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Systematic Meta Analysis

Clinical Effects of Postoperative Parenteral Glutamine-Dipeptide Supplementation in Surgical Intensive Care Unit Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Glutamine plays a vital role as an energy substrate the inflammatory response, prevention of organ injury and renal acid buffering. Parenteral glutamine supplementation could reduce in-hospital and ICU morbidity and mortality.

Objective: Aim of this systematic review and meta-analysis is to investigate the effects of parenteral administration of GLN in adult surgical critically ill ICU patients.

Study selection: Two-arm studies about adult surgical ICU patients undergoing postoperative glutamine-enriched parenteral nutrition (experimental cohorts) vs control ones.

Endpoints: Primary endpoint was in-hospital outcome (mortality, length of stay, length of mechanical ventilation). Secondary endpoint was the evaluation of nosocomial infections.

Results: According to PRISMA ® 2020 flow diagram, eight randomized controlled trials were included for a total of 603 patients. No significant differences about in-hospital and ICU mortality were found (p=0.16 and p=0.53, respectively). Parenteral glutamine-supplementation was associated with a reduction of hospitalization (p=0.02), without influencing nor ICU stay (p=0.35) neither postoperative mechanical ventilation (p=0.18). Finally, dipeptide administration did not reduced cumulative incidence of nosocomial infections (p=0.41); however, a protective role for postoperative pneumonia was reported (p=0.05).

Conclusions: Excepting for a reduction in hospital stay and incidence of nosocomial pneumonia, glutamine-dipeptide parenteral supplementation does not add any benefit in surgical ICU patients.

Keywords: Glutamine, parenteral nutrition, intensive care unit, surgery, prognosis

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Glutamine (GLN), a conditionally essential L-α -amino acid, plays a vital role as an energy substrate for cellular proliferation pathways, modulation of the inflammatory response, pathogen recognition, prevention of organ injury and renal acid buffering, especially in catabolic states and critically ill patients.[1-3]

Contrary to long-standing statements, glutamine deficiency becomes clinically evident only after some days after intensive care unit (ICU) admission and up to 35% of patients experience GLN depletion,[4,5] especially in those receiving prolonged parenteral nutrition regimens,[6] as these products do not contain GLN due to instable pharmacological properties in acqueous solutions.[7]

Early studies supported enteral or parenteral dipeptide

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supplementation in critically ill patients as a prevention strategy for bacterial translocation, sepsis and multiorgan failure,[8] although some others reported conflicting results arising skepticism and debate due to speculative positions about unconsistent and even harmful effects of glutamine-supplemented nutrition in ICU patients.[9-11]

The aim of this systematic review and meta-analysis is to investigate the effects of parenteral administration of GLN in adult surgical critically ill ICU patients, excluding burn injury, severe pancreatitis and trauma cohorts from the eligilibilty.

Methods

The systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines for studies including healthcare interventions.[12] Neither ethical approval nor patients' consent were not necessary according to local legislation due to the type of investigation and protocol (meta-analysis).

Study Design

A literature research querying databases, such as PubMed-MEDLINE Embase, Web of Science, Cochrane Library and Google Scholar, was carried out by three investigators from the authors' panel in order to identify relevant articles about parental glutamine dipeptide supplementation in critically ill surgical patients and published from Jan 01, 2000 to March 15, 2023, in order to homogenize patient sampling, parenteral nutrition protocols and administered pharmaceutical compositions.

According the Medical Subject Heading (MeSH) report, the Boolean function was as follows: ((Glutamine) and (L-glutamine) and (dipeptide) or (L-alanine glutamine) and (nutrition) and (parenteral) or (intravenous) and (support) and (critically ill) OR (critical) and (surgical) OR (surgery) and (intensive care unit) or (ICU) and ("2000/01/01" [Date - Publication]: "2022/08/31" [Date - Publication])). Additional manual research including unindexed sources was included via a three-step approach run on March 20, 2023, April 10, 2023 and April 30, 2023 in order to expand reference lists selected for further title, abstract and full-text evaluation. In the event of overlapping data from the same studies (e.g. subgroup analyses or preliminary results), the most recent and exhaustive study was included.

Study Selection Criteria

All the potentially relevant articles were reviewed and checked by a five-phase process according to source reliability, titles' eligibility or ineligibility, abstract evaluation, duplicates removal and full-text evaluation if they met the following inclusion criteria: (I) Adult patients (< 18 years of age); (II) Critically ill Intensive Care Unit patients with clearly-defined admission criteria, undergoing non-traumatic and non-pancreatic elective or emergency surgery and supplemented with glutamine dipeptide-based parental nutrition in the postoperative period; (III) Patients' allocation in experimental (Gln-dipeptide) and control (placebo or no intervention) cohort analysis; (IV) Clearly defined inclusion and exclusion criteria and settings; (V) Well-described parental nutrition protocol administration; (VI) Randomized controlled clinical trials; (VII) Clear definition of study design, according to reference Country, year of publication, mono-multicentricity and possible endorsements from National Societies; (VIII) Rigorous demographic sample stratification; (IX) An exhaustive description of patients' outcome according to mortality rate, hospital stay, infectious complications and nosocomial infections; (X) Studies written only in English. Articles, such as letters to editors, opinions, reviews, guidelines and proceedings were excluded.

Endpoints

In order to evaluate the effects of glutamine dipeptide parental nutrition in critically ill surgical ICU patients, primary endpoints were overall in-hospital and ICU mortality, length of stay and length of mechanical ventilation; secondary endpoints dealt with infectious complications (overall incidence, post-operative pneumonia, blood stream and urinary tract infections) and nosocomial infections according to pathogens and Gram classification.

Data Extraction and Management

Decisions about inclusion and data extraction from elected studies were carried out in duplicate according to a standardized protocol. All original trials were reviewed by two investigators from the authors' panel. Any disagreement was solved by discussion, whereby a consensus was then reached and estimated by Cohen's k parameter.[13]

In the case lack of continuous variables and relative estimated means or standard deviations (e.g. hospital stay), data were derived in accordance with the method proposed by Hozo et al.[14]

An evaluation for the fulfillment of the inclusion criteria, design of the experimental population for predicted clinical outcomes was carried out preliminarily with reference to the randomization criteria, intention-to-treat (ITT)-based analysis, comparability among cohorts, follow-up and parenteral nutritional administration protocols.

Inclusion Investigators' Consensus

The degree of accuracy and inter or intra-reliability during selection of primary studies for definitive eligibility resulted into a substantial agreement with a Cohen's k of 0.75.

Risk of Bias Assessment

The presence of publication bias was assessed by a two-step process: Jadad qualitative score[15] and quantitative visual funnel plot Egger's rank correlation test.

Statistical Analysis

The analysis was conducted with Microsoft Excel 2016 (Microsoft®, Redmond, USA), with IBM SPSS version 20.0 (IBM ®, Segrate MI, Italy) and Revman 5.4.1 (Cochrane Collaboration). Data were reported as absolute numbers (N), percentages (%), mean (MD) and standard deviation (SD) with their relative 95% confidence interval (95% CI). The effect size was estimated by the Relative Risk (RR) according to the Mantel-Haenszel method.

For continuous variables expressed in median and interquartile range, the mean and standard deviation were derived according to the method of Hozo et al.[14] and any correlations were estimated by means of Mean Difference (MD). Heterogeneity (I^2), Cochrane Q tests and Tau-squared tests (τ^2) among studies' variances were carried out. A threshold to establish the presence of heterogeneity was 50%. An $I^2<50\%$, indicating the absence of any statistical heterogeneity, resulted in a fixed-effect model analysis; while an $I^2\geq50\%$ confirmed the presence of heterogeneity eligible for an analysis with random-effect model.

Results

The MeSH Boolean function query terms via the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (https://prisma-statement.org/prismastatement/flowdiagram.aspx) yielded 655 potentially eligible records retrieved via databases and register interrogation. Results from additional manual research for unindexed papers from Google Scholar were also included. After a primary evaluation based on title or abstract ineligibility (n= 501) and duplicates removal (n=24), 130 studies were sought for further retrieval according to a strict three-step protocol based on study design, enrolled population and application limits. Only 8 randomized clinical controlled trials[6, 16-22] were included for the meta-analysis (Fig. 1).

Methodological and inclusive ineligibility was found in: (I) 3 studies not written in English (n=2 Chinese, n=1 Russian); (II) 35 articles due to study design incompatibility (review articles [n=11], mono- multicentric retrospective studies [n=16], protocols [n=4], editorial [n=3], European Society for Clinical Nutrition and Metabolism guidelines [n=1]); (III) 74 papers enrolling unfitted cohorts of patients (not critically ill or ICU patients [n=23], mixed groups [n=14], medical samples [n=6], trauma or burn patients [n=19] and paediatric cases [n=12]); moreover, (IV) preliminary studies reporting subgroup analyses [n=4], combined enteral and parenteral glutamine supplementation protocol [n=1] and articles lacking of exhaustive data or outcomes [n=5] were also excluded from systematic review. At the end of this process, 603 patients (306 experimental vs 297 control) were enrolled.

The elected trials showed a high-quality score (mean Jadad Score: 4.00±0.93, range: 3-5) and double-blind investigation methodology. Common exclusion criteria were: pregnancy, lactation, renal or hepatic failure, history of cancer, immunosuppression (innate or acquired), malnutrition, hemodynamic instability and life expectancy less than seven days.

Three studies did not report the parenteral amino acid formula; while, in the remainings, the nutritional protocol provided for the infusion of 15% GLN-free amino acid solutions at a dose of 1.5g/kg/day and dipeptide amino acid formulas (L-glutamine-alanine) at an average dosage of 0.48 ± 0.05 g/kg/day. Table 1 and Table 2 refer to protocols, data extraction and outcomes for each elected study.

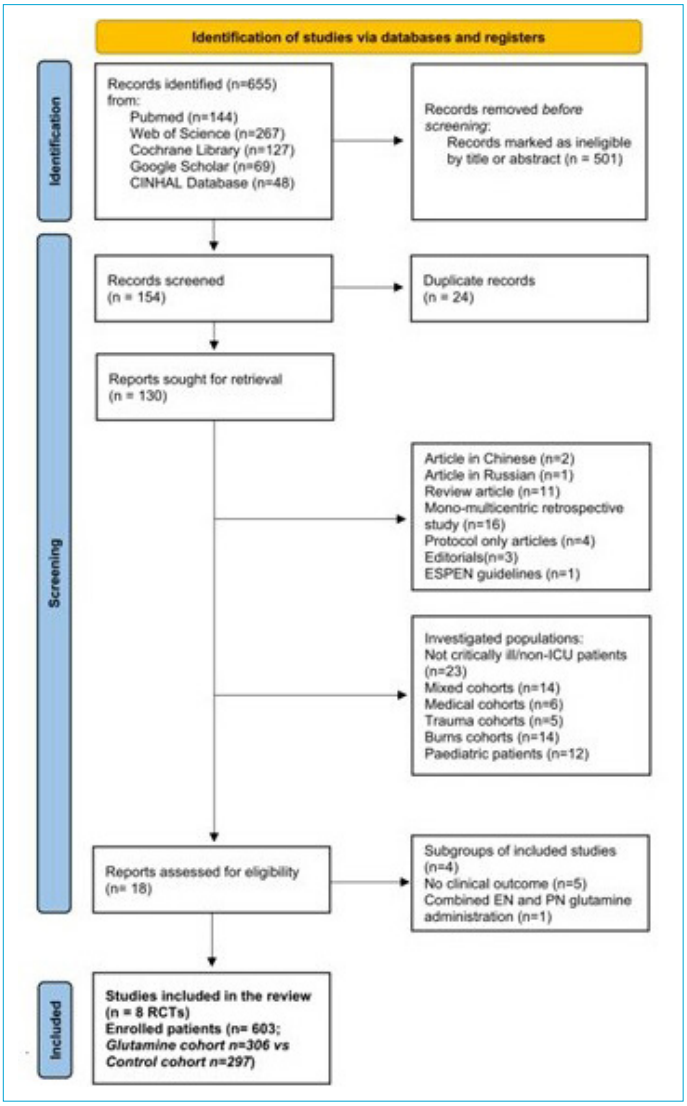

Figure 1. PRISMA ® 2020 flow diagram for systematic reviews and meta-analysis.

Table 1. Summary of included studies assessing glutamine parenteral supplementation in critically ill surgical ICU patients: protocols, designs and quality evaluation scores

Author (year)	Country	Study design	Exclusion criteria	Enrolled patients (N)			Glutamine supplementation protocols					Jadad Score
				Total	L-Gln[a]-dipeptide	Control	Route of administration	PNb formula	PN dosage (g/kg/day)	L-Gln supplementation formula	L-Gln dosage (g/kg/day)	
Goeters[17] (2002)	Germany	RCT	pregnancy, lactation, inborn disorders of aminoacid metabolism	68	33	35	Parenteral	NR	1.5	L-Gln-Alanyl	0.30	3
Fuentes-Orozco[18] (2004)	Mexico	RCT	renal failure, hepatic failure, severe neutropenia, chemotherapy, radiation, steroid therapy, hemodynamic instability	33	17	16	Parenteral	NR	1.5	L-Gln-Alanyl	0.40	3
Ziegler[19] (2005)	USA	RCT	NR	29	15	14	Parenteral	GLN-free aminoacid solution (15%)	1.5	L-Gln-Alanyl	0.50	5
Déchelotte[6] (2006)	France	RCT	malnutrition, severe obesity, pregnancy, lactation, hemodynamic instability, renal failure, hepatic failure, sepsis, persistent acidosis, immunosuppressive therapy, HIV, life expectancy <7 days	114	58	56	Parenteral	NR	NR	L-Gln-Alanyl	0.34	5
Kumar[20] (2007)	India	RCT	NR	120	63	57	Parenteral	NR	NR	NR	0.47	3
Estivariz[21] (2008)	USA	RCT	hepatic failure, sepsis <24h; malignancies; renal failure or dialysis	59	30	29	Parenteral	GLN-free aminoacid solution (15%)	1.5	NR	0.50	4
Cekmen[22] (2011)	Turkey	RCT	sepsis, hepatic failure, renal failure, life expectancy <7 days	30	15	15	Parenteral	GLN-free aminoacid solution (15%)	NR	L-Gln-Alanyl	0.50	4
Ziegler[23] (2016)	USA	RCT	pregnancy; clinical sepsis; malignancies; history of seizures; cirrhosis; cronic renal failure or dialysis; previous organ trasplant; HIV/AIDS; burn or trauma; previous GLN enriched nutrition; administration refuse to follow-up	150	75	75	Parenteral	GLN-free aminoacid solution (15%)	1.5	L-Gln-Alanyl	0.50	4

[a]Gln: glutamine; [b]PN: parental nutrition; NR: not reported.

Table 2. Summary of included studies assessing glutamine parenteral supplementation in critically ill surgical ICU patients: primary and secondary endpoints. Data extraction.

Author (year)	Country	Enrolled patients (N)			Mortality (N)	Lenght of stay (mean±SD)	Lenght of mechanical ventilation (mean±SD)	Nosocomial infections (N)				Pathogenes (N events)		
					In-hospital (ICU)	In-hospital (ICU)		Overall	Pneumonia	Urinary tract infections	Bloodstream	Gram positive	Gram negative	Fungi
		Total	L-Glna-dipeptide	Control	Gln/Control	Gln/Control	Gln/Control	Gln/Control	Gln/Control	Gln/Control	Gln/Control	Gln/Control	Gln/Control	Gln/Control
Goeters[17] (2002)	Germany	68	33	35	7/11 (7/10)	46±49.1/ 39.4±31.3 (21.30±13.50/ 20.80±9.10)								
Fuentes-Orozco[18] (2004)	Mexico	33	17	16	2/3	16.52±8.9/ 16.69±7.04 (7.17±9.20/ 7.25±4.46)	4.88±8.20/ 4.47±4.40	4/12						
Ziegler[19] (2005)	USA	29	15	14		29.7±14,85/ 33.30±16.65 (15.70±7.87/ 17.40±8.70)	11.1±5.50/ 15.80±7.87							
Déchelotte[6] (2006)	France	114	58	56	2/2 (2/2)	30.00±139.75/ 26.00±100.75 (12.50±107.25/ 11.5±29.50)		19/31	10/19	0/4				
Kumar[20] (2007)	India	120	63	57	8/5	13.29±6.75/ 25.74±20.00		44/37						
Estivariz[21] (2008)	USA	59	30	29	1/5	20.00±2.00/ 30.00±6.00 (12.00±2.00/ 23.00±6.00)	9.00±2.00/ 21.00±5.00		13/16	6/9	4/10	18/24	22/29	8/20
Cekmen[22] (2011)	Turkey	30	15	15	3/6									
Ziegler[23] (2016)	USA	150	75	75	11/13			52/39	10/12	7/3	18/13	35/32	33/18	21/13

SD= Standard Deviation; ICU= Intensive Care Unit; Gln=glutamine.

Glutamine Dipeptide Supplementation and Hospital Mortality

Table 3 reports evidences coming from meta-analysis. Seven of the eight elected trials for a total of 574 patients (291 experimental vs 283 control ones) speculated about hospital mortality. With a cumulative incidence of 13.76% (79/574), no significant statistically differences between cohorts were reported (GLN-dipeptide vs control cohorts: 11.68% vs 15.90%, 95%CI: -1.44 – 9.92; p=0.142). No significant heterogeneity among studies (I^2=0%) when the fixed effect model was adopted, confirming any protective role of parental nutritional dipeptide administration on patients' prognosis (RR: 0.75, 95%CI: 0.50-1.12; p=0.16) (Fig. 2a, 3a).

Also the subgroup analysis concerning with ICU mortality, including two RCTs and 182 patients (91 experimental vs 91 control) yielded any significant difference in outcome (GLN-dipeptide vs control cohorts: 11.68% vs 15.90%, 95%CI: -1.44 – 9.92; p=0.142) and, without any heterogeneity between included studies (I^2=0%), any augmented risk between groups (RR: 0.78, 95%CI: 0.36-1.69; p=0.53) (Fig. 2b, 3b).

Length of Stay and of Postoperative Mechanical Ventilation

Aggregating six trials reporting on length of hospital stay (GLN-dipeptide vs control cohorts: 216 vs 207), parental GLN-dipeptide supplementation was associated with a significant trend toward a reduction of hospitalization (MD: -6.18, 95%CI: -11.52 - -0.85; p=0.02). Heterogeneity among studies (I^2=68%, τ^2=22.64) at random effect analysis was reported (Fig. 4a, 5a).

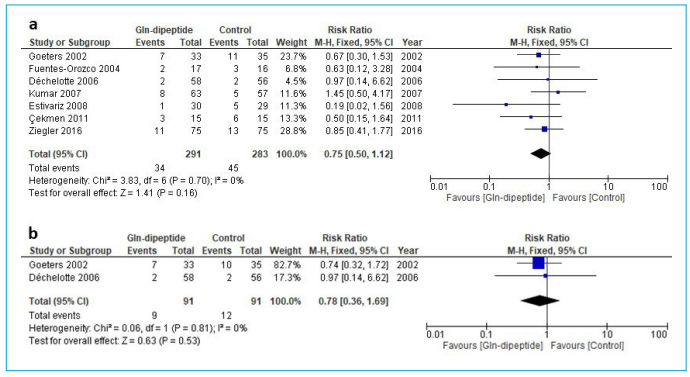

Figure 2. Meta-analysis for glutamine-dipeptide parenteral supplementation and **(a)** overall in-hospital mortality; **(b)** ICU mortality. Forrest plots (Gln=glutamine; M-H= Mantel-Haenszel test).

However, neither significant reduction in ICU hospital stay (Gln-dipeptide vs control cohorts: 153 vs 150; MD: -3-15, 95%CI: -9.80 – 3.51; I^2=87%, τ^2=42.28, p=0.35) (Fig. 4b, 5b) nor duration of postoperative mechanical ventilation (Gln-dipeptide vs control cohorts: 62 vs 59; MD: -5.62, 95%CI: -13.77 – 2.53; I^2=93%, τ^2=47.75, p=0.18) was reported (Fig. 4c, 5c).

Nosocomial Infections

Four of the elected articles reported on nosocomial infections for a total of 417 patients (GLN: 213 vs control 204).

Dipeptide administration did not reduce cumulative incidence or postoperative risk of such complications (Gln-

Table 3. Summary of evidences from systematic review and meta-analysis

Outcome	Studies included N	Enrolled patients N	Statistical Method	RR (MD)	95%CI	p
Mortality						
Hospital mortaliy	7	574	Risk Ratio (M-H, Fixed)	0.75	0.50 - 1.12	0.16
ICU mortality	2	182	Risk Ratio (M-H, Fixed)	0.78	0.36 - 1.69	0.53
Hospital stay						
In-hospital stay	6	423	Mean Difference (IV, Random)	(-6.18)	-11.52 - -0.85	0.02
ICU	5	303	Mean Difference (IV, Random)	(-3.15)	-9.80 - 3.51	0.35
Lenght of mechanical ventilation	3	121	Mean Difference (IV, Random)	(-5.62)	-13.77 - 2.53	0.18
Nosocomial infections						
Overall	4	417	Risk Ratio (M-H, Random)	0.83	0.52 - 1.30	0.41
Pneumonia	3	323	Risk Ratio (M-H, Fixed)	0.68	0.47 - 0.99	0.05
Urinary tract infections	3	323	Risk Ratio (M-H, Random)	0.80	0.22 - 2.91	0.73
Bloodstream infections	2	209	Risk Ratio (M-H, Random)	0.72	0.15 - 3.57	0.69
Pathogen isolation						
Gram positive bacteria	2	209	Risk Ratio (M-H, Random)	0.69	0.58 - 1.35	0.57
Gram negative bacteria	2	209	Risk Ratio (M-H, Random)	1.15	0.36 - 3.60	0.82
Fungi	2	209	Risk Ratio (M-H, Random)	0.79	0.19 - 3.23	0.75

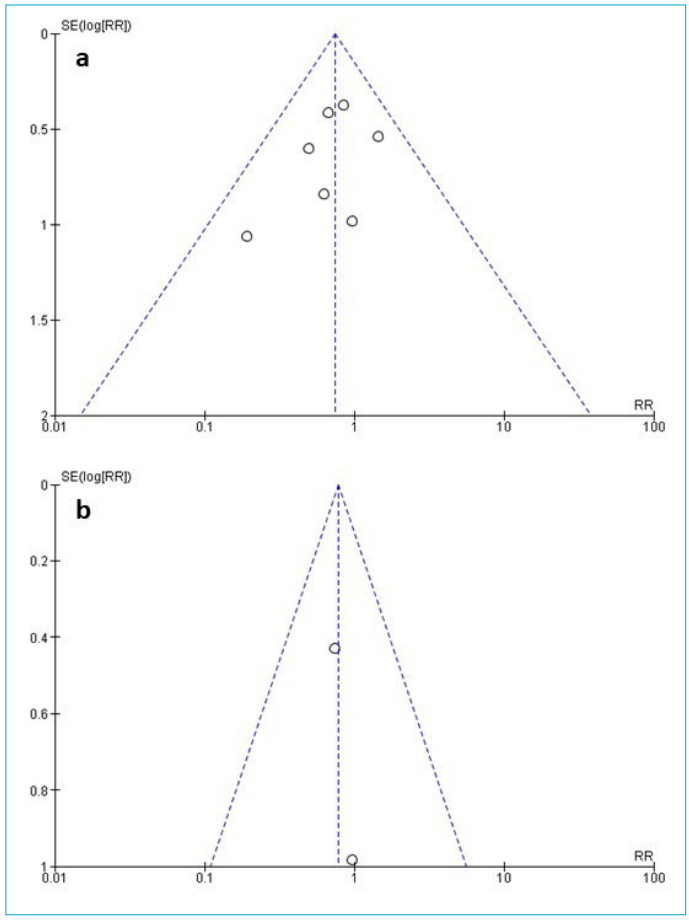

Figure 3. Asymmetry rank correlation funnel plot of included articles for **(a)** overall in-hospital mortality; **(b)** ICU mortality (SE: standard error; RR: relative risk).

dipeptide vs control cohorts: 55.86% vs 58.33%, RR: 0.83, 95% CI: 0.52-1.30, I^2=83%, τ^2=0.16, p=0.41) (Figs. 6a, 7a). Although aggregating data referring to postoperative pneumonia amino-acid supplementation showed a trend

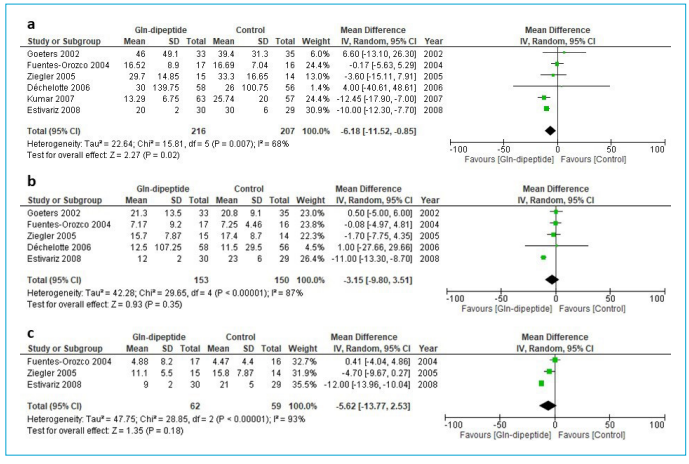

Figure 4. Meta-analysis for glutamine-dipeptide parenteral supplementation and **(a)** length of stay; **(b)** ICU stay; **(c)** length of mechanical ventilation. Forrest plots (Gln=glutamine; M-H= Mantel-Haenszel test).

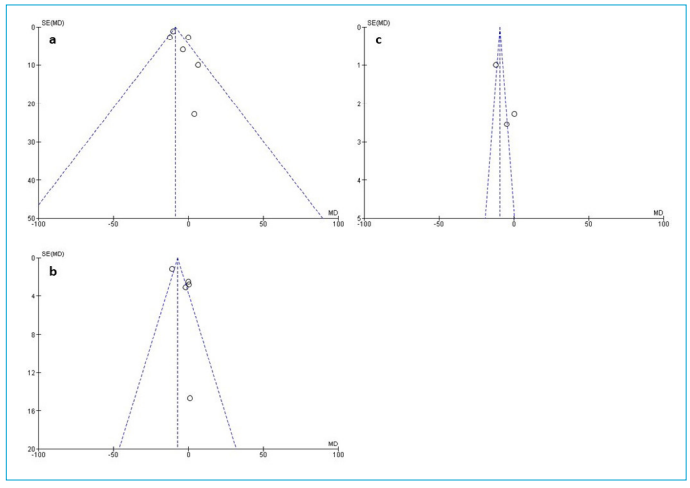

Figure 5. Asymmetry rank correlation funnel plot of included articles for **(a)** length of stay; **(b)** ICU stay; **(c)** length of mechanical ventilation. (SE: standard error; RR: relative risk).

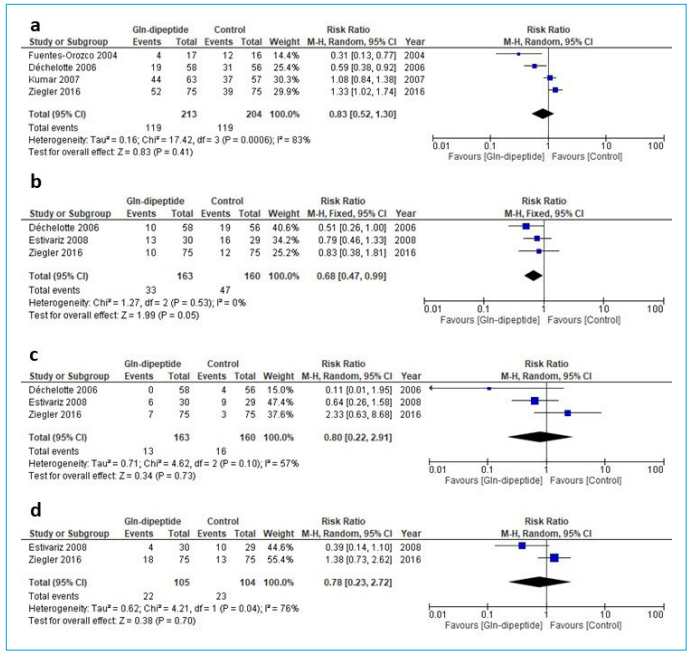

Figure 6. Meta-analysis for glutamine-dipeptide parenteral supplementation and **(a)** overall infection complications; **(b)** nosocomial pneumonia; **(c)** urinary tract infections; **(d)** bloodstream infections. Forrest plots (Gln=glutamine; M-H= Mantel-Haenszel test).

towards a protective effect (GLN-dipeptide vs control cohorts: 20.24% vs 29.37%, RR: 0.68, 95% CI: 0.47-0.99, I^2=0%, p=0.05) (Figs. 6b, 7b), the studies included in the meta-analysis provided no evidences for any benefit neither for urinary tract infections (GLN-dipeptide vs control cohorts: 7.97% vs 10.00%, RR: 0.80, 95% CI: 0.22-2.91, I^2=57%, τ^2=0.71, p=0.73) (Figs. 6c, 7c) nor bloodstream infections (GLN-dipeptide vs control cohorts: 7.97% vs 10.00%, RR: 0.72 , 95% CI: 0.15-3.57, I^2=77%, τ^2=0.16, p=0.69) (Figs. 6d, 7d). In detail, reporting data of two trials (GLN-dipeptide:

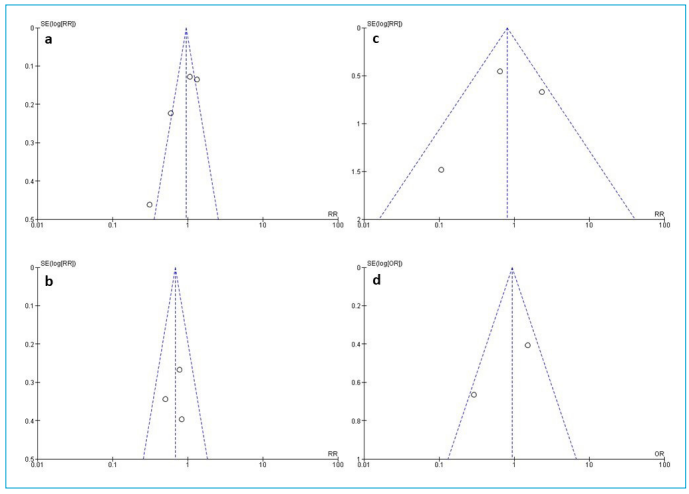

Figure 7. Asymmetry rank correlation funnel plot of included articles for **(a)** overall infection complications; **(b)** nosocomial pneumonia; **(c)** urinary tract infections; **(d)** bloodstream infections (SE: standard error; RR: relative risk).

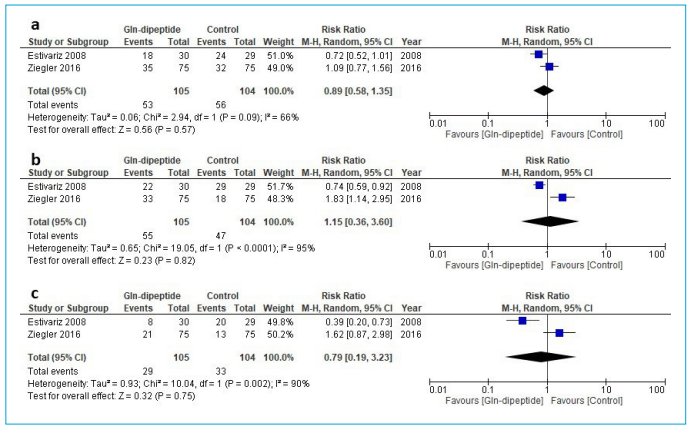

Figure 8. Meta-analysis for glutamine-dipeptide parenteral supplementation and **(a)** Gram positive infections; **(b)** Gram negative infections; **(c)** Fungemias. Forrest plots (Gln=glutamine; M-H= Mantel-Haenszel test).

105 vs control 104), the administration of supplementary amino acids did not have any immunoprotective impact on Gram positive bacteria (RR: 0.89, 95% CI: 0.58-1.35, I^2=66%, τ^2=0.06, p=0.57), Gram negative infections (RR: 1.15, 95% CI: 0.36-3.60, I^2=95%, τ^2=0.65, p=0.82) and fungemias (RR: 0.79 , 95% CI: 0.19-3.23, I^2=90%, τ^2=0.93, p=0.75) (Figs. 8a-c, 9a-c).

Discussion

Glutamine is the most abundant free amino-acid, whose bioavailability depends upon the balance of endogenous muscle production and consumption for inflammatory modulation and response to oxidative stress.[23]

Although ancestral evidences have long suggested an increased endogenous production in catabolic intensive

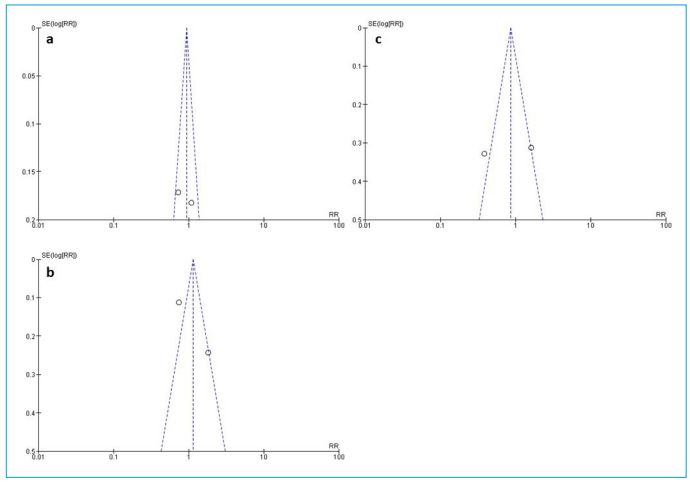

Figure 9. Asymmetry rank correlation funnel plot of included articles for **(a)** Gram positive infections; **(b)** Gram negative infections; **(c)** Fungemias (SE: standard error; RR: relative risk).

care unit patients with a proportional increased risk of in-hospital mortality such to justify strategies to attenuate the peptide pool efflux,[24] recent observations have challenged this hypothesis. In fact, plasma glutamine levels are extremely variable in the ICU population[25,26] and only severe hyperglutamineemia is an independent predictor for mortality.[5] Contrast release strategies, therefore, appear quite inconclusive and the demonstration of putative beneficial effects of exogenous glutamine supplementation on immune effector cells as well as high-demanding tissues does not appear so obvious.[27-29]

Our results reveal glutamine supplementation offers no prognostic advantage in cohorts of critically ill surgical patients (in-hospital or ICU mortality [RR: 0.75, 95%CI: 0.50-1.12, p=0.16 and RR: 0.78, 95%CI: 0.36-1.69, p=0.53]). In addition, glutamine supplementation was not associated with statistically significant differences between the remaining primary (except for intrahospital stay: MD: -6.18, 95%CI: -11.52- -0.85, p=0.02) nor secondary endpoints (except a statistically significant reduction in the incidence of nosocomial pneumonia [RR: 0.68, 95%CI: 0.47-0.99, p=0.05]). However, evidences deserve a precise contextualization. From emerging results, it was not possible to find any nutripharmaceutical rationale for dipeptide infusion to a standard parenteral regimen in surgical patients.

In particular, a substantial absence of any putative clinically advantageous and evident immunomodulatory effect was found. Results that, beyond a reduction in pneumonia with the same duration of post-operative mechanical ventilation (MD: -5.62, 95%CI: -13.77-2.53. p=0.18), were substantially confirmed by similar incidence for urinary tract (RR: 0.80, 95%CI: 0.22-2.91, p=0.73) and bloodstream infections (RR: 0.72, 95%CI: 0.15-3.57, p=0.69). Chen et al.[30] reported

no significant reduction in mortality in dipeptide-supplemented patients. Interestingly, the Authors demonstrated maximal doses of glutamine administration resulted into a significant increase in mortality (relative risk (RR) 1.18; 95% confidence interval (CI), 1.02 to 1.38; p=0.03); while, in contrast of our results, a significant reduction in nosocomial infections was reported in the surgical ICU subgroup (RR 0.70; 95% CI, 0.52 to 0.94; p=0.04). In a blinded multicenter 2-by-2 factorial trial, Heyland et al.[4] reported a trend toward an increased both short-term (OR: 1.29, 95%CI: 1.00-1.64, p=0.05) and long-term mortality among patients receiving glutamine, as far as no effects on infectious complications. In reality, evidences require clarification regarding some peculiarities of the enrolled population (surgical patients) and the absence of a subsequent specific subdivision by pathology and/or surgical procedure. Therefore, our results could have been translated into a rather generalizable cohort of surgical patients needing post-operative ICU.

With regard to the peculiarities of surgical patients, the absence of a real therapeutic and immunonourishing advantage is in agreement with what has been reported by recent studies. Ziegler et al.,[22] in a parallel group muticenter double blind trial in adults undergoing gastrointestinal, vascular or cardiac surgery requiring parenteral nutrition and ICU care without hepatic, renal failure or shock at admission, receiving isonitrogenous isocaloric PN and alanyl-GLN dipeptide (0.5 g/kg/day), reported no difference in in-hospital mortality (14.7% in GLN vs 13/75 control group, 17.3%; difference, −2.6%; 95% CI: −14.6 - 9; p=0.66) and mid-term mortality 31.4% in the GLN-PN group and 29.7% in the STD-PN group (p=0.88). Bloodstream infection incidence was 9.6 and 8.4 per 1000 hospital days in the GLN-PN and STD-PN groups, respectively (p=0.73). PN supplemented with GLN dipeptide was safe but did not alter clinical outcomes among ICU patients. In contrast Pimental et al.[31] in a systematic review of seven elected RCTs, while confirming the absence of any prognostic advantage, reported a reduction in infectious complications supporting the immunomodulatory effect of exogenous glutamine administration. Our results, although conflicting, allowed for a peculiar analysis not found in other studies. Two included studies[20,22] reported a complete taxonomy of isolated microorganisms in ICU surgical infected patients. Secondary analysis did not reveal any statistically significant differences regarding any augmented risk for Gram positive, Gram negative and fungal infections. In particular, the incidence of bacterial infections did not differ between the experimental and the control groups, allowing to indirectly derive an underlying real ineffectiveness in prevention of any translocative event in a specific subgroup of patients, such as surgical ones.

Clinical effects, however, do not appear subordinated to the supplement dosage. The patients enrolled in our systematic review received medium-high dose parenteral addition (Mean-SD, min-max) with comparable results to what emerged for low-dose strategies such as in the SIGNET trial.[10] In this double-blinded multicenter controlled trial enrolling 502 ICU patients, the primary intention to treat analysis showed no effect on prognosis, length of stay, days of antibiotic use, new infection and modified SOFA score in patient receiving low-dose (0.2 mg/kg/day) GLN-supplemented parenteral nutrition. The REDOX study,[4] a large multicenter trial, similar demonstrated early administration of high dose glutamine could have adverse effects reflecting in an augmented mortality.

Controversial evidence in the literature therefore suggests that certain subgroups of patients could benefit from GLN-parenteral nutrition in the ICU setting due to specific metabolic needs that can be identified a priori to predict a cluster defined as "responder". On the other hand, surgical groups appear to be “non-responders” and therefore not deserving of any dipeptide supplementation even at supermaximal dosages.[32-34]

Limitations of the Study

The study was conducted based upon a rigorous statistical methodology (PRISMA® statements, Cochrane Collaboration Tools, Quality assessment tools). Notwithstanding analyses showed population heterogeneity and only high-quality randomized controlled trial (mean Jadad Score: 4.00±0.93, range: 3-5), a number of these key trials have non-negligible strengths and weaknesses that could justify conflicting evidences with previous driving meta-analyses claiming a critical appraisal.

First all studies included small sample size of patients (range: 29–150). Second, two studies[18,19] lacked of exclusion criteria. Third, three RTCs[6,20,22] lacked of PN dosage protocol and two did not declare parenteral GLN-supplementation formula.[20,21] In addition, conceptual and design limitations emerge from inadequate interpretation of concurrent factors such as type of surgery, surgical subspecialities and preoperative SOFA score assessment, in order to homogenize the enrolled population and test the real immunomodulatory and related clinical effects of glutamine parenteral administration.

Conclusion

Notwithstanding glutamine represents an immunomodulator and organ damage prevention substrate, a stringent therapeutic rationale for its administration still appears controversial. Although the absence of a harmfull effect is

shown in selected cohorts of surgical patients, supplementation does not entail any clinical benefit with the exception of a reduced hospitalization and a lower incidence of nosocomial pneumonia. Its ineffectiveness, in prognostic terms, raises several doubts about a rationale for a daily administration. Surprisingly, the secondary analysis showed a statistically significant absence regarding infectious complications, downsizing the putative prophylactic role of glutamine as a protective substrate of translocation events.

However, results need to be critically read and contextualized facing with the heterogeneity of a subset of surgical patients, where independent factors (demographics, type of surgery, indications, risk stratification at admission) could have influenced the emerged evidences.

Disclosures

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