Glutamine supplementation in serious illness: a systematic review of the evidence

Authors' objectives
To assess the effect of glutamine supplementation in elective surgical and critically ill patients.

Searching
The Cochrane Controlled Trials Register (from 1985 to Issue 2, 2000), MEDLINE (from 1985 to April 2000), EMBASE (from 1985 to February 2000), BIOSIS Previews (from 1985 to April 2000), CINAHL (from 1985 to April 2000) and CAB Abstracts (from 1985 to December 1999) were searched. The search terms were stated. The following journals were handsearched: Clinical Nutrition, volumes 4 to 19(2); Critical Care Medicine, volumes 13 to 28(3); Intensive Care Medicine, volumes 11 to 26(1); Journal of Parenteral and Enteral Nutrition, volumes 9 to 24(2); Proceedings of the Nutrition Society, volumes 1 to 59(1); and Nutrition, volumes 5 to 16(5). Additional published and unpublished studies were sought by contacting major manufacturers of glutamine products and the authors of trial reports. In addition, the reference lists from original studies, review articles and the authors' personal files were examined, and abstract proceedings of recent scientific meetings were searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Comparisons of glutamine with placebo or standard care were eligible for inclusion. Studies in which glutamine was one of several nutritional supplements, and studies of glutamine keto-analouges or metabolites, were excluded. The included studies used L-glutamine in total parenteral nutrition or enteral nutrition. The doses ranged from 0.16 to 0.57 g/kg per day. All the studies of enteral glutamine were in critically ill patients.

Participants included in the review
Studies of elective surgical or critically ill adults were eligible for inclusion. The included studies were of patients undergoing elective surgery, patients with burns or trauma, and patients in medical or surgical intensive care units.

Outcomes assessed in the review
Studies that assessed complications, length of hospital stay and mortality were eligible for inclusion. Studies that only evaluated nutritional or other biological mechanistic outcomes were excluded. The primary outcomes assessed in the review were mortality and the number of patients with new infectious complications. Hospital stay was a secondary outcome.

How were decisions on the relevance of primary studies made?
Two authors selected the studies for inclusion.

Assessment of study quality
Study validity was assessed and scored using the following criteria: concealment of randomisation, blinding, intention-to-treat analysis, patient selection, baseline comparability of the treatment groups, extent of follow-up, description of treatment protocol, description of cointerventions (antibiotics, enteral nutrition, ventilation, oxygen and transfusions), and description of outcomes. The maximum possible score was 14 points. Two authors independently assessed validity and resolved any disagreements through discussion. If required, the authors of primary studies were contacted for missing information.

Data extraction

Two authors independently extracted data on the study methods and outcomes. The tabulated data included the year of publication, population characteristics, details of the intervention and results.

**Methods of synthesis**

How were the studies combined?
The pooled relative risk (RR) and 95% confidence interval (CI) were calculated for mortality and infectious complications using a random-effects model, after adding one half to each cell to adjust for sparse data. The pooled difference for hospital stay was calculated, weighted by the inverse of the squared standard error of the difference.

How were differences between studies investigated?
Statistic heterogeneity was tested. A subgroup analysis was used to explore the influence of several factors on the results: type of patient (elective surgical versus critically ill), route of glutamine administration (enteral versus parenteral), dose of L-glutamine (greater than 0.2 versus less than 0.2 g/kg per day), and study quality (validity score of 8 versus less than 8). A sensitivity analysis was undertaken by re-analysing the data after excluding studies published in abstract form. A P-value of less than 0.20 was taken as indicating a trend, while a P-value of less than 0.05 was taken to indicate statistical significance using Student's t-test.

**Results of the review**

Fourteen RCTs (around 757 patients) were included.

Validity: the validity scores for 12 RCTs ranged from 4 to 11 (out of 14); it was not possible to assign a score to the other 2 RCTs. It was not possible to extract data on an intention-to-treat basis for most of the studies.

Mortality: there was no significant difference in mortality between glutamine and no glutamine; the RR was 0.78 (95% CI: 0.58, 1.04). No significant heterogeneity was found (P=0.99). The results were similar after the exclusion of studies published in abstract form; the RR was 0.79 (95% CI: 0.59, 1.05).

Infectious complications (7 RCTs, 326 patients): glutamine significantly reduced infectious complications; the RR was 0.80 (95% CI: 0.64, 1.00). No significant heterogeneity was found (P=0.43).

Hospital stay (10 RCTs, 541 patients): glutamine significantly reduced the length of hospital stay in comparison with no glutamine; the difference was -2.6 days (95% CI: -4.5, -0.7). Significant heterogeneity was found (P=0.002). There was no significant difference between glutamine and no glutamine after abstracts were excluded; the difference was -2.1 days (95% CI: -5.0, +0.83).

Subgroup analyses.

There was no significant difference in mortality for studies of surgical patients or those of critically ill patients. The RR was 0.99 (95% CI: 0.27, 3.58) for surgical versus 0.77 (95% CI: 0.57, 1.03) for critically ill patients (P=0.71).

There was a trend towards an increased reduction in infectious complications for surgical patients compared with critically ill patients. The RR was 0.36 (95% CI: 0.14, 0.92) for surgical versus 0.86 (95% CI: 0.68, 1.08) for critically ill patients (P=0.14, indicating a trend). Glutamine significantly reduced hospital stay for surgical patients, but there was no significant difference between glutamine and no glutamine for critically ill patients. The difference was -3.54 days (95% CI: -5.3, -1.76) for surgical versus -0.9 days (95% CI: -4.9, +6.8) for critically ill patients (P=0.19, indicating a trend).

Parenteral glutamine significantly reduced mortality for surgical patients, but there was no significant difference between enteral glutamine and no glutamine. The RR was 0.71 (95% CI: 0.51, 0.99) for parenteral versus 1.08 (95% CI: 0.57, 2.01) for enteral glutamine (P=0.27). Parenteral glutamine significantly reduced hospital stay, but there was no significant difference between enteral glutamine and no glutamine. The difference was -2.8 days (95% CI: -4.8, -0.7) for parenteral versus -1.09 (95% CI: -5.4, +3.2) for enteral glutamine (P=0.50).

High-dose glutamine significantly reduced mortality for surgical patients, but there was no significant difference...
between low-dose glutamine and no glutamine. The RR was 0.71 (95% CI: 0.51, 0.99) for high-dose versus 1.02 (95% CI: 0.52, 2.01) for low-dose glutamine (P=0.40). High-dose glutamine significantly reduced infectious complications, but there was no significant difference between low-dose glutamine and no glutamine. The RR was 0.58 (95% CI: 0.43, 0.80) for high-dose versus 0.57 (95% CI: 0.08, 3.90) for low-dose glutamine (P=0.98). There was no significant difference in hospital stay between high-dose and low-dose.

There was no significant difference in mortality between glutamine and no glutamine among high-quality or low-quality RCTs. The RR was 0.77 (95% CI: 0.58, 1.03) for high-quality versus 1.07 (95% CI: 0.19, 6.02) for low-quality RCTs (P=0.72). There was no significant difference in hospital stay between glutamine and no glutamine among high-quality RCTs, but glutamine significantly reduced hospital stay among low-quality RCTs. The difference was -3.01 days (95% CI: -6.23, +0.20) for high-quality versus -2.2 days (95% CI: -3.85, -0.55) for low-quality RCTs (P=0.67).

**Authors' conclusions**
Glutamine may reduce infectious complications and the duration of hospital stay in surgical patients without increasing mortality. Glutamine may reduce complications and mortality in critically ill patients. The conclusions are suggestive rather than definitive.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes. Many relevant sources were searched, the search terms were stated and attempts were made to locate unpublished studies. It was not clear whether any language limitations had been applied. Two authors selected the studies, assessed validity and extracted the data; this reduced the potential for bias and errors. Validity was assessed and scored using defined criteria and some relevant data were extracted and tabulated. The duration of the intervention was not reported, and the influence of censoring from death on length of hospital stay was not mentioned. The data were combined in a meta-analysis, statistical heterogeneity was assessed, and the influence of various factors on the results was explored. As the authors correctly state, the conclusions are not definitive in view of the heterogeneity among the studies.

**Implications of the review for practice and research**
Practice: The authors state that seriously ill patients with gastrointestinal failure who are receiving enteral nutrition should probably be given glutamine supplements for at least 6 days.

Research: The authors state that surgical and critically ill patients should be studied separately in adequately powered studies using parenteral glutamine at a dose in excess of 0.2 g/kg per day.

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