

## Original Article

**Running Title:** The Effect of Glutamine Mouthwash on Mucositis Prevention in Pediatric Acute Lymphoblastic Leukemia

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### **The Impact of Glutamine Mouthwash on Preventing Mucositis Following Administration of High Doses of Methotrexate in Children with Acute Lymphoblastic Leukemia: A Randomized Clinical Trial**

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#### **Abstract**

**Background:** Acute lymphoblastic leukemia (ALL) represents the predominant childhood cancer. High-dose methotrexate is integral to leukemia treatment protocols. This study aimed to explore the efficacy of glutamine in preventing mucositis among leukemia patients undergoing high-dose methotrexate therapy.

**Method:** This randomized clinical trial encompassed 45 patients (22 in the glutamine group and 23 in the placebo group). The intervention group was administered a glutamine mouthwash, while the control group received an identical placebo. Data analysis was performed using SPSS version 23, with a significance threshold set at  $P < 0.05$ .

**Results:** No significant difference emerged between the groups concerning the incidence of nausea and vomiting; however, both groups observed a notable reduction in nausea frequency from the first to the fourth days ( $P = 0.0001$  and  $P = 0.040$ , respectively). Grades III and IV mucositis were absent in both groups on the third and seventh days post-treatment. Furthermore, no significant difference was detected in mucositis improvement between the groups ( $P = 0.848$ ).

**Conclusion:** Glutamine mouthwash significantly reduced the incidence of nausea and vomiting, which are common chemotherapy complications. Moreover, up to 95% of patients were free from mucositis by the seventh-day post-chemotherapy.

**Keywords:** Glutamine, Chemotherapy, Mucositis, Child

## **Introduction**

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood, and the B cell type is the most common form of ALL.<sup>1</sup> According to prognosis factors, about 80 to 85% of these patients are cured with new treatment protocols.<sup>2-4</sup> The most important determining factor of prognosis in these patients is the type of treatment received and the protocol used.<sup>5</sup> Different protocols have been used to treat these patients over the years. One of the most commonly used protocols worldwide for treating these patients is the COG (children's oncology group) protocol.<sup>5,6</sup> One of the drugs that is used in this protocol is methotrexate. Methotrexate is a folic acid antagonist used as an effective drug in treating many malignancies like leukemia and lymphoma; this drug works by inhibiting DNA synthesis in the S phase of cell division.<sup>7</sup> Mucositis incidence and oral mucosal inflammation are determined as essential side effects in patients treated with high doses of methotrexate.<sup>8</sup> The incidence rate in patients with a standard dose of methotrexate has been reported to be 18 to 52%; in higher doses, the rate is up to 80%.<sup>9</sup> In addition to causing feeding disorders, mucositis leads to depression, increases infection risk, and prolongs hospitalization.<sup>10</sup> So far, different treatments have been proposed for mucositis arising from chemotherapy. Glutamine is an unnecessary amino acid essential in catabolic conditions such as malignancy.<sup>11</sup> Glutamine is essential for the proper function of the mucus membrane, and studies in adults have proved that using glutamine supplements can reduce the mucositis caused by chemotherapy.<sup>12</sup> The immunity of glutamine consumption in human and cancerous patients has been thoroughly proven.<sup>13</sup> Despite the systemic use of glutamine in preventing mucositis, few studies have been done on using this material as a mouthwash in mucositis prevention so far. The goal of the

present study is to evaluate the rate of glutamine mouthwash effect in the decrease of incidence and severity of mucositis in children receiving methotrexate in high doses with a clinical random trial study.

## **Material and Methods**

### ***Study design***

This randomized clinical trial was conducted at the Hematology-Oncology Department of Bou Ali Sina Hospital, Sari, Iran.

### ***Participants***

Children aged 5 to 10 years, diagnosed with ALL and undergoing treatment within the Hematology-Oncology Department of Bou Ali Sina Hospital were enrolled. Eligible participants were those in the first level of Interim Maintenance of the Children's Oncology Group (COG) chemotherapy protocol, receiving high doses of intravenous methotrexate (5 grams/m<sup>2</sup> over a 24-hour infusion).

### ***Inclusion criteria***

Eligibility was determined by the following criteria: age between 5 and 10 years, diagnosis of ALL, undergoing the COG chemotherapy protocol, treatment with high-dose methotrexate, absence of mucositis and nausea/vomiting before methotrexate administration, platelet count above 100×10<sup>3</sup>/μL, absolute neutrophil count above 1500/μL, hemoglobin levels exceeding 8 g/L, and the capability to retain mouthwash for 30 seconds every 8 hours.

### ***Exclusion criteria***

Exclusion criteria encompassed failure to use mouthwash as prescribed, occurrence of fever, administration of systemic or local antibiotics, non-study mouthwash, absence of dental examination on the fourth day, and presence of mucositis at the initial dental visit.

### ***Randomization***

Based on convenience sampling, participants were allocated into two groups receiving either glutamine (intervention group) or

placebo (control group). Random Allocation software was utilized for assignment, with each patient receiving a unique identifier.

### **Blinding**

The study implemented a double-blind approach, with the participating dentists and patients' parents unaware of the treatment allocation. Mouthwashes, indistinguishable in taste and color, were coded as either group one or group two.

### **Implementation**

Following group assignment via Random Allocation software, the project executor dispensed the designated mouthwash to the nursing staff. Nurses were responsible for monitoring the parents' adherence to mouthwash protocols at each usage.

### **Interventions**

The treatment plan was done from the start of a 24-hour infusion of methotrexate every 8 hours and at least 30 seconds of mouthwash in the mouth. In the witness group, patients received the standard mouthwash without glutamine as a placebo. In the case group, a mouthwash in a dish similar to the placebo was used for every patient, including placebo mouthwash material added to 16 grams per 260 milliliters of glutamine prepared by the project co-worker pharmacist in the pharmacy faculty. Project co-worker nurses monitored the proper usage of mouthwash, and if the patient was omitted from the study, the patient was omitted. In both groups, the frequency of nausea and vomiting and food consumption were registered daily. Patients were visited by the project co-worker's dentist again on the 4<sup>th</sup> day after receiving methotrexate and mucositis, registered according to the WHO criteria.<sup>14</sup> The patient was re-evaluated on the 7<sup>th</sup> day by the project co-worker's dentist in terms of the presence and severity of mucositis. When patients could not manage an adequate oral diet due to severe mucositis, nutrition supplementation was provided.

### **Sample size**

The required sample size was calculated to be 23 individuals in each group using the formula for estimating the sample size for comparing the two means and considering the 95% confidence level, the 80% power, the standard deviation of the cognitive impairment score obtained in other studies<sup>15</sup> by about 1.28, and the least significant difference between the two groups which was considered as 0.8.

### **Statistical methods**

Data analyses were performed using SPSS version 23. Quantitative data were presented as mean  $\pm$  standard deviation (SD), and comparisons between groups were conducted using the Independent T-test for continuous data and the chi-square test for categorical data. A *P*-value of less than 0.05 was deemed statistically significant. Welch's t-test was used to analyze continuous variables, while Fisher's exact test was used for categorical variables. The Kaplan-Meier method was applied to evaluate the time to onset of mucositis.

### **Ethical considerations**

Informed consent was obtained from all participants' parents or guardians before inclusion in the study. This research received ethical approval from the Ethical Committee of the Medical Sciences University of Mazandaran under the code IR.MAZUMS.REC.1398.1183 was registered at the Registration Center of Clinical Trials of Iran (IRCT) with the identifier IRCT20190202042583N2.

### **Results**

This study, a randomized clinical trial, aimed to assess the efficacy of glutamine mouthwash in preventing mucositis following high-dose methotrexate administration in children diagnosed with ALL at the Hematology-Oncology Department of Bou Ali Sina Hospital, Sari, Iran. A total of 45 patients participated,

divided into 22 patients in the glutamine intervention group and 23 in the placebo group. Patient recruitment is detailed in figure 1.

The demographic breakdown revealed that 54.5% of the glutamine group and 52.2% of the placebo group were male, indicating no significant gender difference ( $P = 0.783$ ). The mean age was  $5.57 \pm 2.97$  years in the glutamine group and  $6.21 \pm 2.83$  years in the placebo group, with no statistically significant difference ( $P = 0.574$ ). Examination of serum biochemical and hematological parameters showed no significant differences between the two groups, except for Blood Urea Nitrogen (BUN) levels, which were significantly lower in the glutamine group ( $P = 0.021$ ), suggesting a potential protective effect of glutamine mouthwash on serum BUN levels. Regarding nausea, no statistically significant difference was observed between groups from day one to day four. However, a significant reduction in nausea frequency was noted in both groups over the initial four days ( $P = 0.0001$  and  $P = 0.040$ , respectively), as analyzed by Generalized Estimating Equations (GEE). Vomiting frequency decreased significantly in both groups during the same period ( $P = 0.030$  and  $P = 0.0001$ , respectively) (Table 1).

Liquid and solid food intake from day one to day four showed no significant difference in liquid food consumption between the groups. However, the glutamine group exhibited a significant improvement in liquid ( $P = 0.0001$ ) and solid ( $P = 0.0001$ ) food intake by day four, as per GEE analysis, while no such improvement was noted in the placebo group for liquid food intake during the first four days ( $P = 0.111$ ) (Table 2).

Regarding mucositis severity, on day three, most patients in both the glutamine and placebo groups were classified as Grade I (86.4% and 69.6%, respectively,  $P = 0.327$ ). By day seven, 95% of the glutamine group

had Grade 0 mucositis, and 4.5% had Grade I, compared to 100% of the placebo group at Grade 0 mucositis. There were no Grade III or IV mucositis instances in either group on days three or seven. GEE analysis revealed no statistically significant difference in mucositis treatment outcomes between the glutamine and placebo groups ( $P = 0.848$ ) (Table 3).

## Discussion

This study was a randomized clinical trial study to investigate the effect of glutamine mouthwash on mucositis prevention following high doses of methotrexate in children with ALL. There was no statistically significant difference in mucositis improvement between the two groups, but in the glutamine group, the amount of nutrition in liquids and solids significantly improved. Mucositis and stomatitis are common side effects related to cancer chemotherapy. Although this is a common side effect that influences patients' quality of life, there are only a few treatments to reduce its severity or duration.

In a study that was performed on 32 patients with head and neck cancer going through chemoradiotherapy treatment, the effect of glutamine compared to placebo (normal saline) in reducing mucositis was evaluated. In the glutamine group, no patient developed grade 4 mucositis, whereas in the control group, 33% of patients developed grade 4 mucositis.<sup>16</sup> Like the mentioned study, the study also indicated that none of the patients developed grade 3 or 4 mucositis on days three and seven, and more than 95% of patients in the glutamine group showed that they were mucositis-free on day seven. Studies that were conducted on the efficacy of glutamine on chemotherapy side effects such as mucositis and diarrhea have been inconsistent and controversial.<sup>17-20</sup>

In a Taiwan study, intravenous glutamine's effect on mucositis reduction in patients

under 18 with ALL following high doses of methotrexate was evaluated. Out of 96 patients in the study, 72 were placed in the control group and 24 in the glutamine-receiving group. 48 hours after stopping methotrexate, the glutamine started at a dose of 0.4 g per kilogram of body weight and lasted for 3 days. In the glutamine-receiving group, mucositis was significantly lower compared with the control group (3.8% in the glutamine group versus 17.6% in the control group). However, in the study, no statistically significant difference was observed between mucositis incidence and its recovery rate in the glutamine and placebo groups. In the mentioned study, other side effects such as abdominal pain, diarrhea, nausea, and vomiting were reported less in the glutamine-receiving group.

In contrast, in the study, there was no statistically significant difference in the frequency of nausea and vomiting between the two glutamine and placebo groups. Moreover, in the mentioned study, no patients with grade 3 or 4 mucositis were seen from the glutamine-receiving group either, and the results of that study are similar to ours.<sup>21</sup> Studies on animal models have also provided methods on how glutamine can function to control cancer.

Some research has shown that glutamine dietary supplements increase the effectiveness of chemotherapy against rhabdomyosarcoma and reduce chemotherapy-related toxicity.<sup>22,23</sup> The effect of glutamine on malignant tumor growth has been extensively investigated.<sup>24</sup> Therefore, it seems that glutamine boosts the immune system, especially the activity of natural killer cells (NK), and consequently, it sustains balance and shrinks tumor growth.<sup>25,26</sup> Thus, from the studies that were primarily conducted on animals, it seems that glutamine has a therapeutic effect against cancer, and it can improve the host's immune

system and raise the ability to tolerate chemotherapy.<sup>27-29</sup>

In another study, the effects of oral glutamine on managing mucositis in children under chemotherapy were examined. In this study, 76 children who have gone through similar chemotherapy at least two times, once with oral glutamine and once without it, were investigated. This study also showed that there was not a significant correlation between the two groups in terms of mucositis incidence, and the findings of the study are similar to ours. Moreover, this study indicated that consumption of oral glutamine in high doses does not affect reducing nausea, stomach pain, vomiting, and chemotherapy-induced diarrhea,<sup>30</sup> however, in the study, there was a significant decrease in the number of nausea and vomiting episodes during the first four days in the group treated with glutamine. Additionally, a significant improvement in liquid and solid (foods) intake was seen in patients.

In another study, the effect of intravenous glutamine on 12 children aged 48 to 120 months suffering from Hodgkin's lymphoma was scrutinized. Thirty chemotherapy sessions with an intravenous glutamine dose of 0.04 milligrams per kilogram of body weight per day for seven days and then 31 sessions without glutamine were investigated. The results showed that 70% of the group that received glutamine experienced mucositis, while 74% of the group that did not receive glutamine also experienced mucositis. However, no significant difference was observed between the two groups.<sup>31</sup>

Generally, the frequency of mucositis incidence in their study was higher than ours after seven days. In fact, in the current study, only 4.5% of patients had mucositis grade 1, and 95.5% were mucositis-free on day seven. In a study conducted in 2000 in Taiwan, the effectiveness of glutamine as a mouthwash in reducing mucositis caused by chemotherapy

and radiotherapy in children was examined. Seventeen children with head and neck malignancies who received radiotherapy were evaluated in this pilot study. Eight patients in the study group used a 30cc glutamine solution containing 16 grams of glutamine in 240cc normal saline as a mouthwash for 3 minutes before each meal and before bedtime. The study's results indicated that the average maximum grade of severe mucositis in the glutamine group was significantly lower than in the control group. Also, the duration of mucositis was significantly shorter in all three grades of mucositis (grades 1, 2, and 3) in the glutamine group,<sup>32</sup> while in the study, no significant correlation was observed between the severity of mucositis in the two groups receiving glutamine and placebo.

In 2008, Sornsuvit et al. conducted a study on the effectiveness of intravenous glutamine supplementation in preventing chemotherapy-induced side effects in patients with acute myeloid leukemia (AML). They conducted a clinical trial study on 16 patients suffering from ALM. The patients were randomly included in two groups, one receiving intravenous glutamine supplementation (30 grams per day) and the other receiving an equivalent amount of a standard amino acid mixture (25 grams per day) on day 1 to day 5 of chemotherapy. In patients undergoing treatment with glutamine, the percentage of neutrophil phagocytosis was significantly higher than the placebo group. Also, patients undergoing treatment with glutamine had significantly less mucositis than the placebo group. This study demonstrated that intravenous glutamine supplementation enhances the performance of the phagocytic neutrophils, sustains nutritional status, and reduces mucositis.<sup>33</sup> However, that study was not consistent with ours regarding the effectiveness of glutamine on mucositis. The reported findings in the Sornsuvit study

demonstrated that the glutamine had a positive impact on mucositis, and that is perhaps because most of the patients in the glutamine group had less severe mucositis for a shorter period compared to the control group and given the small number of participants in the study, it was not possible to demonstrate a significant effect.

Choi et al. conducted another study on the effectiveness of oral glutamine on mucositis/stomatitis induced by chemotherapy. 51 patients with advanced or metastatic cancer undergoing chemotherapy with 5-FU and Leucovorin were included in the study. Also, 18 healthy individuals were included in the control group. After chemotherapy was stopped, mucositis and stomatitis were examined on day 7. Of 51 patients, 22 received oral glutamine (30 grams per day), and 29 received only supportive healthcare. Mucositis was seen in only 9% of patients receiving glutamine, as well as 38% of the patients in the control group, and glutamine supplements led to a mucositis and stomatitis incidence reduction in patients undergoing chemotherapy.<sup>34</sup>

Our study has some limitations. First, due to the lack of facilities, we could not study the pharmacokinetics of glutamine. Second, we conducted the study in a single center with a limited larger sample size. Further studies with larger sample sizes are recommended to scrutinize the effect of glutamine mouthwashes and other forms of glutamine, such as oral and topical. Also, it is recommended to scrutinize glutamine with various doses and concentrations.

## **Conclusion**

This investigation found no statistically significant difference in mucositis outcomes between children treated with glutamine mouthwash and those receiving placebo, nor were differences observed in the incidence of nausea and vomiting between the groups in the initial four days. However, both groups

experienced a significant reduction in nausea within the same timeframe. Notably, the glutamine group significantly improved liquid and solid food intake by the fourth day. These findings suggest that while glutamine mouthwash may not significantly alter mucositis severity or the frequency of nausea and vomiting, it could enhance nutritional intake in pediatric patients undergoing high-dose methotrexate treatment for ALL.

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### Conflict of Interest

None declared.

### References

1. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. *Pediatr Clin North Am.* 2015;62(1):61-73. doi: 10.1016/j.pcl.2014.09.006.
2. Hunger SP, Raetz EA. How I treat relapsed acute lymphoblastic leukemia in the pediatric population. *Blood.* 2020;136(16):1803-12. doi: 10.1182/blood.2019004043.
3. Bordbar M, Jam N, Karimi M, Shahriari M, Zareifar S, Zekavat OR, et al. The survival of childhood leukemia: An 8-year single-center experience. *Cancer Rep (Hoboken).* 2023;6(4):e1784. doi: 10.1002/cnr2.1784.
4. Elgarten CW, Aplenc R. Pediatric acute myeloid leukemia: updates on biology, risk stratification, and therapy. *Curr Opin Pediatr.* 2020;32(1):57-66. doi: 10.1097/MOP.0000000000000855.
5. Goudarzi Pour K, Eshghi P, Naderisorki M. A comparison of two chemotherapeutic regimens in children with B-cell acute lymphoblastic leukemia. *J Compr Ped.* 2018;9(4):e64153. doi:10.5812/compreped.64153.
6. Fish JD, Lipton JM, Lanzkowsky P. Lanzkowsky's manual of pediatric

hematology and oncology. 6<sup>th</sup> ed. London, United Kingdom: Academic Press; 2016.

7. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. *Haematologica.* 2020 Nov 11;105(11):2524.
8. Mohammed AI, Celentano A, Paolini R, Low JT, McCullough MJ, O' Reilly LA, et al. Characterization of a novel dual murine model of chemotherapy-induced oral and intestinal mucositis. *Sci Rep.* 2023;13(1):1396. doi: 10.1038/s41598-023-28486-3.
9. Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, Filipauskas A. Prevention and treatment of chemotherapy and radiotherapy induced oral mucositis. *Medicina.* 2019;55(2):25. doi: 10.3390/medicina55020025
10. Zobeck M, Bernhardt MB, Kamdar KY, Rabin KR, Lupo PJ, Scheurer ME. Novel and replicated clinical and genetic risk factors for toxicity from high-dose methotrexate in pediatric acute lymphoblastic leukemia. *Pharmacotherapy.* 2023;43(3):205-14. doi: 10.1002/phar.2779.
11. Cluntun AA, Lukey MJ, Cerione RA, Locasale JW. Glutamine metabolism in cancer: understanding the heterogeneity. *Trends Cancer.* 2017;3(3):169-80. doi: 10.1016/j.trecan.2017.01.005.
12. Peng TR, Lin HH, Yang LJ, Wu TW. Effectiveness of glutamine in the management of oral mucositis in cancer patients: a meta-analysis of randomized controlled trials. *Support Care Cancer.* 2021;29(8):4885-92. doi: 10.1007/s00520-021-06060-9.
13. Matés JM, Campos-Sandoval JA, Santos-Jiménez JL, Márquez J. Dysregulation of glutaminase and glutamine synthetase in cancer. *Cancer Lett.* 2019;467:29-39. doi: 10.1016/j.canlet.2019.09.011.
14. Villa A, Vollemans M, De Moraes A, Sonis S. Concordance of the WHO, RTOG, and CTCAE v4.0 grading scales for the evaluation of oral mucositis associated with

- chemoradiation therapy for the treatment of oral and oropharyngeal cancers. *Support Care Cancer*. 2021;29(10):6061-8. doi: 10.1007/s00520-021-06177-x.
15. Sayles C, Hickerson SC, Bhat RR, Hall J, Garey KW, Trivedi MV. Oral glutamine in preventing treatment-related mucositis in adult patients with cancer: a systematic review. *Nutr Clin Pract*. 2016;31(2):171-9. doi: 10.1177/0884533615611857.
16. Cerchietti LC, Navigante AH, Lutteral MA, Castro MA, Kirchuk R, Bonomi M, et al. Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2006;65(5):1330-7. doi: 10.1016/j.ijrobp.2006.03.042.
17. Anderson PM, Lalla RV. Glutamine for amelioration of radiation and chemotherapy associated mucositis during cancer therapy. *Nutrients*. 2020;12(6):1675. doi: 10.3390/nu12061675.
18. Huang CJ, Huang MY, Fang PT, Chen F, Wang YT, Chen CH, et al. Randomized double-blind, placebo-controlled trial evaluating oral glutamine on radiation-induced oral mucositis and dermatitis in head and neck cancer patients. *Am J Clin Nutr*. 2019;109(3):606-14. doi: 10.1093/ajcn/nqy329.
19. Yokota T, Ogawa T, Takahashi S, Okami K, Fujii T, Tanaka K, et al. Efficacy and safety of rebamipide liquid for chemoradiotherapy-induced oral mucositis in patients with head and neck cancer: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II study. *BMC Cancer*. 2017;17(1):314. doi: 10.1186/s12885-017-3295-4.
20. Tang G, Huang W, Zhang L, Wei Z. Role of glutamine in the management of oral mucositis in patients with cancer: a meta-analysis of randomized controlled trials. *Nutr Cancer*. 2022;74(2):482-95. doi: 10.1080/01635581.2021.1889623.
21. Chang YH, Yu MS, Wu KH, Hsu MC, Chiou YH, Wu HP, et al. Effectiveness of parenteral glutamine on methotrexate-induced oral mucositis in children with acute lymphoblastic leukemia. *Nutr Cancer*. 2017;69(5):746-51. doi: 10.1080/01635581.2017.1324995.
22. Issaq SH, Mendoza A, Fox SD, Helman LJ. Glutamine synthetase is necessary for sarcoma adaptation to glutamine deprivation and tumor growth. *Oncogenesis*. 2019;8(3):20. doi: 10.1038/s41389-019-0129-z.
23. Lee P, Malik D, Perkons N, Huangyang P, Khare S, Rhoades S, et al. Targeting glutamine metabolism slows soft tissue sarcoma growth. *Nat Commun*. 2020;11(1):498. doi: 10.1038/s41467-020-14374-1.
24. Choi YK, Park KG. Targeting glutamine metabolism for cancer treatment. *Biomol Ther (Seoul)*. 2018;26(1):19-28. doi: 10.4062/biomolther.2017.178.
25. Suardi C, Cazzaniga E, Graci S, Dongo D, Palestini P. Link between viral infections, immune system, inflammation and diet. *Int J Environ Res Public Health*. 2021;18(5):2455. doi: 10.3390/ijerph18052455.
26. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: metabolism and immune function, supplementation and clinical translation. *Nutrients*. 2018;10(11):1564. doi: 10.3390/nu10111564.
27. Ramezani Ahmadi A, Rayyani E, Bahreini M, Mansoori A. The effect of glutamine supplementation on athletic performance, body composition, and immune function: A systematic review and a meta-analysis of clinical trials. *Clin Nutr*. 2019;38(3):1076-91. doi: 10.1016/j.clnu.2018.05.001.
28. Newsholme P, Diniz VLS, Dodd GT, Cruzat V. Glutamine metabolism and optimal



- immune and CNS function. *Proc Nutr Soc.* 2023;82(1):22-31. doi: 10.1017/S0029665122002749.
29. Perna S, Alalwan TA, Alaali Z, Alnashaba T, Gasparri C, Infantino V, et al. The role of glutamine in the complex interaction between gut microbiota and health: a narrative review. *Int J Mol Sci.* 2019;20(20):5232. doi: 10.3390/ijms20205232.
30. Ward E, Smith M, Henderson M, Reid U, Lewis I, Kinsey S, et al. The effect of high-dose enteral glutamine on the incidence and severity of mucositis in paediatric oncology patients. *Eur J Clin Nutr.* 2009;63(1):134-40. doi: 10.1038/sj.ejcn.1602894.
31. Yildirim ZK, Bidev D, Buyukavci M. Parenteral glutamine supplementation has no effect on chemotherapy-induced toxicity in children with non-Hodgkin lymphoma. *J Pediatr Hematol Oncol.* 2013;35(5):371-6. doi: 10.1097/MPH.0b013e318282daf4.
32. Huang EY, Leung SW, Wang CJ, Chen HC, Sun LM, Fang FM, et al. Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. *Int J Radiat Oncol Biol Phys.* 2000;46(3):535-9. doi: 10.1016/s0360-3016(99)00402-2.
33. Sornsuvit C, Komindr S, Chuncharunee S, Wanikiat P, Archararit N, Santanirand P. Pilot study: effects of parenteral glutamine dipeptide supplementation on neutrophil functions and prevention of chemotherapy-induced side-effects in acute myeloid leukaemia patients. *J Int Med Res.* 2008;36(6):1383-91. doi: 10.1177/147323000803600628.
34. Choi K, Lee SS, Oh SJ, Lim SY, Lim SY, Jeon WK, et al. The effect of oral glutamine on 5-fluorouracil/leucovorin-induced mucositis/stomatitis assessed by intestinal permeability test. *Clin Nutr.* 2007;26(1):57-62. doi: 10.1016/j.clnu.2006.07.003.

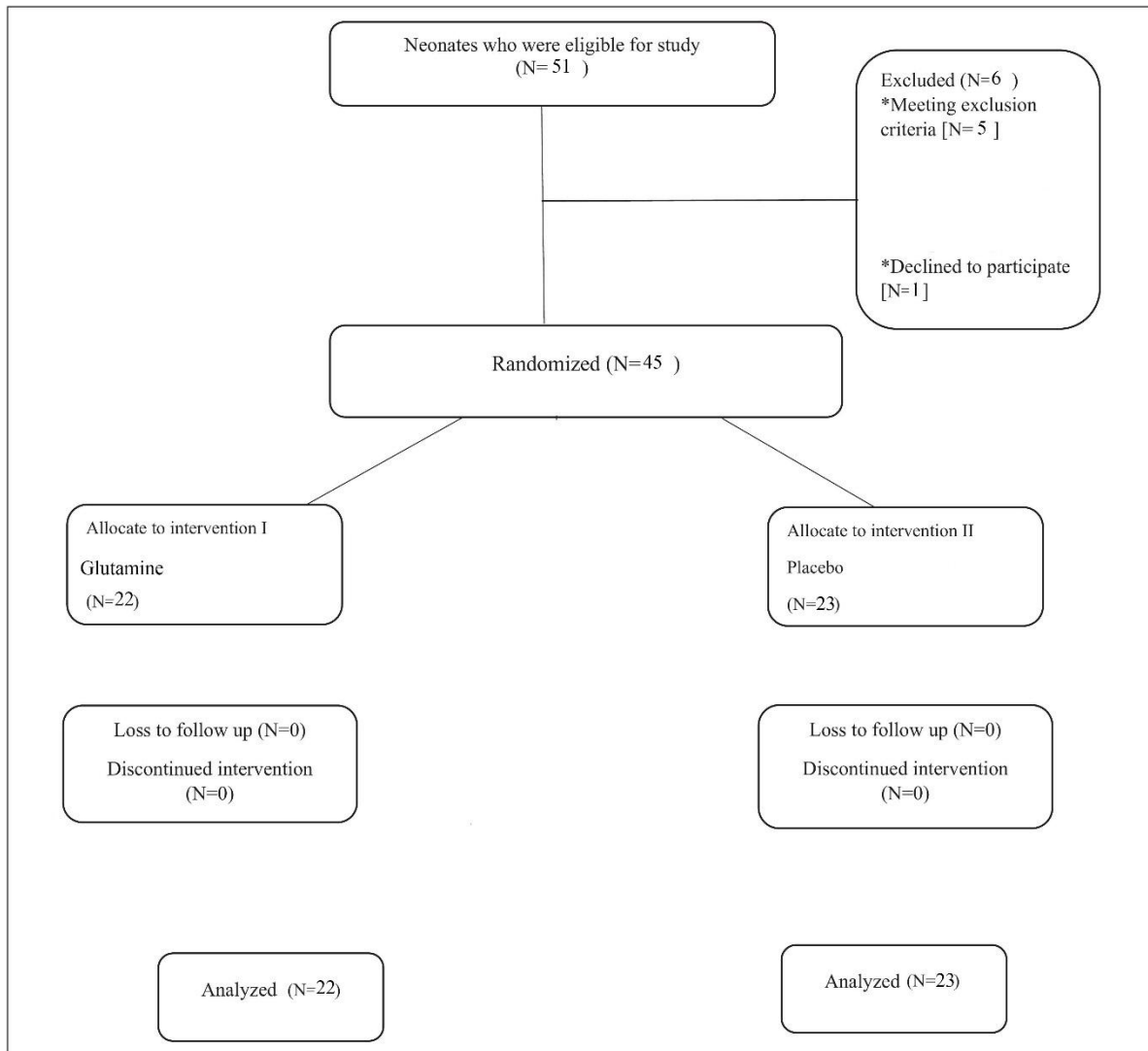


Figure 1. This Flow diagram shows the participants' progression through the trial.

Table 1. The frequency distribution of nausea and vomiting from day one to day four in the glutamine and placebo groups

	Number of times	Studied groups		P value
		Placebo group	Glutamine group	
<b>Nausea on the first day</b>	0	17 (73.9%)	16 (72.7%)	0.577
	1	5 (21.7%)	3 (27.3%)	
	5	1 (4.3%)	0 (0%)	
<b>Nausea on the second day</b>	0	16 (69.6%)	19 (86.4%)	0.237
	1	6 (26.1%)	2 (9.1%)	
	2	1 (4.3%)	0 (0%)	
	3	0 (0%)	1 (4.5%)	
<b>Nausea on the third day</b>	0	19 (82.6%)	21 (95.5%)	0.354
	1	3 (13%)	1 (4.5%)	
	2	1 (4.3%)	0 (0%)	
<b>Nausea on the fourth day</b>	0	21 (91.3%)	22 (100%)	0.368
	3	1 (4.3%)	0 (0%)	
	4	1 (4.3%)	0 (0%)	
<b>Vomiting on the first day</b>	0	16 (69.6%)	19 (86.4%)	0.386
	1	4 (17.4%)	2 (9.1%)	
	2	3 (13%)	1 (4.5%)	
<b>Vomiting on the second day</b>	0	18 (78.3%)	18 (81.8%)	0.679
	1	2 (7.8%)	2 (9.1%)	
	2	0 (0%)	0 (0%)	
	3	2 (7.8%)	1 (4.5%)	
	4	0 (0%)	1 (4.5%)	
	5	1 (4.3%)	0 (0%)	
<b>Vomiting on the third day</b>	0	16 (96.6%)	21 (95.5%)	0.130
	1	3 (13%)	1 (4.5%)	
	2	1 (4.3%)	0 (0%)	
	3	3 (13%)	0 (0%)	
<b>Vomiting on the fourth day</b>	0	19 (82.6%)	22 (100%)	0.241
	1	1 (4.3%)	0 (0%)	
	2	1 (4.3%)	0 (0%)	
	3	2 (7.8%)	0 (0%)	

Table 2. Daily intake of liquid and solid foods from day one to day four in the glutamine and placebo groups

Feeding times according to the number of times of feeding that can be swallowed	Studied groups		P value
	Placebo group	Glutamine group	
Liquid foods /day 1	3 (1-10)	3 (1-6)	0.805
Liquid foods /day 2	2 (0-8)	3 (1-7)	0.916
Liquid foods /day 3	3 (0-8)	3 (1-7)	0.899
Liquid foods /day 4	3 (0-8)	4 (2-8)	0.100
Solid foods/day 1	4 (2-20)	3 (1-6)	0.879
Solid foods/day 2	4 (2-18)	4 (2-9)	0.855
Solid foods/day 3	4 (2-18)	4 (2-6)	0.265
Solid foods/day 4	4 (2-18)	4 (2-6)	0.855

Table 3. Mucositis severity frequency in the glutamine and placebo groups

	Grade	Studied Groups		P value
		Placebo group	Glutamine group	
Severity of mucositis on day 3	0	1 (4.3%)	0 (0%)	0.327
	I	16 (69.6%)	19 (86.4%)	
	II	6 (21.6%)	3 (13.6%)	
	III	0 (0%)	0 (0%)	
	IV	0 (0%)	0 (0%)	
Severity of mucositis on day 7	0	23 (100%)	21 (95.5%)	0.301
	I	0 (0%)	1 (4.5%)	
	II	0 (0%)	0 (0%)	
	III	0 (0%)	0 (0%)	
	IV	0 (0%)	0 (0%)	