ORIGINAL RESEARCH

Clinical Study of Glutamine Combined with Early Enteral Nutrition Support on Nutritional Status of Gastric Cancer Patients Undergoing Neoadjuvant Chemotherapy

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ABSTRACT

Objective • To explore the clinical study of glutamine combined with early enteral nutrition support on the nutritional status of gastric cancer patients undergoing neoadjuvant chemotherapy.

Methods • Divided into control and observation groups, a control group received routine enteral nutrition, while the observation group received an additional 0.5 g/kg/d of glutamine. The researchers measured nutritional indicators, immunoglobulins, T lymphocyte subsets, and stress indexes such as fasting blood sugar and C-reactive protein throughout the study.

Results • Before nutritional support, there was no significant difference in the HGB, TP, and ALB levels. During nutritional support, however, the observation group began registering significantly higher levels of HGB, TP, and ALB, suggesting that glutamine intervention can improve the nutritional status of patients. Throughout the study, the CD4+ level showed a consistent increase in the observation group. The levels of IgA and IgG in the observation group also grew significantly higher. Both groups had higher blood glucose levels before nutritional support. However, on day 8 and day 15, the levels decreased. The observation group had significantly lower fasting blood glucose (FBG) levels than the control group. By day 15, the FBG levels in the observation group were close to normal. The CRP level showed a consistent decrease in the observation group compared to the control group on day 8 and day 15. Glutamine intervention appears to improve the stress capacity of gastric cancer patients undergoing neoadjuvant chemotherapy. Overall, the findings suggest that glutamine intervention in enteral nutrition can significantly improve immune function, nutritional status, and stress capacity in gastric cancer patients undergoing neoadjuvant chemotherapy and appears to be more effective than conventional enteral nutrition.

Conclusion • The combination of glutamine and early enteral nutrition support can significantly improve gastric cancer patients undergoing neoadjuvant chemotherapy's nutritional status and immune function levels. It is a safe and reliable enteral nutrition support method worthy of clinical promotion. (*Altern Ther Health Med.* 2024;30(7):122-127).

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INTRODUCTION

Gastric cancer is a malignant tumor originating from the epithelium of gastric mucosa. Statically, gastric cancer ranked second in incidence rate and mortality among various malignant tumors in China in 2015.[1] Gastric cancer has no apparent symptoms at the early stage or has non-specific symptoms such as abdominal distension and abdominal pain, belching, acid regurgitation, which are often similar to chronic gastric diseases such as gastritis, dyspepsia, reflux Esophagitis, resulting in a low early detection rate. The early diagnosis rate of gastric cancer in China is low, with less than 10% of early gastric cancer patients. Therefore, most Chinese gastric cancer patients have advanced gastric cancer.[2] The treatment of gastric cancer patients tends to be surgical resection of the tumor, but the rate of radical resection is low, and there are many postoperative complications with severe grading, resulting in poor overall efficacy.

In recent years, the treatment of gastric cancer has gradually developed into a comprehensive treatment mode with radical surgery at its core. Many auxiliary treatments such as postoperative adjuvant chemotherapy, neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, and

molecular targeted therapy have begun to emerge and play an important role in clinical efficacy. However, the stimulation of chemotherapy in the gastrointestinal tract has adverse effects on gastrointestinal function. The effects can lead to a decrease in patient nutrient intake, nutritional deficiency, malnutrition, and ultimately hinder the tolerance of malignant tumor patients towards treatment. Consequently, they may be unable to tolerate conversion chemotherapy, ultimately leading to treatment failure.[3] It is crucial for gastric cancer patients undergoing chemotherapy to receive proper nutritional support to help protect their normal gastrointestinal function and improve their overall nutritional status. By enhancing their tolerance to chemotherapy, patients can complete preoperative chemotherapy and enter surgery in good physiological condition, facilitating a speedy recovery post-surgery.[4]

Glutamine (Gln) is a primary immune nutrient that can provide a nitrogen source for synthesizing amino acids, proteins, nucleic acids, and carbon chain oxidation like glucose. It is the most abundant amino acid in the human blood and free amino acid pool and serves as an energy source and precursor for nucleic acid synthesis for immune cells and various tissue cells such as the intestinal mucosa, liver, and kidneys. Usually, Gln is synthesized in large quantities in the body and is a non-essential amino acid.[5] However, animal experiments and clinical studies have shown that Gln becomes essential under stressful conditions. It serves as the primary energy source for cells in the small intestine and is crucial for promoting intestinal repair. The body's demand for Gln greatly increases with severe consumptive diseases such as trauma, major surgery, and tumors. If there is insufficient supplementation of this amino acid, it can lead to a depletion of Gln in the body.[6] Consequently, this depletion can damage the intestinal mucosa's structure and function, weaken immune function, and disrupt protein metabolism, among other notable changes.

Many literature reports have shown that the immune nutrient glutamine significantly improves severely injured rat models' nutritional status, immune function, and intestinal barrier function. Researchers have extensively examined the intestinal clinical effect of glutamine, and there have been numerous reports both domestically and internationally regarding its widespread utilization in clinical settings, including its application in critical illnesses, hematological disorders, and cancer cases.[7,8] However, there are few reports on the combined use of glutamine in critically ill patients. This project establishes a control group to add glutamine to enteral nutrition for patients receiving neoadjuvant chemotherapy for gastric cancer, observe the effect of the combination of the two, explore its mechanism of action, provide a reasonable and scientific nutritional support plan for gastric cancer patients, and provide a theoretical basis for the development of nutritional preparations in the future.

In summary, this study examined the effectiveness of glutamine in supporting immunonutrition for patients with gastric cancer after surgery, as well as its impact on immune function and quality of life. The goal was to investigate how glutamine regulates cellular and humoral immunity by assessing changes in immune markers, thereby offering new insights and approaches for the clinical treatment of gastric cancer patients. Additionally, the study sought to establish a scientific foundation for enhancing these individuals' postoperative recovery and quality of life. By further exploring the immunomodulatory effects of glutamine in gastric cancer patients, this research seeks to contribute to a more comprehensive treatment strategy to improve overall health outcomes and prognoses for affected individuals.

MATERIALS AND METHODS

Basic Information

The researchers' hospital studied 80 gastric cancer patients admitted from January 2020 to January 2023. Before admission, all patients underwent gastroscopy, pathological examination, and imaging examination to confirm their diagnosis. The multidisciplinary team (MDT)[i] decided that neoadjuvant chemotherapy was necessary. The researchers randomly divided the patients into an observation group (n=40) and a control group (n=40). The control group consisted of 22 male and 18 female patients, aged 47-70 years, with an average age of 60.06 (±3.27). The observation group consisted of 23 male and 17 female patients, aged 48-70 years, with an average age of 60.11 (±3.32). When analyzing the fundamental patient details in both groups, there were no significant differences in the data ($P > .05$).

To ensure the clinical relevance and consistency of selected patients with gastric cancer, patient diagnosis rested on clinical symptoms, imaging, pathological examination, and clinical staging performed using the TNM system to assess tumor characteristics. To ensure the accuracy and utility of the study, all patients were required to meet the following inclusion criteria: (1) a preoperative diagnosis of gastric cancer through gastroscopy and radical surgery for gastric cancer; (2) no other heart, liver, kidney dysfunction, or other diseases had occurred before surgery; (3) no immune disease, hyperthyroidism, or diabetes; (4) their tumor had not undergone distant metastasis; (5) the patient had not received radiotherapy, chemotherapy, or immunosuppressive drug treatment within half a year before surgery; (6) and no preoperative malnutrition had occurred. Exclusion criteria required that the patient (1) not have other infections, (2) not have a mental illness, and (3) can cooperate actively in the study.

Methods

Treatment Methods

This study was a prospective randomized controlled trial in which researchers randomly assigned gastric cancer patients who met the study's inclusion criteria to observation and control groups. The observation group received glutamine immunonutrition support, while the control group received

i. MDT is a collaborative approach to health care involving physicians and specialists in multiple medical specialties who jointly discuss a patient's condition, diagnosis, treatment plan, and follow-up management.

standard postoperative supportive treatment. Through randomization, the researchers intended to explore the immunomodulatory effects of glutamine in patients with gastric cancer and its effects on immune function and quality of life.

The control group received routine enteral nutrition support. On the first day, control group patients received a routine enteral nutrition tube infused 500 mL of 5% glucose. Enteral nutrition proceeded if there was no apparent discomfort, and the patient received an infusion of conventional enteral nutrition support preparations. On the second day, the patient received an injection of 500 mL of nutritional preparations, and from day three to seven, each patient received a 1000 mL injection of nutritional preparations. The control group received continuous enteral nutrition supplementation for a week, with a daily calorie intake of 104.6 kJ/kg and a nitrogen content of 0.16 g/kg.

The observation group received glutamine-enhanced enteral nutrition support. The patient received 500 mL of 5% glucose on the first day. If tolerated, the researchers proceeded with enteral nutrition supplementation and glutamine preparations (0.5 g/kg/d). On the second day, the researchers administered 500 mL of nutritional preparations, followed by the administration of 1000 mL of nutritional preparations on days three through seven. For the same consecutive week, the daily calorie intake reached 104.6 kJ/kg, and the nitrogen content reached 0.16 g/kg. All patients used the Fulkai 800 infusion pump for receiving nutritional preparations. The infusion process controlled the speed and dosage within the appropriate range, using 25 mL/h, 50 mL/h, and 100 mL/h for the first three days.

Observation Indicators and Detection Methods. The researchers took 3 ml of venous blood from the patient after a 12-hour fast in the morning on three different days: day 1, day 8, and day 15. They measured and analyzed the blood within three hours of collection to obtain the following indicators: (1) fasting blood sugar (FBG) using the glucose oxidase method, as measured by the Beckman LX-20[ii] automatic biochemical analyzer using a test kit produced by Zhongsheng Beikong Biotechnology and the Chinese Academy of Sciences[iii]; (2) hemoglobin (HGB) determined using a Coulter[iv] HXM five classification blood cell analyzer; (3) serum albumin (ALB) and total serum protein (TP) detected using the double reduction dolphin colorimetric method using the Beckman LX-20 fully automatic biochemical analyzer; (4) immunoglobulin (Ig): immunoglobulin (IgG, IgM, IgA) measured using enzyme-linked immunosorbent assay; and (5) T lymphocytes and their subpopulations ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$) measured by flow cytometry. It was necessary to follow closely the instrument's instructions and take effective quality control measures to ensure the integrity of the experimental research.

Statistical Analysis

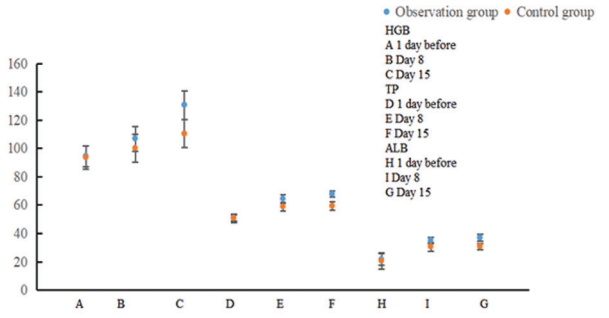
IBM SPSS Statistics 20.0[v] software processed the study's statistics. Measurement data included the mean standard deviation ($\bar{x} \pm s$) for analysis of variance and t test. The researchers used the χ^2 test to compare counting data to $\alpha = 0.05$ as the inspection level. The researchers used the t test to compare continuous variables between the two groups, such as differences in immune indicators between the observation group and the control group at specific time points, and the chi-square (χ^2) test to analyze differences in categorical variables between the two groups.

Table 1. Comparison of Nutritional Indicators Between Two Groups of Patients Before and After Nutritional Support ($\bar{x} \pm s$)

Indicators	Date	Observation group	Control group	t	P value
HGB	1 day before	94.56±7.23	93.73±8.35	0.47	.64
	Day 8	107.00±8.79	100.23±9.93	3.18	<.01
	Day 15	130.76±10.22	110.38±9.89	8.95	<.01
TP	1 day before	50.96±2.23	50.78±3.05	0.30	.76
	Day 8	64.39±3.09	58.93±3.03	7.85	<.01
	Day 15	67.86±2.22	59.38±3.01	14.16	<.01
ALB	1 day before	21.56±4.23	20.60±5.53	0.86	.39
	Day 8	35.00±2.29	30.63±3.02	7.20	<.01
	Day 15	36.86±2.42	30.78±2.34	11.28	<.01

Note: The units of HGB, TP, and ALB are g/L.

Figure 1. Comparison of Nutritional Indicators Between Two Groups of Patients Before and After Nutritional Support



RESULTS

Impact on Patient Nutritional Indicators

There was no difference in hemoglobin, total protein, and albumin between the two groups of patients before nutritional support ($P > .05$). On the 8th and 15th days of nutritional support, the values of HGB, TP, and ALB in the observation group were higher than those in the control group, with significant differences ($P < .01$). After glutamine intervention, the HGB, TP, and ALB levels in the enteral nutrition group with enhanced immune nutrients were higher than in the conventional enteral nutrition group. (See Table 1, Figure 1)

Impact on Patient Immune Indicators

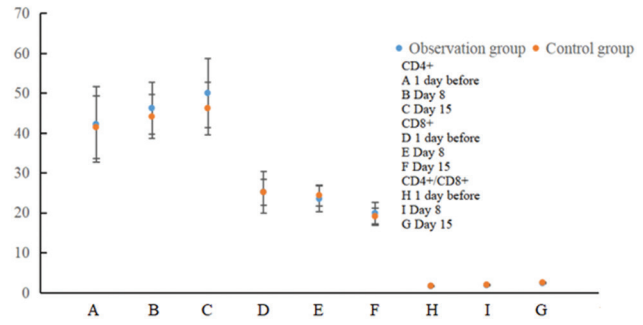
Impact on Patient T Lymphocyte Subpopulations. Before nutritional support, there was no statistically significant difference in $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ($P > .05$). $CD4^+$ remained elevated throughout the entire period of nutritional support. On the 8th day, the level of $CD4^+$ in the observation group was comparable to that in the control group, with no

ii. Beckman Coulter, Inc., Brea, CA, USA.
iii. Zhonsheng Beikong Biotechnology Co., Ltd., Beijing, China and the Chinese Academy of Sciences, Beijing, China.
iv. Beckman Coulter, Inc., Brea, CA, USA.
v. SPSS Statisics is a popular and widely used software package used for analysis of statistical data. Originally named SPSS or Statistical Package for Social Sciences, IBM (Armonk, NY, USA) acquired the software in 2010 and now maintains and sells the software as IBM SPSS Statistics.

Table 2. Comparison of T Lymphocyte Subpopulations Between Two Groups of Patients Before and After Nutritional Support ($\bar{x} \pm s$)

Indicators	Date	Observation group	Control group	*t*	*P* value
$CD4^+$	1 day before	42.20±9.51	41.45±7.86	0.38	.71
	Day 8	46.23±6.47	44.11±5.49	1.56	.12
	Day 15	50.01±8.63	46.21±6.59	2.19	.03
$CD8^+$	1 day before	25.21±5.26	25.18±3.31	0.03	.97
	Day 8	23.50±3.25	24.39±2.58	1.33	.18
	Day 15	19.93±2.67	19.12±2.16	1.47	.14
$CD4^+/CD8^+$	1 day before	1.62±0.07	1.68±0.06	0.37	.54
	Day 8	1.85±0.04	1.96±0.06	2.97	.09
	Day 15	2.36±0.07	2.52±0.07	0.13	.71

Figure 2. Comparison of T Lymphocyte Subpopulations Between Two Groups of Patients Before and After Nutritional Support



difference (46.23 ±6.47 vs. 44.11 ±5.49, $P > .05$). On the 15th day, the observation group was significantly higher than the control group (50.01 ±8.63 vs. 46.21 ±6.59, $P < .05$). There was no statistically significant difference between the $CD8^+$ and $CD4^+/CD8^+$ groups at any time (1.62 ±0.07 vs. 1.68 ±0.06, 1.85 ±0.04 vs. 1.96 ±0.06, 2.36 ±0.07 vs. 2.52 ±0.07 $P > .05$). This indicates that glutamine-enhanced enteral nutrition positively improved the immune function of gastric cancer patients undergoing chemotherapy compared to conventional enteral nutrition. (See Table 2, Figure 2)

Impact on Patient Immunoglobulins. There was no significant difference in immunoglobulins (IgA, IgG, IgM) between the two groups of patients before nutritional support ($P > .05$). On the 8th day of nutritional support, the levels of IgA and IgG in the observation group were significantly higher than those in the control group ($P < .01$). The levels of IgM in the observation group were comparable to those in the control group, but the difference was not statistically significant ($P > .05$). On the 15th day of nutritional support, the levels of IgA and IgG increased, and the observation group was higher than the control group, with a significant difference ($P < .01$). The levels of IgM increased compared to the day before support and the 8th day of support. However, there was no statistically significant difference between the observation group and the control group ($P > .05$), indicating that glutamine-enhanced enteral nutrition effectively improved the immune function of gastric cancer patients. (See Table 3, Figure 3)

Impact on Patient Stress Indicators. Table 4 shows the two groups' fasting blood sugar and C-reactive protein changes.

Table 3. Comparison of Immunoglobulins Between Two Groups of Patients Before and After Nutritional Support ($\bar{x} \pm s$)

Indicators	Date	Observation group	Control group	*t*	*P* value
IgA	1 day before	2.21±0.68	2.20±0.64	0.06	.94
	Day 8	2.88±0.73	2.34±0.99	2.74	.01
	Day 15	3.31±0.68	2.43±0.52	6.42	<.01
IgG	1 day before	10.41±2.58	10.49±3.02	0.13	.90
	Day 8	13.60±2.20	11.23±2.54	4.40	<.01
	Day 15	15.10±3.86	12.03±3.83	3.52	<.01
IgM	1 day before	1.40±0.48	1.25±0.43	1.45	.15
	Day 8	1.50±0.32	1.45±0.49	0.53	.59
	Day 15	1.78±0.46	1.68±0.54	0.88	.38

Note: The units of IgA, IgG, and IgM are g/L.

Figure 3. Comparison of Immunoglobulins Between Two Groups of Patients Before and After Nutritional Support

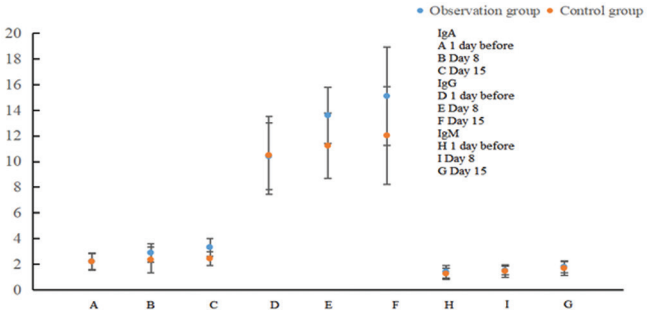


Table 4. Comparison of Blood Glucose and C-Reactive Protein Levels Between Two Groups of Patients Before and After Nutritional Support ($\bar{x} \pm s$)

Indicators	Date	Observation group	Control group	*t*	*P* value
FBG	1 day before	14.56±2.13	14.63±2.32	0.13	.89
	Day 8	12.56±2.19	14.23±2.48	3.15	<.01
	Day 15	8.12±2.05	10.80±1.32	6.86	<.01
CRP	1 day before	6.52±1.34	6.50±1.45	0.06	.95
	Day 8	4.23±1.06	6.21±1.26	7.51	<.01
	Day 15	1.50±0.38	6.00±2.10	13.16	<.01

Note: The unit of FBG is mmol/L, and the unit of CRP is mg/L.

Before nutritional support, the blood glucose values of the two groups had no statistical significance ($P > .05$) and were higher than the normal level. The blood glucose values decreased on the 8th and 15th days of nutritional support. The FBG in the observation group was lower than that in the control group, with a statistically significant difference ($P < .01$). On the 15th day, the FBG levels in the observation group were close to normal, much lower than those in the control group. There was no statistically significant difference in C-reactive protein between the two groups of patients before nutritional support ($P > .05$). CRP decreased in both groups on the 8th and 15th day of nutritional support, and the observed group showed a significant decrease ($P < .01$). The enteral nutrition intervention with glutamine improved gastric cancer patients' hyperglycemic response after chemotherapy and alleviated their stress response. (See Table 4)

DISCUSSION

Gastric cancer is more common in clinical practice; its incidence rate has gradually increased in recent years. Most patients with gastric cancer suffer from bleeding, gastrointestinal obstruction, and difficulty in eating. Therefore, malnutrition

and other conditions likely occur, especially after surgery or chemotherapy, and patients' immune ability will gradually decrease. Tumor patients are a high-risk population for malnutrition, and the mechanisms by which they experience malnutrition include the impact of tumors on human metabolism, leading to increased catabolism.[9] Tumors can also lead to relative nutritional deficiencies by affecting food intake. Both factors simultaneously affect gastric cancer patients. According to research reports, preoperative malnutrition is an independent risk factor for postoperative complications in gastric cancer patients. Severe complications can increase mortality, prolong hospital stay, increase patients' physical and psychological burden, reduce quality of life, and affect the implementation of postoperative adjuvant treatment, even affecting long-term survival.[10]

As a common digestive system tumor, the low rate of early diagnosis of gastric cancer is a serious problem, resulting in a late diagnosis for many patients. Early diagnosis is essential for the treatment and prognosis of patients with gastric cancer, as an intervention at an early stage can significantly improve patient survival and quality of life. On the other hand, malnutrition is a common problem in gastric cancer patients, especially during treatment. Malnutrition may lead to physical exhaustion, decreased immune function, and reduced treatment tolerance, which may affect the treatment effect and survival rate. Therefore, reasonable nutritional support is also crucial in the treatment of gastric cancer, in addition to standardized anticancer treatment.

Currently, most people in clinical practice believe that the safe and effective nutritional support method is enteral nutrition support, which has the characteristics of easy operation, physiological compliance, and fewer complications. Research has confirmed that enteral nutrition support can fully meet the nutritional needs of gastric cancer patients, effectively reducing the high metabolic rate caused by surgical trauma and significantly reducing the occurrence of intestinal infections, helping patients recover their intestinal function as soon as possible.[11,12] However, some scholars believe routine nutritional support cannot effectively reduce the body's catabolism, immune function benefits, and inflammatory reactions.[13] At the same time, it is proposed to adopt immune enhancement measures for enteral nutrition preparations, which can use special nutrients such as glutamine and nucleotides to enhance, thereby changing the metabolic response of the patient's body during stress, effectively enhancing their immune function, and improving their prognosis.[14]

Glutamine, a special type of nutrient categorized as a free amino acid, is plentiful within the human body, accounting for as much as 50% of human amino acids. Therefore, it is necessary to supplement patients with glutamine to provide them with essential nutrients. Glutamine plays a crucial role as one of the main nutrients for rapidly proliferating cells, improving the function of immune cells in patients. In the presence of patients outside the body, neutrophils can strengthen their bactericidal ability, enabling macrophages to kill Candida albicans.[2] The high utilization rate of glutamine plays an important role in maintaining and regulating the immune function of macrophages. A reasonable nutritional support plan can increase the concentration of glutamine in patients' muscles and hematoma, and immune function inhibition under stress can be improved.

The immune-enhancing effect of glutamine in patients with gastric cancer involves the regulation of cellular immunity and humoral immunity. In terms of cellular immunity, glutamine helps activate and expand T cells, improve their ability to fight pathogens and tumor cells, and enhance immune cells' killing effect by regulating cytokine secretion, such as increasing the production of interferon-γ (IFN-γ). In terms of humoral immunity, glutamine can promote the activity of B cells, increase the production and secretion of antibodies, and, thereby, strengthen the body's immune defense and improve the resistance to infection and tumor. However, further studies are needed to reveal its specific regulatory mechanism and explore its application prospects in gastric cancer immunotherapy.

Hemoglobin, total serum protein, and albumin are common indicators used to evaluate the nutritional status of human protein. Their operation is simple, and they are necessary biochemical tests in clinical practice. After the observation group received enteral nutrition supplemented with immune nutrients, the levels of HGB, TP, and ALB increased significantly compared to the control group, indicating that glutamine can improve the nutritional status of gastric cancer chemotherapy patients. Immunoglobulin reflects the body's ability to resist diseases and the prognosis level.

After receiving enteral nutrition fortified with immune nutrients, the levels of IgA and IgG in the observation group significantly increased, indicating that glutamine can improve the immunity of gastric cancer patients undergoing chemotherapy. C-reactive protein (CRP) indicates stress response, and hyperglycemia is a part of physiological stress response. The blood glucose level directly affects the prognosis of trauma patients, which is the basis for clinical prognosis evaluation. After receiving enteral nutrition fortified with immune nutrients, the observation group showed a significant decrease in CRP levels, a significant decrease in blood glucose, and FGB levels approaching normal levels, indicating that glutamine can alleviate stress levels in gastric cancer chemotherapy patients and effectively lower their blood glucose levels. The above results indicate that glutamine combined with enteral nutrition support is a safe and reliable nutritional support method. Xu et al.[4] used glutamine combined with enteral nutrition support for postoperative chemotherapy patients with gastric cancer, and the results showed that the nutritional status and immunity of gastric cancer patients were effectively improved, similar to the results of this study. This nutritional support method is a practical and effective measure.

Patients with advanced gastric cancer have a high nutritional risk during the conversion treatment process, so sufficient and reasonable nutritional support is essential. Nutritional support improves gastrointestinal digestion and absorption function, promotes nutrient absorption in the

body, corrects malnutrition in patients, reduces the probability of losing surgery opportunities due to malnutrition or poor chemotherapy tolerance, and helps gastric cancer patients undergoing conversion therapy recover quickly after surgery.[15] In recent years, many clinical studies have proven that glutamine positively affects the comprehensive treatment of tumors.[16] Therefore, this study provides a basis for the combination of glutamine and enteral nutrition support to improve nutritional status during the conversion chemotherapy period for advanced gastric cancer and also has a certain guiding significance for the application of glutamine in clinical treatment.

Study limitations include the small sample size and geographic limitations, which may have limited the generalizability of the results. In addition, although studies have found that glutamine has a potential positive effect on immune function, further studies are required to confirm its molecular mechanism and any direct impact on patient treatment outcomes. Future research directions can include expanding the sample size, exploring the molecular mechanism, further evaluating the clinical effect, realizing individualized treatment, and studying the influence of other nutritional factors to understand more fully the immune-enhancing effect of glutamine in patients with gastric cancer and to provide more accurate support for the treatment of patients.

ETHICAL COMPLIANCE

The medical ethics committee within the hospital reviewed and approved this study. All patients were informed of the research purpose and process and signed an informed consent form.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

YD and LW designed the study and performed the experiments, JH and LC collected the data, XY, YL and XL analyzed the data, YD and LW prepared the manuscript. All authors read and approved the final manuscript.

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