Current evidence and ongoing trials on the use of glutamine in critically-ill patients and patients undergoing surgery

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CRD summary
This review concluded that parenteral glutamine in critical illness was associated with a non-significant reduction in mortality and may reduce infections. This conservative conclusion reflected the results of the review and the poor quality of the evidence. Despite limited reporting of some aspects of the review, the conclusions may be reliable.

Authors' objectives
To assess the use of parenteral and enteral glutamine in critically ill patients and in patients undergoing surgery.

Searching
MEDLINE, EMBASE and CINAHL were searched without language or publication status restrictions up to August 2008. Search terms were not reported. Four relevant journals were handsearched and previous reviews were checked. Studies undertaken in China were excluded from the review.

Study selection
RCTs that compared parenteral or enteral nutrition containing glutamine with control feeding in adults who were critically ill or undergoing surgery were eligible for inclusion in the review. Studies of immunonutrition that administered several specified nutrients such as arginine and n-3 fatty acids were excluded from the review. Primary outcomes were mortality, infection and organ failure.

Most of the included trials were in critically ill patients with a range of aetiologies including burns, trauma, pancreatitis, surgical complications and mixed intensive care. Surgical trials enrolled patients who underwent elective gastrointestinal surgery. Information provided on the included studies in terms of intervention and populations was extremely limited.

The authors did not state how the papers were selected for the review.

Assessment of study quality
It appeared that the authors assessed aspects of validity, including allocation concealment, blinding of outcome assessment and use of intention-to-treat (ITT) analysis.

The authors did not report how validity assessment was conducted.

Data extraction
Data on outcomes were extracted using the last available time of follow-up to permit the calculation of risk ratios (RR), with 95% confidence intervals (CI).

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Studies were combined in separate random-effects meta-analyses for critically ill and surgical patients. Statistical heterogeneity between trials was assessed using the I^2 statistic with greater than 50% indicating significant heterogeneity. Publication bias was assessed by examination of funnel plots. Subgroup analyses were conducted to assess the impact of glutamine dose and of acute pancreatitis in patients.

Results of the review
Thirty-one RCTs were included in the review: 22 in critically ill patients; eight in surgical patients; and one in a mixed
hospital population. Trial validity was considered to be limited in most cases.

Overall there was no statistically significant difference in mortality between groups given glutamine and controls (RR 0.84, 95% CI 0.66 to 1.07). There was a non-significant reduction in mortality associated with parenteral glutamine in critical illness (RR 0.71, 95% CI 0.49 to 1.03). There was no statistically significant difference in trials of enteral glutamine in this patient group or in trials in surgical patients and a mixed hospital population.

There was a statistically significant overall reduction in infections in patient groups treated with parenteral glutamine (RR 0.81, 95% CI 0.70 to 0.93). The reduction in infections was also statistically significant in trials in critically ill patients (RR 0.78, 95% CI 0.63 to 0.97) and in patients following surgery (RR 0.43, 95% CI 0.27 to 0.69).

The overall proportion of patients who experienced multi-organ or renal failure was significantly lower in groups given glutamine (RR 0.75, 95% CI 0.56 to 0.99) and in groups given parenteral glutamine (RR 0.60, 95% CI 0.42 to 0.85).

Further analyses including exploration of the impact of glutamine dose were reported, but did not show statistically significant effects.

There was some evidence of publication bias in trials that assessed infections.

**Authors’ conclusions**
Parenteral glutamine in critical illness was associated with a non-significant reduction in mortality and may have reduced infections. There was no evidence to suggest that glutamine was harmful in terms of organ failure. Parenteral glutamine may have reduced the development of organ failure. These results should be interpreted with caution given poor study quality and the possibility of publication bias.

**CRD commentary**
The review question and the inclusion criteria were clear. The authors searched three relevant databases and additional sources without language restrictions, which reduced chances of bias and omission of relevant studies. No use of methods designed to reduce reviewer bias and error was reported at any stage of the review process. It appeared that an assessment of study validity was undertaken and that this was used to inform the conclusions, but few details were reported. Use of meta-analyses appeared appropriate. Heterogeneity was assessed. The authors’ conclusions were conservative with respect to the results of the review and may be reliable, despite limited reporting of some aspects of the review.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research, but noted that two large RCTs examining glutamine in critically ill patients were underway.

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