Letter to the Editor

Glutamine in critically ill patients: Trial-sequenceal analysis

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1. Background

Glutamine supplementation has long been used in patients receiving parenteral nutrition, but a sound evidence in support of its effectiveness is lacking. A meta-analysis of 22 studies (2126 patients) conducted from 1997 to 2011 reported a decrease in mortality in patients given this supplementation, but a subsequent meta-regression pointed out that benefits were found only in earlier trials whereas the most recent ones showed no improvement. More recently, the debate has been fuelled by the publication of a large trial that enrolled 1223 patients. Mortality was higher in patients given glutamine than in placebo controls, and the difference was at limits of statistical significance (odds ratio = 1.28; 95% confidence interval: 1.00–1.64). Post-hoc explanations for this paradoxical finding have been proposed (eg, effect of single-center studies), but they clearly remain hypothetical.

2. Objective

Our analysis was aimed at synthetizing the results of randomized studies focused on glutamine supplementation in critically ill patients (including also the recent large-scale trial). Since trial-sequenceal analysis (TSA) can contribute to better interpret controversial findings from meta-analyses, this statistical technique was employed for our study. One advantage of TSA is that this technique can improve interpretation of meta-analyses into one of four mutually exclusive categories: a) superiority; b) inferiority; c) futility; d) inconclusive.

3. Methods and findings

We applied TSA to re-examine the 22 trials previously mentioned plus the recent trial. The end-point was mortality. We assumed two-sided testing, type-1 error = 5%, power = 80%, event frequency for controls = 24.8% (i.e. the arithmetic cumulative event rate in the 23 control groups), and relative risk reduction (RRR) = 25%. Boundaries for superiority, inferiority or futility calculated according to the O’Brien-Fleming alpha-spending function. The graph of TSA was plotted according to a specific software (User Manual for TSA, Copenhagen Trial Unit 2011).

Figure 1 shows the results of our analysis. The number of patients enrolled in the 23 trials (N = 3344) exceeded the optimal number (N = 2155) estimated to avoid an inconclusive finding. In the graph, after estimating that 2155 patients would be needed to reach a conclusion, the curve crossed the green boundaries at the cumulative number of 1606 patients (after 19 trials in chronological order) and reached the area of futility. Hence, the conclusion of TSA was proof of no effectiveness (or “futility”); this result remained unchanged assuming RRR = 20% (data not shown).

4. Discussion

On the basis of these results, glutamine in critical illness is ineffective and may even be toxic. Since futility of this supplementation is proven, no further trials should be carried out to study its benefit in these patients. Furthermore, in consideration that the hypothesis of a toxic effect of this treatment has been made, this is another reason why its use should be abandoned also in clinical practice.

Conflict of interest

None declared.

References


