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META-ANALYSIS

Impact of Glutamine Supplemented Total Parenteral Nutrition in Surgical patients: A systematic review of the evidence

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ABSTRACT

BACKGROUND: The importance of the metabolic role of glutamine has been demonstrated in several laboratory and clinical studies. A number of publications have addressed issues relevant to the benefits of the parenteral use of glutamine in patients with a variety of conditions.

OBJECTIVE: To review published evidence of the relationship between glutamine supplemented total parenteral nutrition (TPN) and infection rates, length of hospital stay, nitrogen balance, total lymphocyte count and mortality in patients undergoing elective surgery.

MATERIAL AND METHODS: 146 titles, abstracts, and articles were reviewed. Those primary studies were included that were randomized trials of surgical patients requiring TPN. The effect of glutamine enriched TPN (Gln-enriched TPN) regimen vs. standard TPN regimen on clinical and biological outcomes was evaluated.

RESULTS: Eight randomized trials were found. When the results of these trials were analyzed with respect to infection, Gln-enriched TPN was associated with a relative risk ratio (RR) of 0.368 (95% CI, 0.162-0.832, p=0.016). Gln-enriched TPN was also associated with reduced length of hospital stay (1.191 days less; 95% CI 0.395-1.986, p=0.004), better cumulative nitrogen balance (2.568gr; 95% CI 1.274-3.863, p=0.000), an increase in total lymphocyte count (2.246 /μL; 95% CI 0.416-4.076, p=0.017), and a reduction in mortality rate (RR 0.723; 95% CI 0.174-3.012, p=0.656). No side-effects were reported.

CONCLUSION: There is strong evidence that a benefit from Gln-enriched TPN may exist for surgical patients in terms of length of hospital stay, infection rate, total lymphocyte count and cumulative nitrogen balance. The benefit from glutamine-enriched TPN on mortality was not found to be statistically significant.

KEY WORDS: *glutamine, total parenteral nutrition, surgery, review, meta-analysis, randomized trials*

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INTRODUCTION

Glutamine is a five-carbon amino acid with two amino moieties, and accounts for 30-35% of all the amino acid nitrogen that is transported in the plasma [1]. It is a non-essential amino acid, which occupies a central role in many metabolic pathways. It comprises more than 50% of the body's free amino acid pool and is a precursor that donates nitrogen (N) for the synthesis of nucleic acids, purines, pyrimidines, amino sugars and glutathione. It is also the most important substrate for renal ammoniagen-

esis. Glutamine is considered as a nitrogen "shuttle" between tissues and as a fuel for enterocytes, colonocytes, lymphocytes and proliferating cells [2,3]. It is also often considered to be of prime importance for immunomodulation [4]. Numerous studies in patients and animals have demonstrated that glutamine feeding increases immune function and can result in better nitrogen homoeostasis [5].

Although glutamine is not an essential amino acid, glutamine deficiency with its severe complications that commonly occur during periods of metabolic stress, has led to the reclassification of glutamine as a conditionally essential amino acid [6-8].

In hypercatabolic conditions, even though glutamine can be readily synthesized de novo within many tissues, the demand may exceed the body's capacity to synthesize it. There is enough evidence that hypercatabolic and hypermetabolic situations are accompanied by marked reduction in blood and skeletal muscle intracellular glutamine. The intracellular concentration of glutamine may decline by more than 50% and the plasma level may fall by up to 30% [6,7]. This has been observed after elective operations, surgical trauma, major injury, burns, infections and pancreatitis, irrespectively of nutritional efforts at its repletion. Tissue and plasma glutamine remains reduced up to 7 days after surgery. It also appears that the magnitude of reduction is unrelated to the severity of trauma [9,10].

The etiology of the fall of muscle glutamine is not yet known, but the mechanism may well include a loss of the ability of the glutamine transporter to maintain a concentration gradient across the muscle [11].

Moreover, recently published data show that, during a critical illness, there is an average loss of lean body mass of 1% /day extrapolated to a skeletal muscle loss of 2%/day, and consequently a loss of muscle glutamine [12]. The decline in muscle glutamine is particularly important since 80% of the free amino acids of the body reside within the intracellular compartment of skeletal muscle, and glutamine accounts for approximately two-thirds of these free amino acids [6]. It has further been postulated that there is a change in the "setting" of the muscle transport system of glutamine, resulting in a lowered plasma/muscle concentration ratio despite an increased net flow of glutamine from muscle to plasma. Thus, the decrease in muscular glutamine concentration presumably reflects a pronounced increase in the clearance of glutamine by the liver, kidney, and mostly the gut [11]. It seems that the lost glutamine from skeletal muscle and blood is primarily used by visceral organs for a variety of purposes [13].

During catabolic states, glutamine is used for renal ammoniagenesis, but it also serves as "fuel" for stimulated lymphocytes, macrophages and intestinal mucosal cells [14].

More specifically, glutamine is the preferred fuel for oxidative metabolism by the enterocytes. Animal studies have demonstrated that enterocytes of the gastrointestinal tract use glutamine as a respiratory fuel and during critical illness the consumption of glutamine by the gut significantly increases [15]. A study by McAnena et al (1991) confirmed that, for the first time in humans, selective uptake of glutamine occurs in the gut of patients with major trauma. During critical illness, intestinal consumption of glutamine seems particularly important, since normal intestine protects the host from intraluminal bacteria and their toxins, and disruption in the bowel's barrier function may result in a chronic hypermetabolic state and contribute to multi-organ failure [16].

Moreover, lymphocytes require glutamine in order to proliferate in response to antigenic challenge. Macrophages may consume glutamine as a source of energy and as a precursor for nucleotides [5]. Rohde et al (1996), in their in vitro study, concluded that glutamine influences the production of some T-cell-derived cytokines, and is, thereby, important for optimal lymphocyte proliferation [17]. Heberer et al (1996) evaluated the dependence of human lymphocyte functions on the exogenous provision of glutamine in a series of in vitro experiments. They found that later events of lymphocyte activation including cytokine production, proliferation of lymphocytes and lymphokine-activated killer cell activity depends on exogenous glutamine provision [18].

Furthermore, renal glutamine consumption becomes appreciable during acidosis, when additional circulating glutamine is needed to support renal ammoniagenesis (regulation of the acid-base balance) [5].

Glutamine depletion might lead to severe complications, such as infections, poor wound healing, impaired immunity, increased intestinal permeability, and, finally, multiple organ failure [1,13]. Thus, glutamine replacement seems necessary. The striking direct correlation between free muscle glutamine concentration and the rate of protein synthesis suggests that maintenance of the intracellular glutamine pool may promote conservation of muscle protein during catabolic stress [19].

Thus, there is an obvious indication for use of glutamine supplements in the parenteral nutrition regimen of hypercatabolic patients. Glutamine supplements might be beneficial in the treatment of stressed and malnourished patients [8]. A number of publications have addressed issues relevant to the parenteral use of glutamine in a variety of patients. However, the routine inclusion of glutamine in parenteral nutrition was delayed until 1995 due to concerns about its spontaneous degradation, which results in the formation of pyroglutamic acid and ammonia [20].

When this problem was solved, concerns were raised about the beneficial role of glutamine used in routine clinical practice. A number of questions were posed such as: "Does glutamine affect the clinical outcome?", "Is parenteral glutamine beneficial to a wide range of patients or should it be confined to a specific category of patients?", "What is the optimal dose?".

The objective of the present review is to examine the ef-

fect of parenteral glutamine supplementation on certain nutritional, clinical and biological endpoints in surgical patients. Specifically, the relationship between parenteral glutamine supplementation and specific outcomes such as hospital length of stay, infection rates, mortality, total lymphocyte count, mortality and N balance is examined in patients undergoing elective surgery.

MATERIAL AND METHODS

Computerized searches were performed looking for relevant articles on MEDLINE (1966-2005), PUBMED (1990-2005), CINAHL and MEDLINE (In-Process, Other Non-Indexed Citations). The text words used were *parenteral nutrition and glutamine and surgery* limiting references to human studies. The main manufacturers of glutamine products were contacted for additional published and unpublished studies.

Primary studies were retrieved and selected in this review if they met the following criteria:

1. Research design: randomized clinical trial
2. Population: elective surgery, adult subjects who fulfilled all the criteria for receiving total parenteral nutrition (TPN) before and/or after surgery.
3. Intervention: glutamine enriched TPN (Gln-enriched TPN) versus standard care in the post-operative period or even one day pre-operatively. Patients did not receive any other form of nutritional support at the time of the study. TPN with glutamine was compared with an isocaloric, isonitrogenous TPN formulae with no glutamine (standard practice). Basic selection criteria was that both intervention and standard TPN regimen contained all three macronutrients (fat, carbohydrates, protein) in the same proportions, in both study and control groups. Studies with both peripheral and central TPN were included.
4. Outcomes: hospital length of stay, infection rate, mortality, total lymphocyte count and cumulative N balance.

Studies evaluating the impact of Gln-enriched-TPN on other biological or mechanistic endpoints were excluded.

Immunonutrition interventions in studies in which glutamine was one of several nutrients given together (e.g. with arginine and omega-3 fatty acids) were not included. Studies evaluating the effects of glutamine keto-analogues or metabolites (namely glutamate) were also not included. Because of issues of clinical heterogeneity, studies of pediatric, or neonatal patients, or studies referring to adults undergoing chemotherapy, and bone-marrow transplantation were excluded.

ANALYSIS OF DATA AND STATISTICS

The methodological quality of all selected studies was assessed using a scoring system [21-23] presented in Table 1. An effort was made to contact the authors of the included studies and to request further information not contained in the published articles.

The outcomes of primary interest were length of hospital stay, infection rate, total lymphocyte count and cumulative N balance. Relative Risks (RR) and associated confidence intervals (CIs) were estimated for all these parameters. Heterogeneity across trials was examined. A random effects model was used to estimate the overall relative risks regardless of whether there is evidence of homogeneity or heterogeneity across trials. A sensitivity analysis was performed. In interpreting subgroup differences a p value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 146 titles, abstracts and articles were identified. Initial eligibility screening resulted in 26 original articles describing randomized trials of parenteral glutamine supplementation in surgical patients, which were selected for further evaluation. Of these potentially eligible studies, 12 met all the inclusion criteria. There were two duplicate studies with different data analyses and measured outcomes which were both included. Three studies did not contain sufficient data for their results to be incorporated into the meta-analysis and were excluded. Reasons for excluding relevant randomized studies included duplicate publications, and insufficient data for analysis.

Eligible studies included surgical patients undergoing elective resection of carcinoma of the colon or rectum, gastric cancer patients, patients with biliary diseases, patients undergoing elective open cholecystectomy, patients with secondary peritonitis, abdominal-thoracic surgery patients with pancreatic carcinoma, adenocarcinoma of the duodenum and hepatoma undergoing surgery. The details of each individual study, including the methodological quality score are described in table 1.

When the results of these trials, involving 291 analyzable patients (the study population of the two duplicate studies were considered only once), were aggregated with respect to infection, Gln-enriched TPN was associated with an RR of 0.368 (95% CI 0.162-0.832, $p=0.016$). The test for heterogeneity was not significant ($p=0.893$). There was, therefore, a significant reduction in the infectious complication rate in surgical patients who received Gln-enriched TPN as reported in four studies, and in a total of 166 study patients (Figure 1).

Six studies reported length of hospital stay in 231 analyzable patients. Overall, TPN with glutamine supplementation was associated with a significantly shorter hospital stay (1.191 days less; 95% CI 0.395-1.986, $p=0.004$). The test for heterogeneity was significant ($p<0.05$) (Figure 2).

Four studies reported cumulative N balance on the fifth postoperative day in 110 patients. Overall, Gln-enriched TPN

TABLE 1. Randomized studies evaluating Gln-enriched TPN in surgical patients

Study	score	Patient Population (No. of patients)	Dose of L-Glutamine (g/kg/day)	Mortality No/n		Infectious complications No/n		Hospital stay days means±SD		Cumulative N balance mean in grams means±SD (5th day)		Total Lymphocyte Count/μL±SD (6th day)	
				Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control
Stehle et al.[11] (1989)	5	Resection of colon/rectum carcinoma (12)	0.28	---	---	---	---	---	---	-7.1±2.2	-18.1±1.7	---	---
Morlion et al.[24] (1998)	8	Elective colon/rectum carcinoma resection (28)	0.30	0/15	0/13	---	---	15.5±0.72	22.1±1.54	-7.44±4.04	-23.04±2.62	2410±170	1520±140
Jiang et al.[25] (1999)	7	Major abdominal surgery (60)	0.50	---	---	0/30	3/30	12.5±5.1	16.4±7.1	---	---	---	---
Mertes et al.[26] (2000)	9	Major abdominal surgery (37)	0.50	---	---	---	---	12.8±2.6	17.5±6.4	-14.1±9.1	-21.7±11.4	---	---
Neri et al.[27] (2001)	7	Major abdominal surgery (33)	0.30	---	---	1/16	4/17	11.5±2.5	15±3	-8.1±4.3	-19.9±4	2350±280	2100±400
Lin et al.[28] (2002)	9	Major abdominal surgery (48)	0.417	0/25	0/23	---	---	---	---	---	---	1141.9±106.8	1306±152.9
Fuentes-Orozco et al.[29] 2004	12	Secondary peritonitis (33)	0.40	2/17	3/16	4/17	12/16	16.52±8.9		---	---		
Xiang et al.[30] (2005)	8	Gastrointestinal surgery (40)	0.50	---	---	0/20	2/20	11.7±2	10.6±1.2	---	---	---	---
Lin et al.[31] (2005)	9	Major abdominal surgery (48)	0.417	---	---	---	---	---	---	-3.2±1.6	-6.5±2.7	---	---

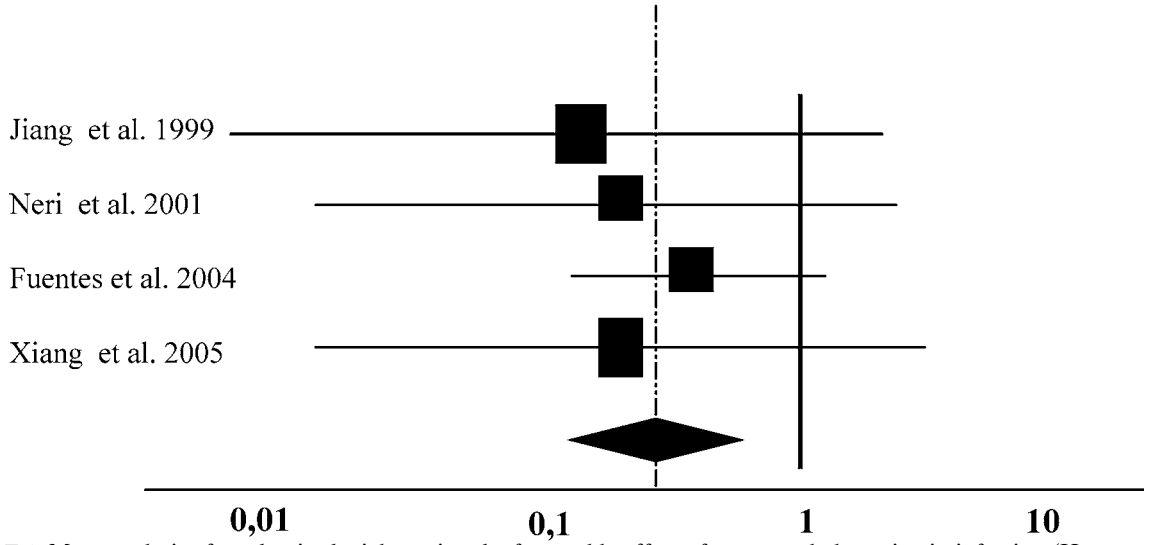

FIGURE 1. Meta-analysis of randomised trials testing the favourable effect of parenteral glutamine in infection (Heterogeneicity tet: p = 0.893; random effect model: RR = 0.368 with 95% CI: 0.162-0.832 and p <0.05).

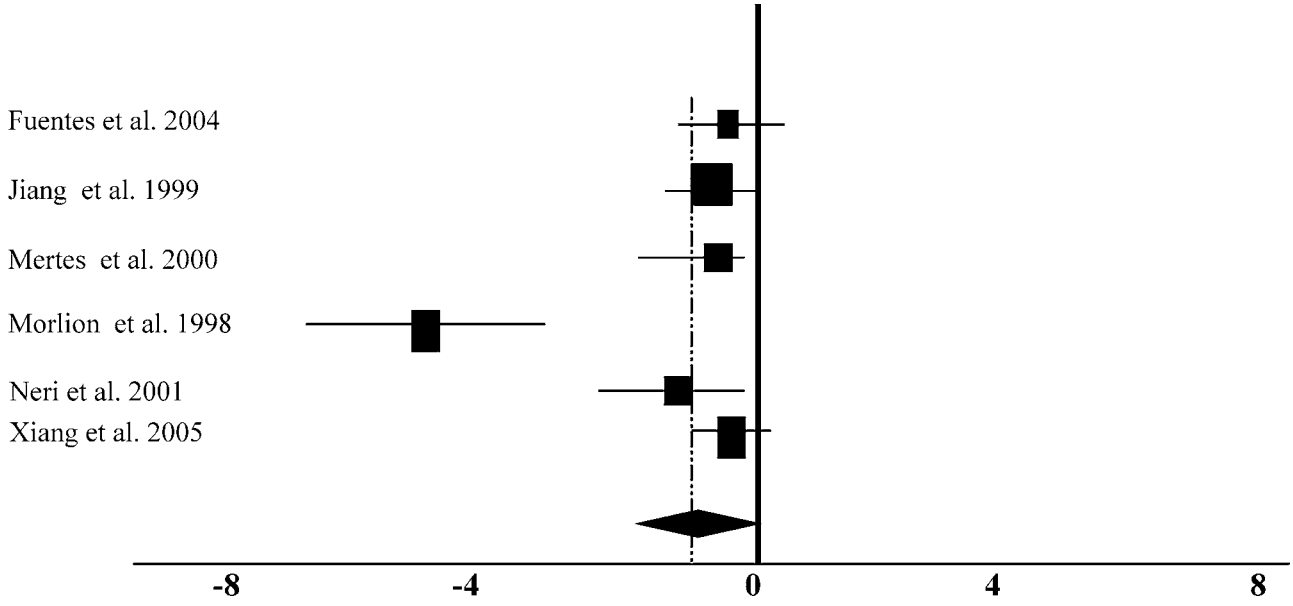

FIGURE 2. Meta-analysis of randomised trials testing the favourable effect of parenteral glutamine in length of hospital stay (Heterogeneicity test: p <0.05; random effect model: Difference in means = -1.191 with 95% CI: -1.986, -0.395 and p <0.05).

was associated with a better cumulative N balance (2.568gr; 95% CI 1.274-3.863, p=<0.05). The test for heterogeneity was significant (p<0.05) (Figure 3).

Three studies referring to total lymphocyte count on the sixth postoperative day in a total of 109 patients, demonstrated that Gln-enriched TPN was associated with a significant increase in total lymphocyte count (2.246 /μL; 95% CI 0.416-4.076, p=0.017). The test for heterogeneity was significant (p<0.05) (Figure 4).

Mortality was studied in three trials. Gln-enriched TPN was associated with a non-significant reduction in mortality rate (RR 0.723; 95% CI 0.174-3.012, p=0.656). The test for heterogeneity was not significant (p=0.983) (Figure 5).

Two studies referred to side-effects and reported no adverse-effects attributable to the Gln-enriched TPN regimen.

Due to concerns of clinical heterogeneity, and since statistical heterogeneity was present in most of the results, we

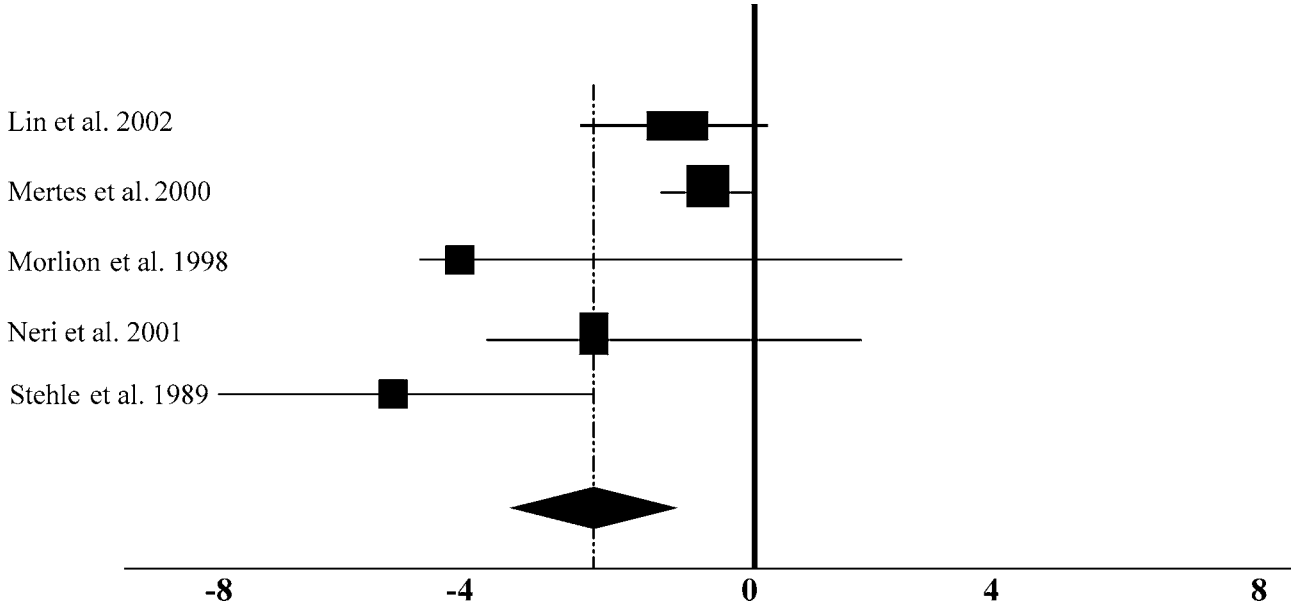

FIGURE 3. Meta-analysis of randomised trials testing the favourable effect of parenteral glutamine in cumulative N balance (Heterogeneicity test: $p < 0.05$; random effect model: Difference in means = -2.568 with 95% CI: -3.863, - 1.274 and $p < 0.05$).

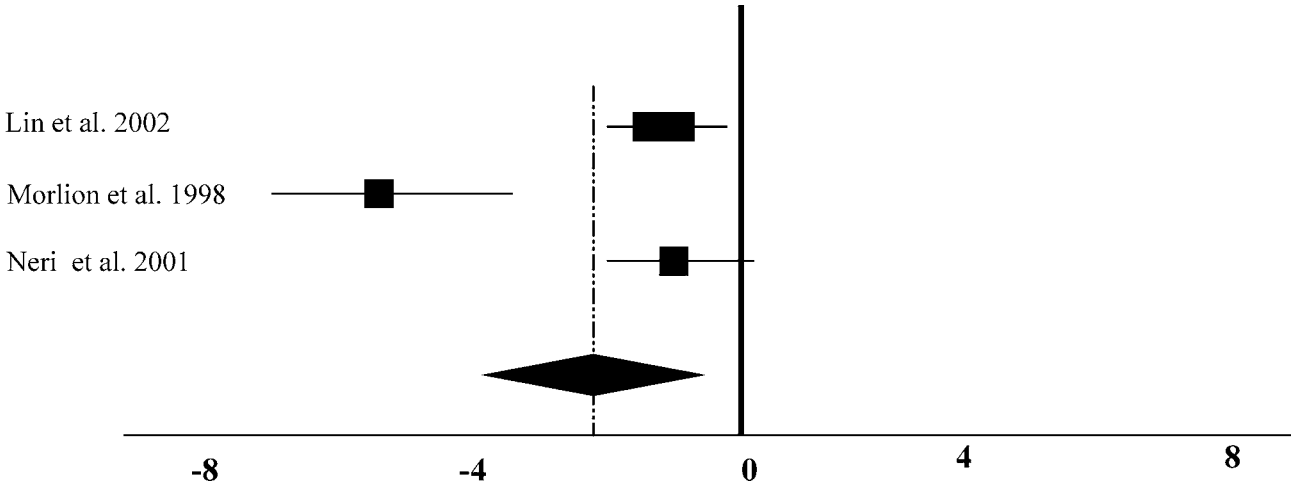

FIGURE 4. Meta-analysis of randomised trials testing the favourable effect of parenteral glutamine in total lymphocyte count (Heterogeneicity test: $p < 0.05$; random effect model: Difference in means = -2.246 with 95% CI: -4.076, - 0.416 and $p < 0.05$).

divided the analysed studies in two groups: those with a methodological quality score of ≥8 and those with a methodological score of <8. Trials with a higher methodological score demonstrated a significant association between Gln-enriched TPN and reduced length of hospital stay (1.506 days less; 95% CI 0.151-2.861, p=0.030), better cumulative N balance (2.038gr; 95% CI 0.485-3.592 p=0.011) and a trend toward increased total lymphocyte counts (3.292/ μL; 95% CI -0.964 to 7.548 p=0.127). Trials with lower methodological score also demonstrated reduced length of hospital stay (0.864 days less; 95% CI 0.272-1.457, p=0.005) and better cumulative N balance (3.607gr; 95% CI 1.312-5.903, p=0.003) in the patients with the glutamine-supplemented regimen. They also demonstrated a trend towards reduced rates of infections (RR=0.245; 95% CI 0.045-1.347, p=0.106). Both subgroups presented significant associations between Gln-enriched TPN, better cumulative N balance and reduced length of hospital stay. All other associations were found to be non-significant.

The dose-dependent effect of glutamine supplementation was also evaluated. High dose glutamine (≥40g/kg/BW/day)

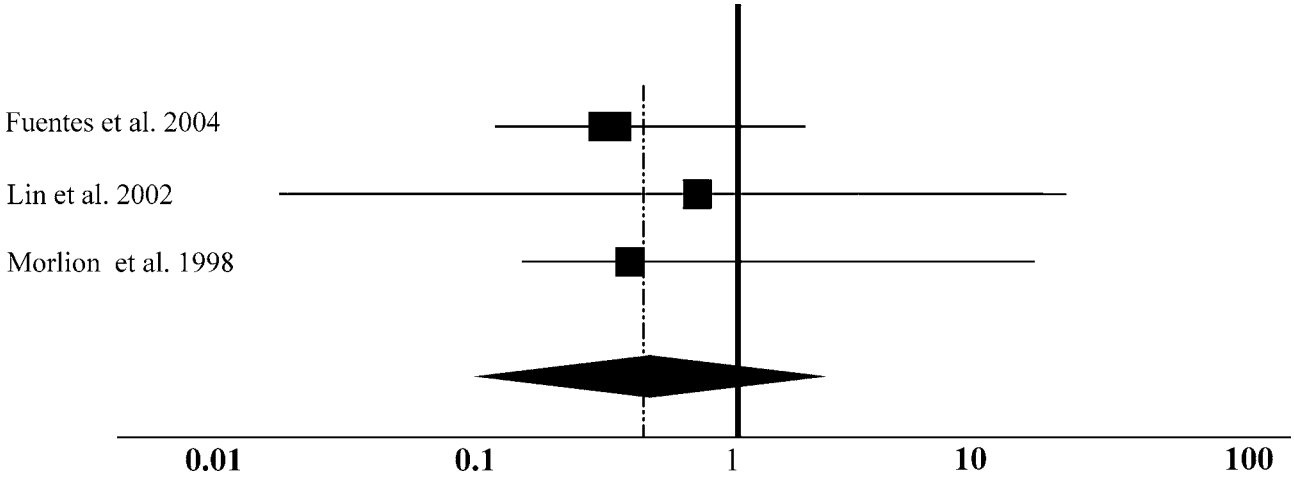

FIGURE 5. Meta-analysis of randomised trials testing the effect of parenteral glutamine in mortality, Results are not statistically significant (RR = 0.723 with 95% CI: 0.174, 3.012 and p >0.05).

was associated with a reduction in length of hospital stay (0.716 days less; 95% CI 0.366-1.067, p<0.05) and increased cumulative N balance (1.106gr; 95% CI 0.355-1.857, p=0.004). Lower dose glutamine (<40g/kg/BW/day) was associated with better cumulative N balance (3.791 gr; 95% CI 2.354-5.227 p <0.05), a trend towards a reduction in length of hospital stay (3.277 days less; 95% CI -0.957 to 7.511 p=0.127), and a non-significant increased total lymphocyte count (3.038/μL; 95% CI -1.768 to 7.845 p=0.211). Both subgroups showed a significantly better cumulative N balance with glutamine. A strong association between Gln-enriched TPN and reduced hospital stay was found only in the high-dose glutamine group.

Subgroup comparisons with respect to any other outcomes were not possible due to insufficient number of patients and trials.

DISCUSSION

The importance of the metabolic role of glutamine has been demonstrated in several laboratory and clinical studies [32-34]. In critical illness, the increased demand in glutamine for protein synthesis depletes the amino acid pool, thereby reducing glutamine levels in plasma and intracellular muscle concentration [35]. The stress response to surgery has been shown to increase the release of glutamine from the muscle pool and to activate de novo synthesis of glutamine, which causes insufficient levels of glutamine in tissue and plasma [36]. It was found that critically ill patients with low plasma glutamine levels had a higher mortality rate than those with normal glutamine levels (even when adjusted for Acute Physiology and Chronic Health Evaluation II score) [23]. Consequently, in surgical patients, the administration of Gln-enriched TPN might have beneficial effects [37], by correcting the deficit in conventional amino acid solutions.

There are several randomized clinical trials evaluating the effect of Gln-enriched TPN in seriously ill patients. Individually the majority of theses studies are underpowered to evaluate an effect on clinically important end points. In the present meta-analysis the role of Gln-enriched TPN was specifically evaluated in the seriously ill surgical patients. An attempt was made to combine results of similar studies in order to determine a more precise estimate of treatment effect.

In the aggregated estimates, there was no adverse effect associated with Gln-enriched TPN. Overall, Gln-enriched TPN regimens were associated with a strong trend toward a reduction in infections, a shorter hospital stay, a better N balance, and an increased total lymphocyte count. There was no significant association with mortality.

Because of the small number of studies and the few clinical end points examined, the findings should be considered as hypothesis-generating rather than solid indications for the routine use of glutamine supplemented TPN. Only three studies examined mortality, and only four infectious complications rate.

Recent multi-centre trials and meta-analysis on systemic glutamine delivery in a number of seriously ill patients support these results. In a French multi-centre randomized control trial, one hundred and fourteen ICU patients demonstrated a significant reduction in frequency of infections, and pneumonias [38]. Glyceamic control was improved with significantly less hyperglycaemia (20 vs 30 p<0.05). Another study, in Germany, including 144 ICU patients showed that in those patients receiving Gln-enriched TPN for more than nine days, the survival rate at six months was significantly better (22/33 vs

13/35 p<0.05) [39]. A recent meta-analysis strongly supports the hypothesis that parenteral glutamine has an advantageous effect on reducing mortality (RR 0.71; 95% CI 0.51-0.99) [23]. The meta-analysis also found that glutamine via the enteral route failed to show any effect on mortality (RR 1.08; 95% CI 0.57-2.01), but glutamine supplementation overall is associated with lower rates of infection (RR 0.81; 95% CI 0.64-1.0) and shorter hospital stay (in the post-operative studies) (-2.6 days; 95% CI -4.5 to -0.7 days). Current recommendations are that parenteral nutrition when used in ICU patients should contain glutamine[40].

We hypothesised that the treatment effect of Gln-enriched TPN may vary on several factors such as the patient population, dose, primary disease and severity of the disease, TPN regimen, nutritional status, age of the patients and the methodological quality of the individual studies. However, the small size and the heterogeneity of the analysed studies do not permit firm conclusions.

The impact of various factors on treatment outcome with Gln-enriched TPN has to be considered in surgical patients. The optimal dose of Gln-enriched TPN in surgical patients deserves further investigation. Human studies suggest that glutamine supplementation up to 0.5gr/kg/day is safe. A meta-analysis by Novak et al on the use of to glutamine in patients with serious illness suggests that a dose higher than 0.2gr/kg/day has greater effect than a lower dose [23]. According to Jackson, the demands in glutamine are high since, in ICU patients, administration of 28 g/day produced only modest correction of plasma levels [41]. Dosing studies show that between 20-40g intravenous glutamine per day are necessary to restore plasma glutamine levels to normal [42].

Other issues than dosage, such as the length of Gln-enriched TPN administration and the disease severity, need further investigation.

In a randomized controlled trial, ICU patients receiving Gln-enriched TPN were divided into two subgroups according to length of nutritional support. It is noteworthy that patients receiving short-term (<5 days) total parenteral nutrition demonstrated no benefit with the addition of glutamine. In contrast, patients receiving Gln-enriched TPN for 5 or more days had fewer catheter infections and a decreased 6-months mortality rate (P<0.05). Outcome analysis showed that, among the various possible outcome determinants, only glutamine was associated with clinical benefit [43].

Furthermore, Lin et al explored the relationship of disease severity and Gln-enriched TPN. They found that Gln-enriched TPN had a beneficial effect on decreasing systemic IL-6 production after surgery in patients with less severe illness at admission, and that low plasma IL-6 may improve N balance in patients undergoing abdominal surgery [28].

CONCLUSIONS

On the basis of the findings of our systematic review, we conclude that there exists strong evidence for a beneficial effect of Gln-enriched TPN in surgical patients in terms of length of hospital stay, infections rate, total lymphocyte count and cumulative N balance. The benefit on mortality was not statistically significant. We consider the results of our meta-analysis as hypothesis-generating and not as definite proof. Nevertheless, since there is no evidence of harm, further clinical trials are warranted in order to establish a definitive relationship between Gln-enriched TPN and its benefits. The specific indications for Gln-enriched TPN and the appropriate protocol of administration need to be defined.

REFERENCES

1. Souba WW. Glutamine: a key substrate for the splanchnic bed. *Annu Rev Nutr* 1991; 11:285-308.
2. Heys SD, Gough DB, Khan L, Eremin O. Nutritional pharmacology and malignant disease: a therapeutic modality in patients with cancer? *Br J Surg* 1996; 83:608-619.
3. Heys S, Ashkanani F. Glutamine (leading article). *Br J Surg* 1999; 86:289-290.
4. Abcouwer SF. Effects of Glutamine on Immune Cells (editorial). *Nutrition* 2000; 16:67-77.
5. Hall JC, Heel K, McCauley R. Glutamine (review). *Br J Surg* 1996; 83:305-312.
6. Kapadia CR, Colpoys MF, Jiang Z-M, Johnson DJ *et al.* Maintenance of skeletal muscle intracellular glutamine during standard surgical trauma. *JPEN J Parenter Enteral Nutr* 1985; 9: 583-9.
7. Lacey JM, Wilmore DW. Is glutamine a conditionally essential amino acid? *Nutr Rev* 1990; 48:297-309.
8. Furst P. Old and new substrates in clinical nutrition. *J Nutr* 1998; 128:789-796.
9. Furst P. New parenteral substrates in clinical nutrition. Part I. Introduction. New substrates in protein nutrition. *Eur J Clin Nutr* 1994; 48:607-616.
10. Greig JE, Keast D, Garcia-Webb P, Crawford P. Inter-relationships between glutamine and other biochemical and immunological changes after major vascular surgery. *Br J Biomed Sci* 1996; 53:116-121.
11. Stehle P, Mertes N, Puchstein C, Zander J, *et al.* Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. *Lancet* 1989; 1: 231-233.
12. Finn PJ, Plank LD, Clark MA, Connolly AB, *et al.* Progressive cellular dehydration and proteolysis in critically-ill patients. *Lancet* 1996; 347:654-656.
13. Wilmore DW. Catabolic illness: strategies for enhancing recov-

ery. *N Engl J Med* 1991; 325:695-702.
14. Ziegler TR, Young LS, Benfell K, Scheltinga M, *et al.* Clinical and Metabolic Efficacy of Glutamine-supplemented Parenteral Nutrition after Bone Marrow Transplantation. *Ann Intern Med* 1992; 116:821-828.
15. McAnena OJ, Moore FA, Moore EE, Jones TN, *et al.* Selective uptake of glutamine in the gastrointestinal tract: confirmation in a human study. *Br J Surg* 1991; 78:480-482.
16. Souba WW, Wilmore DW. Postoperative alternation of arteriovenous exchange of amino acids across the gastrointestinal tract. *Surgery* 1983; 94:342-350.
17. Rohde T, MacLean DA, Klarlund PB. Glutamine, lymphocyte proliferation and cytokine production. *Scand J Immunol* 1996; 44:648-650.
18. Heberer M, Babst R, Juretic A, Gross T, *et al.* Role of glutamine in the immune response in critical illness. *Nutrition* 1996; 12:S71-S72.
19. MacLennan PA, Smith K, Weryk B, Watt PW, *et al.* Inhibition of protein breakdown by glutamine in perfused rat skeletal muscle. *FEBS Lett* 1988; 237:133-136.
20. Hornsby-Lewis L, Shike M, Brown P, Klang M, *et al.* L-Glutamine supplementation in home total parenteral nutrition patients: stability, safety, and effects on intestinal absorption. *JPEN J Parenter Enteral Nutr* 1994; 18:268-273.
21. Heyland DK, MacDonald S, Keefe L, Drover JW, *et al.* Total parenteral nutrition in the critically ill patient: A meta-analysis. *JAMA* 1998; 280:2013-2019.
22. Heyland DK, Novak F, Drover JW, Jain M, *et al.* Should immunonutrition become routine in critically ill patients: A systematic review of the evidence. *JAMA* 2001; 286:944-953.
23. Novak F, Heyland DK, Avenell A, Drover JW, *et al.* Glutamine supplementation in serious illness: A systematic review of the evidence. *Crit Care Med* 2002; 30:2022-2029.
24. Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, *et al.* Total parenteral nutrition with glutamine dipeptide after major abdominal surgery. *Annals of Surg* 1998; 227:302-308.
25. Jiang ZM, Cao JD, Zhu XG, Zhao WX, *et al.* The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of 120 patients. *JPEN J Parenter Enteral Nutr* 1999; 23:62S–66S.
26. Mertes N, Schulzki C, Goeters C, Winde G, *et al.* Cost containment through L-alanyl-L-glutamine supplemented total parenteral nutrition after major abdominal surgery: A prospective randomized double-blind controlled study. *Clin Nutr* 2000; 19: 395-401.
27. Neri A, Mariani F, Piccolomini A, Testa M, *et al.* Glutamine-Supplemented total parenteral nutrition in major abdominal surgery. *Nutrition* 2001; 17:968-969.
28. Lin MT, Kung SP, Yeh SL, Lin C, *et al.* The effect of glutamine-supplemented total parenteral nutrition on nitrogen economy depends on severity of diseases in surgical patients. *Clin Nutr* 2002; 21:213-218.
29. Fuentes-Orozcoa C, Anaya-Pradoa R, Gonzalez-Ojeda A, Arenas-Marquez H, *et al.* L-Alanyl-L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. *Clin Nutr* 2004; 23:13–21.
30. Guo-Xiang Y, Xin-Bo X, Zhu-Ming J, Nai-Fa Y, *et al.* Effects of perioperative parenteral glutaminedipeptide supplementation on plasma endotoxin level, plasma endotoxin inactivation capacity and clinical outcome. *Clin Nutr* 2005; 24:510–515.
31. Lin MT, Kung SP, Yeh SL, Liaw KY, *et al.* Glutamine-supplemented total parenteral nutrition attenuates plasma Interleukin-6 in surgical patients with lower disease severity. *World J Gastroenterol* 2005; 11:6197-6201.
32. Furukawa S, Saito H, Fukatsu K, Hashiguchi Y, *et al.* Glutamine-enchanced bacterial killing by neutrophils from postoperative patients. *Nutrition* 1997; 13:863-869.
33. van der Hulst, Rene RWJ, van Kreel, Bernard K, *et al.* Glutamine and the preservation of gut integrity. *Lancet* 1993; 341: 1363-1365.
34. O'Riordain MG, Fearon KCH, Ross JA, Rogers P, *et al.* Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. *Ann Surg* 1994; 220:212-221.
35. Souba WW, Austgen TR. Interorgan glutamine flow following surgry and infection. *JPEN J Parenter Enteral Nutr* 1990; 14: 90S-93S.
36. Kuhn KS, Shuhmann K, Stehle P, Darmaun D, *et al.* Determination of glutamine in muscle protein facilitates accurate assessment of proteolysis and de novo synthesis-derived exogenous glutamine production. *Am J Clin Nutr* 1999; 70:484-489.
37. Furst P, Pogan K, Stehle P. Glutamine dipeptides in clinical nutrition. *Nutrition* 1997; 13:731-737.
38. Dechelotte P, Bleichner G, Hasselmann M, Dassonville J, *et al.* Improved clinical outcome in ICU patients receiving alanyl-glutamine (Depeptiven) supplemented total parenteral nutrition (TPN). A french double-blind multicenter study. *Clin Nutr* 2002; 21:1a.
39. Goeters C, Wenn A, Mertes N, Wempe C, *et al.* Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002; 30:2032-2037.
40. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, and the Canadian Critical Care Clinical Practice Guidelines Committee. Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients. *JPEN J Parenter Enteral Nutr* 2003; 27: 355-373.
41. Jackson NC, Carroll PV, Russell-Jones DL, Sφnksen PH, *et al.* Effects of glutamine supplementation, GH, and IGF-1 on glutamine metabolism in critically ill patients. *Am J Physiol Endocrinol Metab* 2000; 278:E226-E233.
42. Tjðder I, Rooyackers O, Forsberg A-M, Vesali RF, *et al.* Effects on skeletal muscle intravenous glutamine supplementation to ICU patients. *Intensive Care Med* 2004; 30:266-275.
43. Griffiths R, Jones C, Palmer T. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997; 13:295-302.