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Current evidence and ongoing trials on the use of glutamine in critically ill and surgical patients

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Synopsis

The amino acid glutamine has numerous important roles including particularly antioxidant defence, immune function, the inflammatory response, acid-base balance and nitrogen economy. This systematic review of randomised controlled trials of nutrition support with glutamine up to August 2008 found that parenteral glutamine in critical illness is associated with a non-significant reduction in mortality (risk ratio 0.71, 95% CI 0.49 to 1.03) and may reduce infections. However, poor study quality and the possibility of publication bias mean that these results should be interpreted with caution. There is no evidence to suggest that glutamine is harmful, in terms of organ failure, and parenteral glutamine may reduce the development of organ failure in ventilated patients.

Background

There are many potential mechanisms by which supplementation with the amino acid glutamine could prove beneficial in critical illness. Plasma glutamine levels fall in patients with critical illness, and glutamine is released from muscle to be used by rapidly dividing cells (such as the gut and immune system) and for renal acid-base homeostasis (1). The fall in glutamine levels may suggest that glutamine becomes a 'conditionally essential' amino acid in critical illness. Glutamine supplementation improves nitrogen balance in parenteral nutrition support (2). Glutamine is particularly important as a precursor of glutathione and thus antioxidant defence.

Glutamine also plays a role in intracellular signalling, enhances heat shock protein expression (3), prevents apoptosis in injury, and attenuates hyper-inflammation (1). There is some evidence to suggest that glutamine may reduce gut injury and inflammation in critical illness, thus influencing bacterial translocation across the gut wall (4). Glutamine may also improve insulin sensitivity in critical illness (5).

With the ability now to provide glutamine in parenteral nutrition, as well as additional supplements enterally, randomised controlled trials have evaluated whether glutamine provides clinical benefits.

Guidelines for the use of glutamine in critical illness have recommended enteral glutamine for patients with burns or trauma, and parenteral glutamine, where parenteral nutrition is required (6). However, not all guidelines for critical illness have supported the use of parenteral glutamine for all patients requiring parenteral nutrition, and the quality of trials has been considered poor for guideline recommendations (7).

Heyland and Dhaliwal (8) have shown that surgery causes some cytokine activation and some depression of cellular defences, but the systemic inflammatory response of critical illness is best represented by hyper-inflammation and marked cellular immune dysfunction at the same time. Thus responses to glutamine supplementation may differ between surgical and critically ill patients. This systematic review examines the use of glutamine parenterally and enterally in critical illness and surgical groups of patients separately.

Methods

A systematic review and meta-analyses of randomised controlled trials (RCTs) were undertaken using a prespecified protocol. RCTs compared glutamine containing parenteral or enteral nutrition compared with control feeding in adult patients undergoing surgery or with critical illness. It was assumed that regimes given to intervention and control groups were isonitrogenous and isocaloric, but whether this was the case was not always clear in the reports. RCTs of immunonutrition, where glutamine was one of several nutrients, e.g. with arginine or ω-3 fatty acids, were not included.

RCTs were identified by searching three databases (MEDLINE, EMBASE, CINAHL), hand searching four journals (Clinical Nutrition, Journal of Parenteral and Enteral Nutrition, Intensive Care Medicine, Critical Care Medicine) and from previous reviews, including that by Novak *et al*. (9). Full published reports, conference proceedings and abstracts provided data. Details of the search strategy can be provided by contacting the author. There were no language exclusions, but the review did not include trials from China, because of continuing concerns over the authenticity of randomised trial designs from China (10). The last date for the search was August 2008.

Data on deaths, participants with infection and participants with organ failure are presented. A conservative method of data handling was used. Outcomes were taken from the last available time of follow-up, with a random effects model for meta-analysis (except in the case of the data used in the funnel plot). Data are presented with all participants randomised as the denominator. *Post hoc* subgroup analyses examined mortality in critical illness for glutamine dose calculated as dose/kg x days of ≥ 4.2g/kg compared with <4.2g/kg, and for patients with acute pancreatitis.

Heterogeneity amongst trials was assessed by the I^2 statistic (11), where ≥50% was taken as indicating significant heterogeneity. Publication bias was examined by funnel plot analysis. Meta-analyses were undertaken using Review Manager version 4.2.7 software, Cochrane Collaboration, 2004. Risk ratios (RR) and 95% confidence intervals (CI) are reported.

Results

Data are presented from 31 RCTs that provided data (12-42). Twenty-two trials were identified in patients with critical illness (burns two trials, mixed intensive care unit population nine trials, trauma patients three trials, patients with pancreatitis four trials, and patients with surgical complications four trials). Eight trials were in elective gastrointestinal surgical patients, where parenteral nutrition support post-operatively would not normally be provided. One trial evaluated glutamine containing parenteral nutrition in a mixed hospital population cared for by the nutrition team (37).

Trial quality, as reported, was often limited, particularly in terms of reporting concealment of randomisation, intention to treat analysis and blinding of outcome assessment (although this is not likely to be a problem for reporting of deaths).

Mortality (Figure 1)

Parenteral glutamine in critical illness was associated with a non-significant reduction in mortality (RR 0.71, 95% CI 0.49 to 1.03, P = 0.07). For enteral glutamine in critical illness the risk ratio was 1.05 (95% CI 0.71 to 1.54, P = 0.81). Two surgical trials reported mortality and one trial reported for a mixed hospital population, in neither case was there a statistically significant reduction. Overall, if all population groups are combined the risk ratio for mortality was 0.84 (95% CI 0.66 to 1.07, P = 0.17). Thus there was a trend for a beneficial effect, most clearly for parenteral glutamine in critical illness.

Participants with infection (Figure 2)

For enteral glutamine in critical illness the risk ratio was 0.91, 95% CI 0.74 to 1.10, P = 0.33). Parenteral glutamine in critical illness was associated with a statistically significant reduction in infections (RR 0.78, 95% 0.63 to 0.97, P = 0.03). In surgical patients given parenteral nutrition containing glutamine, whether they required parenteral nutrition or not, there was a statistically significant reduction in participants with infection (RR 0.43, 95% 0.27 to 0.69, P < 0.001). Overall, for all the patient groups there was a statistically significant reduction in participants with infection (RR 0.81, 95% 0.70 to 0.93, P = 0.003).

For the outcome of participants with infection which provided the most data, a funnel plot examining for suggestion of publication bias was undertaken (Figure 3). The individual data points should be evenly distributed in an inverted V on either side of the vertical axis. The

plot shows fewer data points to the top right of the line, suggesting that small trials with negative results, not in favour of glutamine, were less likely to be published.

Participants with multiorgan or renal failure (Figure 4)

Few trials reported multiorgan or renal failure. Combining all parenteral glutamine trials there was a statistically significant reduction (RR 0.60, 95% 0.42 to 0.85, P = 0.004), but not for enteral glutamine (RR 1.15, 95% 0.70 to 1.87, P = 0.59). Overall there was no suggestion that glutamine was harmful in terms of multiorgan or renal failure (RR 0.75, 0.56 to 0.99, P = 0.04).

Participants with pancreatitis (Figures 5 and 6)

Parenteral glutamine was associated with a statistically significant reduction in mortality (RR 0.36, 95% CI 0.13 to 0.99, P = 0.05) and a non-significant reduction in infection (RR 0.49, 95% 0.20 to 1.16, P = 0.10) in participants with pancreatitis.

Examination of dose effects in critical illness (Figure 7)

For trials providing ≥0.42g glutamine/kg as total dose over time the risk ratio for mortality was 0.66 (95% 0.43 to 1.01, P = 0.06), and for doses less than this RR 0.91 (0.66 to 1.27, P = 0.59). Suggesting that higher doses may be more effective, but there was no statistically significant difference between the sub groups in the interaction test (P = 0.27). However, the trials with the higher dose of glutamine showed high heterogeneity (I^2 = 57%).

Conclusions

Compared with a previous systematic review three years before (43), there have been some changes to the results for the outcomes. The effect of glutamine on mortality is very similar to previously, with a risk ratio of 0.71 (95% CI 0.49 to 1.03) for parenteral glutamine. Although this result is not statistically significant, the confidence intervals do not exclude the possibility of benefit on mortality.

Parenteral glutamine now appears to reduce infections in critical illness, but the evidence for enteral glutamine in critical illness is less strong. This is the reverse of the results from the previous review. The possibility of publication bias for this outcome remains a concern. The methodological quality of nutrition support trials in critical illness, particularly with regard to intention to treat analysis, concealment of allocation, and blinding of outcome assessment, also requires improvement (44).

Categorisation into critical illness or surgical trials was difficult. Trials where participants had pancreatitis or surgery followed by complications, e.g. peritonitis, were classified as critical illness. All the other surgical trials of parenteral glutamine gave parenteral nutrition after uncomplicated elective surgery, when it would not generally have been provided. Given that parenteral nutrition itself may be associated with an increased risk of infection, it is not clear how the reduction of infection with parenteral glutamine in this group of surgical patients can be interpreted.

Large multicentre randomised trials, with rigorous methodology, are underway examining the role of glutamine in critical illness (45, 46). The REDOXS© (REducing Deaths due to OXidative Stress) trial (47) is recruiting 1200 patients in North America and Europe with organ dysfunction in critical illness. Participants are randomised to 0.35g/kg/d parenteral glutamine (independent of the need for parenteral nutrition) and 30g/d enteral glutamine and/or parenteral and enteral antioxidants or no supplements, in a factorial design. The main outcome of the trial is 28 day mortality; survival to 6 months and infections are also outcomes. The relatively high doses of glutamine and antioxidants have been established on the basis of reduction in markers of oxidative stress, and greater preservation of glutathione without affecting organ function (46).

The SIGNET (Scottish Intensive care Glutamine of seleNium Evaluative Trial) is examining parenteral nutrition with 20.2g glutamine with or without 500µg parenteral selenium, also in a factorial design with isonitrogenous and isocaloric regimes, in 500 patients who require parenteral feeding in intensive care (45).

There is no suggestion from the data in this review that parenteral or enteral glutamine are harmful, and the meta-analysis suggests that parenteral glutamine may reduce organ failure (other than requiring ventilation), however, few trials reported details of organ failure.

Three small trials suggest that glutamine may reduce mortality in acute pancreatitis. However, only a total of 112 patients were enrolled in these trials and not all trials had patients with severe pancereatitis (33). It is not clear whether enteral nutrition support could have been achieved in these patients (48).

There is some suggestion that higher doses (equivalent to at least 0.42g/kg glutamine for 10 days) may have more effect on mortality.

Two recent Cochrane reviews (49, 50) have also examined the use of parenteral or enteral glutamine in children. Tubman *et al*. (49) found that there was insufficient evidence to support the use of parenteral or enteral glutamine in preterm infants to prevent morbidity and mortality. Grover *et al*. (50) came to the same conclusion for parenteral and enteral glutamine use in young infants with severe gastrointestinal disease.

Acknowledgements and conflict of interest

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Figures

Figure 1 – Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN) nutrition in critical illness and surgery – risk ratios for mortality

Figure 2 – Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN) nutrition in critical illness and surgery – risk ratios for participants with infection

Figure 3 – Funnel plot examination for publication bias from infection data in figure 2

Figure 4 – Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN) nutrition in critical illness and surgery – risk ratios for participants developing organ failure (other than requiring ventilation)

Figure 5 – Meta-analysis of glutamine supplemented parenteral (PN) nutrition in pancreatitis – risk ratios for mortality

Figure 6 – Meta-analysis of glutamine supplemented parenteral (PN) nutrition in pancreatitis – risk ratios for participants with infection

Figure 7 - Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN) nutrition in critical illness and surgery – risk ratios for mortality for high (≥ 0.42g/kg) and lower dose of glutamine (< 0.42g/kg)

Footnote to Figure 3:
SE (log RR) = Standard Error of the log of the Risk Ratio
RR (fixed) = Risk Ratio (fixed effect model)

Footnotes for Figures 1, 2, 4, 5, 6 and 7:
n = number affected in treatment or control group
N = total number in treatment or control group
← and → indicate that values extend beyond range of values shown

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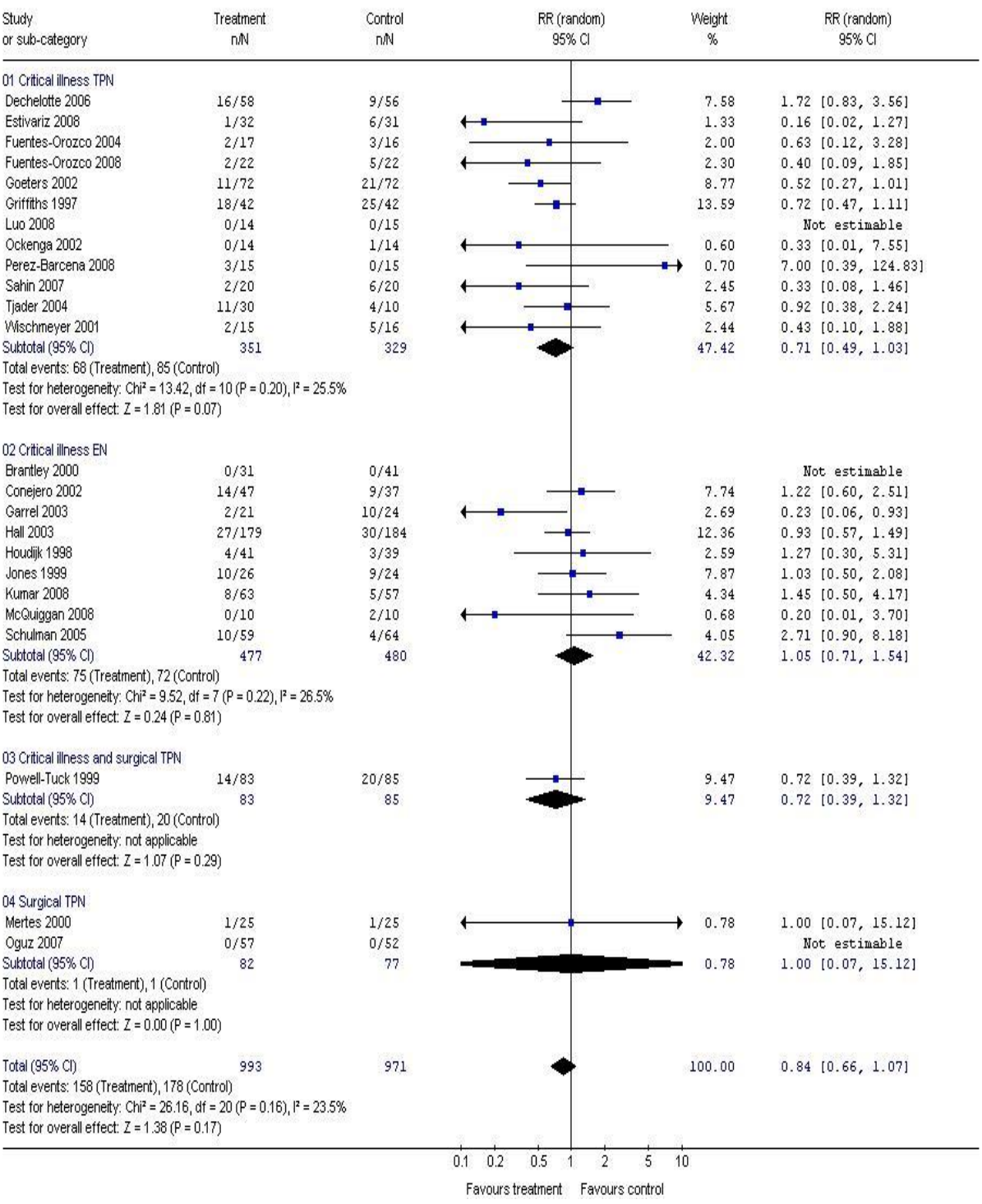
441 Figure 1



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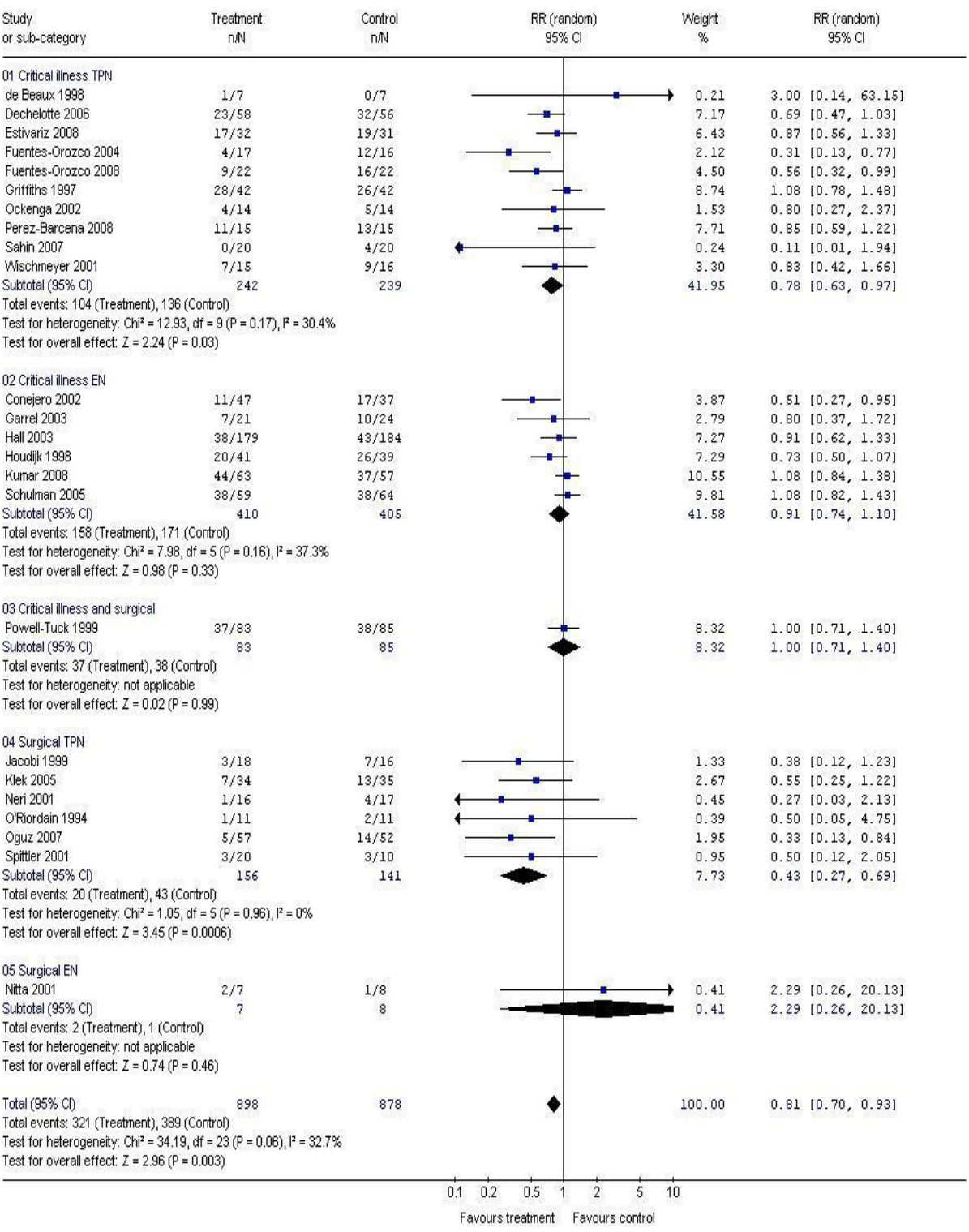

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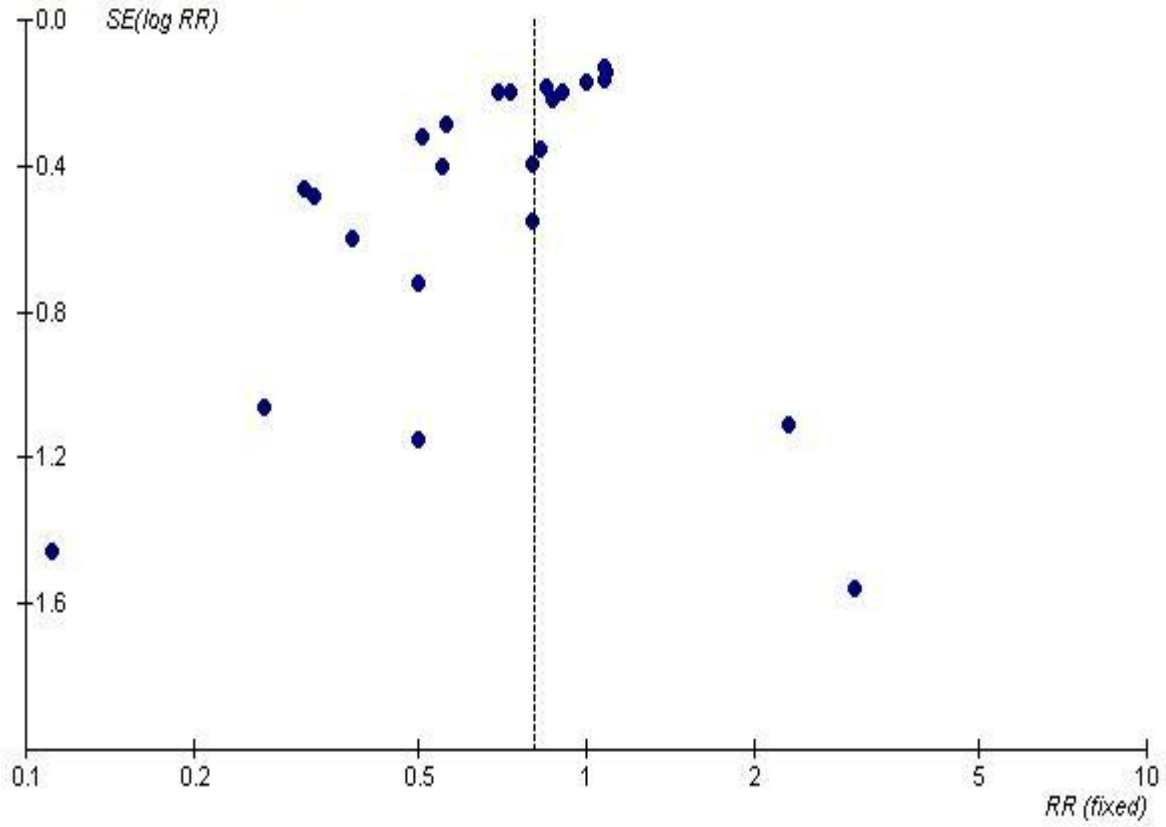

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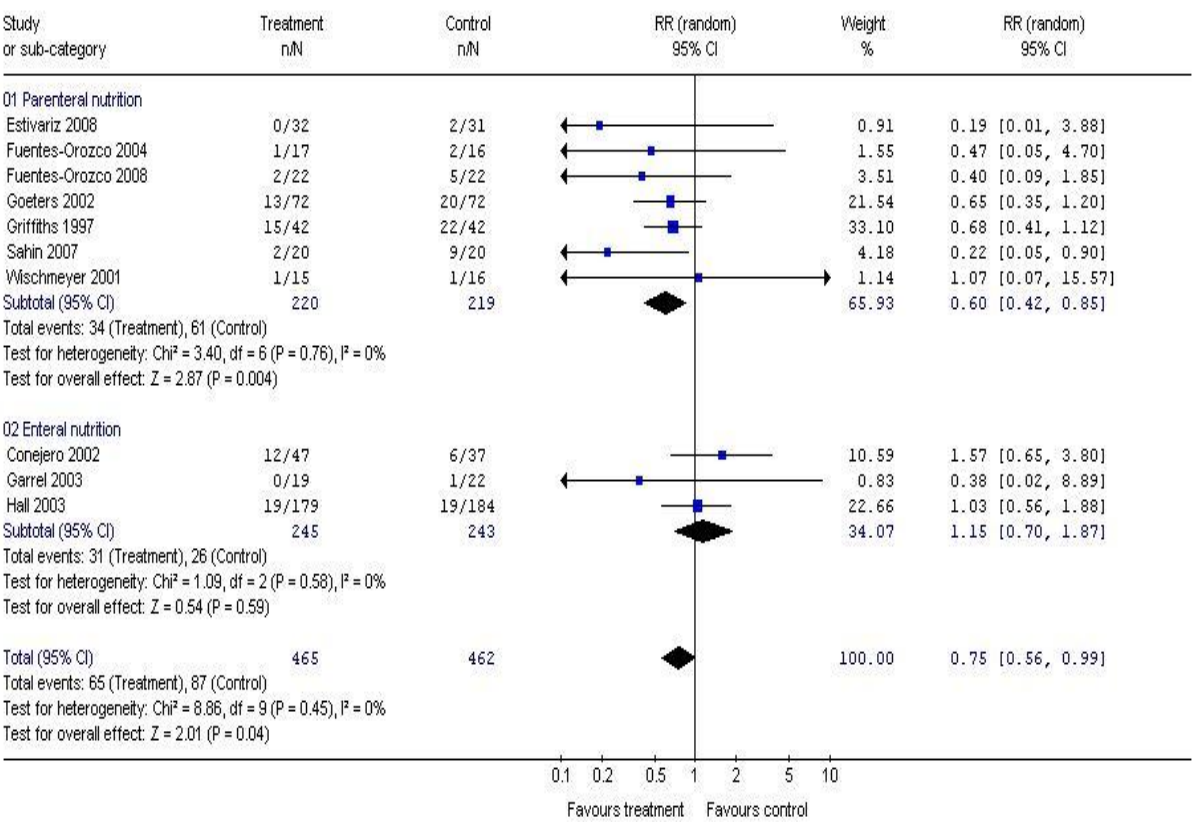

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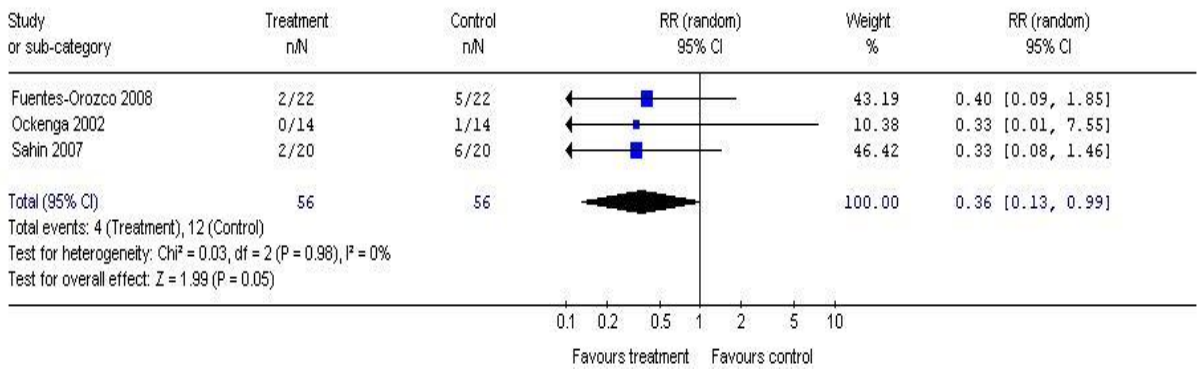

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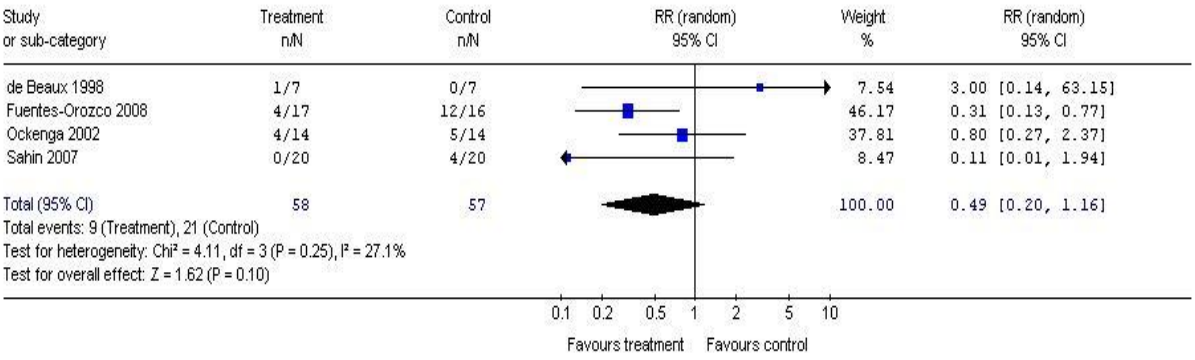

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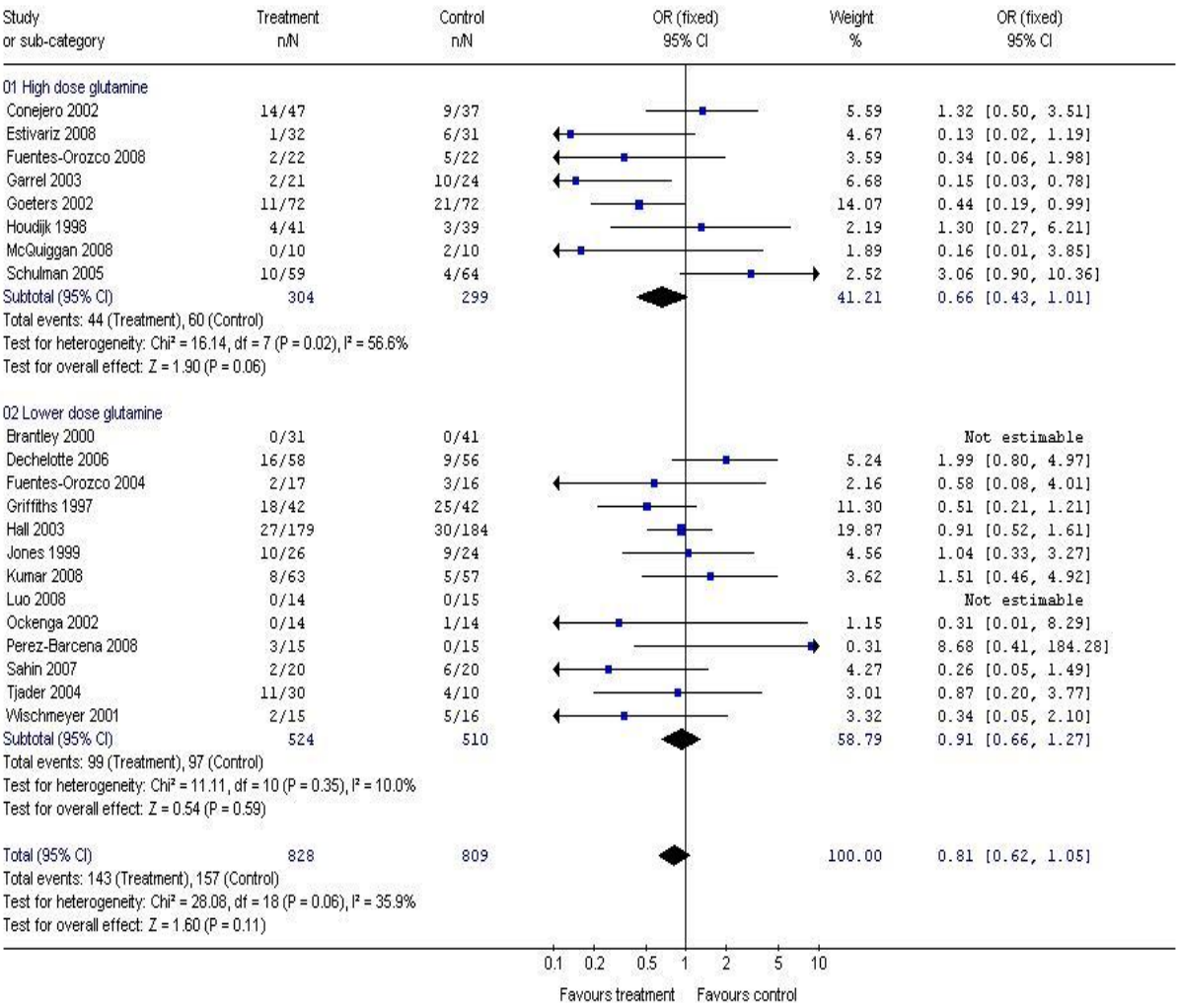

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