ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

ARÁN

Nutrición Hospitalaria

Revisión

Effects of parenteral glutamine in critically ill surgical patients: a systematic review and meta-analysis

Efectos de la glutamina parenteral en pacientes quirúrgicos críticos: revisión sistemática y metaanálisis

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Abstract

Introduction: glutamine (GLN), the most abundant non-essential amino acid in the plasma, tends to be rapidly depleted in cells in situations of metabolic stress. Some studies have demonstrated the benefits of GLN supplementation on mortality, infection, and length of hospital stay. The objective of this review was to analyze whether parenteral supplementation with GLN has any relevant effect in critically ill surgical patients.

Methods: based on a systematic database search, randomized clinical trials (RCTs) published since 1985 were included if they had evaluated the effect of parenteral GLN supplementation in critical surgical patients. The statistical analysis was performed using the RevMan 5.3 software.

Results: seven RCTs were eligible for the meta-analysis. Parenteral glutamine supplementation was associated with a non-significant 24 % reduction in mortality (RR = 0.76; 95 % CI: 0.50-1.15). Infections were significantly reduced (RR = 0.60; 95 % CI: 0.45-0.80), and length of hospital stay was 4.09 days shorter (95 % CI: -6.71 to -1.46).

Conclusion: parenteral GLN usage in critical surgical patients seems to decrease infection and length of hospital stay, but we could not demonstrate a significant reduction in mortality.

Keywords:

Glutamine. Parenteral nutrition. Critical surgical patients. Meta-analysis.

Resumen

Introducción: la glutamina (GLN), el aminoácido no esencial más abundante en el plasma, tiende a agotarse rápidamente en las células en situaciones de estrés metabólico. Algunos estudios han demostrado beneficios de la suplementación con GLN en términos de reducción de la mortalidad, las infecciones y la duración de la hospitalización. El objetivo de esta revisión es analizar si la suplementación parenteral de GLN tiene algún efecto relevante para los pacientes quirúrgicos en estado crítico.

Métodos: basado en una búsqueda sistemática de bases de datos, se incluyeron ensayos clínicos aleatorizados (ECA) publicados desde 1985 si estos habían evaluado el efecto de la suplementación parenteral de GLN en pacientes quirúrgicos críticos. El análisis estadístico se realizó utilizando el software RevMan 5.3.

Resultados: siete ECA fueron elegibles para el metaanálisis. La suplementación parenteral de glutamina se asoció a una reducción no significativa del 24 % en la mortalidad (RR = 0,76; IC 95 %: 0,50-1,15). Las infecciones se redujeron significativamente (RR = 0,60; IC 95 %: 0,45-0,80) y la duración de la estancia de hospitalización fue 4,09 días menor (IC 95 %: -6,71 a -1,46).

Conclusión: el uso de GLN parenteral en pacientes quirúrgicos críticos parece disminuir las infecciones y la duración de la estancia hospitalaria, pero no pudimos demostrar una reducción significativa de la mortalidad.

Palabras clave:

Glutamina. Nutrición parenteral. Pacientes quirúrgicos críticos. Metaanálisis.

Received: 16-11-2019 • Accepted: 26-12-2019

Conflict of interest: The authors declared no conflicts of interest.

Pimentel RFW, Fernandes SL. Effects of parenteral glutamine in critically ill surgical patients: a systematic review and meta-analysis. Nutr Hosp 2020;37(3):616-621

DOI: http://dx.doi.org/10.20960/nh.02949

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INTRODUCTION

Glutamine (GLN) is the most abundant non-essential amino acid in the plasma, and it is involved in a wide variety of processes in the body. Despite its possibility to be synthesized, GLN has been described as conditionally essential in the catabolic state (1). This amino acid is the preferential substrate of fast-dividing cells such as enterocytes and lymphocytes. In situations of metabolic stress, especially after surgery, GLN tends to be rapidly depleted in muscle cells and transported to the liver in order to optimize gluconeogenesis, as well as to favor immune system cells in the healing phases (2,3).

Clinical studies have demonstrated that GLN plays a fundamental role in the induction of cellular protective pathways, also acting in the modulation of inflammatory response and preventing organic lesions (4). In contrast, other studies raised doubts about the true efficacy and safety of supplementation with this amino acid in critically ill patients (5,6). Recently, some meta-analyses reaffirmed that GLN supplementation seems to reduce mortality and length of hospitalization in critically ill patients (7-10).

Faced with such a diverse scenario and conflicting results, the objective of this systematic literature review was to analyze whether parenteral GLN supplementation, as a part of nutritional therapy, has any relevant effect on clinical outcomes for critically ill surgical patients.

METHODS

This is a systematic literature review (SLR) performed through a retrospective analysis of primary studies that focused on the use of parenteral GLN in critical surgical patients. Articles published from 1985 until May 2019 were surveyed in the MEDLINE database. Search terms included: *Glutamine*, *Randomized*, *Blind*, *Clinical Trial*, *Nutrition*, *Nutritional Support* or *Dietary Supplementation* or *Parenteral Nutrition* or *Parenteral Nutrition Solutions* and *Surgical ICU Patients* or *Surgical Critical Illness*. The results obtained were reviewed for identification of those studies that used intravenous or parenteral GLN supplementation. Only articles written in English, Spanish or Portuguese were eligible. Bibliographical references of important literature reviews were also reviewed. As this was a systematic review of the literature, no ethics board approval or patient consent was required.

Only original articles that met the following criteria were included in this SLR: a) Study design: randomized clinical trials; b) Population: adult patients undergoing surgical procedures admitted to the intensive care unit (ICU); c) Intervention: parenteral use of GLN versus a control group using an isonitrogenated amino acid solution or placebo; d) Outcomes: having included one of the following outcomes: mortality, length of hospitalization, infection-related complications or other significant clinical condition. Assays that used only GLN via enteral or combined enteral/parenteral routes were excluded.

The analysis of the studies was performed by an independently reviewer. The first outcome of this SLR was general mortality. As secondary outcomes, we included the occurrence of infection and length of hospital stay (LOHS).

The Revman 5.3 software was used to perform the meta-analysis. The data extracted from the studies were combined to estimate the relative risk, and a 95 % confidence interval (CI) was stipulated for the categorical variables (mortality and occurrence of infection). For continuous variables (LOHS), the weighted mean difference and 95 % CI were estimated as results of the effect. Heterogeneity was calculated using the χ^2 test. A random effects model was used to estimate the overall effect. To justify a possible heterogeneity statistic, it was taken into consideration that the form or dose of the dipeptide provided might influence treatment outcome.

RESULTS

One hundred and twenty-three articles were found using the above-mentioned search terms. After initial screening through titles and abstracts 24 papers were selected. Among these, and after analyzing important reviews, seven studies were included (11-17). The articles that were excluded in this SLR did not have the necessary outcomes delimited or did not include accurate information on patient stay in the ICU after the surgical procedure.

The samples of the studies ranged from 30 to 150 patients. The GLN used in these investigations included alanyl-glutamine (ALA-GLN) (six studies) (11-15,17). Two of them also used glycyl-glutamine (GLY-GLN) for a second experimental group (12,13). Only one study did not report the type of dipeptide used (16). For the studies that included three groups (two experimental arms and a control arm) we chose to pool together the events concerning the categorical variables of both GLN groups (ALA-GLN and GLY-GLN) in one single intervention group to avoid event duplication in the control group.

The details for each of the included studies are described in table I.

Five studies (11,14-17) described the mortality rate of participants in each group. The combination of the results of these studies shows that glutamine supplementation in parenteral nutrition seems to have no effect on mortality reduction (RR = 0.76; 95 % CI: 0.50-1.15; p = 0.19) (Fig. 1). This is evidenced by the partial deviation of the diamond in the chart. The heterogeneity test was not significant ($\chi^2 = 2.78$; p = 0.60).

Regarding the occurrence of infection five articles described the rates of this complication (Fig. 2) (12,14-17). There was no heterogeneity among the five articles ($\chi^2 = 5.69$; p = 0.22). The combined analysis of the data showed that there seems to be a reduction in the rates of infectious complications in the patients who received parenteral glutamine supplementation (RR = 0.60; 95 % CI: 0.45-0.80; p = 0.0005), as shown in the left deviation of the diamond in the graph (in favor of glutamine use).

All seven studies reported LOHS (11-17). One of them (17) recorded LOHS as a median value, which could not be combined with the results of the other studies, and was therefore excluded from the analysis (Fig. 3).

Table I. Clinical characteristics of the selected studies

Study	Surgical procedure	N (GLN/Con)	Dose of GLN (g/kg/d)	Dipeptide type	Duration of treatment (d)	Infection (N)		LOHS (d ± SD)		Mortality	
						GLN	Con	GLN	Con	GLN	Con
Mertes et al., 2000	Large abdominal or torus-abdominal surgery	37 in (19/18)	0.34	ALA-GLN	1-5 post op.	--	--	12.8 ± 2.6	17.5 ± 6.3	1	1
Spittler et al., 2001	Large abdominal surgery	30 (10/10/10 in)	0.5	ALA-GLN	1-2 post op.	3	3	12.6 ± 1.1	20.1 ± 5.1	--	--
			0.5	GLY-GLN	1-2 post op.	0	3	14.6 ± 1.1	20.1 ± 5.1	--	--
Exner et al., 2003	Large abdominal surgery	45 in (15/15/15)	0.5	GLY-GLN	Pre-op. and 1-2 post op.	--	--	12.8 ± 5.6	17.3 ± 1.8	--	--
				ALA-GLN	Pre-op. and 1-2 post-op.	--	--	17.0 ± 1.3	17.3 ± 1.8	--	--
Fuentes-Orozco et al, 2004	Abdominal surgery	33 in (17/16)	0.4	ALA-GLN	1-10 post-op.	4	12	16.52 ± 8.9	16.69 ± 7.04	2	3
Styvariz et al., 2008	Pancreatic necrosis	52 in (15/17)	0.34	ALA-GLN	> 5 post-op.	10	9	32 ± 4	31 ± 5	0	0
	Other	52 in (15/12)	0.34	ALA-GLN	> 5 post-op.	7	10	20 ± 2	30 ± 6	1	5
Orfila et al., 2011	Gastrointestinal surgery	67 in (27/21)	0.4	--	Post-op.	12	13	28.62 ± 25.96	32.57 ± 27.3	4	4
		67 in (19/21)	0.4	--	Pre-op. and post-op.	5	13	24.78 ± 11.48	32.57 ± 27.3	3	4
Ziegler et al., 2016	Cardiac, non-neurological or vascular intestinal surgery	150 in (75/75)	0.5	ALA-GLN	< 28 post-op.	28	52	19 (14-28)*	17 (10-28)*	22	25

*ALA-GLN: alanyl-glutamine; Con: control group; GLN: glutamine group; GLY-GLN: glycyl-glutamine; LOHS: length of hospital stay; Pre-op: preoperative; Post-op: postoperative; SD: standard deviation. *These values are presented as median (variation).*

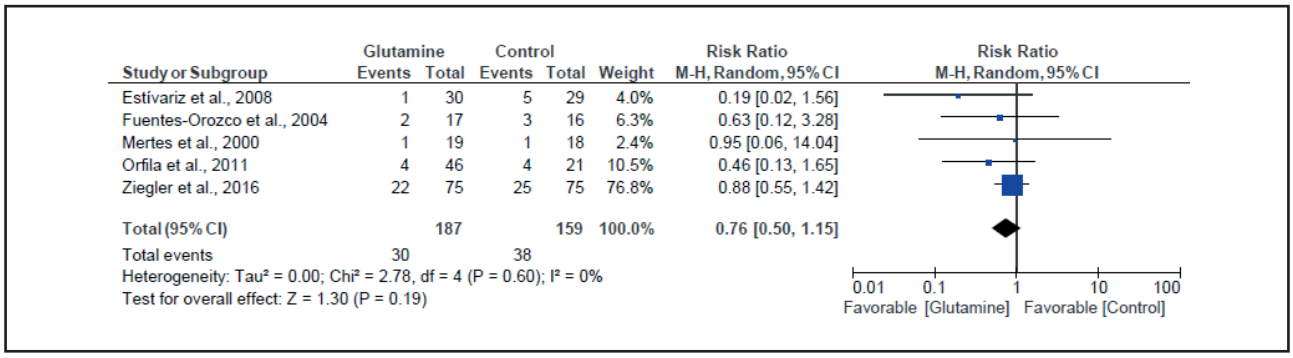

Figure 1.

Effect of parenteral glutamine supplementation on mortality.

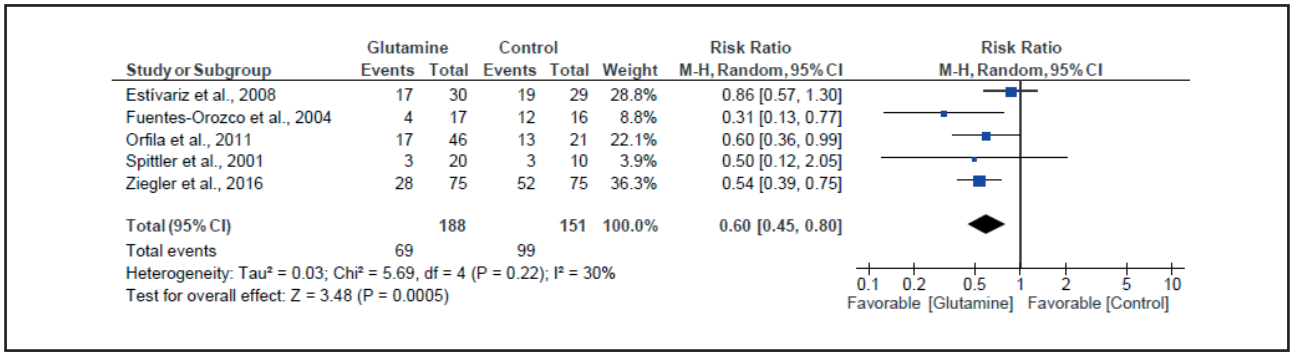

Figure 2.

Effect of parenteral glutamine supplementation on the occurrence of infectious complications.

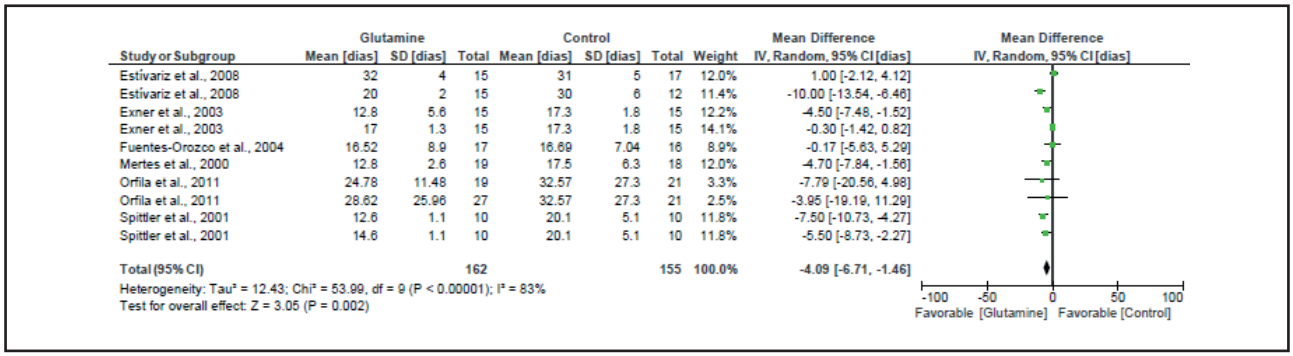

Figure 3.

Effect of parenteral glutamine supplementation on the length of hospital stay.

In the studies where this information was stratified between the two experimental groups, each intervention group was independently associated with the single control group. The heterogeneity test was significant ($\chi^2 = 53.99$; $p < 0.00001$). The use of parenteral glutamine seems to be associated with a shorter length of hospital stay (RR = -4.09; 95 % CI: -6.71 to -1.46; p = 0.002), as shown in the left deviation of the graph diamond (in favor of glutamine use).

DISCUSSION

In the last 20 years several studies were conducted and some of them reported that there seemed to be a reduction in length of hospital stay for patients who used GLN supplementation, in addition to reduced mortality and fewer infectious complications. Two large randomized, multicenter clinical trials (REDOX and METAPLUS) showed that patients in the early phase of sepsis,

using vasopressor drugs, on mechanical ventilation, or with renal insufficiency should not receive GLN because of a potential increase in mortality (5,6).

This study demonstrated that the use of parenteral glutamine does not seem to have the ability to significantly decrease mortality rate in patients having undergone surgery who required intensive care. These data are consistent with other findings in the literature about general surgical patients and critically ill patients regardless of disease type. Wang and collaborators demonstrated in their meta-analysis that general surgical patients did not have a reduction in mortality with the parenteral usage of this dipeptide (18). The same was concluded by Avenell and collaborators, who observed only a tendency towards mortality reduction with the use of parenteral glutamine in critically ill patients (19). Bollhalder and their group of researchers also confirmed in their meta-analysis this trend towards reduced mortality only in patients admitted to the ICU, with no such tendency being observed among non-ICU patients (7).

Coëffier and collaborators reported in their review that GLN has a protective effect on cells, stimulating the production of heat shock proteins (HSPs), which would protect cells against toxic and pathological agents, thus minimizing their deleterious effects (1). These proteins would serve as inflammatory messengers in the plasma. Recently, Wischmeyer and collaborators demonstrated that the level of these proteins in the serum could be used as a predictor of mortality in severely ill patients. They also reported that GLN supplemented in parenteral nutrition was not able to reduce serum HSP levels, reinforcing the low impact of this nutrient on reducing mortality for critically ill patients (20).

Our analyses also demonstrated that the use of parenteral glutamine seems to have a protective effect against infections during hospitalization among critical surgical patients, due to a lower incidence (40 % less) of events with this supplementation. This information seems to be in accordance with what was reported in the meta-analysis by Wang et al. and in the article by Zheng et al. about the use of parenteral GLN in general surgical patients (10,18). Wischmeyer et al. and Bollhalder et al. also demonstrated this tendency in their meta-analyses about the use of this dipeptide in critically ill patients (7,21).

In the surgical patient the metabolic response to uncontrolled trauma seems to have a deleterious effect on wound healing and organic defenses. This response involves cardiac hyperdynamics, pulmonary repercussion, insulin resistance, hyperglycemia, muscle protein catabolism, and use of lipid reserves for accelerated gluconeogenesis, ultimately increasing oxidative stress and inflammatory mediators. This cascade of events tends to culminate in organ failure and immunosuppression, which falicitates infection (22). The use of GLN has been shown to be effective in reducing hyperglycemia and use of insulin in critically ill patients, but the mechanism of action through which this dipeptide exerts this regulation remains unknown (1). In addition, GLN proved to be effective in reducing the expression of interleukin 8 (IL-8) and C-reactive protein (CRP), thus influencing inflammatory response. Additionally, the parenteral use of GLN has been shown to induce a reduction in IL-6, improving immunodepression (23), and a strengthening of the gastrointestinal mucosal barrier, in this way preventing bacterial translocation (24).

In this meta-analysis we have also shown that the use of parenteral GLN seems to have decreased hospital stay by approximately four days among critical surgical patients. This is consistent with the data reported in the meta-analyses that evaluated the use of parenteral GLN supplementation in general surgical or general critical patients (7,10,18,21). This information is relevant since a reduction in hospital stay has a direct impact on decreasing costs. Despite this fact, the way GLN may reduce LOHS remains unknown. Some authors believe that nitrogen balance cannot in and by itself decrease hospital stay. It seems that the metabolic response to GLN induces an improvement in organ functioning, which would then minimize infection, and optimize patient mood, as well as other parameters influencing the decision to discharge (25).

CONCLUSION

Based on the analyses of this study, we conclude that the parenteral use of GLN in critical surgical patients seems to reduce infections and length of hospital stay. Supplementation with this dipeptide, however, did not result in a significant reduction in mortality among these patients. Although these results seem to be promising, it is still difficult to generalize the use of this nutrient for this population due to the heterogeneity found among clinical trials in the literature (different doses used and lack of surgery type stratification).

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