Glutamine in critically ill patients

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SUMMARY

This multinational, blinded, randomized, controlled trial aimed to prove that glutamine supplementation would reduce mortality in critically ill patients. In a 2-by-2 factorial design, 1223 mechanically ventilated patients with multiorgan failure in 40 intensive care units (ICUs) were enrolled and randomized to receive either intravenous glutamine (0.35 g/kg of ideal body weight) and enteral glutamine (30 g) supplementation, a supplement of anti-oxidants, both or placebo within the first 24 hours of admission to the ICU. The primary outcome was 28-day mortality. Secondary outcomes included in-hospital and 6-month mortality, time to discharge alive from the ICU and hospital, and ICU length of stay and duration of mechanical ventilation. Plasma glutamine levels were measured at admission and on days 4 and 7 of supplementation in a sample of patients.

Patients who were supplemented with glutamine showed a trend towards increased 28-day mortality (32.4% vs. 27.2%, OR 1.28, 95% CI 1.00–1.64, p=0.05) compared with those not supplemented with glutamine. Among the secondary outcomes, in-hospital mortality (37.2% vs. 31.0%, p=0.02) and mortality at 6 months (43.7% vs. 37.2%; p=0.02) were significantly higher among patients who received glutamine, as was also the median time to discharge alive from the ICU and hospital. Glutamine supplementation had no significant effect on the outcomes of organ failure or infections. Plasma glutamine levels were normal at baseline among the groups but were significantly higher in the supplemented group on days 4 and 7 (p<0.01). The number of serious adverse events was not different among the groups, and the results were not different in several pre-specified subgroups.

COMMENT

Glutamine, an amino acid synthesized in large amounts by the human body, is capable of generating both glucose and glycogen and is the non-toxic transport form of nitrogen and ammonia. It is considered to be ‘conditionally essential’ in serious catabolic states. Release of glutamine in large amounts from muscles during serious illness is hypothesized to serve as a ‘stress signal’ leading to gene activation to promote cellular protection and immune regulation. In animal experiments, Wischmeyer et al. showed that parenteral glutamine is protective against pro-inflammatory induced injury via induction of heat shock proteins (HSP). Proliferating lymphocytes, monocytes and macrophages need glutamine for synthesis of nucleotides and expression of cell surface activation markers (CD25, CD45RO). Glutamine is preferred over glucose as a source of fuel for enterocytes, in settings of gut ischaemia. Human studies show that glutamine supplementation improves insulin sensitivity, leads to preservation of skeletal muscle, improves nitrogen balance, enhances immune cell function and is not pro-inflammatory. Further, it has antioxidant properties via metabolism to glutathione.

Glutamine deficiency, defined as low plasma concentration (<420 mmol/L), at ICU admission was found to be an independent predictor of mortality. Parenteral glutamine supplementation results in uniform uptake of glutamine across splanchnic areas whereas enteral glutamine absorption occurs principally through the proximal jejunum; the rest of the gut is unsupported by enteral glutamine. After uptake by enterocytes and immune cells only a fraction of enteral glutamine is detected in the portal blood. A further first pass elimination of 40%–90% of enteral glutamine occurs in the liver, resulting in low plasma concentration after enteral supplementation. Intravenous glutamine supplementation of 0.3–0.5 g/kg/day normalizes the plasma concentration in most critically ill patients.

Several studies on glutamine supplementation were available at the beginning of this century and Novak et al. did a systematic review of 14 randomized trials (including 751 patients) from 1993 to 2001. Overall, this review supported the view that glutamine supplementation was associated with a strong trend towards a reduction in mortality (RR 0.78, 95% CI 0.58–1.04), lower rates of infectious complications (RR 0.8, 95% CI 0.64–1.00, p=0.003) and shorter hospital stay (~2.6 days; 95% CI −4.5 to 0.7). As there was statistical heterogeneity in the studies, and to better understand the findings, the authors further looked at outcomes in pre-
specified subgroups. All the studies on critically ill patients were with enteral glutamine, with no treatment effect. Parenteral supplementation was beneficial, high dose (>0.2 g/kg) was better than low dose and glutamine supplementation in post-surgical patients resulted in significant benefits as compared to that in critically ill patients. However, the authors opined that the studies included in this meta-analysis had their own limitations such as insufficient sample size, non-concealed study drug allocation, analysis not done in subgroups, end-points not defined a priori and intention-to-treat analysis not done. Hence, they considered this meta-analysis as hypothesis-generating regarding safety of glutamine supplementation rather than confirming the hypothesis that glutamine has beneficial effects in seriously ill patients.

Subsequent reviews further stressed the beneficial role of parenteral glutamine supplementation. Nutritional guidelines of various societies recommended 0.35–0.5 g/kg per day of parenteral glutamine supplementation for use in critically ill patients requiring parenteral nutrition. This is in spite of the fact that publication bias was seen as a major limitation of the quality of available trials.

The first well-designed study was by Andrews et al., who did a randomized, double-blind, 2-by-2 factorial, controlled trial on parenteral glutamine supplementation in 502 critically ill patients in 10 Scottish ICUs (SIGNET trial). Critically ill patients, who required ≥50% of their nutritional requirement parenterally, were supplemented with 20.2 g/day of glutamine or 500 µg/day of selenium or both. The intervention was started at a median of 2.6 days after ICU stay and continued for at least 5 days. In an intention-to-treat analysis, no evidence of beneficial effect on new infections was seen. Contrary to what was expected, this study showed higher ICU (OR 1.21, 95% CI 1.02–1.44, p=0.02) and parenteral glutamine supplementation. 11 Nutritional guidelines of various societies recommended 0.35–0.5 g/kg per day of parenteral glutamine supplementation for use in critically ill patients requiring parenteral nutrition. This is in spite of the fact that publication bias was seen as a major limitation of the quality of available trials.

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The findings in the present study by Heyland et al. are very different from what was expected. Several factors may have accounted for this discrepancy as identified by the authors. First, prior meta-analysis involved smaller, less methodologically robust studies. Second, patients in this study received a higher dose of glutamine. Third, glutamine supplementation was both enteral and parenteral in this study whereas in previous studies either enteral or parenteral glutamine was used. Fourth, a majority of patients in this study were in multiorgan failure with shock; whereas previous studies excluded these patients. Fifth, initiation of supplements started within 24 hours after ICU admission, i.e. much earlier in comparison to previous studies. Sixth, patients with gastrointestinal failure, a major cause of mortality in critically ill patients, were excluded in this study and all patients received at least partial enteral nutrition. Apart from these, plasma glutamine concentrations on day 1 were not low in either group (494.5 vs. 480.5 mmol/L) of critically ill patients.

We can only speculate as to why glutamine supplementation resulted in higher mortality. Possibly, low plasma glutamine levels during acute critical illness reflect an adaptive response rather than a true intracellular deficiency and interfering with such adaptation could be deleterious. Enteral supplementation also increases plasma concentration of arginine. 15 Arginine, in turn, may act as a substrate for inducible nitric oxide synthase, which is usually upregulated in haemodynamically unstable patients, resulting in an unfavourable outcome.

Considering the high quality of evidence obtained from this last trial, we can confidently say that glutamine supplementation in critically ill patients does not improve outcome, rather it may be harmful. This study only exemplifies what is well known but often overlooked: that all interventions in medicine need to be tested rigorously before applying them in clinical practice.

REFERENCES