Editorial

# Uncertainty about the safety of supplemental glutamine: an editorial on "A randomized trial of glutamine and antioxidants in critically ill patients"

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**Abstract:** Previously small randomized clinical trials and several meta-analyses have suggested improved patient outcomes from parenteral glutamine supplementation. A recent large multi-center randomized trial conducted in critically ill patients with documented multiple organ failure at enrollment demonstrated an increase in mortality among those receiving supplemental glutamine. This article discusses the discrepancies in trial outcomes and the risks associated with glutamine administration during critical illness.

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## Introduction

Glutamine is a non-essential, free amino acid that is primarily generated by skeletal muscle. During critical illness, glutamine can become a conditionally essential amino acid as the body's ability to produce glutamine is reduced (1). Low plasma glutamine concentrations at ICU admission in critically ill patients are associated with higher mortality rates. Thus, many trials have been conducted to determine if glutamine supplementation improves outcomes in this patient population (1-3).

## Evidence leading up to REDOXs

Enteral glutamine supplementation at doses of 11-40 g/day has demonstrated beneficial effects on morbidity and mortality in general ICU, burn, and trauma patients primarily in small, single-center, randomized studies (4). However, trials conducted in patients requiring parenteral nutrition have used intravenous (IV) glutamine supplementation at doses of 0.3-0.5 g/kg/day. Intravenous glutamine was found to significantly decrease hospital length of stay, infectious complications, risk of multi-system organ failure, and even mortality in meta-analyses involving critically ill and surgical patients (1). Until recently, the safety of glutamine supplementation has only been questioned in patients with underlying renal and hepatic dysfunction. Elevated liver function tests and serum ammonia concentrations have been noted in glutamine-supplemented patients with hepatic insufficiency while worsening azotemia may occur in patients with renal dysfunction; thus, caution is advised for the use of glutamine in these populations (1). No studies had demonstrated truly harmful effects of glutamine supplementation until the publication of the REDOXS trial.

## Summary of REDOXs and possible explanation for findings

In a multicenter, randomized, placebo controlled trial (REDOXs), Heyland *et al*. compared 28-day mortality among four groups of patients (5): combination IV and enteral glutamine (0.35 g/kg/day and 30 g/day, respectively), combination IV and enteral antioxidants (selenium 500 µg/day and 300 µg selenium, 20 mg zinc, 10 mg beta carotene, 500 mg vitamin E, 1,500 mg vitamin C, respectively),

combination antioxidants plus glutamine, and placebo. Only critically ill patients with multisystem organ failure requiring mechanical ventilation were included. This study included 1,223 patients from 40 ICU's across Europe, Canada, and the United States, making it the largest trial on intravenous glutamine to date (5).

Unexpectedly, there was a trend toward increased mortality at 28 days in patients who received glutamine compared with those who did not (32.4% *vs*. 27.2%, P=0.05). In-hospital mortality and 6-month mortality were significantly higher for patients receiving glutamine compared with those who did not (37.2% *vs*. 31%, P=0.02; and 43.7% and 37.2%, P=0.02, respectively). This was surprising due to the largely positive results seen in previous trials and numerous meta-analyses.

Among the possible reasons for these findings, authors hypothesized that patients included in this study were more acutely ill than patients in previous trials and may have received the study drug too early. Greater than 90% of patients had both respiratory failure and clinical evidence of hypoperfusion. While hepatic failure was an exclusion criterion, roughly 36% of participants had renal dysfunction. These characteristics have not been previously included in other studies. Perhaps this is a patient population that does not need glutamine supplementation. In fact, a post hoc analysis of this trial revealed that mortality at 28 days was significantly higher in patients in the glutamine-only group with baseline renal dysfunction who did not receive dialysis during the study period compared with placebo [odds ratio (95% CI) =3.91 (1.71-8.96)] (6).

The timing of supplementation may have also affected the outcomes of the REDOXs trial. To avoid the development of glutamine deficiency in this critically ill study population, glutamine was initiated early (e.g., within 24 hours of admission). Other studies have initiated treatment between 48-72 hours and even greater than one week after (7-9). Thus, later initiation of glutamine may be more appropriate as this is when glutamine deficiency is more likely to have developed.

Another possibility is that the dose was too high. An average of 0.6-0.8 g/kg/day of glutamine was administered using a combination of both IV and enteral routes, which is much higher than previously studied doses. This may have resulted in harmful effects from elevated plasma glutamine concentrations. In a recent study by Rodas *et al*., baseline glutamine concentrations >930 μmol/L were associated with mortality in ICU patients (3); however, glutamine concentrations were not routinely measured in the REDOXs trial (5). Baseline glutamine concentrations were only reported for a subgroup of 61 patients, and the majority of these patients had normal or above-normal concentrations of glutamine at the time of study enrollment. Unfortunately, results from a subgroup analysis of this size cannot be extrapolated to the rest of this large study population. It should also be noted that patients in the REDOXs trial were significantly underfed during the study period. Whether this is harmful or insignificant in the early course of critical illness is still debated; however, it is possible that providing minimal calories from enteral nutrition in combination with doses of up to 0.8 g/kg/day of glutamine is harmful in the setting of multisystem organ failure in an elderly patient population (10,11).

An alternative perspective is that glutamine supplementation simply is not beneficial in all critically ill patients. Other large, randomized trials have failed to show a benefit of glutamine supplementation in trauma, surgery, and medical ICU patients (12-14). In a randomized, double-blind, multicenter trial, 142 trauma patients were randomized to receive 0.5 g/kg/day of IV glutamine (n=71) or placebo (n=71) for five days. Baseline glutamine concentrations were low in 58% of the treatment group and 62% of the placebo group. Repeat glutamine concentrations drawn on day 6 revealed low glutamine concentrations in 39% of the treatment group and 57% of the placebo group. The treatment group had significantly higher mean glutamine concentrations at 6 days (380 versus 322 μmol/L, respectively; P=0.012), but there was no difference in infection rates, length of stay, or mortality between groups (12). In another randomized, multicenter trial, 428 patients undergoing major abdominal surgery for cancer were randomized to receive either 0.4 g/kg/day (n=212) of IV glutamine or no supplementation (n=216) (13). Treatment began the day prior to surgery and continued for at least five days. Investigators found no difference between infectious morbidity, length of stay, or post-operative complications. The SIGNET study also failed to show any beneficial effect of parenteral glutamine in critically ill patients (14). This trial was conducted in ten Scottish intensive care units using a randomized, double blind, factorial design. A total of 502 medical and surgical ICU patients were randomized to one of four groups with gastrointestinal failure requiring PN: IV glutamine (20.2 g/day; n=126), IV selenium (500 μg/day; n=127), combination glutamine and selenium (n=124), or placebo (n=125). Treatment continued for up to seven days. Glutamine supplementation (either with monotherapy or in combination with selenium) did not affect infection rate,

 

6-month mortality, length of stay, antibiotic use, or modified SOFA scores. This study has been criticized because of its low dose of glutamine supplementation (~0.25 g/kg/day) and other methodologic issues such as patient drop-out numbers, missing values, and complete follow-up data. Nutrition support in the United Kingdom is not individualized for each patient so parenteral nutrition formulations were designed to meet average estimated requirements for most patients. No data on the amount of parenteral nutrition received *vs.* prescribed was reported and the median duration of parenteral nutrition for glutamine formulations with or without selenium ranged from 5-5.1 days. Patient severity of illness was characterized with APACHE II and SOFA scores. Median APACHE II and SOFA scores were 20 (interquartile range, 16-25) and 5 (interquartile range, 3-8), respectively (14). In comparison, median APACHE II and SOFA scores in REDOXs trial patients were 26.6 and 8.4, respectively (6). In contrast to the REDOXs trial, no worsening of organ dysfunction or survival was attributed to glutamine supplementation. The discrepancies in patient outcomes may be related to differences in severity of illness and the low dose of glutamine administered over such a short time period.

## Conclusions

The discrepancy between results from the REDOXs trial and previously published data emphasizes the necessity for conducting large, multicenter, prospective randomized clinical trials rather than basing clinical practice on hypothesis-generating data from meta-analyses. It also creates additional questions about the safety and efficacy of providing parenteral glutamine supplementation to critically ill patients. The optimal dose and timing of glutamine supplementation is yet to be determined. The patient population (i.e., surgical, medical, trauma) that stands to benefit the most from glutamine supplementation is also unknown. Based upon the current evidence, we believe 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. Furthermore, care should be taken to ensure that parenteral glutamine is used as a supplement to complete nutrition support regimens rather than as an independent nutrient. Attempting to use parenteral glutamine as a pharmacologic agent may create an amino acid imbalance when the actual nutritional delivery is less than 50% of that prescribed for patients and inadequate to meet their energy and protein needs. If parenteral nutrition is supplemented with intravenous glutamine, doses of 0.3-0.5 g/kg/day should be used after resolution of the acute phase of critical illness in patients with no clinical evidence of significant hypoperfusion or impending renal dysfunction.

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