

Glutamine in the critically ill

Nutrition, immune function and Health

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Introduction

Infection and sepsis are complicating features of most critically ill intensive care unit (ICU) patients. Although early death in ICU from a single organ failure is usually due to the primary organ insult (e.g. trauma or sepsis) later death occurs due to multiple organ failure and is “associated” with the development of secondary infections. Although the intensity of the initial inflammatory response may correlate to tissue injury it is now appreciated that restoring an optimised immune system still capable of mounting a normal inflammatory signalling is a feature of survival. Glutamine is an example where a nutritional deficiency arises¹ and whereby its correction improves survival from Multi Organ Failure (MOF)^{2,3}. Even a low plasma glutamine has been shown to be an independent predictive factor for a poor outcome⁴. Key effects of a deficiency are the mechanisms responsible for cellular defence and the cells of the immune system.

Demand exceeds the endogenous supply of Glutamine

Glutamine is very abundant since under most situations it is readily synthesised and this classifies it as a dietary non-essential amino acid, however during situations of extreme stress, particularly of prolonged duration the endogenous supply cannot match increased demand and a conditional deficiency develops. Vinnars *et al.* in 1975⁵ showed that following surgery, trauma or sepsis the free glutamine pool in muscle is depleted. Despite the rapid fall in the intramuscular concentration of free glutamine, transport out of muscle is maintained and clearance from the plasma by other tissues increased indicating activated transport mechanisms⁶ perhaps linked to disturbances in the sodium electrochemical gradient across the muscle cell membrane⁷. Depending on the demands increased utilisation occurs by the gut, liver, spleen, kidney and immune cells. The process of muscle glutamine release is not fully understood but is intimately related to the stress response, particularly cortisol. Stable isotope studies of glutamine metabolism in critically ill patients appear to support the extensive and robust large animal studies that show net flux of glutamine occurs from skeletal muscle to vital organs⁸. Demand is high as even with 28 g/day of glutamine infusions in ICU patients there was only modest correction of low plasma levels⁹. Dosing studies show that amounts between 20-40 g glutamine per day IV were necessary to restore plasma glutamine levels to normal¹⁰.

Glutamine: restoring cellular protective mechanisms

A major demand for glutamine via glutamate is for the production of the major cellular anti-oxidant glutathione¹¹. Low intramuscular glutathione levels are correlated with low glutamine and glutamate levels in the critically ill, but surprisingly the cysteine and glycine levels are maintained¹². Mice fed glutamine supplemented enteral diets and then challenged with endotoxin showed maintenance of glutathione levels with increased numbers of T cells. Glutamine but not arginine, glycine or n-3 fatty acids prevented the apoptosis of B cells in the Peyer's patches¹³. Glutamine has been shown protective to intestinal cells through HSP70 generation¹⁴. Glutamine infusions, over a range of doses (0.15-0.75 g/kg bw), is able to increase HSP 72 and HSP 25 expression in multiple organs of the rat¹⁵. Enhanced HSP 72 and 25 expression was protective against endotoxin-induced septic shock in the rat and could markedly decrease end-organ injury and overall mortality. Pharmacological doses of glutamine, achieving 4 mM levels could decrease TNF-alpha release and increase HSP 72 expression in human peripheral blood mononuclear cells¹⁶. Such large doses of glutamine given intravenously to patients with severe burns, who were nevertheless fed enterally, showed a significant reduction in septicemia¹⁷.

Glutamine: linked to improved immune function and fewer infections

Delivery of 30g/day of glutamine jejunally in multiple-trauma patients led to a significant reduction in pneumonia, bacteraemia, and severe sepsis¹⁸. Glutamine has been shown to modulate and restore immune function; following colorectal surgery glutamine TPN restored T-

cell DNA synthesis¹⁹, and in severe acute pancreatitis reduced mononuclear cell interleukin-8 release²⁰, and shown a significant increase in lymphocyte count, and decrease in C-reactive protein²¹. In patients with secondary peritonitis alanyl-glutamine significantly reduced infectious complications and improved nitrogen balance and faster IgA restoration to normal along with a trend to improved CD4/CD8 lymphocytes²².

It has been shown that non-surviving critically ill patients compared with those that survived show an inability to generate the potent inflammatory mediator, leukotriene C₄²³. TPN with glutamine following bowel surgery restores cysteinyl-leukotrienes generation from peripheral leukocytes indicative of improved immune function²⁴. Impaired polymorphonuclear neutrophil function has been shown to be an antecedent of acquired nosocomial infections in the critically ill²⁵. It is now recognised that in immune failure disturbance of inflammatory and anti-inflammatory processes co-exist in time²⁶. For instance the expression of mononuclear cell HLA-DR, a prerequisite for the presentation of processed foreign antigens to specifically activate T cells, is impaired in sepsis. Contrary to the view this is a late feature of sepsis this suppression of monocyte HLA-DR expression occurs from the outset reaching its nadir coincident with the maximum inflammatory response. Survivors showed a recovery within 10 days while non-survivors showed a failure of recovery. The association of poor recovery and sustained impaired mononuclear cell HLA-DR expression in septic patients underlines the important mechanism linking the initial innate immune response with the necessary controlled and targeted acquired immune response associated with healing. That this is amenable to nutrition therapy is shown by a randomised clinical trial (RCT) with 55 multi-trauma patients given a glutamine enriched enteral feed compared with a control feed both having a depressed HLA-DR expression on monocytes which with glutamine showed an enhanced recovery in the second week²⁷.

Enteral glutamine delivery

In a study of 84 ICU patients given 14g glutamine the incidence of new acquired infection was reduced RR 0.5 (95% CI 0.3-0.9) with a reduction in nosocomial pneumonia from 33% to 14%²⁸. However another study of 363 critically ill patients randomised to 19g of glutamine²⁹ neither mortality nor severe sepsis incidence was affected. If correcting a deficiency is central to any effect of glutamine then the failure of enteral studies can be explained by the limited systemic availability of glutamine from a continuous enteral feed. Even the intestinal cells and the gut associated lymphoid tissue (GALT) can be maintained by systemic glutamine. Furthermore the sicker the patient the greater the likelihood of deficiency, and therefore increased mortality risk, yet the more difficult it is in practice to deliver adequate enteral feed with sufficient glutamine to significantly influence survival. A high risk-of-mortality population of patients with severe burns given enteral glutamine showed a reduction in systemic infections and a significantly reduced intention-to-treat mortality rate 2 v 12 (p=0.05). Most importantly the supplemented glutamine was not given as a slow infusion but dosed as boluses of 4.3g every 4 hours to a total of 26g³⁰. Bolus delivery is more likely to alter glutamine levels in the systemic circulation. At day 14 serum glutamine levels were still abnormally low 388 umol/l in the control compared with a normal level of 696 umol/l in the glutamine recipients (p=0.009).

Systemic glutamine delivery

In predominantly septic multi-organ failure patients with non-functioning gastrointestinal tracts six months survival was increased with glutamine to 57% from 33% in controls (p=0.049). It was promotion of recovery from infection and multiple organ failure that was most important rather than simply the prevention of infection although glutamine recipients do show a lower incidence of catheter-related infections (p=0.026). The difference in survival noted was almost all explained by reduced death within intensive care from MOF in those patients requiring a minimum of five days of parenteral feed (p=0.05). Fewer glutamine recipients acquired *Candida* infections and none died, whereas more control patients acquired *Candida* infections and died from multiple organ failure (p=0.02). This is a clinical demonstration of how

glutamine may restore the impaired immune functioning, particularly the T cell mediated acquired immunity, to allow optimal recovery.

114 ICU patients in a French multi-centre RCT, showed a significant reduction in complicated outcomes related to reduced infectious rate and pneumonias³¹. Glycaemic control was improved with significantly less hyperglycaemia (20 v 30 p<0.05). A study of 144 ICU patients in Germany³² showed that in those fed for more than nine days the survival measured at six months was significantly better 22/33 v 13/35 p<0.05. A recent meta-analysis strongly supports the hypothesis that parenteral glutamine has an advantageous effect on reducing mortality (RR 0.71, 95% CI 0.51-0.99)³³. The meta-analysis confirms that glutamine via the enteral route has failed to show any effect on mortality (RR 1.08, 95% CI 0.57-2.01), but glutamine supplementation overall is associated with lower rates of infection (RR 0.81, 95% CI 0.64-1.0) and shorter hospital stays (in the post-operative studies) (-2.6 days, 95% CI -4.5 to -0.7 days). Current recommendations are that where available parenteral nutrition when used in ICU should contain glutamine³⁴.

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