

The clinical role of glutamine supplementation in patients with multiple trauma: a narrative review

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SUMMARY

Glutamine is considered an essential amino acid during stress and critical illness. Parenteral glutamine supplementation in critically ill patients has been shown to improve survival rate and minimise infectious complications, costs and hospital length-of-stay. However, glutamine supplementation in patients receiving enteral nutrition and the best method of administration are still controversial. The purpose of this article is to provide a narrative review of the current evidence and trials of enteral and parenteral glutamine supplementation in multiple trauma patients.

A search in PubMed and EMBASE was conducted and relevant papers that investigated the effect of enteral or parenteral glutamine supplementation in patients with multiple trauma were reviewed.

Although recent nutritional guidelines recommend that glutamine supplementation should be considered in these patients, further well-designed trials are required to provide a confirmed conclusion. Due to the inconclusive results of enteral glutamine supplementation trials in patients receiving enteral nutrition, future trials should focus on intravenous glutamine supplementation in patients requiring enteral nutrition and on major clinical outcome measures (e.g. mortality rate, infectious complications).

Key Words: trauma, head injury, glutamine, alanyl-glutamine, supplementation, enteral, parenteral, intravenous

Multiple traumas are life-threatening, not only from the initial insult itself but also from the subsequent extensive immunological impairment and metabolic dysfunction¹. Major trauma is characterised by alteration and depression of the immune response^{2,3}, which is associated with an elevated rate of infectious complications, sepsis, multiple organ failure and death^{4,5}. In fact, the prevalence of infectious complications in critically ill patients continues to be a serious problem and is independently associated with higher rates of hospital mortality⁶.

The role and effectiveness of glutamine supplementation in critically ill patients has been extensively

studied and debated in literature for at least the 15 years. A number of systematic reviews and meta-analyses have shed light on this interesting topic⁷⁻⁹. Some of these reviews grouped critically ill patients with surgical patients; the latest considered them as separate groups. The critically ill patient population is haemodynamically and immunologically different from the surgical population. Furthermore, the critically ill patient population is clinically heterogeneous, hence results from one subgroup of patients cannot be generalised to the whole population, even in nutrition support interventions.

Many of the studies that have investigated the effect of intravenous or enteral glutamine supplementation includes multiple trauma patients with other critically ill patients as one population group and have utilised many different outcome measures, not all of which are likely to be of clinical relevance. As the heterogeneity of published trials would have limited the usefulness of a standard meta-analysis approach, and the large outcome measures in these trials made it difficult to pool effect sizes, we decided to undertake a narrative review. Therefore, the purpose of this narrative review was to focus on the trials conducted specifically to investigate the effect of glutamine or glutamine dipeptide as a single pharmacological nutrient in adult multiple

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trauma patients, including head injury patients, and develop recommendations for future perspectives on glutamine supplementation in this homogeneous group of patients.

Search strategy and selection criteria

The patient group in this review represents the critically ill patients with multiple trauma that require enteral or parenteral nutrition support. Searches on PubMed and EMBASE from 1990 to 2011 were used to identify trials that evaluated enteral and parenteral glutamine supplementation in trauma patients. Search terms included “glutamine”, “alanyl-glutamine”, “trauma”, “injury” or “head injury”. Only English language papers were reviewed. Search parameters were limited to human clinical trials. Studies in which glutamine was used in combination with other immunonutrients and safety trials were excluded. Additional articles were identified through searching the bibliography of practice guidelines, systematic reviews and meta-analyses of glutamine supplementation in critically ill patients.

BACKGROUND

Immune and metabolic response to trauma and injury

Multiple trauma and severe injury evoke reproducible immune and metabolic responses that correlate with the extent and duration of the injury. The immune (inflammatory) response starts within minutes and is characterised by increased release of pro-inflammatory cytokines. In parallel, there is a concurrent production of anti-inflammatory cytokines. This response is required to restore homeostasis as soon as possible¹⁰. In uncomplicated trauma and injury, there is an equilibrium between the pro and anti-inflammatory cytokines. However, if the pro-inflammatory mediators predominate, this results in a systemic inflammatory response syndrome. Alternatively, if the anti-inflammatory mediators predominate, this results in compensatory anti-inflammatory response syndrome¹⁰. An imbalance between systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome, depending on the severity and duration of the trauma and stress, may be responsible for increased susceptibility to infectious complications, multiple organ dysfunction syndrome and multiple organ failure, which are associated with a higher mortality rate^{11,12}.

In conjunction, there is an escalated production of catabolic and counter-regulatory hormones¹³. These neuroendocrine changes trigger the metabolic response that is characterised by hypermetabolism¹⁴, insulin resistance associated with hyperglycaemia¹⁵,

increased fat breakdown (lypolysis)¹⁶ and accelerated protein catabolism (proteolysis)^{14,17,18}. Proteolysis, which may reach up to 16%, is mainly derived from the skeletal muscle and can last for up to 21 days^{14,18}. There is also an increase in the rate of protein synthesis, but this does not match the increased rate of proteolysis. Indeed, in critically ill patients, protein catabolism is elevated despite aggressive nutritional support and increased protein intake^{19,20}. Although muscle catabolism is important for providing substrates for acute phase protein synthesis and gluconeogenesis in the liver, severe and prolonged depletion of lean body mass has deleterious effects such as irreversible muscle wastage, impaired wound healing and delayed recovery from illness²¹. Protein catabolism is also associated with the release of glutamine from the skeletal muscle and this results in a marked and prolonged depletion of glutamine levels in plasma and the skeletal muscle^{17,22}.

Glutamine metabolism during stress and critical illness

Glutamine is the most abundant amino acid in the body and is synthesised in sufficient amounts under normal physiological conditions, and therefore has been considered as a non-essential amino acid for decades. It is involved in a wide range of metabolic and biochemical processes in the body^{23–26}. These functions are summarised in Table 1.

As the preferred fuel for enterocytes, it has been suggested that glutamine may have a role in reducing bacterial translocation across the gastrointestinal tract and thus reduce the risk of infections and sepsis³⁷. In fact, enteral glutamine administration has been associated with reduced intestinal permeability and bacterial translocation in some animal studies^{38,39}. Also, some clinical trials showed that glutamine supplementation maintained gastrointestinal structure in critically ill patients and was associated with reduced intestinal permeability^{40,21}. However, other trials could not reproduce this finding⁴².

TABLE 1
Glutamine functions in the human body^{23–36}

Nitrogen transport
Acid-base homeostasis
Gluconeogenesis
Fuel for immune cells (lymphocytes and macrophages)
Arginine synthesis in the kidney (being a precursor for citrulline)
Fuel for enterocytes
Glutathione synthesis (antioxidant defence)
Enhance heat shock protein expression (prevent apoptosis)
Enhance insulin sensitivity

TABLE 2
Trials of enteral glutamine supplementation in trauma patients

Study	Design	Route	Commencement and duration		Intervention		Main outcomes
			Gln	Control	Gln	Control	
Long et al 1995, 1996 ^{3,64}	DB RCT, n=30	EN (NG)	Approximately 24 h after admission; 3 d	Gln-enriched EN, mean intake 0.35 g Gln/kg/d, n=16	Isotrogenous, isocaloric EN, n=14	ND NB, protein turnover, synthesis and breakdown ND glucose turnover, oxidation and recycling ND plasma Gln levels EAA conc. ↑↑ in both groups NEAA ↑↑ in control group	
Houdijk et al 1998, 1999 ⁶⁶	DB RCT, n=72 (60 received feeding ≥5 d)	EN (NJ)	Within 48 h of trauma and until tolerating oral feeding (study period 15 d)	Gln-enriched EN provides 30.5 g Gln/100 g protein, n=35	Isocaloric, isotrogenous feed, n=37	Mean plasma levels of Gln, citrulline and arginine ↑↑ in Gln group Mean serum levels of TNF-receptors ↓↓ in Gln group ↓↓ pneumonia (17 vs 45%; $P < 0.02$), ↓↓ bacteraemia (7 vs 42%; $P < 0.005$), ↓↓ sepsis (3 vs 26%; $P < 0.02$) in Gln group No gram-negative bacteraemia in Gln group vs 54% in control group. ND ICU or hospital length-of-stay, mechanical ventilation days. Glucose levels above normal fasting levels in both groups Plasma levels of stress hormones (cortisol and glucagon) ↑ to high normal levels in both groups ($P = NS$) Growth hormone levels were in normal range throughout study and ND between groups $\alpha 1$ -antitrypsin ↑↑ on day 2; $P < 0.05$, days 3, 7 and 10; $P < 0.01$ vs baseline in both groups CRP ↑↑ and reached peak levels on day 3 ($P < 0.05$ vs baseline) in both groups	
Brantley et al 2000 ⁸³ (Abstract)	RCT unblinded? (not mentioned in abstract), n=70	EN	7 d	0.5 g/kg Gln + supplemented EN formula, n=32	Isocaloric, isotrogenous formula, n=38	Prealbumin ↑↑ in Gln group on day 7 NB balance better in Gln group (NS) ND infections, total costs, ICU and hospital length-of-stay	
Boelenes et al 2002 ²⁴	DB RCT, n=108	EN (NJ)	Within 48 h of trauma and until tolerating oral feeding (pts fed at least 5 d enterally were included in results; study period 15 d)	Gln-enriched EN; provides 30.5 g Gln/100 g protein, n=28	Isocaloric, isotrogenous EN (control), n=27 Age-matched healthy people, n=53	On day 1 HLA-DR expression much lower in Gln and control groups compared to healthy volunteers group HLA-DR expression ↑↑ on day 5 ($P < 0.05$), day 9 ($P < 0.05$) and day 14 ($P < 0.05$) in Gln group compared with day 1 but did not restore normal values Fc γ RI/CD64 expression in monocytes in Gln and control groups = expression in healthy volunteers	

TABLE 2
Trials of enteral glutamine supplementation in trauma patients (continued)

Study	Design	Route	Commencement and duration	Gln	Intervention	Control	Main outcomes
Schulman et al 2005, 2006 ^{66,68}	Sequential rotating assignment, unblind, n=185 (175 trauma)	EN (NJ) and some converted to PEG	EN continued until oral diet was tolerated or TPN was required	0.6 g/kg/d Gln + Standard EN (Group 2), n=59 0.6 g/kg/d Gln + Immune-modulated EN (Group 3), n=62	Standard EN (Group 1), n=64	Isocaloric, isonitrogenous standard EN feed (Group 1), n=64	ND mean number of infections, incidence of infections, antibiotic use between groups ND mechanical ventilation days, ICU and hospital length-of-stay In-hospital mortality was 6.3% (Group 1) vs 16.9% (Group 2; P=0.09) and 16.1% (Group 3; P=0.09) ND in-hospital mortality between groups (after controlling for age and severity of illness, P≤0.11)
McQuiggan et al 2008 ⁷¹	Pilot, unblinded RCT, n=20	EN (NG)	Start during the first 24 h of resuscitation; 10 d	0.5 g/kg/d glutamine(boluses 2-3 times daily (NG) + immune-enhancing EN (NJ) which started on post-injury day 1, n=10	0.5 g/kg/d isonitrogenous whey protein + immune-enhancing, n=10		Gln well tolerated during resuscitation, no adverse events Gln group had ↓↓ instances of high gastric output (5 vs 23; P=0.01), abdominal distension (3 vs 12; P=0.021) and total instances of intolerance (8 vs 42; P=0.011) ND in CRP on day 4 between groups Total UUN ↑↑ in Gln group vs control (P=0.012)

Gln=glutamine, DB=double-blind, RCT=randomised clinical trial, EN=enteral nutrition, NG=nasogastric, h=hours, d=days, ND=no significant difference, NB=nitrogen balance, EAA=essential amino acid, NEAA=non-essential amino acid, ↑↑=significant increase, NJ=nasojejunal, TNF=tumor necrosis factor, ↓↓=significant decrease, ICU=intensive care unit, ↑=increased, NS=not significant, CRP=C-reactive protein, HLA-DR=human leukocyte antigen DR, FeγRI/CD64=Fc receptor, PEG=percutaneous endoscopic gastrostomy, TPN=total parenteral nutrition, UUN=urinary urea nitrogen.

TABLE 3
Trials of parenteral glutamine supplementation in trauma patients

Study	Design	Route	Commencement and duration		Intervention		Main outcomes
			Gln	Control			
Bakalar et al 2006 ²	Pilot, unblinded RCT, n=40	IV	Started 24 h after injury for 7 d	0.4 g/kg/d Alanyl-Gln + PN or EN, n=20	Isonitrogenous amino acids control + PN or EN, n=20	ND protein breakdown between groups ND SOFA score Energy expenditure ↓ in Gln group Insulin-mediated glucose disposal ↑↑ in Gln group at day 4 (P=0.044) and day 8 (P<0.001) Endogenous insulin secretion was ↑↑ in control group on day 8 Gln group had a better insulin sensitivity (statistically significant)	
Yang et al 2007 ²	RCT	IV	Started within 24 h for 2 w TPN started on day 3 after injury, EN gradually replaced TPN in the first week	Alanyl-Gln (2 mg/kg body weight) + PN, n=23	Standard nutritional therapy, n=23	Mortality rate in first 2 w and ICU length-of-stay ↓↓ in Gln group ND GCS between groups Patients with lung infection and alimentary tract hemorrhage ↓↓ in Gln group ND urinary tract infection between groups Total serum protein and total lymphocyte count ↑↑ in Gln group	
Eroglu 2009 ²⁴	DB RCT, n=40	IV	7 d	0.5 g/kg/d Alanyl-Gln + standard EN, n=20	Control (normal saline) + standard EN, n=20	Total plasma glutathione levels ↑↑ in Gln group on days 7 and 10 ND CRP, prealbumin, glucose levels between groups ND SOFA score ND infections, ICU length-of-stay between groups ND 1 m mortality rate between groups	
Perezé-Bárcena 2010 ⁵	SB RCT, n=43	IV	5 d	0.5 g/kg/d Alanyl-Gln + TPN, n=23	Isonitrogenous, isocaloric TPN, n=20	TLR4 levels were not different between groups before treatment (glutamine supplemented TPN doesn't improve the expression or the functionality of TLRs in peripheral blood monocytes)	

Gln=glutamine, RCT=randomised clinical trial, IV=intravenous, h=hours, d=days, PN=parenteral nutrition, EN=enteral nutrition, ND=no significance difference, SOFA=sequential organ failure assessment, ↓=decrease, ↑↑=significant increase, w=weeks, TPN=total parenteral nutrition, ICU=intensive care unit, ↓↓=significant decrease, GCS=Glasgow Coma Score, DB=double-blind, CRP=C-reactive protein, m=month, SB=single-blind, TLR=toll-like receptor.

Under catabolic conditions, such as critical illness, glutamine is released from the skeletal muscle in large quantities⁴³. Although glutamine synthesis is not impaired during critical illness, plasma and intramuscular glutamine levels are severely depleted in conditions^{22,44} such as major surgery⁴⁵, burn injury^{46,47} and multiple trauma^{24,48,49} because of increased demand. Therefore, glutamine has been proposed as an essential amino acid in these situations⁵⁰.

Clinical trials of glutamine supplementation in multiple trauma patients

A number of trials have been conducted to investigate the effect of glutamine supplementation in a homogeneous group of multiple trauma patients. Table 2 and 3 summarise the trials of enteral and parenteral glutamine supplementation in trauma patients, which are subsequently discussed.

Clinical trials of enteral glutamine supplementation in multiple trauma patients

The benefits of glutamine supplementation in patients receiving enteral nutrition and the best route of administration are still controversial. Research indicates that initiation of early enteral nutrition (i.e. within the first 24–48 hours following intensive care unit admission) in critically ill patients, including trauma patients, is recommended when the gastrointestinal tract is functioning as it is associated with decreased infectious morbidity, hospital length-of-stay and improved overall clinical outcome^{51–56}. Therefore, the concept of enteral glutamine supplementation in multiple trauma patients is attractive and advocated when enteral nutrition is required⁵⁷. However, it has been documented that the systemic bioavailability of glutamine through the enteral route is lower than the parenteral route³⁰. Most enterally administered glutamine is utilised and oxidised by the splanchnic organs^{58–60}. Furthermore, before considering glutamine supplementation via the enteral route, it is important to recognise that most enteral trials failed to reach the target prescribed dose due to delayed feeding, feeding intolerance and interruption of feeding due to extubation or surgery^{61,62}.

One of the early trials that have been conducted to investigate the effect of enteral glutamine supplementation in 30 trauma patients by Long et al⁶³ found that there were no significant differences in outcomes including nitrogen balance, protein synthesis and breakdown, and muscle proteolysis between the glutamine supplemented and the control groups. Also, glucose turnover, oxidation and recycling were not significantly different between the two groups. The same trial attempted to see the effect of glutamine supplementation on hypoaminoacidaemia⁶⁴, which results in an increased

concentration of essential amino acids and a decrease in nonessential amino acids in the intracellular pool. However, it was reported that total essential amino acids concentration was significantly increased in both groups, while the nonessential amino acids concentration was increased significantly only in the control group. This increase was explained by the added amino acids to the control formula to make it isonitrogenous. Plasma glutamine level was not influenced by supplementation. These results suggested that a short period of glutamine provision (i.e. three days) has no effect on nutritional or metabolic outcomes and a longer period is required. The authors explained the negative results by altered glutamine absorption in critically ill patients and glutamine being mostly oxidised by the gut and liver^{58–60}. On the other hand, Houdik et al showed that enteral glutamine supplementation significantly increased plasma glutamine concentration, which was associated with an increased plasma arginine concentration suggesting that enteral glutamine stimulated renal production of arginine⁶⁵.

Mortality as a primary outcome was investigated in one of the largest trials of enteral glutamine supplementation in trauma patients⁶⁶. The in-hospital mortality rate was higher in the treatment group compared with the control group, but the results were not significant ($P=0.09$), particularly after controlling for age and severity of illness ($P \leq 0.11$). This trial suggested that enteral glutamine might have negative effects with a trend toward increased mortality. The authors theorised that enteral administration of glutamine makes it available to the bacteria in the gastrointestinal tract⁶⁷.

The effect of enteral glutamine supplementation on infectious morbidity was investigated in two main trials^{65,68}. Houdijk and colleagues⁶⁵ reported that glutamine-enriched enteral feed resulted in a significant decrease in pneumonia (17 vs 45%; $P < 0.02$), bacteraemia (7 vs 42%; $P < 0.005$) and sepsis (4 vs 26%; $P < 0.02$). Gram-negative bacteraemia occurred in 54% of the cases of bacteraemia in the control patients and was not reported in any of the glutamine supplemented patients, suggesting that glutamine might prevent bacterial translocation from the gut. In contrast, Schulman et al⁶⁸ found that enteral glutamine had no significant effect on reducing infectious complications and the use of antibiotics. In both trials there were no significant differences in mechanical ventilation days, intensive care unit and hospital length-of-stay between the supplemented and the control groups.

In an attempt to explain the relationship between the reduction in infectious morbidity by enteral glutamine supplementation and endocrine responses,

Houdijk et al reported in a subsequent paper⁶⁹ that enteral glutamine had no influence on metabolic and endocrine changes in trauma patients. Hyperglycaemia was sustained in both glutamine and control groups, and plasma levels of stress hormones (cortisol and glucagon) increased to high normal levels in both groups, but this was not significant. Growth hormone levels were within the normal range and did not differ between groups. In both groups there was a significant increase in α 1-antitrypsin levels and the inflammatory marker C-reactive protein. It was concluded that the reduction in infectious complications by glutamine supplementation was not related to the changes in the metabolic and hormonal responses.

It has been reported by Boelens et al²⁴, as part of the trial by Houdijk et al⁶⁵, that glutamine-enriched enteral nutrition can restore and modulate immune function. It investigated the effect of glutamine supplemented enteral nutrition versus isocaloric, isonitrogenous enteral nutrition on human leukocyte antigen (HLA)-DR and Fc receptor (Fc γ RI/CD64) expression on monocytes which are severely depleted in trauma patients^{4,70}. Both groups' results were compared with healthy volunteers. As expected, HLA-DR expression was much lower in both groups compared to the healthy volunteers. However, glutamine-enriched enteral nutrition resulted in significantly increased expression of HLA-DR but still did not restore normal values. There was no difference in the Fc γ RI/CD64 expression between both groups and the healthy volunteers. It was concluded that glutamine had beneficial effects on increasing HLA-DR expression and thus improving cellular immune function and this may play a role in reducing infectious complications in trauma patients.

In a pilot study, 20 patients with severe trauma were randomised to receive enteral glutamine or an isonitrogenous placebo during the first 24 hours of resuscitation, before even starting enteral feeding for ten days⁷¹. The supplementation was given as a bolus two to three times daily, dissociated from enteral feed as a pharmacological dose. The study demonstrated that glutamine was well-tolerated during resuscitation with no adverse events. It was reported that the glutamine group had significantly fewer instances of high gastric output (5 vs 23, $P=0.01$) and abdominal distension (3 vs 12; $P=0.021$). These results suggested that enteral glutamine can be safely given during active shock resuscitation and enhances gastrointestinal tolerance. However, this was a pilot study and a larger trial is required to investigate the effect of enteral glutamine administered to haemodynamically unstable patients on other clinical outcomes.

Clinical trials of parenteral glutamine supplementation in multiple trauma patients

There are a few trials that have investigated the effect of parenteral glutamine supplementation in trauma patients receiving parenteral nutrition. Limitations of glutamine supplementation via the enteral route triggered researchers to investigate the effect of intravenous glutamine supplementation in patients receiving enteral nutrition.

The effect of parenteral alanyl-glutamine on insulin resistance was investigated by Bakalar et al³², who showed significantly improved insulin sensitivity and insulin-mediated glucose disposal in the glutamine supplemented patients. There was no significant difference in the Sequential Organ Failure Assessment score between groups. The rate of protein breakdown was not different between groups during the study, but hypermetabolism was attenuated in the glutamine supplemented patients by reducing energy expenditure. It was concluded that glutamine supplementation was associated with significantly better insulin sensitivity in trauma patients, offering a new approach to glycemic control in this group of patients. The authors concluded that this trial should be considered as a pilot study and further trials are required to gain further understanding about the mechanisms by which glutamine improves insulin resistance.

The effect of intravenous alanyl-glutamine supplementation in 46 patients with severe traumatic brain injury receiving total parenteral nutrition was investigated in a randomised trial⁷². The authors demonstrated that alanyl-glutamine supplementation resulted in a significant decrease in infectious complications ($P < 0.05$). It was reported that glutamine supplementation was associated with a significant decrease in two-week mortality rate and alimentary tract haemorrhage ($P < 0.05$). There was a significantly shorter intensive care unit length-of-stay with glutamine supplementation ($P < 0.05$). This study was the first to investigate the effects of glutamine supplementation in head injury patients. However, there are number of limitations of this paper. First, in terms of a standard basic treatment protocol, no stress ulcer prevention was provided, which is not an accepted standard management⁷³. The main cause of death in the second week (six patients in the control group versus one in the glutamine group) was uncontrolled alimentary tract haemorrhage, which is not common in head injury patients and is potentially related to lack of stress ulcer prevention. The results suggest that glutamine might play a role in prevention of alimentary tract haemorrhage but only if patients are not receiving standard management (i.e. stress

ulcer prevention). Furthermore, this was a single trial and the number of recruited patients was relatively small, limiting the ability to make clear conclusions and recommendations. It is also important to mention that the dose used was relatively low (2 mg/kg) compared with other trials that found beneficial effects.

There is no evidence for beneficial effects of intravenous glutamine supplementation in trauma patients receiving enteral nutrition. However, in a pilot, randomised, double-blind trial, Eroglu⁷⁴ investigated the effect of intravenous supplementation of alanyl-glutamine in 40 severe trauma patients receiving enteral nutrition. It was reported that total plasma glutathione levels increased significantly in the glutamine group on day 7 and 10 ($P < 0.001$). As reported by the author, the limitations of this trial were the small number of recruited patients and the short follow-up period.

The effect of parenteral glutamine on toll-like receptors (TLR2 and TLR4), which are key receptors sensing infections, was investigated in a single-blind, randomised trial in trauma patients receiving parenteral nutrition⁷⁵. It was reported that the expression levels of TLR2 on monocytes were similar between groups before and after supplementation. There was also no significant difference in TLR4 levels between groups before and after treatment. Although the study was not powered to investigate the clinical effect of glutamine on reducing infectious complications, there was a decreased incidence of infections and hospital length-of-stay in the glutamine group, which did not reach significance. It was concluded that glutamine-supplemented parenteral nutrition in trauma patients had no influence on the expression or functionality of TLRs on monocytes.

In summary, from the previous trials, positive and consistent findings were demonstrated in patients receiving glutamine-supplemented parenteral nutrition and with higher doses.

Limitation of glutamine trials in multiple trauma patients

Like other nutritional interventions, there are limitations in the existing trials of glutamine supplementation in trauma patients that make recommendations inconclusive. These are as follows:

- The quality of many trials was low and did not meet the CONSORT (consolidated standards of reporting trials) guidelines^{76,77} in terms of random allocation concealment, blinding of assessors or care-givers and presenting results in an intention-to-treat analysis.
- Most trials had a small number of subjects and

were not sufficiently powered to investigate major clinical outcomes such as mortality⁷⁸⁻⁸⁰.

- The doses varied between trials which makes clear comparison between trials problematic.
- Some trials used a mixture of immunonutrients concurrently as an intervention^{81,82}, which makes it impossible to make a clear judgment about the exact beneficial effect of each nutrient.
- Other trials used a historical group as a control⁸⁷.
- In enteral feeding it is often difficult to deliver the supplemented feed effectively due to feeding intolerance, which is present in many critically ill patients^{63,65}.
- The period of supplementation was very short in some trials (e.g. three to seven days)^{32,63,74,83}.

These limitations were also highlighted in a European roundtable⁸⁴. As mentioned earlier, some recent trials gave the enteral supplementation as a separate supplementation and not as part of the enteral feeding formula⁸¹. Others investigated the effect of intravenous supplementation in patients receiving enteral feeds⁷⁴. This represents an advance from the traditional 'immunonutrition' paradigm to a new 'pharmaconutrition' one⁸⁵⁻⁸⁷.

CONCLUSION

While there is emerging evidence that glutamine supplementation should be considered as a potential therapeutic regimen in patients with multiple trauma, adequately powered, multi-centre well-designed trials are needed to provide robust clinical evidence. The trials that have been conducted in homogeneous trauma patients are limited and the results are inconclusive. Due to the difficulty and uncertainty of enteral supplementation of glutamine in patients receiving enteral nutrition, future trials should focus on delivering glutamine intravenously to these patients. Investigating significant outcome measures such as mortality, organ dysfunction and infectious complications, rather than short-term surrogate measures, are also required.

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