The Role of Glutamine in Intensive Care Unit Patients: Mechanisms of Action and Clinical Outcome

Moïse Coëffier and Pierre Déchelotte

Patients in the intensive care unit are at high risk of glutamine depletion and subsequent complications. Several controlled studies and a meta-analysis have concluded that glutamine supplementation has beneficial effects on the clinical outcome of critically ill and surgical patients. These results may be explained by glutamine’s influences on the inflammatory response, oxidative stress, cell protection, and the gut barrier. In addition, glutamine may also improve glucose metabolism by reducing insulin resistance.

Key words: glutamine, nutritional support, critical care, nosocomial infections, insulin resistance.

Introduction

Glutamine is the most abundant amino acid in plasma and is involved in a wide variety of metabolic and biochemical processes. Although initially classified as a non-essential amino acid (since it can be synthesized de novo), glutamine has more recently been considered as conditionally essential in catabolic states. Glutamine contributes to the regulation of the redox status, is a precursor of glutathione and other amino acids, and also regulates protein synthesis. In addition, glutamine contributes to the synthesis of puric and pyrimidic bases and consequently of nucleic acids. Glutamine is also the preferential substrate of rapidly dividing cells such as enterocytes and immune cells, and thus can stimulate their proliferation. In hypercatabolic conditions, it has been reported that glutamine plasma levels are decreased, which is associated with a bad prognosis.

Critically ill patients and patients after major surgery are at risk of malnutrition, bacterial translocation, and acquired infections. Up to 40% of patients in the intensive care unit (ICU) may acquire nosocomial infections. As a result, their lengths of stay and mortality risks, in addition to hospital costs, are increased.

Several studies have addressed the efficacy of parenteral or enteral supplementation with glutamine in reducing complication rates in critically ill and postoperative patients. Enteral supplementation with glutamine reduced infectious complications in critically ill patients and in trauma patients. Parenteral glutamine supplementation also reduced infectious complications in severely burned patients fed enterally and during secondary peritonitis. Glutamine supplementation has been associated with a decrease in mortality in some studies. Griffiths et al. reported that parenteral glutamine improved six-month outcome, and that the severity of complications and the associated in-ICU death rates were reduced in glutamine-treated patients.

In a randomized, controlled, double-blind multicenter trial, parenteral glutamine supplementation was evaluated in 114 critically ill patients admitted for multiple trauma, complicated surgery, pancreatitis, or sepsis. The patients did not differ at inclusion. Glutamine supplementation was associated with a lower incidence of complications: 41.4% compared with 60.7%, (p < 0.05, intention-to-treat), which was mainly due to a reduced infectious rate per patient (mean ± SD = 0.45 ± 0.6 vs 0.71 ± 0.73; p < 0.05) and a reduced incidence of pneumonia (10 vs 19; p < 0.05). Hyperglycemia was less frequent in glutamine-treated patients (20 vs 30; p < 0.05), and the need for insulin therapy was reduced. Thus, in this study, total parenteral nutrition supplemented with Dipeptiven in critically ill patients was associated with an improved clinical outcome and better metabolic tolerance. In additional studies of critically ill patients, glutamine plasma level was depleted and restored after supplementation with parenteral glutamine.
The mechanisms possibly contributing to the beneficial effects of glutamine in ICU patients are summarized in Figure 1 and discussed below.

**Glutamine and the Gut Barrier**

The gut barrier plays a critical role in the defense of an organism, and alterations of this barrier may contribute to the incidence of infection. The gut barrier is regulated by a balance between cell proliferation and apoptosis and between protein synthesis and degradation. It has been reported that glutamine stimulates enterocyte proliferation and decreases human intestinal epithelial cell apoptosis. Glutamine also stimulates intestinal protein synthesis in epithelial cell lines, in animals, and in human duodenal mucosa. In addition, glutamine may decrease intestinal proteolysis by the inhibiting ubiquitin-ATP-dependent proteolytic pathway. Finally, van der Hulst et al. reported that glutamine limits the increase of intestinal permeability in critically ill patients.

**Glutamine and Immune Function**

Immune function is altered in critical illness, and decreases have been reported in trauma patients compared with healthy volunteers; D-related human leukocyte antigen (HLA-DR) expression plays a critical role in the induction of the cellular immune response. In trauma patients, parenteral glutamine supplementation restored HLA-DR expression in monocytes. Glutamine also stimulated lymphocyte proliferation in mice, and parenteral glutamine increased lymphocyte count during acute pancreatitis. Thus, glutamine may improve the cellular immune response during critical illness.

**Glutamine and Glutathione**

Glutamine provides the source of glutamate, an amino acid precursor of glutathione. The glutathione system is one of the major mechanisms protecting against oxidative stress in the cells. Reduced glutathione (GSH) content is decreased in the skeletal muscle of surgical patients and in the intestinal mucosa during inflammatory disease. Experimental data have reported that glutamine increases splanchnic GSH production, as well as tissue concentrations of GSH in catabolic animals. Glutamine also prevents GSH depletion of Peyer’s patch in endotoxemic mice. In surgical patients, glutamine maintains muscle and plasma GSH concentrations to the preoperative level.

**Glutamine and Heat Shock Proteins**

Glutamine has a protective effect on cells by inducing the production of heat shock proteins, which protect cells against toxic agents or pathologic insults. Indeed, experimental data have shown that glutamine enhances heat shock protein expression in human peripheral blood mononuclear cells, in intestinal epithelial cell lines, and in several organs in rats. We have previously reported that enteral glutamine increases hsp32 (or heme oxygenase-1) expression in human duodenal mucosa. Heme oxygenase-1 induction is considered to be a protective response because of its anti-inflammatory, anti-apoptotic, and antioxidant effects. An enhancement of heat shock protein expression is usually associated with an attenuation of tissue lesions.

**Glutamine and Inflammatory Response**

During acute pancreatitis, glutamine-supplemented parenteral nutrition decreases the inflammatory response, as shown by a decrease in IL-8 or CRP. Experimental data have also shown that glutamine influences the intestinal inflammatory response. Indeed, glutamine decreases IL-8 production by the intestinal epithelial cell line Caco-2, and IP-10 and ITAC chemokines by the intestinal epithelial cell line HCT-8. Using a model of

![Figure 1: Potential mechanisms explaining the benefits of glutamine in critically ill and surgical patients.](image)
cultured duodenal mucosa, we showed that enteral glutamine reduces IL-6 and IL-8 basal production, in a specific manner compared with isonitrogenous and isosmolar controls. In inflammatory conditions, glutamine reduces IL-6 and IL-8 production but also increases anti-inflammatory cytokine IL-10 production. This result is in accordance with previous data in parenteral-fed rats. In this latter study, glutamine-supplemented parenteral nutrition maintained IL-4 and IL-10 production by lamina propria mononuclear cells and also maintained intestinal and extra-intestinal IgA levels in rats. On the other hand, glutamine did not affect intestinal nitric oxide production.

Glutamine and Glucose Metabolism

In addition to the regulation of the inflammatory response, pro-inflammatory cytokines such as IL-6 and IL-8 can play a major role in the mechanism of insulin resistance, since they are up-regulated in adipose cells from insulin-resistant individuals. Thus, modulation of the inflammatory response should influence insulin sensitivity. Indeed, glutamine supplementation reduces hyperglycemia episodes and insulin needs in critically ill patients. It has been reported that pronounced hyperglycemia may increase the risk of complications in such patients and in patients with diabetes, and that intensive insulin therapy with tight glycemic control decreases mortality and morbidity in ICU patients. Nevertheless, the mechanisms of action of this beneficial effect remain unclear; both insulin by itself and the reduction of hyperglycemia may contribute to the clinical effect. Therefore, modulation of glucose metabolism could improve outcome in severe illness.

Studies in healthy subjects have indicated that enteral infusion of glutamine increases the insulin level, but data on the effects of glutamine on insulin resistance are still limited. Supplementation of obese mice with glutamine resulted in persistent reductions in both plasma glucose and insulin levels. In dogs, glutamine infusion increased whole body glucose utilization (mainly muscular and hepatic) markedly and whole-body glucose production to some extent. In addition, parenteral alanine-glutamine administration attenuates insulin resistance in multiple trauma patients. Thus, glutamine may have potential benefits during clinical situations associated with insulin resistance.

Conclusion

Several clinical studies performed in critically ill and surgical patients have indicated that provision of supplemental glutamine reduces the rate of infectious complications and lengths of hospital stay. These beneficial effects may be explained by several mechanisms, including the modulation of inflammatory and oxidative responses, as well as the induction of heat shock proteins and the reduction of insulin resistance.

References


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