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Conference on 'Malnutrition matters'

Symposium 4: Hot topics in parenteral nutrition
Current evidence and ongoing trials on the use of glutamine in critically-ill patients and patients undergoing surgery

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The amino acid glutamine has numerous important roles including particularly antioxidant defence, immune function, the inflammatory response, acid–base balance and N economy. The present systematic review of randomised controlled trials of nutrition support with glutamine up to August 2008 has found that parenteral glutamine in critical illness is associated with a non-significant reduction in mortality (risk ratio 0·71 (95% CI 0·49, 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.

Glutamine: Systematic review: Critical illness

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 N balance in parenteral nutrition support[2]. Glutamine is particularly important as a precursor of glutathione and thus in antioxidant defence.

Glutamine also plays a role in intracellular signalling, enhances heat-shock protein expression[3], prevents apoptosis in injury and attenuates hyperinflammation[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 enteral supplements, 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].

It has been shown that surgery causes some cytokine activation and some depression of cellular defences[8], but the systemic inflammatory response of critical illness is best represented by hyperinflammation and marked cellular immune dysfunction at the same time. Thus, responses to glutamine supplementation may differ between patients undergoing surgery and critically-ill patients. The present 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 were undertaken using a prespecified

Abbreviation: RR, risk ratio.

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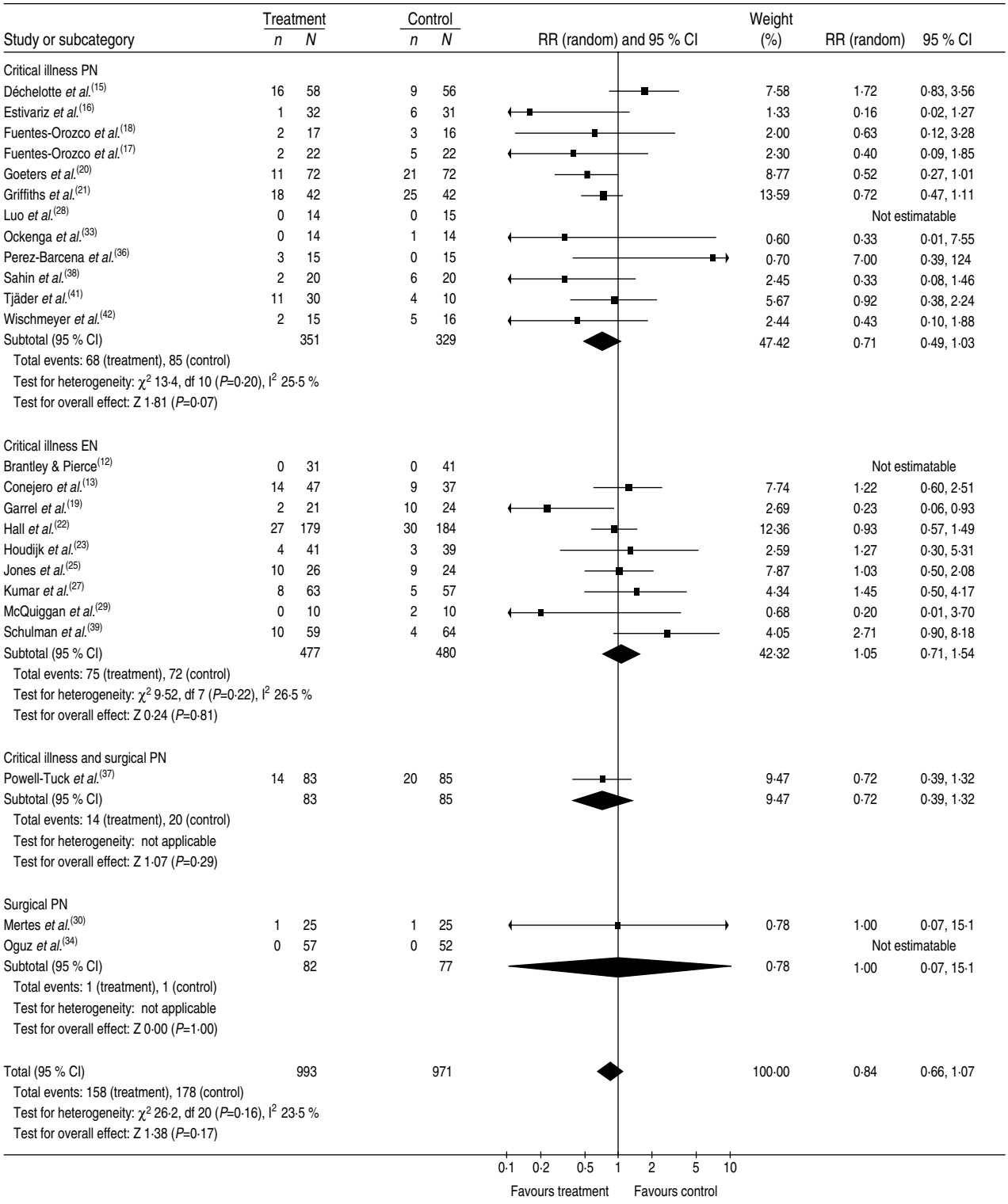

Fig. 1. Meta-analysis of glutamine-supplemented parenteral (PN) or enteral (EN) nutrition in critical illness and surgery; risk ratios (RR) for mortality. n, No. of patients affected in treatment or control group; N, total no. of patients in treatment or control group; ←, →, values extend beyond the range of the values shown.

protocol. Randomised controlled trials compared glutamine-containing parenteral or enteral nutrition with control feeding in adult patients undergoing surgery or with critical illness. It was assumed that regimens given to intervention and control groups were isonitrogenous and isoenergetic, but whether this assumption reflected practice was not always clear from the reports. Randomised controlled trials of immunonutrition, in which glutamine was

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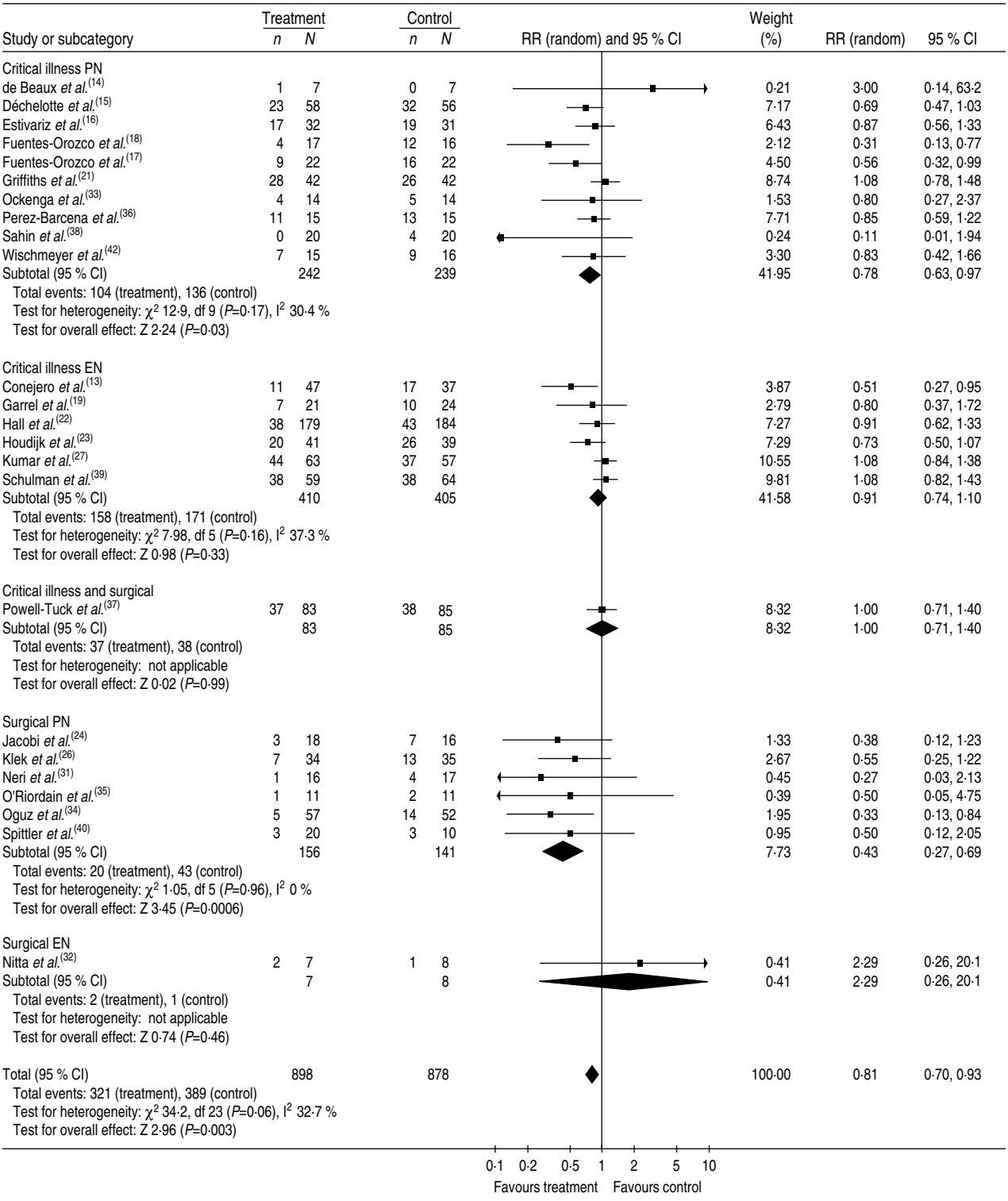

Fig. 2. Meta-analysis of glutamine-supplemented parenteral (PN) or enteral (EN) nutrition in critical illness and surgery; risk ratios (RR) for participants with infection. n, No. of patients affected in treatment or control group; N, total no. of patients in treatment or control group; ←, →, values extend beyond the range of the values shown.

one of several nutrients, e.g. with arginine or *n*-3 fatty acids, were not included.

Randomised controlled trials 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. There were no language exclusions, but the review did not

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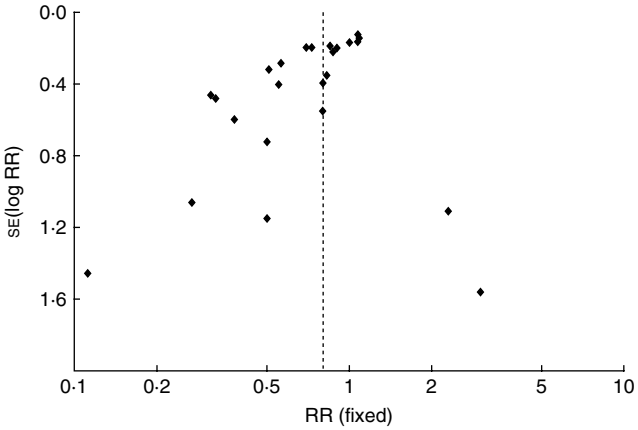

Fig. 3. Funnel plot examination for publication bias from infection data shown in Fig. 2. SE (log RR), SE of the log of the risk ratio; RR (fixed), risk ratio (fixed effect model).

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 body weight × period (d) of ≥4·2 g/kg body weight compared with <4·2 g/kg body weight, 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, Oxford, UK). Risk ratios (RR), OR and 95% CI are reported.

Results

Data are presented from thirty-one randomised controlled trials 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; patients with trauma, three trials; patients with pancreatitis, four trials; patients with surgical complications, four trials). Eight trials were in patients undergoing elective gastrointestinal surgery, for whom parenteral nutrition support post-operatively would not normally be provided. One trial

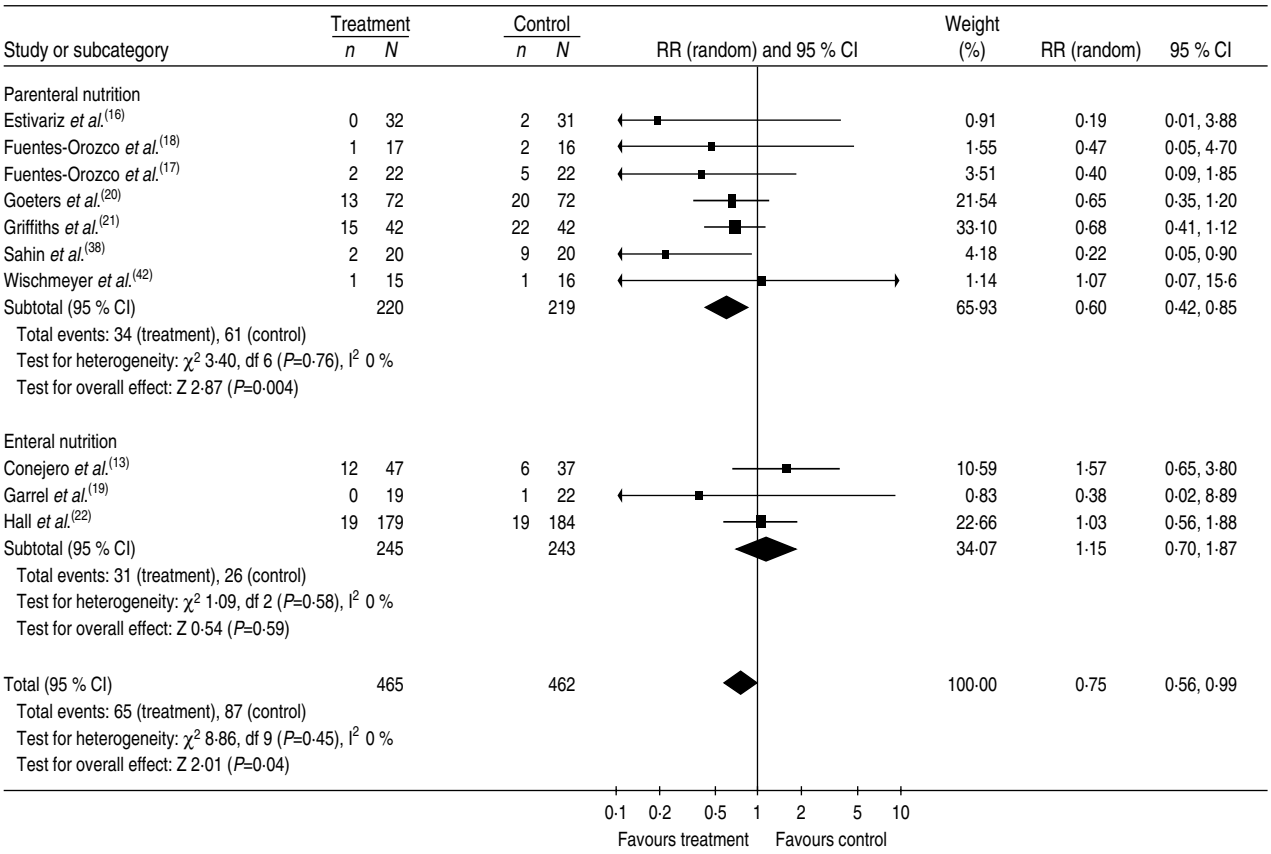

Fig. 4. Meta-analysis of glutamine-supplemented parenteral or enteral nutrition in critical illness and surgery; risk ratios (RR) for participants developing organ failure (other than requiring ventilation. n, No. of patients affected in treatment or control group; N, total no. of patients in treatment or control group; ←, →, values extend beyond the range of the values shown.

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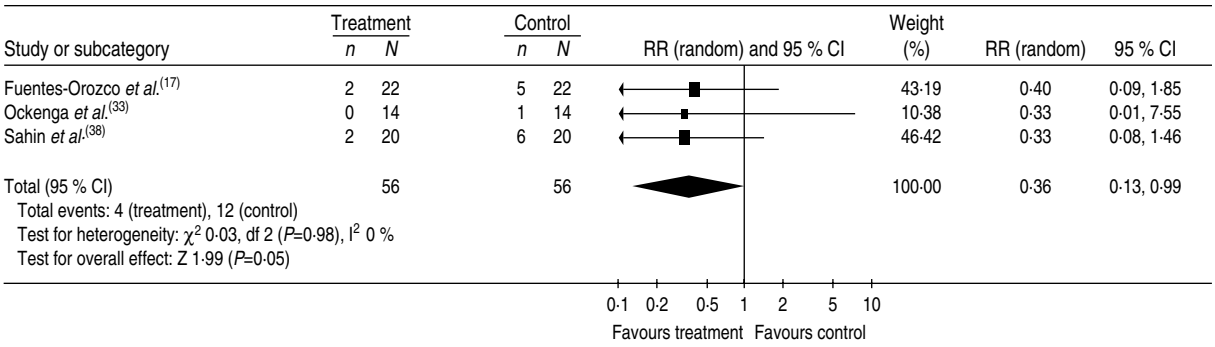

Fig. 5. Meta-analysis of glutamine-supplemented parenteral nutrition in pancreatitis; risk ratios (RR) for mortality. n, Number affected in treatment or control group; N, total no. of patients in treatment or control group; ←, →, values extend beyond the range of the values shown.

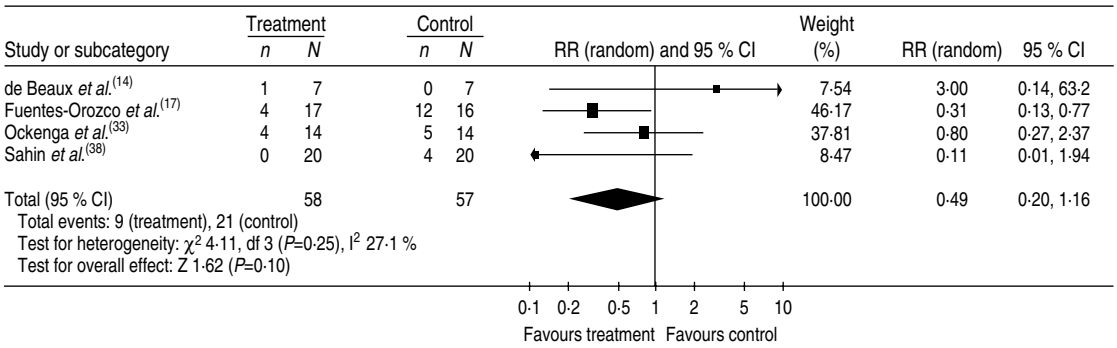

Fig. 6. Meta-analysis of glutamine-supplemented parenteral nutrition in pancreatitis; risk ratios (RR) for participants with infection. n, No. of patients affected in treatment or control group; N, total no. of patients in treatment or control group; ←, →, values extend beyond the range of the values shown.

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 factor is not likely to be a problem for reporting of deaths).

Mortality

Parenteral glutamine in critical illness was associated with a non-significant reduction in mortality (RR 0·71 (95% CI 0·49, 1·03); $P = 0·07$; Fig. 1). For enteral glutamine in critical illness the RR was 1·05 (95% CI 0·71, 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 significant reduction. Overall, if all population groups are combined the RR for mortality was 0·84 (95% CI 0·66, 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

For enteral glutamine in critical illness the RR was 0·91 (95% CI 0·74, 1·10; $P = 0·33$; Fig. 2). Parenteral glutamine in critical illness was associated with a significant reduction in infections (RR 0·78 (95% CI 0·63, 0·97); $P = 0·03$). In patients following surgery who were given parenteral nutrition containing glutamine, whether they required parenteral nutrition or not, there was a significant reduction in participants with infection (RR 0·43 (95% CI 0·27, 0·69); $P < 0·001$). Overall, for all patient groups there was a significant reduction in participants with infection (RR 0·81 (95% CI 0·70, 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 (Fig. 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 multi-organ or renal failure

Few trials reported multi-organ or renal failure. Combining all parenteral glutamine trials there was a significant reduction (RR 0·60 (95% CI 0·42, 0·85); $P = 0·004$; Fig. 4), but not for enteral glutamine (RR 1·15 (95% CI 0·70, 1·87); $P = 0·59$). Overall, there was no suggestion that glutamine was harmful in terms of multi-organ or renal failure (RR 0·75 (95% CI 0·56, 0·99); $P = 0·04$).

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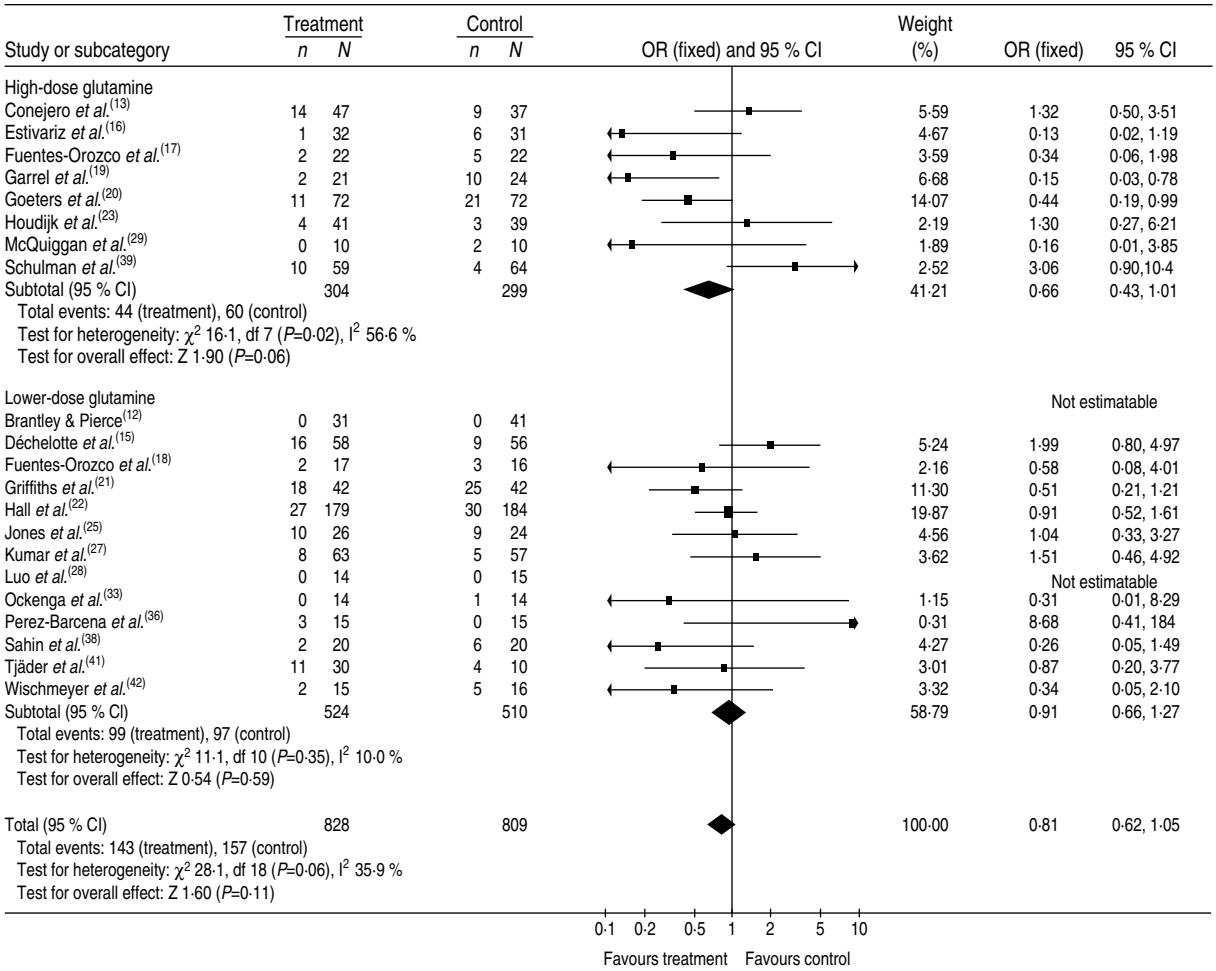

Fig. 7. Meta-analysis of glutamine-supplemented parenteral or enteral nutrition in critical illness and surgery with OR for mortality for the high-dose (≥4·2 g/kg body weight) and lower-dose (<4·2 g/kg body weight) glutamine. n, No. of patients affected in treatment or control group; N, total no. of patients in treatment or control group; ←, →, values extend beyond the range of the values shown.

Participants with pancreatitis

Parenteral glutamine was associated with a significant reduction in mortality (RR 0·36 (95% CI 0·13, 0·99); $P = 0·05$; Fig. 5) and a non-significant reduction in infection (RR 0·49 (95% CI 0·20, 1·16); $P = 0·10$; Fig. 6) in participants with pancreatitis.

Examination of dose effects in parenteral and enteral glutamine-supplemented critical illness

For trials providing ≥4·2 g glutamine/kg body weight as the total dose over time the OR for mortality was 0·66 (95% CI 0·43, 1·01; $P = 0·06$) and for doses <4·2 g glutamine/kg body weight OR was 0·91 (95% CI 0·66, 1·27; $P = 0·59$; Fig. 7). These findings suggest that higher doses may be more effective, but there was no significant difference between the subgroups 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 systematic review conducted 3 years previously[43] there have been some changes to the results for the outcomes. The effect of glutamine on mortality is very similar to that reported previously, with an RR of 0·71 (95% CI 0·49, 1·03) for parenteral glutamine. Although this result is not significant, the confidence intervals do not exclude the possibility of benefit on mortality.

The data now appear to suggest that parenteral glutamine reduces infections in critical illness, but the evidence for enteral glutamine in critical illness is less strong. This finding 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 in relation to intention-to-treat analysis, concealment of allocation and blinding of outcome assessment, also requires improvement[44].

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Categorisation into critical illness or surgical trials was difficult. Trials in which 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 surgical group of patients can be interpreted.

Large multicentre randomised trials, with rigorous methodology, are underway to examine the role of glutamine in critical illness[45,46]. The REDOXS© trial is recruiting 1200 patients in North America and Europe with organ dysfunction in critical illness[47]. Participants are randomised to 0·35 g glutamine/kg body weight per d administered parenterally (independent of the need for parenteral nutrition) and 30 g glutamine/d administered enterally and/or parenteral and enteral antioxidants or no supplements in a factorial design. The main outcome of the trial is 28 d 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 Scottish Intensive care Glutamine or seleNium Evaluative Trial is examining parenteral nutrition with 20·2 g glutamine with or without 500 µg parenteral Se/d, also in a factorial design with isonitrogenous and isoenergetic regimens, in 500 patients who require parenteral feeding in intensive care[45].

There is no suggestion from the data in the present review that parenteral or enteral glutamine is harmful and the meta-analysis suggests that parenteral glutamine may reduce organ failure; 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 pancreatitis[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 ≥0·42 g glutamine/kg body weight for 10 d) may have more effect on mortality.

Two recent Cochrane reviews[49,50] have also examined the use of parenteral or enteral glutamine in children. One review has found insufficient evidence to support the use of parenteral or enteral glutamine in preterm infants to prevent morbidity and mortality[49]. The other review comes to the same conclusion for parenteral and enteral glutamine use in young infants with severe gastrointestinal disease[50].

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