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Effects of Ala-Gln dipeptide parenteral nutrition on rehabilitation and infection of liver transplantation patients

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Abstract: This study aimed to explore the application and effect of alanyl-glutamine (Ala-Gln) dipeptide parenteral nutrition support in liver transplantation patients. A randomized controlled trial was performed, including and analyzing 96 patients who underwent liver transplantation surgery in our hospital from March 2019 to February 2023. These 96 patients were randomly divided into an experimental group and a control group, with 48 cases in each group. The control group was supplied with branched-chain amino acids (BCAAs) as a nitrogen source, and the experimental group was supplied with BCAAs + Ala-Gln. The results indicated that the levels of prealbumin (PA), serum albumin (ALB), and transferrin (TRF) in the experimental group were higher than those in the control group ($P<0.05$). The duration of care at the intensive care unit (ICU) and hospitalization of the experimental group were shorter than the control group ($P<0.05$). The incidence of infection events of the experimental group was lower than that in the control group ($P<0.05$). Collectively, the use of Ala-Gln in parenteral nutrition support for liver transplantation patients can significantly improve the nutritional status of the body, shorten the length of hospitalization time and reduce the incidence of infection.

Keywords: Liver transplantation; alanyl-glutamine; parenteral nutrition support; infection

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INTRODUCTION

Liver transplantation is the most effective treatment for end-stage liver disease ("EASL Clinical Practice Guidelines on liver transplantation," 2024). In China, more than 5,000 liver transplantation surgeries are carried out every year, and the overall survival rates of recipients at 1, 3 and 5 years after the operation are approximately 84.60%, 76.36%, and 71.31%, respectively (Sunbin *et al.*, 2022). Infection is the most common complication after liver transplantation. According to the survey data from European Research Institutes, the incidence of early infection after liver transplantation is about 37.9% ~ 66.0%, and infection-related death accounts for 20% of all liver transplantation deaths (Ferrarese *et al.*, 2020). Malnutrition is a common problem in liver transplant patients, with an incidence rate of up to 80% to 10% before surgery (Trigui *et al.*, 2023). Moreover, malnutrition can aggravate the immunosuppressive condition, and increase the risk of infection, and it is also a risk factor for sepsis after liver transplantation (Brooke *et al.*, 2020). Therefore, actively improving the nutritional status of liver transplant recipients is of great significance in reducing the risk of infection and promoting early recovery.

Parenteral nutrition is one of the main nutritional support methods during perioperative period of liver transplantation. It is applicable to patients who are unable to eat or have severe gastrointestinal diseases (Cuerda *et al.*, 2021). Compared with enteral nutrition, parenteral nutrition can meet the requirements of different nutritional components (Berlana, 2022). However, during the process of parenteral nutrition, the gastrointestinal tract lacks nutritional stimulation, and the decrease of peristalsis leads to intestinal mucosa atrophy, thereby increasing the risk of intestinal flora displacement and indirectly raising the rate of intestinal infections (Elisabeth *et al.*, 2020). Alanyl-Glutamine (Ala-Gln) is an unconditionally essential amino acid, which can promote the synthesis of substances and energy metabolism in intestinal mucosal cells, and help maintain the balance of intestinal flora and protect the function of the gastrointestinal tract (Hu *et al.*, 2022). At present, Ala-Gln has been proven to be able to improve the nutritional status and immune regulation of the body (Xiaolei *et al.*, 2021), but whether it can reduce the risk of infection after liver transplantation still requires further research.

In this study, Ala-Gln was used in parenteral nutrition of liver transplantation patients to explore the prevention and treatment strategy for perioperative infection of liver transplantation.

MATERIALS AND METHODS

Research design

A randomized controlled trial was performed, including and analyzing 96 patients who underwent liver transplantation surgery in our hospital from March 2019 to February 2023. These 96 patients were randomly divided into an experimental group (EG) and a control group (CG) using a double-blind method, with 48 cases in each group. No significant difference was seen in baseline data between the 2 groups ($P>0.05$, table 1).

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Inclusion and exclusion criteria
Inclusion criteria: (1) Planned liver transplantation; (2) Over 18 years old; (3) Nutritional risk screening table 2002 (NRS 2002) ≥3 points (Cattani *et al.*, 2020); (4) Enteral nutrition did not reach the target feeding amount, and parenteral nutrition was simulated; (5) The donor liver was well preserved and repaired. Exclusion criteria: (1) Past or current recipients of other organ transplants; (2) Autoimmune disease, or long-term immunosuppressive treatment; (3) Severe anemia and hypoproteinemia need to be corrected in time; (4) Congenital anemia or autoimmune anemia; (5) There were acute complications during enrollment, including acute upper gastrointestinal bleeding and acute infection; (6) All-cause death during perioperative period; (7) Acute liver failure after transplantation; (8) Parenteral nutrition support should be suspended for nutrient intolerance; (9) Patients withdrew from the study initiatively.

Sample size calculation
Power analysis was carried out in this study using G*Power 3.1.9.7 software to determine the sample size required to detect statistical differences. With an alpha level of 0.05 and 90% power analysis, the research revealed that a sample size of 48 patients per group was required. Therefore, to draw reliable conclusions, the study sample sizes were 48 patients per group.

Randomization and blinding
A group randomization design was adopted for random grouping. The random allocation sequence was generated by a computer. The allocation confidentiality measures were achieved through sequential numbering, sealing, and opaque envelopes. After being deemed to meet the inclusion criteria, patients were randomly assigned to a control group or an experimental group in a 1:1 ratio. This study was single-blind, and the participants were unaware of the allocation.

Nutritional support methods
After achieving hemodynamic stability following liver transplantation, both groups received the same heat and nitrogen content nutritional support regimen. The specific details were as follows: 25 calories per kilogram per day, nitrogen content of 0.15 grams per kilogram, and a sugar-to-fat ratio of 6:4. Water-soluble vitamins, fat-soluble vitamins, electrolytes, and trace elements were added to the parenteral nutrition solutions of both groups, which were mixed in a 3-liter infusion bag and administered intravenously at a constant rate for 12 to 18 hours per day. The "blood glucose control strategy" was adopted, such as using insulin to control blood glucose within 5.5 to 8 millimoles per liter, with negative or weakly positive urine glucose. Insulin was continuously intravenously infused through a micro-pump to ensure its activity.

The nitrogen source for control group was supplied by branched-chain amino acids (BCAAs). The nitrogen source for the experimental group was supplied with BCAAs +Ala-Gln (20% dipeptiven supply), where the nitrogen content provided by the dipeptide accounted for approximately 35% of the total nitrogen content, and the nitrogen content in non-protein calories was 653 kilojoules per 1 gram. Both groups received 7 days of nutritional support.

Observation indicators
Nutritional indexes: 3~6 ml of blood was drawn from the patient's peripheral vein. The blood was then subjected to centrifugation at 1200 × g to obtain the serum, and the levels of albumin (ALB), transferrin (TRF) and prealbumin (PA) were detected by enzyme-linked immunosorbent assay (ELISA) provided by Sangon Biotech (Shanghai, China).

Rehabilitation indicators: intensive care unit (ICU) care duration, mechanical ventilation time, gastric tube removal time, and hospitalization time of patients in two groups were recorded.

Infection: The incidence of infection during hospitalization of the two groups was recorded, including any type of infection such as lung infection, abdominal infection and urinary system infection.

Ethical approval
The study protocol was approved by the medical Ethics Committee of Inner Mongolia Baogang Hospital No. 2024-MER-177. Both the patient and their legal representative signed the informed consent form.

STATISTICAL ANALYSIS

The data were processed by SPSS 25.0 statistical software, and statistical data were represented by n (%) and chi-square (χ^2) test. Normal distribution data were represented by "x±s", paired sample t test was applied for intra-group comparison, independent sample t test was employed for inter-group comparison. Skew distribution data were represented by [M (P25, P75)] and non-parametric Mann-Whitney U test was applied. P<0.05 meant that the difference was statistically significant.

RESULTS

Comparison of nutritional indexes between 2 groups
After intervention, the levels of serum ALB, PA and TRF in 2 groups were higher compared to those before intervention, and the levels of serum ALB, PA and TRF in the EG were higher compared to those in the CG, and the difference was statistically significant (P<0.05, table 2).

Comparison of recovery time between 2 groups
The duration of ICU care and hospitalization in the EG were shorter than those in the CG, and the difference was significant (P<0.05). No significant differences were seen

Table 1: Comparison of baseline data between 2 groups

Groups	Age	gender		Body Mass Index (kg/m^2)	Etiology		Child-Pugh class	
		male	female		primary liver cancer	liver cirrhosis	B	C
EG (n=48)	53.56±8.22	36	11	25.84±2.62	17	31	11	37
CG (n=48)	51.35±8.63	43	5	26.64±2.25	23	25	15	33
t/χ2	1.284	2.700		1.605	1.543		0.844	
P	0.202	0.100		0.112	0.214		0.358	

Table 2: Comparison of nutritional indexes between 2 groups

Group	ALB (g/L)		PA (mg/L)		TRF (g/L)	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
EG (n=48)	25.33±3.85	38.32±4.15	83.22±9.53	306.35±21.33	1.17±0.13	2.54±0.48
CG (n=48)	24.66±3.53	33.83±3.62	85.66±8.87	282.55±18.44	1.22±0.15	2.12±0.37
t	0.877	5.542	1.299	5.847	1.704	4.746
P	0.383	<0.001	0.197	<0.001	0.092	<0.001

Note: Comparison of pre- and post-intervention: *P < 0.05.

Table 3: Comparison of recovery time between 2 groups

Group	ICU stay (d)	Gastric tube removal time (h)	Drainage tube removal time (d)	Hospitalization stay (d)
EG (n=48)	4.00 (3.00, 4.00)	24.32±5.35	6.50 (6.00, 7.75)	14.44±3.60
CG (n=48)	6.00 (6.00, 7.00)	25.60±4.98	7.00 (6.00, 8.00)	18.63±3.57
t/Z	8.293	1.224	1.839	5.720
P	<0.001	0.224	0.066	<0.001

Table 4: Comparison of infection incidence between 2 groups

Group	Pulmonary infection	Abdominal infection	Urinary system infection	Infection of biliary tract	Total incidence
EG (n=48)	6	3	2	2	13 (27.08)
CG (n=48)	11	3	3	5	23 (47.92)
χ^2					4.444
P					0.035

in the gastric tube removal time and recovery time between the 2 groups (P>0.05, table 3).

Comparison of infection incidence between 2 groups

The incidence of infection events in the EG was lower than that in the CG, and the difference was significant (P<0.05, table 4).

DISCUSSION

Malnutrition is one of the common causes of death after liver transplantation. For patients with malnutrition, the intense stress response brought about by liver transplantation will lead to a relatively high level of catabolism and anabolism in the body, thereby causing hypoproteinemia, emaciation and even cachexia, which is not conducive to postoperative recovery (Maitreyi *et al.*, 2020). During the perioperative period of liver transplantation, enteral nutrition is the preferred option. However, due to the gastric congestion and decreased nutritional absorption capacity of patients with end-stage liver disease, simple enteral nutrition is unable to meet the nutritional needs of the patients (Ronald, 2023). Therefore, during the rehabilitation process after liver transplantation, parenteral nutrition support is particularly important, especially for those patients who have problems with enteral nutrition intolerance.

As an important component of parenteral nutrition, Ala-Gln can be decomposed into alanine and glutamic acid after entering the body, which can protect the intestinal mucosal barrier, improve the body's immune function, and promote protein synthesis (Sean *et al.*, 2020). At present, most of the amino acid solutions used for parenteral and enteral nutrition do not contain Gln. The reason is that Gln is less stable in aqueous solutions, and will decompose into pyroglutamic acid and ammonia within a short period of time (Pająk *et al.*, 2023). Furthermore, free glutamine has a relatively low solubility and, once absorbed into the body, it will excessively increase the fluid load within the body (Wang *et al.*, 2024). Therefore, the use of Gln-containing dipeptides (i.e. Ala-Gln) can effectively avoid these problems. Ala-Gln has been on the market as an intravenous nutrition agent for over 20 years, and its efficacy and safety have been widely confirmed. It can not only provide raw materials for the synthesis of amino acids, proteins and nucleic acids, but also release energy through oxidation reactions, and can be used as dyes for other rapidly proliferating cells (Jing *et al.*, 2023). Wu *et al.* showed that Gln was the most important energy source for intestinal mucosal cells and colonic mucosal cells, which can promote protein synthesis and glycogen synthesis, and is a metabolic fuel necessary for rapid cell recovery (Wu *et al.*, 2023). Therefore, Ala-Gln has a significant nutritional improvement effect. In this study, the levels of serum ALB, PA and TRF in the EG were significantly higher than the CG after intervention, implying that Ala-Gln could significantly improve the nutritional status of liver transplantation patients.

Liver transplantation is characterized by high complexity, significant trauma and large blood loss. After the operation, patients usually need to be transferred to the intensive care unit for observation, and the hospital stay is relatively long, which greatly increases the treatment burden on patients. Although the concept of enhanced recovery is widely used in liver transplantation rehabilitation, its effect still needs to be further improved (Pollok *et al.*, 2023). Therefore, it is of great significance to promote early rehabilitation after liver transplantation to reduce the burden of treatment. In this study, the duration of ICU stay and hospitalization time in EG were shorter than CG, suggesting that the use of Ala-Gln in parenteral nutrition for liver transplant patients could shorten the recovery time. A pharmacological study has shown that Ala-Gln can help the liver and kidneys remove waste from the body, promote the growth of the pancreas, reduce muscle breakdown, and facilitate wound healing (Zheng *et al.*, 2023). According to Su *et al.*, Ala-Gln could reduce the expression of postoperative inflammatory factors, counteract the cell damage caused by inflammatory responses, promote cell repair, and shorten the recovery time (Su *et al.*, 2021). Therefore, the use of Ala-Gln parenteral nutrition support in this study had the significance of promoting post-liver transplantation rehabilitation.

Infection is one common cause of death after liver transplantation. Liver transplantation patients need to take immunosuppressants for a long time, which often leads to repeated infection that is difficult to cure (Mouch *et al.*, 2022). Therefore, it is particularly important to control nosocomial infection in the liver transplant ward. In this research, the occurrence rate of infection events in the experimental group was lower than the control group, suggesting that Ala-Gln could prevent the infection in patients after liver transplantation. Studies have shown that Gln is the precursor for the synthesis of glutamic acid in glutathione, and supplementation of glutamine can protect the storage of glutathione in liver and intestinal mucosa, help maintain normal immune function, and reduce immunosuppressive effects (Cirle *et al.*, 2023). In the study of Newsholme *et al*., the supplementation of glutamine was possibly the most widely recognized immunonutrient, playing key roles in immune regulation (Newsholme *et al.*, 2023). Therefore, the reduced incidence of infection in the experimental group of this study may be related to the immune regulatory mechanism of Ala-Gln.

CONCLUSION

For patients after liver transplantation, the use of Ala-Gln dipeptide parenteral nutrition support can correct the malnutrition condition, shorten the length of stay in the intensive care unit and the total hospital stay, and reduce the incidence of infection. For cases where the nutritional needs cannot be met through enteral nutrition after liver transplantation, it is recommended to use Ala-Gln dipeptide for parenteral nutrition support. This can correct the malnutrition condition, shorten the recovery time and prevent infection, and has certain significance for improving the rehabilitation quality of liver transplant patients.

Conflict of interest

There is no conflict of interest.

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