Original Article

Glutamine for chemotherapy induced diarrhea: a meta-analysis

Juxian Sun MD[1], Hui Wang MD[2], Heping Hu MD[2]

[1]*Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China*
[2]*Department of Liver disease, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China*

The clinical efficacy of glutamine in the control of chemotherapy-induced diarrhea remains controversial. We conducted a meta-analysis, including as many randomized control trails (RCTs) as possible, to clarify the effectiveness of prophylactic glutamine in patients requiring chemotherapy. Methods: the Embase, MEDLINE, Cochrane Library, and BIOSIS databases were searched, and the included studies were RCTs that compared the use of prophylactic glutamine versus placebo in patients receiving chemotherapy. The main outcomes were diarrhea severity and duration. Results: a total of 298 patients in eight RCTs were reviewed (147 patients who received glutamine, and 151 patients who received placebo). There was a statistically significant difference in the duration of diarrhea (weighted mean difference (WMD), -1; 95% confidence interval (CI), -1.73, -0.26) between the two groups, but there was no significant difference in the severity of diarrhea (WMD, -0.49; 95% CI, -1.36, 0.39) between the groups. Conclusion: we concluded that glutamine could reduce the duration of diarrhea but could not improve its severity.

Key Words: glutamine, diarrhea, chemotherapy, meta-analysis, prophylactic

INTRODUCTION

Most commonly, chemotherapy is a systemic therapy, which means that it affects the entire body via the bloodstream. Chemotherapy targets rapidly dividing cells, meaning that it also harms normal cells with high turnover rates such as those lining the digestive tract. Many of the major adverse effects of chemotherapy are related to the loss of the mucosal integrity of the gut epithelium, which might be associated with increased risks of bacteremia and endotoxemia.[1,2] The primary clinical manifestation of this adverse effect is diarrhea. To prevent chemotherapy-induced diarrhea and improve the quality of life of patients, it is important to promptly provide powerful treatment. Traditionally, medical treatment of chemotherapy-induced diarrhea has included the use of nonspecific agents, such as the opiate preparations paregoric, atropine, and loperamide.

Glutamine is the major energy source for rapidly dividing cells such as enterocytes[3] and plays important roles in gut integrity and immunologic responses. It might be useful in healing the gastrointestinal mucosa after chemotherapy-induced damage and may ameliorate the clinical manifestation of this damage.[4] In addition, a number of clinical studies have attempted to clarify its anti-diarrheal effects.[1,3,5-7]

However, the clinical efficacy of glutamate in the control of chemotherapy-induced diarrhea remains controversial; some investigators have reported the efficacy of glutamine in alleviating diarrhea to be disappointing,[1, 5, 8-12] whereas others found it to be ineffective.[2,13] The common shortcoming of these studies has been small sample sizes, making these trials less representative. Therefore, we conducted the current meta-analysis, including as many randomized control trails (RCTs) as possible, to clarify the effectiveness of prophylactic glutamine in patients requiring chemotherapy. Bone marrow transplant (BMT) patients were also included in our protocol.

METHODS

A meta-analysis of relevant RCTs comparing the effects of glutamine and placebo on chemotherapy-induced diarrhea was undertaken. The Embase, MEDLINE, Cochrane Library, and BIOSIS databases were searched using the following combinations of search terms: glutamine/Gln, chemotherapy or BMT, diarrhea, RCTs, and human subjects. Only studies written English or Chinese were searched. The papers were retrieved to identify relevant studies for inclusion in the meta-analysis.

The criteria for inclusion in the meta-analysis were as follows: the patients were randomized; the groups differed in that one group received glutamine and the other group served as control; and the results were reported clearly. All studies were examined to identify parameters

Corresponding Author: Dr Heping Hu, Department of Liver disease, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, No.225 Changhai Road, Shanghai, China, 200438.
Tel: +862181875254; Fax: +862165566851
Email: heping_hu@126.com.
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that could be compared. The data were extracted from the text and tables within the studies. Data from the studies were independently examined by the authors of this study. If data were not available in the original publication, the authors of those studies were contacted via email to request this information.

The eligible studies were graded using a 5-point scale in which a score of 1 was given for each of the following components, as described by Jadad *et al*[14]: the description of the study as randomized; the description of an appropriate method of randomization; the description of the study as double-blind; the description of an appropriate method of double-blinding; and a statement of withdrawals. As non-randomized studies were excluded, the minimum score was 1, and the maximum score was 5. All studies were scored individually, compared and discussed where the scores were different. We were able to compare the therapeutic results between the studies.

Quantitative analyses were performed using Review Manager software (RevMan for Windows, version 5.0; The Cochrane Collaboration, Oxford, UK, 2008), which calculates the odds ratio for dichotomous data or the weighted mean differences (WMDs) for continuous data between the experimental and control groups for each study, with an overall estimate of the pooled effect. Review Manager was used to perform heterogeneity analyses; data that were not significantly heterogeneous ($p>0.05$) were analyzed using a fixed effects model, and heterogeneous data ($p<0.05$) were analyzed using a random effects model.

RESULTS

There were 20 English research studies identified by our search strategies. All full-text articles were reviewed. Finally, eight studies[2,5,8-13] were included in the meta-analysis. A total of 298 patients were included in these eight RCTs: 147 patients received glutamine, and 151 patients received placebo. The characteristics of the included studies are shown in Table 1. Based on the overall results of the meta-analysis, we found that glutamine nificantly reduced the duration of diarrhea compared with placebo (WMD, −1; 95% confidence interval (CI), −1.73, −0.26; Figure 1). In the subgroup analysis, we found that oral glutamine significantly reduced the duration of diarrhea (WMD, −1.06; 95% CI, −2.01, −0.11; Figure 1), but intravenous glutamine was ineffective in this regard (WMD, −0.89; 95% CI, −2.07, 0.28; Figure 1).

The common toxicity criteria grades for diarrhea were defined as follows: grade 0, none; grade 1, increase of <4 stools/day over pretreatment; grade 2, increase of 4–6 stools/day or nocturnal stools; grade 3, increase of >7 stools/day, incontinence, or the need for parenteral support for dehydration; and grade 4, physiological consequences requiring intensive care or hemodynamic collapse. Our findings suggested that glutamine could not improve the severity of diarrhea (WMD, −0.49; 95% CI, −1.36, 0.39; Figure 2). Statistical heterogeneity was identified for overall rates ($p<0.00001$), and thus, a random effects model was utilized ($p<0.00001$).

DISCUSSION

It has been proven that chemotherapy can induce bacterial translocation and intestinal barrier dysfunction in animal studies.[15] Glutamine is the most abundant free amino acid in the human body, and it is essential for the growth of normal and rapidly proliferating cells. Maintaining the the integrity of the intestine.[13,16] During episodes of catabioenergetics of these cells is fundamental to maintaining

Table 1. Controlled prospective trials of the effects of glutamine on chemoradiotherapy-induced diarrhea

Study (Jadad score)	Year of publication	Indication	No. of patients	Dose/route	Duration	Response	
						Diarrhea Score	Duration of Diarrhea (d)
Li Y et al[2] (Jadad score 4)	2009	Gastrointestinal cancer	T† 22 P‡ 22	Gln§ 20 g/d I.V¶ Placebo	5d††	1.31±0.25 2.82±0.34	NA NA
Sornsuvit C et al[5] (Jadad score 2)	2008	Acute Myeloid Leukemia	T 8 P 8	Gln 30 g/d I.V Standard amino acid mixture	5d	1.5±1.0 1.1± 1.4	5.0±3.7 4.3±5.7
Pytlík R et al[8] (Jadad score 4)	2002	Autologous transplant	T 21 P 19	Gln 20 g/d I.V Isonitrogenous aminoacide	NA	NA NA	3.3±4 4.3±3
Daniele B et al[13] (Jadad score 4)	2001	Colorectal cancer	T 29 P 33	Gln 18 g/d Oral Placebo	20d	0.76±1.1 0.97±1.07	3.7±2.5 4.9±2.3
Coghlin Dickson TM et al [9] (Jadad score 4)	2000	Bone marrow transplants	T 29 P 29	Gln 30 g/d Oral Placebo	Until discharge	NA NA	2±3.5 3±2.25
Bozzetti F et al[12] (Jadad score 2)	1997	Advanced breast cancer	T 33 P 32	Gln 30 g/d I.V Placebo	8d	NA NA	2±3 3±3
Jebb SA et al[11] (Jadad score 2)	1995	Bone marrow transplants	T 12 P 12	Gln 16 g/d Oral Placebo	Until discharge	NA NA	3.1±3.5 3.3±3.7
van Zaanen HC et al[10] (Jadad score 2)	1994	Hematologic patients	T 10 P 10	Gln 40 g IV Placebo	3 weeks	0±0.3 0.3±0.35	NA NA

Data are shown as the mean ± SD; †T, treatment; ‡P, placebo; §Gln: Glutamine; ¶IV: Intravenously; ††d, days.

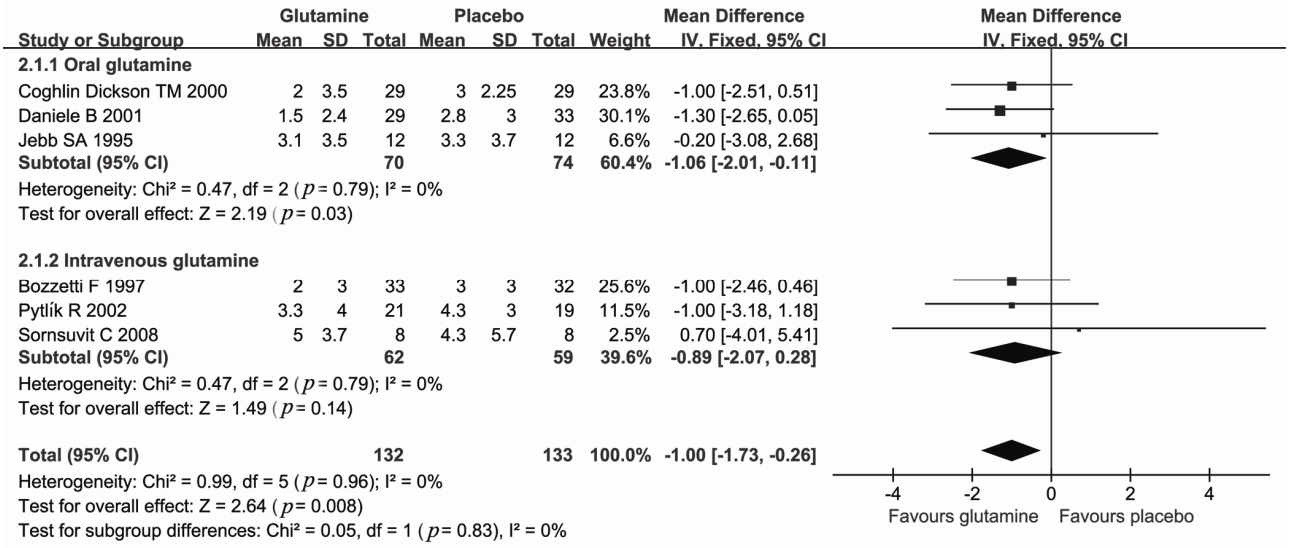

Figure 1. Meta-analysis of the duration of diarrhea in randomized controlled trials comparing glutamine and placebo. The results revealed a benefit of glutamine in reducing the duration of diarrhea, particularly in the oral glutamine subgroup. CI, confidence interval. Chi^2, Chi-square.

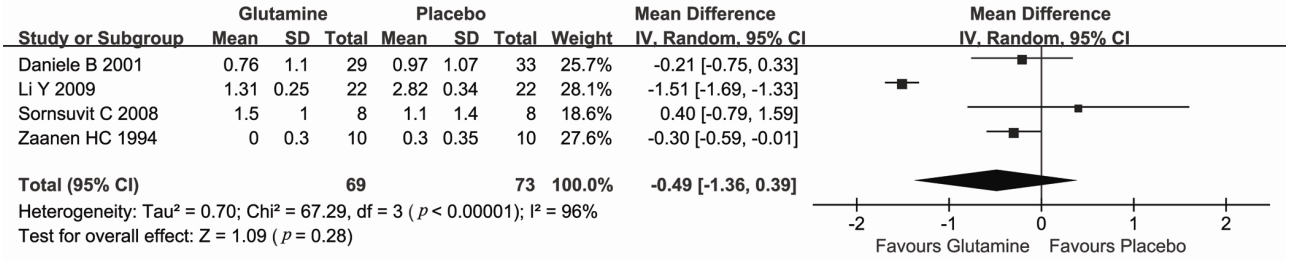

Figure 2. Meta-analysis of diarrhea scores in randomized controlled trials comparing glutamine and placebo. The results indicated that glutamine did not improve the severity of diarrhea. CI, confidence interval. Chi^2, chi-square.

bolic stress, there is a marked intracellular depletion of glutamine.[17]

Glutamine has been demonstrated in numerous studies to reduce intestinal permeability, which can be increased by chemotherapy.[2,18] Therefore, we believe that glutamine would be effective for controlling chemotherapy-induced diarrhea. However, the effects of glutamine in patients with diarrhea induced by chemotherapy remain controversial. Many RCTs have discussed this topic, but the findings have been inconsistent for a number of reasons. Thus, we conducted this meta-analysis, which included eight RCTs, to clarify this issue. In this study, we concluded that glutamine can reduce the duration of diarrhea, but it could not improve its severity.

Li *et al.*[2] evaluated the use of glutamine for chemotherapy-induced diarrhea in gastrointestinal cancer patients in a randomized cross-over study. In this study, patients with gastric or colorectal cancer who exhibited grade 2 or higher side effects according to the WHO side-effect grading system were randomly assigned to receive a dose of 20 g of glutamine or placebo intravenously. According to their findings, glutamine reduced plasma endotoxin levels and the severity of diarrhea. One serious concern of this trial was that endotoxin levels were used to assess intestinal permeability instead of the lactulose-mannitol test. Another clinical study[1] conducted by this group demonstrated that oral glutamine could not ameliorate stomatitis and diarrhea, although it did reverse chemotherapy-induced increases in intestinal permeability.

Sornsuvit *et al* [5] used a somewhat higher dose of glutamine (30 g, IV) for diarrhea prevention in acute myeloid leukemia patients receiving chemotherapy. The prophylactic use of glutamine did not significantly reduce the severity or duration of diarrhea, although it enhanced neutrophil phagocytic function and maintain nutritional status. However, this study only included eight patients in each group, which decreased its reliability.

A study by Pytlík *et al.*[8] evaluated the effects of glutamine in autologous transplant patients. Their study was a randomized trial of 20 g per day of parental glutamine given at the start of chemotherapy. Although patients in the glutamine group had a longer hospital stay, more severe oral mucositis, and a more costive condition, they had fewer days with diarrhea. In addition, this study included a heterogeneous patient population. Other studies also discussed the use of glutamine in BMT patients; however, we were primarily concerned with its diarrhea-preventing effects. Despite the mostly disappointing results, the data from these studies tended to support the idea that parenteral glutamine supplementation reduced the duration of diarrhea. The small number of patients in these trials is a possible cause of the lack of significant differences.

Bozzetti *et al* [12] assessed the efficacy of glutamine in

preventing doxifluridine-induced diarrhea in a double-blind randomized trial including 65 patients. Patients received 30 g of glutamine per day (divided into three doses of 10 g each) or placebo for 8 consecutive days between chemotherapy. The glutamine group tended to have fewer days with diarrhea. Although this article assessed the severity of diarrhea in these patients, no accurate data were found or calculated, and thus, we were unable to include the data of this study in Figure 2.

Daniele *et al* [13] evaluated the efficacy of glutamine in preventing FU(fluorouracil)-induced intestinal toxicity in a double-blind, placebo-controlled, randomized trial. Patients treated with fluorouracil were randomly assigned to receive either 18 g of oral glutamine per day or placebo 5 days before chemotherapy. Though the duration and severity of diarrhea were not statistically different between the two groups, the researchers found that glutamine could prevent FU-induced changes in intestinal absorption and permeability, supporting the protective effect of glutamine on chemotherapy-induced diarrhea.

The four randomized controlled trials [2,5,10,13] assessing the effects of glutamine on the severity of diarrhea differed significantly from each other, suggesting that combining them for statistical analysis may not be valid. These trials differed in terms of the internalizing standard, the doses used, and the routes and duration of glutamine administration. Ultimately, our results were disappointing.

We cannot precisely explain why glutamine decreased the duration of diarrhea without improving its severity, but a possibility is that although glutamine could not prevent the death of enterocytes induced by chemotherapy, it did accelerate mucosal regeneration. Leitão *et al* [19] also revealed that glutamine accelerates mucosal recovery, increasing mucosal tissue glutathione stores and hastening re-epithelization. Other mechanisms by which glutamate improves gastrointestinal toxicity have been investigated, such as its down regulation of Toll-like receptor-4 and myeloid differentiation gene 88 expression and improvement of intestinal recovery after intestinal mucosal damaged caused by LPS endotoxemia.[20]

In the subgroup analysis, oral glutamine, but not intravenous glutamine, significantly reduced the duration of diarrhea. This finding does not appear to be related to the small numbers of clinical trials and patients included in this meta-analysis It is well established that the presence of food in the gut lumen is an important stimulus for mucosal cell growth, and MacFie[21] reported that the energy source of enterocytes was primarily located in the intestinal lumen and not in blood. Glutamine can exert an atrophic effect on mucosal cells, and oral glutamine reduced the severity of enterocolitis induced by toxic doses of methotrexate in rats.[22] Another paper reported that intravenous glutamine could not preserve small-bowel mucosal height.[23] The aforementioned reason might be the cause of this finding, but there is not sufficient clinical evidence to support the view that oral glutamine would be better. Additional clinical trials comparing the effects of oral and intravenous glutamine on chemotherapy-induced diarrhea are necessary.

Studies have provided limited evidence that glutamine supplementation has a benefit for patients with radiation-induced diarrhea.[24] Studies of high-quantity with large sample sizes should be conducted in the future; however, glutamine should not be used at present to prevent diarrhea during radiotherapy, but this agent can be administered prophylactically to patients receiving chemotherapy. It can reduce the duration of diarrhea, thus reducing hospital stay.

Human hepatoma cells consume glutamine at a 5–10-fold faster rate than normal hepatocytes.[25] This finding indicated that parental glutamine would stimulate tumor growth. However, RCTs revealed that glutamine did not have any impact on the tumor response to chemotherapy.[1,9]

Allocation concealment, an important source of bias, was commonly unclear, whereas many studies did not utilize double-blinding. Negative studies are less likely to be submitted or accepted for publication, and considerable variation can exist between studies in terms of interventions and clinical circumstances. Quantitative meta-analyses are limited by heterogeneity in study design and small study sizes. However, despite these weaknesses, meta-analysis is considered a reliable source of evidence. Furthermore, a large, well-designed, prospective, randomized trial is necessary to confirm these findings.

Conclusion

We concluded that glutamine could reduce the duration of diarrhea, but it could not improve its severity.

AUTHOR DISCLOSURES

The authors report no conflicts of interest.

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Juxian Sun MD[1], Hui Wang MD[2], Heping Hu MD[2]

[1]*Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China*
[2]*Department of Liver disease, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China*

谷氨酰胺与化疗相关性腹泻的荟萃分析

摘要:谷氨酰胺在预防化疗相关性腹泻中的临床疗效仍存在争议，因此本次荟萃分析纳入了尽可能多的临床随机对照研究，来明确谷氨酰胺在预防化疗性腹泻中的疗效。方法：搜索 EMBASE 数据库、Medline 数据库、Cochrane 图书馆和 BIOSIS 数据库，所有比较谷氨酰胺与安慰剂对预防化疗相关性腹泻作用的随机对照研究均纳入本次荟萃分析。主要分析结果为腹泻评分和腹泻天数。结果：8 个随机对照研究，共 298 名患者纳入了本次研究，其中谷氨酰胺组 147 名，安慰剂对照组 151 名。两组腹泻天数有很大差别(WMD, -1; 95%可信区间: -1.73, -0.26)，但是腹泻评分无明显差别(WMD, -0.49; 95%可信区间: -1.73, 0.39)。结论：谷氨酰胺可以减少化疗相关性腹泻的天数，但可能无法减轻腹泻程度。

關鍵字：谷氨酰胺、腹泻、化疗、荟萃分析、预防性