

Original Article

Efficacy of glutamine-enriched enteral feeding formulae in critically ill patients: a systematic review and meta-analysis of randomized controlled trials

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Critically ill patients usually suffer from catabolic stress that could lead to malnutrition and nutritional support therefore is essential to maintain lean body mass, improve metabolic and immune response and decrease rate of mortality and comorbidity in these patients. This meta-analysis was aimed to evaluate effect of glutamine-enriched enteral nutrition in critically ill patients. In order to obtain randomized clinical trial studies (RCTs), international databases including MEDLINE and Google scholar and also electronic resources in Iran, including IRAN MEDEX, IRAN DOC, SID, Magiran were systematically searched without language and publication restriction before December 2014. The final included number of studies for meta-analysis was 10. The methodological quality of eligible studies was assessed by four investigators using the Jadad 5-point scale, a scale containing three items describing randomization, blinding and fate of participants. We analyzed data from the included studies using STATA version 12.0, and calculated a pooled odds ratio for dichotomous data and mean differences for continuous data with 95% confidence intervals (CIs). There was no significant difference in mortality in elevated pooled odds ratios (p -value=0.070). A funnel plot was drawn for evaluation of publication bias, but none was found. The fixed effect model shows significant reduction in gut permeability in who received enteral feeding enriched with glutamine (-0.84, 95% CI=-1.25 to -0.44), moreover the funnel plot did not show publication bias. Based on the available data, our meta-analysis showed that enteral glutamine (Gln) supplementation increased mortality rate, though non-significantly, but decreased gut permeability significantly.

Key Words: glutamine, enteral, immune-enhancing formula, critically ill patients, systematic review

INTRODUCTION

Critically ill patients usually suffer from catabolic stress that could lead to malnutrition.^{1,2} In these patients the risk of sepsis, infection, prolonged hospitalization, rate of mortality and intestinal permeability are high due to oxidative stress stimulation and immune system suppression.^{3,4} Nutritional support therefore is essential to maintain lean body mass, improve metabolic and immune response and decrease rate of mortality and comorbidity in these patients.^{1,2} Previous clinic studies have shown that parenteral and enteral nutrition are effective after surgery, trauma, infection and injuries,⁵ however, enteral nutrition is more beneficial than parenteral nutrition for improving intestinal endothelium function.^{3,6} Enteral nutrition plays a role in integrity and function of the gut tract via maintenance of mucosal mass and villi height, proliferation of enterocytes and production of gastrointestinal (GI) enzymes and hormones.¹

Studies have indicated that immune-enhancing formula decrease rate of mortality and infection. So, critically ill

patients benefit from immune-enhancing nutrients, it had suggested that glutamine (Gln), an immune nutrient,⁵ is a dispensable amino acid that plays a pivotal role in the synthesis of neucleotides and supplying fuel for enterocytes. It contributes in musin production and integrity of GI membrane via synthesis of N-acethyl glucose amine and N-acethyl galactose amine.^{5,7} In stress and critically illness conditions consumption of Gln is higher than de novo synthesis and Gln plays a role as an indispensable

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amino acid.¹ Animal studies have reported that Gln supplementation reduces risk of bacterial translocation, atrophy of intestinal mucosa, intestinal permeability and clinical infection,⁸ However, human clinical trials are inconsistent.^{1,3,5,8} Therefore, conduction a meta-analysis in order to clarification of glutamine effectiveness is required. This meta-analysis was aimed to evaluate effect of Gln-enriched enteral nutrition in critically ill patients.

METHODS

Literature search strategy

In order to obtain randomized clinical trial studies (RCTs), international databases including MEDLINE and Google scholar and also electronic resources in Iran, including IRAN MEDEX, IRAN DOC, SID, Magiran were systematically searched without language and publication restriction before December 2014. To achieve the maximum sensitivity of the search strategies and detect all RCTs using enteral feeding supplemented with glutamine in critically ill patients, we appropriately used keywords including: (enteral formula OR enteral nutrition OR enteral feeding) AND glutamine AND (critically ill OR intensive care unit OR severe illness). We also reviewed reference list of selected articles, conference proceedings to identify any articles and data not found using online methods.

Inclusion and exclusion criteria

Studies were eligible for inclusion in the present analysis if they met the following criteria: 1) Study design: Only RCTs with matched control group; 2) Patients characteristics: Only adults who were admitted to ICU or who had APACHE scores equal or above 10; 3) Intervention: Enteral formula supplemented with glutamine; and 4) Outcomes: Intestinal permeability, length of hospital stay, sepsis or infection rate, and mortality rate.

Studies were excluded for the following reason: 1) Studies on children and neonate; 2) Animal and laboratory studies; and 3) Studies with designs other than RCT.

Studies selection

Four investigators independently evaluated all abstracts of relevant studies. If abstracts potentially met the inclusion criteria, full texts of these were requested. Any disa-

greements were resolved through consensus.

Data extraction and quality assessment

Full texts of selected articles were obtained for quality assessment and the following data were extracted by four investigators: first author, year of publication, country, journal name, glutamine dosage, baseline characteristics and previously mentioned outcomes.

The methodological quality of eligible studies was assessed by four investigators using the Jadad 5-point scale, a scale containing three items describing randomization, blinding and fate of participants; we assigned 1 point if randomization was mentioned, 1 additional point if the method of randomization was appropriate and also we deducted 1 point if the method of randomization was inappropriate. Regarding blinding, we assigned 1 point if blinding was mentioned, 1 additional point if the method of blinding was appropriate and again we deducted 1 point if the method of blinding was inappropriate. Finally, we assigned 1 point if the fate of all participants in the trial was known, and if there were no data, the reason should have been stated. The quality scale ranged from 0 to 5. If Jadad score was ≥ 3 points, the article was considered as a high quality research and if Jadad score was ≤ 2 points, it was known as a low quality article.⁹

Statistics

We analyzed data from the included studies using STATA version 12.0 (STATA Corporation, College Station, TX, USA), and calculated a pooled odds ratio for dichotomous data and mean differences for continuous data with 95% confidence intervals (CIs).

To assess heterogeneity across the studies, a statistical test for heterogeneity was performed based on the statistics.¹⁰ If the studies were shown to be homogeneous with $p > 0.05$ for the Q test, the summary of OR was calculated by a fixed-effects model (the Mantel-Haenszel method) when between-study heterogeneity was absent.¹¹ Otherwise, a random-effects model (the DerSimonian and Laird method) was used,¹² publication bias was assessed using funnel plot techniques.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to report the research protocol, outcomes and other

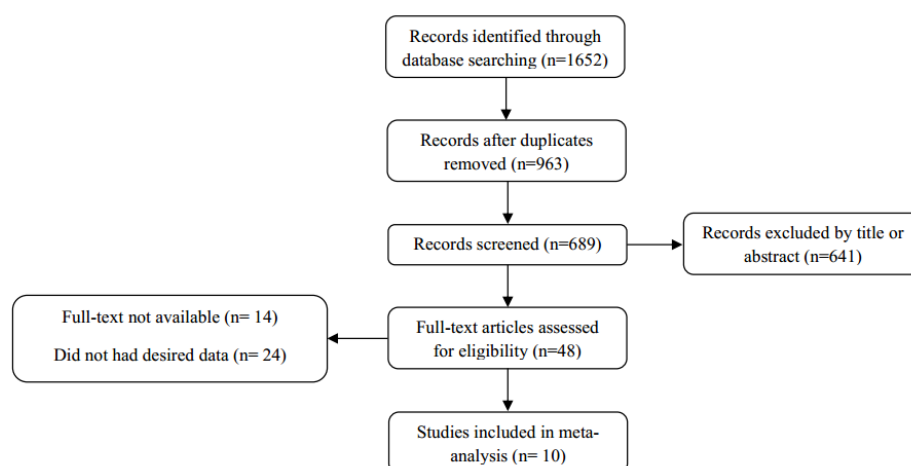


Figure 1. Flowchart illustrating the details of the search and study selection process.

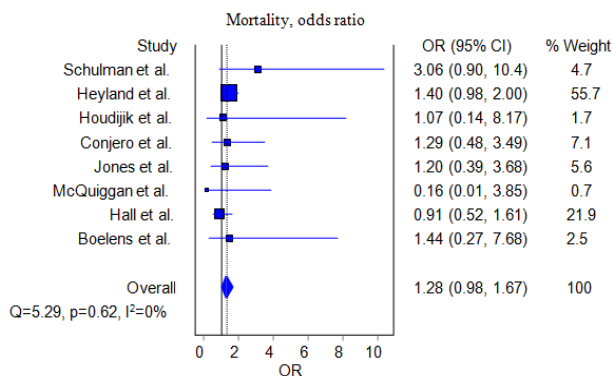


Figure 2. Odds ratios of mortality in patient with glutamine-enriched enteral feeding relative to control group.

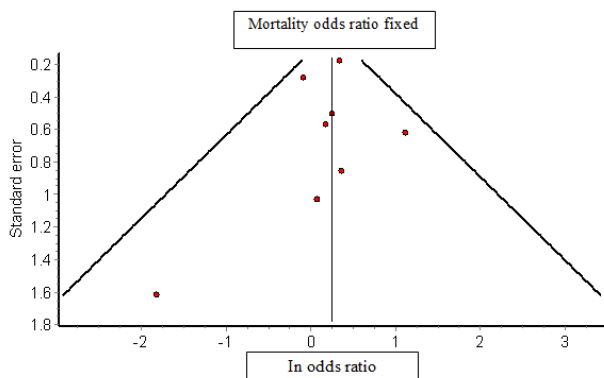


Figure 3. Funnel plot of odds ratio of mortality in patient with glutamine-enriched enteral feeding relative to control group.

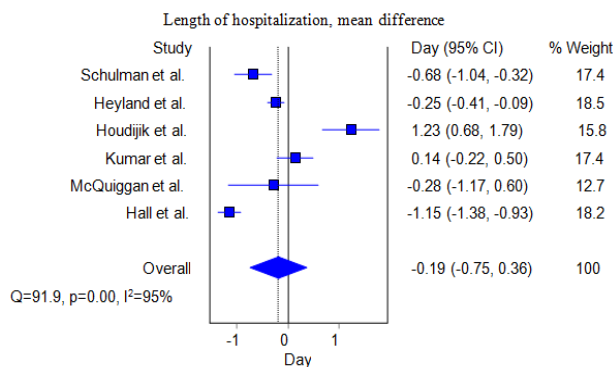


Figure 4. Mean difference of length of hospitalization in patient with glutamine-enriched enteral feeding relative to control group.

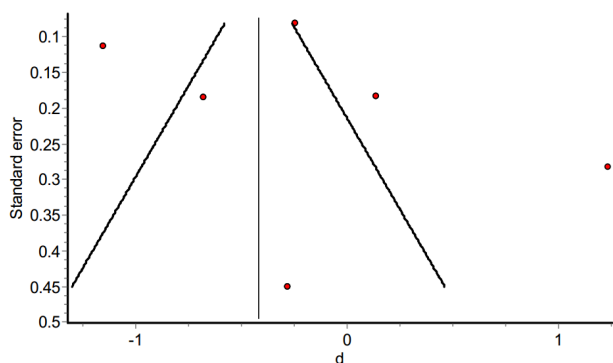


Figure 5. Funnel plot of mean difference of length of hospitalization in patient with glutamine-enriched enteral feeding relative to control group.

relevant items in this systematic review.¹³

RESULTS

Included studies

As shown in Figure 1, according to our inclusion criteria, in total 1652 potentially relevant articles were found. After deleting duplicate and irrelevant articles, post-reading titles and their abstracts, 48 articles remained for assessing eligibility. Of the 48 articles, 38 were excluded for following reasons: 14 articles did not have full-texts available, and the rest lacked relevant data. Finally, 10 RCTs ultimately included in our current systematic review.^{2-4,8,14-19} General information about the included articles is listed in Table 1. According to Jaded scores, nine of the trials were high quality and only one of these was low quality.

Mortality

A total of 10 eligible studies, 8 RCTs presented data of mortality. For each study, the odds ratio of mortality in patients with glutamine-enriched enteral feeding relative to control group was computed (Figure 2). Before carrying out the analysis and pooling the results, a heterogeneity hypothesis was tested using the chi square test, and found no significant heterogeneity between studies (p -value=0.62); hence we pooled estimation of the studies without adjustment for heterogeneity, using the fixed effect model. There was no significant difference in elevated pooled odds ratios (p -value=0.070). A funnel plot was drawn for evaluation of publication bias, but none was found (Figure 3).

Length of hospitalization

Six studies were used for analyzing data about length of hospitalization. The forest plot was used to illustrate mean hospital stay between the two groups in each study (Figure 4). Because of the heterogeneity between studies, the random effect model was used to combine the results of studies ($Q=9.87$, $p<0.001$, $I^2=95%$). The results of the meta-analysis show no significant difference in mean hospital stay between the two treatment groups (-0.19, 95% CI=-0.75-0.36). A funnel plot showed evidence of publication bias (Figure 5). This can be due to the low sample size of studies and probably ignore some of the studies and also estimate the mean and variance.

ICU stay length

In 7 studies comprising 1267 patients, the author reported the ICU stay length. There was no significant difference was observed in any of the studies (Figure 6). A random effect model of studies found that no significant difference between two groups of patients about length of ICU stays (-0.03, 95% CI=-0.53-0.47). The results indicated heterogeneity between studies ($I^2=93%$, $p<0.001$). A funnel plot also showed evidence of publication bias (Figure 7).

Gut permeability

Researchers in three studies reported gut permeability in an aggregate of 107 patients. Significant lower gut permeability was seen in patients who received enteral feeding enriched with glutamine compared to controls in the

Table 1. General information of included articles

Study	Year	Population	Age	Formula	Gln	Control	Randomization Method	Length of supplementation	Jaded score	Glutamine dosage
Boelens et al ¹⁸	2004	Trauma	18-65	Alitra Q	17	17	Randomly allocated	5 days	4	30.5 g/100 g protein
Hall et al ¹⁶	2003	Mixed ICU	Adults	Isocal + Gln	179	183	Randomly allocated	10 days	5	20 g/L
McQuiggan et al ¹⁴	2008	Trauma	Adults	Glutasolve	10	10	Randomly allocated	10 days	3	0.5 g/kg/d
Heyland et al ³	2013	Mixed ICU with organ failure	Adults	Dipeptiven	301	300	Randomly allocated	28 days	5	30 g/d
Schulman et al ¹⁹	2005	Surgical and trauma	Adults	Replete + Gln	59	64	Sequential rotating assignment	13 days	3	0.6 g/kg/d (20-40 g/day)
Houdijk et al ¹⁵	1998	Trauma	18-65	Alitra Q	29	31	Double-blind, randomized, prospective	15 days	3	30.5 g/100 g protein
Velasco et al ⁸	2001	Surgical	19-74	ADN Nutricomp	7	8	Randomly allocated	8 days	1	0.15 g/kg/d
Conjero et al ¹⁷	2002	SIRS	Adults	Juven	43	33	Computer generation randomization	10 days	4	30.5 g/L
Kumar et al ⁴	2007	Peritonitis/ abdominal trauma	18-60	Hospital- made + Gln	63	57	Computer generation randomization	5 days	3	15 g/d
Jones et al ²	1999	Mixed ICU	Adults	Protina MP + Gln	26	24	Block randomization by envelop	5 days	4	20 g/d

Table 2. Main results of RCTs

Study	Gln	Control	Mortality (n)		Length of hospitalization (mean±SD)		Length of ICU stay (mean±SD)		Gut permeability (mean±SD)		Dependence on ventilator (mean±SD)	
			Gln	Control	Gln	Control	Gln	Control	Gln	Control	Gln	Control
Boelens et al ¹⁸	17	17	4/17	3/17	NR	NR	18.8±12.4	14.2±8.3	NR	NR	NR	NR
Hall et al ¹⁶	179	183	27/179	30/184	25±4.33	30±4.33	11±2	13±1.83	NR	NR	NR	NR
McQuiggan et al ¹⁴	10	10	0/10	2/10	32±13.6	39.3±33.6	14.8±6.7	10.4±6.2	NR	NR	NR	NR
Heyland et al ³	301	300	97/301	76/300	16±4.33	17.1±4.6	8.4±1.93	8.9±1.7	NR	NR	NR	NR
Schulman et al ¹⁹	59	64	10/59	4/64	24.1±2.5	25.6±1.9	16.7±1.9	15.2±2.1	NR	NR	10.9±1.3	13.2±1.3
Houdijk et al ¹⁵	29	31	2/29	2/31	32±3	27.4±4.3	NR	NR	NR	NR	7.6±3.37	9±3.13
Velasco et al ⁸	7	8	NR	NR	NR	NR	NR	NR	0.043±0.011	0.075±0.018	NR	NR
Conjero et al ¹⁷	43	33	14/43	9/33	NR	NR	14±14.8	15±24.5	0.109±0.057	0.163±0.087	14±5	14±6
Kumar et al ⁴	63	57	NR	NR	11±6.75	9±20	NR	NR	NR	NR	NR	NR
Jones et al ²	26	24	12/26	10/24	NR	NR	11±12.5	16.5±15.3	NR	NR	NR	NR
Hernandez et al ⁸	8	8	NR	NR	NR	NR	NR	NR	0.065±0.023	0.075±0.018	NR	NR

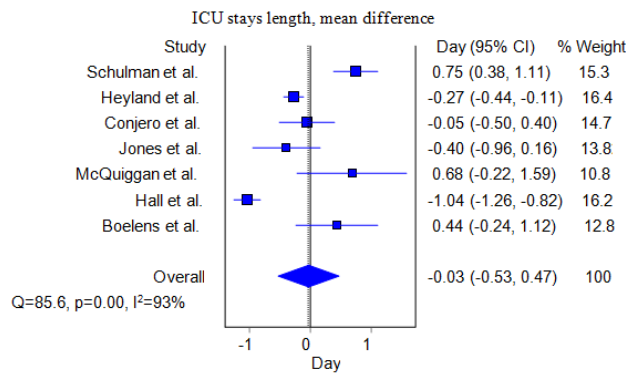


Figure 6. Mean difference of ICU stay length in patient with glutamine-enriched enteral feeding relative to control group.

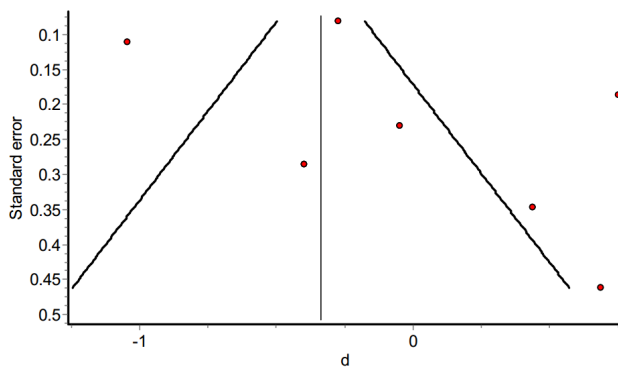


Figure 7. Funnel plot of mean difference of ICU stay length in patient with glutamine-enriched enteral feeding relative to control group.

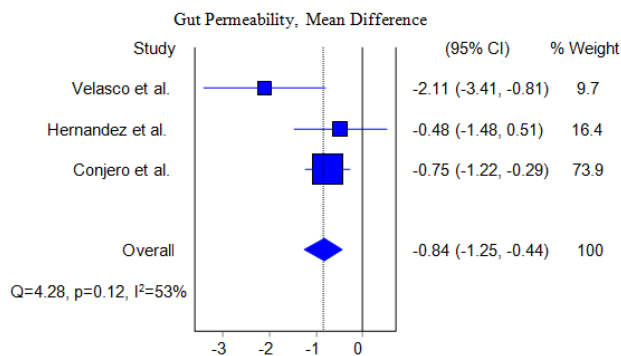


Figure 8. Mean difference of gut permeability in patient with glutamine-enriched enteral feeding relative to control group.

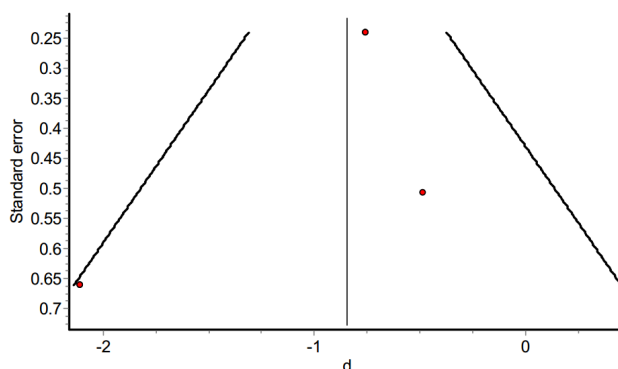


Figure 9. Funnel plot of mean difference of gut permeability in patient with glutamine-enriched enteral feeding relative to control group.

Velasco et al.⁸ study contrary to two other studies. Overall, the fix effect model shows significant reduction in gut permeability in who received enteral feeding enriched with glutamine (-0.84, 95% CI=-1.25 to -0.44) (Figure 8). We evaluated a funnel plot for evidence of publication bias. There was no significant heterogeneity across studies (I²=53%, p-value=0.12). It was symmetrical, indicating no publication bias (Figure 9).

Dependence on ventilator

In three studies comprising a total of 259 patients, the investigators reported data about ventilator dependency. Mean days of dependence on ventilator between two patients groups shows no significant difference in any of the studies; overall, the random effect model showed no significant difference between the groups of patients (-0.74, 95% CI=-1.84-0.37) (Figure 10). The heterogeneity between studies was significant (I²=94%, p<0.001). Publication bias was seen on the funnel plot (Figure 11).

DISCUSSION

Results of the present meta-analysis show that glutamine-enriched enteral feeding significantly decreased gut permeability in critically ill patients and slightly increased mortality rate in these patients, although the latter was not significant. Moreover, it had no significant effect on length of hospitalization, ICU stay length and dependence of ventilator in these patients.

Glutamine is involved in nitrogen transport, nucleotide and arginine synthesis, intestinal mucosal integrity and is also the preferred fuel of enterocytes.²⁰ Studies have suggested that Gln may be a conditionally essential amino acid in critically ill patients due to decrease in the plasma Gln levels of these patients,²¹ decrease of this amino acid in critical illness is associated with immune dysfunction;²⁰ in sepsis and shock conditions, Gln acts as a stress signal in muscles.²²

Results of our study mentioned that a non-significant increase occurred in mortality rate in critically ill patients, similar to which, some RCTs^{3,18,19} demonstrated significant increase in mortality rate of critically ill patients. The possible mechanism of by which glutamine supplementation can decrease mortality rate was discovered. The bowel metabolizes less glutamine during sepsis, a response that may be related to the decrease in the amount of circulating insulin-like growth factor-1 (IGF-1) which is characteristic of sepsis; however, in the absence of glutamine supplementation, protein anabolic effects of growth hormone, which occur via IGF-1, have been associated with an increased mortality rate.²³ A possible mechanism for this, is profound glutamine depletion as a result of the mobilization of glutamine from protein stores; hence, there is interest in combining glutamine supplementation with growth hormone or IGF-1 therapy.²⁴ On the other hand, an experimental Study have indicated that Gln by stimulating expression of heat shock proteins (HSPs) lead to reduction in mortality among critically ill patients.²⁰ Despite the results of these studies, other studies^{25,26} have shown Gln supplementation had no effect on mortality rate, and it even caused increase in mortality rate, However, the possible reason for which was unclear.

In the present meta-analysis, gut permeability signify-

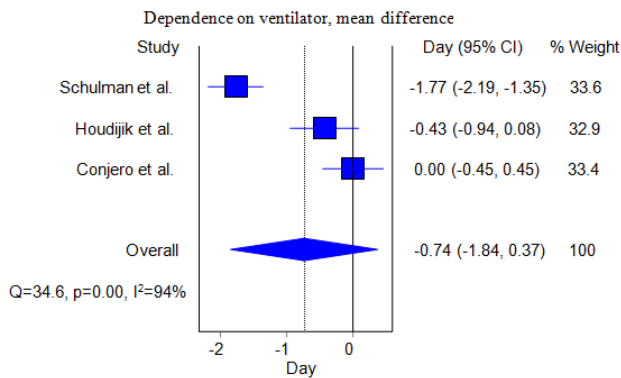


Figure 10. Mean difference of dependence on ventilator in patient with glutamine-enriched enteral feeding relative to control group.

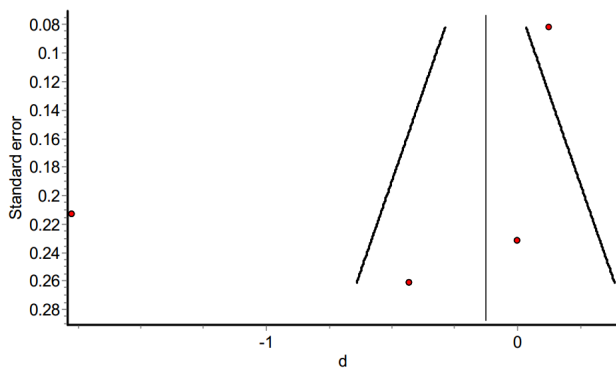


Figure 11. Funnel plot of mean difference of dependence on ventilator in patient with glutamine-enriched enteral feeding relative to control group.

cantly decreased in critically ill patients who received Gln-enriched enteral feeding in compared with control. Gln is an important substrate for enterocytes²⁷ and supplementation of total parenteral nutrition (TPN) with glutamine-containing dipeptides has been shown to prevent mucosal atrophy and decreased permeability associated with long-term TPN.^{28,29} Gut permeability is a risk factor for infection and inflammation among critically ill patients.^{4,20} Studies have documented that lack of Gln contributes to impaired intestinal barrier and immune functions versus Gln supplementation, which enhances GI integrity and intestinal flora and suppresses bacterial translocation in GI, subsequently promoting functions of intestinal barrier.^{17,30} Consistent with our results about gut permeability, some studies showed that glutamine supplementation can reduce gut permeability in critically ill patients.^{8,17,31} Enteral feeding in critically ill patients is the preferred route of nutrition, and glutamine and other substrates seem to preserve intestinal mucosal integrity and lymphoid tissue in the gastrointestinal tract, thus avoiding increased intestinal permeability and bacterial translocation,^{32,33} bacterial translocation could amplify the inflammatory response seen in patients with SIRS and facilitate the appearance of bacteremia and secondary infections by enteric microorganisms.³⁴

However our findings indicated beneficial effects of Gln-enriched feeding on gut permeability in critically ill patients, the American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Parenteral

and Enteral Nutrition (ESPEN) do not advise enteral Gln supplementation in critically ill patients due to lack of conclusive results.³⁰ Future investigations to obtain conclusive results are recommended.

Chen et al in a meta-analysis on 17 RCTs have reported that Gln supplementation had no effect on mortality and length of hospitalization.²⁵ As mentioned earlier in present meta-analysis, Gln supplementation had no any effect on length of hospitalization or length of ICU stay. In a review conducted by Tao et al²⁶ on 53 RCTs, Gln supplementation decreased rate of infection (RR: 0.79, 95% CI: 0.71 to 0.78, $p < 0.001$) and length of hospitalization (MD: -3.46 days, 95% CI: -4.61 to -2.32, $p < 0.001$) in critically ill patients, compared with controls. No significant differences were found in mortality rate of critically ill patients and controls; moreover, both the above studies, RCTs that used Gln supplementation either parenteral or enteral were included in analysis; hence effects of enteral Gln on the outcomes of critically ill patients were unclear. Studies have indicated that parenteral administration of Gln can increase plasma Gln level to normal level, contrary to enteral Gln administration, which elevates plasma Gln levels slightly,^{22,35} indicating that the beneficial effects of Gln supplementation observed in this study, may be related mostly to parenteral Gln supplementation.

To the best of our knowledge, this systematic analysis is the first systematic review on the enteral use of Gln supplementation in critically ill patients. One of the strengths of our meta-analysis is that in this study we included RCTs which used just the enteral route of Gln supplementation. Another positive point of present study is that we had defined rigorous inclusion criteria such as excluding burned, malignant and head traumatic patients and incorporated original studies that enrolled large samples of patients in a randomized controlled design.

Some limitations of our analysis that need to be mentioned are; first, our meta-analyses could only take into account sources written in English. Second, some published trials only reported the median and range, using formulas; we estimated the mean and variance of the length of hospitalization and ICU stay length from the median, range and the size of the trial. Third, there was heterogeneity in kinds of infection reported in patients and because of this the sample size was too small to have substantial power to explore the real association in any subgroup of infections.

Conclusion

In summary, based on the available data, our meta-analysis showed that enteral Gln supplementation increased mortality rate, though non-significantly, but decreased gut permeability significantly. According to recent RCTs and systematic meta-analysis studies on glutamine supplementation the Canadian Critical Care Practice Committee revised the Canadian Critical Care Nutrition Guidelines in 2013.³⁶ The recommendation for parenteral Gln was downgraded from “strongly recommended” to “should be considered” with a warning, ie “strongly recommend that glutamine not be used in critically ill patients with shock and multi-organ failure”. The Committee also added use of strong caution in using enteral glutamine in all critically ill patients with shock

and multi-organ failure because of the results of the recent multicenter study that showed severe complication with the use of combined enteral and parenteral glutamine.³⁷ The current meta-analysis did not provide sufficient evidence for the use of gln-enriched enteral feeding for critically ill patients.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Original Article

Efficacy of glutamine-enriched enteral feeding formulae in critically ill patients: a systematic review and meta-analysis of randomized controlled trials

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谷氨酰胺强化的肠内营养配方对危重症患者的疗效： 随机对照试验的系统综述和 meta 分析

重症患者通常患有代谢应激可以导致营养不良，因此营养支持对保持瘦体重、改善代谢和免疫反应、降低这些病人的死亡率和并发症是必不可少的。本 meta 分析的目的是评估谷氨酰胺强化的肠内营养对重症患者的疗效。为了获得随机临床试验研究 (RCTs)，我们检索了 MEDLINE 和谷歌学术等国际数据库，以及 MEDEX、IRANDOC、SID 和 Magiran 等电子资源中 2014 年 12 月份以前的文献，不受出版语言限制。最终有 10 个研究纳入了 meta 分析。由四个研究者采用包括随机化、盲法和研究对象的合格性三个项目的 Jadad5 点量表来评估合格研究的方法学质量。我们用 STATA12.0 分析纳入研究的数据，计算二分类变量的比值比和连续性变量的标准差及它们的 95% 置信区间 (CIs)。死亡率在升高的合并比值比中无显著差异 (p -value=0.070)。在绘制漏斗图中没有发表偏倚。固定效应模型显示接受谷氨酰胺强化的肠内营养的患者肠道通透性显著降低 (-0.84, 95% CI=-1.25 到 -0.44)，而且漏斗图显示没有发表偏倚。根据现有的资料，我们的 meta 分析表明，肠内谷氨酰胺补充增加死亡率，虽然没有显著性，但显著降低了肠道通透性。

关键词：谷氨酰胺、肠内、免疫增强配方、危重症患者、系统综述