Research Article

Oral L-glutamine as A Shield against Chemotherapy Induced Mucositis: Evidence from A Cross-Sectional Study

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ABSTRACT

Background: Chemotherapy-induced mucositis (CIM) is a notable side effect of cancer therapy, causing painful sores and inflammation throughout the digestive system. L-glutamine, a conditionally essential amino acid, has demonstrated promise in alleviating CIM by supporting mucosal healing and immune function. Nevertheless, ensuring patients consistently take glutamine supplements remains problematic.

Purpose: This research assesses the efficacy of L-glutamine in CIM prevention and investigates its association with mucositis severity and patient compliance.

Methodology: A six-month cross-sectional study was performed at a tertiary healthcare facility. The study included 104 CIM-diagnosed patients. Information was gathered through direct questioning and examined using descriptive statistics and Chi-square test. Mucositis severity was classified using the CTCAE scale, and adherence to glutamine supplementation was evaluated.

Results: Compliant patients did not experience severe mucositis (grade 3/4), while 63% of non-compliant patients developed grade 3 or 4 mucositis ($p < 0.05$). Non-adherence, observed in patients, was primarily due to expense and palpability issues. Glutamine significantly decreased the occurrence of severe CIM ($p < 0.0001$). Mucositis was most frequently observed in the mouth (31%) and intestines (26%).

Conclusion: L-glutamine effectively prevents severe CIM, highlighting its importance as a supportive treatment. Initiatives to enhance adherence, such as reducing costs and educating patients, are essential for improving outcomes. Additional studies are necessary to determine long-term benefits and develop strategies to increase compliance.

Keywords: Chemotherapy, Mucositis, L-glutamine, adherence.

INTRODUCTION

Mucositis, a typical side effect of chemotherapy, is characterised by ulcerative and/or inflammatory lesions of the gastrointestinal system and/or mouth cavity that are typically brought on by various cancer treatments. The expression of mucosal injury along the oral and gastrointestinal mucosa continuum, from the mouth to the anus, is referred to as alimentary tract mucositis[1]. Although the exact pathophysiology of oral mucositis is unknown, both direct and indirect processes are assumed to be involved. The usual 5- to 14-day turnover time of the oral epithelium is disrupted and apoptosis is induced by direct mucosal injury caused by chemotherapy[2].

Some of the guidelines for the prevention of mucositis in receiving chemotherapy are listed below. For patients undergoing bolus 5-FU treatment, oral cryotherapy (30 min) is advised as a preventative measure against oral mucositis [II, A][3]. For patients receiving bolus doses of edatrexate, oral cryotherapy (20–30 min) is advised to reduce mucositis [IV, B]. It is not advised to use acyclovir or its analogues to stop mucositis brought on by standard-dose chemotherapy [II, B][4]. Apart from the March 2019 guidelines published by MASCC/ISOO, a study conducted after the completion of literature reviews proposed the potential benefit of keratinocyte growth factor-1 (palifermin) at a dose of 40 µg/kg/day for three days in preventing oral mucositis in patients undergoing bolus 5-FU plus leucovorin [II, B][5].

One of the nonpharmacologic strategies for preventing oral mucositis is glutamine. Although the exact process by which glutamine shields the oral mucosa is unknown, it is believed to facilitate the mucosal cells' quick growth and act as a precursor to the production of glutamate, glutathione, and nucleotides[6]. It is the most prevalent amino acid in our body. It is a major energy source and a necessary building block for the production of nucleotides in quickly proliferating cells such as lymphocytes, enterocytes, fibroblasts, and macrophages. Consequently, in these cell types, glutamine is categorized as an amino acid that is conditionally necessary. Moreover, glutamine has antioxidant qualities and acts as a substrate for the creation of glutathione[7]. Reduced plasma glutamine levels are the result of the body's inability to synthesise enough of this amino acid during periods of extreme stress. In these circumstances, there is a detrimental impact on mucosal immunity and a reduction in glutamine release from muscle tissues. It has been reported that patients receiving cytotoxic therapy for advanced cancer experience glutamine deficit[8]. Considering the tissue level, glutamine is

crucial for preserving the regular integrity of the intestinal mucosa. Over time, cancer patients experience marked glutamine depletion, which leads to cancer cachexia and compromises immune system function, acid-base balance, and gut epithelial integrity. This has a negative effect on host tissues' ability to function optimally, which depends on glutamine stores[9]. For the prevention of OM, oral (PO) and/or swish and spit glutamine was recommended for patients with H&N cancer undergoing concomitant chemotherapy and radiation treatment. There was no MASCC/ISOO guideline for oral glutamine in other populations, such as patients with solid tumors and patients undergoing HSCT, because of insufficient or contradictory data. According to the recommendations, however, parenteral (intravenous) glutamine should not be used to prevent OM in patients receiving HSCT. With all of the aforementioned considerations in mind, the panel advised against using parenteral glutamine to avoid OM in patients receiving HSCT[10].

The field of therapeutics and preventative care is always changing, and new medications and supportive care techniques could help lessen the severity of mucositis and enhance patient outcomes. In order to reduce the burden of mucositis and improve the general health of cancer patients receiving chemotherapy, further study is necessary to improve current strategies and investigate novel ones.

METHODOLOGY

Study design and setting

This cross-sectional study was conducted for a period of 6 months at a tertiary care hospital. The study protocol was approved by the Institutional Ethics Committee (IEC). All procedures followed ethical guidelines as per the Declaration of Helsinki. The STROBE guideline has been followed for this study design, and the flow chart is shown in Figure 1.

Study population

This study included all the patients who were above the age of 18 years diagnosed with chemotherapy-induced mucositis.

Sample size calculation

The sample size was calculated as 104 using the OpenEpi Software, with a confidence interval of 95%, and margin of error ±5.

Data collection and study procedure

The adherence of the mucositis patient was assessed through direct interviews with patients. The data collected from the patient was documented and analysed.

Statistical analysis

The collected data were analysed using Microsoft Excel and SPSS version-23. Categorical data were presented as frequency and percentage. The patient's adherence is compared with the severity of mucositis using the Chi-square test. P-value < 0.05 was considered statistically significant at a 5% significance level to the confidence interval of 95%.

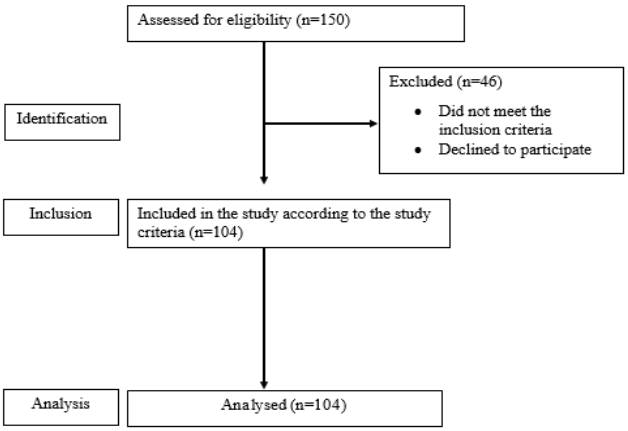

Figure 1: STROBE Flow Chart

RESULTS

A total of 104 patients were included in the study. Table 1 demonstrates the demographics and clinical data of the patients. Most patients were aged 41-60 years (54%) and 75% female. BMI distribution showed that 42% of patients were overweight, while 38% had a normal BMI. A significant portion 53% had a BSA of less than 1.6 m². Mucositis occurred primarily in the mouth (31%) and intestine (26%), with 35% of patients experiencing grade 2 and grade 3 severity.

Table 1: Demographics and Clinical Data of the Study Population

Parameter	Frequency (n=104)	Percentage (%)
Age		
21-40	11	10
41-60	56	54
61-80	37	36
Gender		
Male	26	25
Female	78	75
BMI		
Underweight	6	6
Normal	39	38
Overweight	44	42
Obese	15	14
BSA		
<1.6m^2	55	53
1.6-1.8m^2	23	22
>1.8m^2	26	25
Site of mucositis		
Mouth	32	31
Intestine	27	26
Stomach	9	8
Mouth and Intestine	23	22
Mouth and Stomach	5	5
Others	8	8

Cycle when mucositis was observed		
1	45	43
2	25	24
3	14	13
4	10	10
5	5	5
6	5	5
Severity		
1	18	17
2	36	35
3	36	35
4	14	13

The percentages of adherence and non-adherence to L-glutamine for the prevention of mucositis in chemotherapy patients were assessed, and the majority of the patients (63%) were non-adherent as shown in Table 2.

Table 2: Adherence to L-Glutamine

Adherence	Frequency (n=104)	Percentage (%)
Yes	38	37
No	66	63

Table 3 illustrates the association between the patient's severity of mucositis and their adherence to L-glutamine where the non-adherent patients experienced grades 3 and 4 of severity whereas adherent patients did not experience severe grades and their association was also found to be significant.

Table 3: Association of Adherence to L-Glutamine and Severity of Mucositis

Adherence	Severity				P-value
	1	2	3	4	
Adherent	14(13)	24(23)	0(0)	0(0)	<0.0001*
Non- Adherent	2(2)	11(11)	38(37)	15(14)	

Table 4 illustrates the treatment given to the patients who experienced CIM with the majority of the patients receiving L-glutamine 50 (48%) followed by benzydamine mouthwash 31(30%).

Table 4: Treatment of mucositis

S. No	Treatment	Frequency	Percentage (%)
1	Glutamine	50	48
2	Pantoprazole	18	17
3	Sucralfate	15	14
4	Lactilol+ Isaphagulla	1	1
5	Cremmaffin	3	3
6	Multivitamin	16	15
7	Loperamide	21	20
8	Probiotics	5	5
9	Paracetamol	6	6
10	Choline salicylate + Lidocaine	18	17
11	Benzydamine	31	30
12	Lactulose	8	8
13	Racecadotril	12	12
14	Chlorhexidine	2	2
15	Octreotide	3	3

DISCUSSION

The body's most prevalent free amino acid is glutamine. Its metabolic characteristics are significant and distinct. DNA synthesis, cell division, and cell growth—all of which are required for wound healing and tissue repair—require free and plentiful glutamine in the bloodstream and intracellular pools[11]. Glutamine has been demonstrated to be the primary respiratory fuel for the digestive tract in several animal species. Patients with advanced cancer may develop glutamine deficit as a result of receiving cytotoxic medication[12]. The significance of glutamine in preserving cellular integrity and minimizing tissue damage has been emphasized in a number of studies, particularly when it comes to chemotherapy-induced mucositis (CIM).

The infusion of glutaminase resulted in patchy areas of necrosis, intestinal mucosal ulceration, and oedema due to the lowering of plasma glutamine levels[13]. Glutamine depletion is a common side effect of chemotherapy, especially in patients taking cytotoxic drugs like cisplatin. This can cause a number of harmful side effects, such as intestinal mucosal ulceration, necrosis, and edema. These results are consistent with earlier studies, such as one by Nose et al., which showed that by boosting cellular repair mechanisms and glutamine transport, bolus enteral glutamine injection in rats could prevent cisplatin-induced intestinal mucosal damage[14].

In our study, we sought to evaluate the effectiveness of glutamine supplementation in reducing the severity of chemotherapy-induced mucositis. We used the CTCAE scale to analyse the severity of mucositis in 104 patients and found that 35% of patients had moderately severe grade 2 and grade 3 mucositis, followed by mild grade 1 mucositis in 17% of patients and grade 4 severe mucositis in roughly 13% of patients. In contrast to previous studies by Noriko Nishimura et al. [15], Vagliano L et al.[16], and Seher Cakmak RN

et al.[17], where grade 3 was uncommon—just 4.8% and 21%, respectively—our study had a greater incidence of grade 3.

Because of differences in their genetic manifestations, mucositis can affect any part of the GI tract, but it is more common in the mouth and small intestines. While intestinal mucositis has received relatively little attention, there are numerous research based on oral mucositis. While intestinal mucositis lacks clear diagnostic criteria, oral mucositis can be easily identified through clinical examination. In our study, mucositis was most commonly found in the mouth (31%) and intestinal (26%). Approximately 22% of patients experienced intestinal and oral mucositis. Rarely, the colon and rectum, two sections of the large intestine, were also impacted.

In cases of severe mucositis, therapeutic options include reducing the dosage and stopping the medication. One of the most important aspects of controlling mucositis is symptom control and preventing complications. Symptomatic treatment is administered to patients with mild to severe mucositis. The majority of patients are provided L-glutamine (48%) powder, a mucosal protective agent, and benzydamine (30%) gargles, which are most often prescribed for oral ulcers. To lessen oral pain and discomfort, choline salicylate gel and lidocaine were administered to individuals with grades 2 and 3. Lactulose or combination syrups were used to cure constipation, while loperamide and racecadotril were used to treat diarrhea. Additionally, multivitamins, zinc, and other minerals, particularly vitamin B complex, were prescribed to the patients. Patients were able to continue their chemotherapy and recover more quickly with these symptomatic therapies.

All the 104 patients diagnosed with mucositis were prescribed L-glutamine as a preventive measure. However, only 37% of the patients took l-glutamine as prescribed. None of the adherent patients experienced grade 3 or 4 mucositis, whereas 63% of the non-adherent group experienced grades 3 and 4 mucositis. The factors for non-adherence in this setting was observed to be due to the high cost of the drug, bad taste, and sourness etc. While there was no significant reduction in the overall incidence of mucositis, glutamine dramatically reduced the incidence and duration of grade 3 and grade 4 mucositis (P value 0.000). This aligns with another study by Nur Aisiyah Widjaja et al., only 4.2% of the population who received L-glutamine experienced OM, and their hospital stay was also shortened[18], while 62.5% of the placebo group experienced mucositis. Peng TR et al. (2021) assessed how well glutamine works to treat OM in cancer patients and found that it dramatically lowers the risk of OM while undergoing chemotherapy[19].

The effectiveness of L-glutamine in combating and treating chemotherapy-induced mucositis seems to be strongly related to its capacity to sustain mucosal health and boost cellular regeneration processes. Glutamine, an essential amino acid for rebuilding intestinal and oral mucosa, shows promise as a therapeutic strategy for reducing mucositis severity, especially in patients receiving intensive chemotherapy. Nevertheless, ensuring patient compliance remains a significant hurdle. While our research emphasizes the value of glutamine supplementation, it also highlights the necessity for better patient education and assistance to guarantee consistent adherence to prescribed treatment plans.

CONCLUSION

Glutamine is essential for preserving mucosal health and promoting cell regeneration, making it a potential therapeutic approach for addressing chemotherapy-induced mucositis (CIM). Our research demonstrates the considerable efficacy of glutamine supplements in reducing the severity of grade 3 and 4 mucositis. This is evident from the notable contrast in mucositis severity observed between patients who adhered to the supplementation regimen and those who did not. However, despite its proven advantages, patient non-compliance due to factors such as expense and palatability remains a significant obstacle to overcome.Subsequent studies should concentrate on extensive clinical trials to validate these results across various patient groups and examine the long-term advantages of glutamine supplementation. Investigating innovative delivery methods, such as extended-release formulations or flavor-masked alternatives, could improve adherence. Furthermore, research combining glutamine with other supportive care measures might yield comprehensive strategies to enhance patient outcomes during chemotherapy treatment.

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