gln field has experienced important advances in terms of new clinical data. These studies are showing important findings that support the use of Gln.

Pérez-Bárcena et al (13) in 2014 showed that low doses of Gln IV for 5 days did not show beneficial effects to the intensive care unit (ICU) patients without causing any derogative effect. However, plasmatic Gln measurement in the patients showed that those with lower levels presented a worse outcome (mortality, length of stay, and infections) in which a supplementation with higher doses might be necessary. Lately, Ziegler TR et al also demonstrated the Gln safeness in 50 adults after gastrointestinal, vascular, or cardiac surgery requiring TPN and ICU care and without alterations in clinical outcomes. (14)

In the same year, Grintescu et al (15) showed that Gln supplementation in trauma patients reduced hyperglycemic episodes and improved insulin response. The conclusions suggested a role for Gln as an insulin sensitizer explained by the pathways in the beta pancreatic cells involving intracellular calcium influxes. (4) These clinical observations had been previously suggested by Déchelotte P et al. (16) and Bakalar B et al (17) in patients admitted for multiple trauma complicated surgery or pancreatitis. However, not fully associated with the molecular mechanism currently known.

More recently, Helling et al (18) evidenced the association between liver failure and high plasma Gln levels, a condition not fully reported before that sustains the importance of consider the hepatic dysfunction as a main contraindication parameter for Gln supplementation. Importantly, we might speculate this conditions for the contradictory high plasma values of the small sub-group reported in the REDOXS study prior to dipeptide supplementation.

It is crucial to understand that the REDOXS study gave us important lessons about how not to use the Gln, more than "throwing the baby out with the bathwater", as Wischmeyer eloquently described: (19) the dose has to be appropriate with a balanced mixture with other AA and it is contraindicated to patients with hepatic and/or renal failure. Still, a recent systematic review by the author concluded that parenteral Gln supplementation given in conjunction with nutrition support continues to be associated with a significant reduction in hospital mortality and hospital length of stay (LOS). Parenteral Gln supplementation as a component of nutrition support should continue to be considered to improve outcomes in critically ill patients. (20)

Interestingly, other authors have also evaluated possible explanations for the findings reported by the REDOXS concluding that "high-dose parenteral glutamine (>0.5 g/kg/day) should be avoided during the early stages of critical illness in patients with multiple organ failure or ongoing shock requiring vasopressor support" among other relevant observations. (21)

Our point of view in this matter is that the REDOXS has to be read critically, understanding the particular scope of patients enrolled and the heterogeneous interventional setting selected by the authors and dose.

The poorly designed protocol and the fact that the REDOXS results are irrelevant to routine supplementation of glutamine for the critically ill caused misunderstood and reluctance on the medical community.

New large, multicenter, prospective randomized clinical trials are needed to confirm the beneficial effects of Gln in the mortality, LOS and infections rates as main clinical outcomes highly relevant in the critical care unit. However, it is important to highlight that the research on the Gln field has given important steps in the years after the REDOXS, not only answering and reinforcing basic questions such as the glutamine plasmatic levels in ICU patients and its safe use as supplement to TPN, but also showing new promising beneficial effects that open a whole new perspective for further research and use.

Acknowledgment

Alberto Leguina-Ruzzi and Ricardo Gálvez received consultation honoraria from Fresenius-Kabi in the last 36 months. Marcial Cariqueo received consultation honoraria from 3M in the last 36 months. The authors declare that they do not have other competing interests.

Alberto Leguina-Ruzzi held a grant from the Research Institute for Disease of Old Age, Juntendo University, Japan during the preparation of this manuscript.

References

1. Buchman AL. Glutamine: commercially essential or conditionally essential? A critical appraisal of the human data. Am J Clin Nutr 2001;74:25-32.
2. Rodas PC, Rooyackers O, Hebert C, Norberg Å, Wernerman J. Glutamine and glutathione at ICU admission in relation to outcome. Clin Sci (Lond) 2012;122:591-7.
3. 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.
4. Leguina-Ruzzi A. Therapeutic targets of glutamine in parenteral nutrition: a medical science review. Int J Prev Treat 2015;4:34-9.
5. Goeters C, Wenn A, Mertes N, Wempe C, Van Aken H, Stehle P, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med 2002;30:2032-7.
6. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critical ill patients. N Engl J Med 2013;368:1489-97.
7. Heyland DK, Elke G, Cook D, Berger MM, Wischmeyer PE, Albert M, et al. Glutamine and antioxidants in the critically ill patient: a post hoc analysis of a large-scale randomized trial. JPEN J Parenter Enteral Nutr 2015;39:401-9.
8. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 1997;13:295-302.
9. Abel RM, Beck CH Jr, Abbott WM, Ryan JA Jr, Barnett GO, Fischer JE. Improved survival from acute renal failure after treatment with intravenous essential L-amino acids and glucose. Results of a prospective, double-blind study. N Engl J Med 1973;288:695-9.
10. Zager RA. Amino acid hyperalimentation in acute renal failure: a potential therapeutic paradox. Kidney Int Suppl 1987;22:S72-5.
11. Leguina-Ruzzi A. A commentary on the 2015 Canadian Clinical Practice Guidelines in glutamine supplementation to parenteral nutrition. Crit Care 2016;20:7.
12. 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.
13. Pérez-Bárcena J, Marsé P, Zabalegui-Pérez A, Corral E, Herrán-Monge R, Gero-Escapa M, et al. A randomized trial of intravenous glutamine supplementation in trauma ICU patients. Intensive Care Med 2014;40:539-47.
14. Ziegler TR, May AK, Hebbar G, Easley KA, Griffith DP, Dave N, et al. Efficacy and Safety of Glutamine-supplemented Parenteral Nutrition in Surgical ICU Patients: An American Multicenter Randomized Controlled Trial. Ann Surg 2016;263:646-55.
15. Grintescu IM, Luca Vasiliu I, Cucereanu Badica I, Mirea L, Pavelescu D, Balanescu A, et al. The influence of parenteral glutamine supplementation on glucose homeostasis in critically ill polytrauma patients—a randomized-controlled clinical study. Clin Nutr 2015;34:377-82.
16. Déchelotte P, Hasselmann M, Cynober L, Allaouchiche B, Coëffier M, Hecketsweiler B, et al. L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: the French controlled, randomized, double-blind, multicenter study. Crit Care Med 2006;34:598-604.
17. Bakalar B, Duska F, Pachl J, Fric M, Otahal M, Pazout J, et al. Parenterally administered dipeptide alanyl-glutamine prevents worsening of insulin sensitivity in multiple-trauma patients. Crit Care Med 2006;34:381-6.
18. Helling G, Wahlin S, Smedberg M, Pettersson L, Tjäder I, Norberg Å, et al. Plasma Glutamine Concentrations in Liver Failure. PLoS One 2016;11:e0150440.
19. Wischmeyer P. Glutamine Supplementation in Parenteral Nutrition and Intensive Care Unit Patients: Are We Throwing the Baby Out With the Bathwater? JPEN J Parenter Enteral Nutr 2015;39:893-7.
20. Wischmeyer PE, Dhaliwal R, McCall M, Ziegler TR, Heyland DK. Parenteral glutamine supplementation in critical illness: a systematic review. Crit Care 2014;18:R76.
21. Mulherin DW, Sacks GS. Uncertainty about the safety of supplemental glutamine: an editorial on "A randomized trial of glutamine and antioxidants in critically ill patients". Hepatobiliary Surg Nutr 2015;4:76-9.