Original Article

Benefit of oral nutritional supplements for children with acute lymphoblastic leukaemia during remission-induction chemotherapy: a quasi-experimental study

Rui Liang MM, Gai-Yun Chen BM, San-Xian Fu BM, Jie Zhong PhD, Yan Ma MM

Department of Nutrition, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background and Objectives: To determine the effect of oral nutritional supplements (ONS) on children with acute lymphoblastic leukaemia undergoing remission-induction chemotherapy. **Methods and Study Design:** We included 127 paediatric patients who were diagnosed with acute lymphoblastic leukaemia and undergoing remission–induction chemotherapy in the First Affiliated Hospital of Zhengzhou University. Children from two paediatric wards who met the inclusion criteria were enrolled. One ward was randomly chosen as the intervention group and the other ward as the control group. Children in the two groups were matched for age and sex. The ONS group was administered Peptamen® (n=60) and the control group was administered a low-fat diet (n=67). **Results:** The baseline information before treatment was not significantly different between groups ($p>0.05$). In the control group, weight loss at the end of chemotherapy was significantly higher than that of ONS group ($p<0.05$). The hemoglobin level and the concentrations of total protein, albumin, and pre-albumin were significantly higher in the ONS group than in the control group ($p<0.05$ and $p<0.01$, respectively). The incidences of hypoalbuminaemia, gastrointestinal complications, and infection were lower in the ONS group than in the control group ($p<0.05$). The ONS group also used lower amount of albumin infusion, fewer blood-product infusion, and had lower hospital costs than the control group. **Conclusions:** During remission-induction chemotherapy, oral nutritional supplements can improve the nutritional status of children, reduce the incidence of complications, and decrease the costs of hospitalization.

Key Words: oral nutritional supplements, acute lymphoblastic leukaemia, chemotherapy, child, complications

INTRODUCTION

Malnutrition is a common problem in children with malignant tumour. Abnormal nutritional metabolism is caused by the disease itself or as a side effect of chemotherapy,[1] dysfunction of gastrointestinal function, and other causes that exacerbate malnutrition. Malnutrition has been shown to weaken the tolerance of children to various treatments, increase the risk of complications, reduce the survival rate, and lead to a poor overall outcome.[2-3] In children receiving chemotherapy, appropriate nutrition support can improve the tolerance and sensitivity to chemotherapy, and reduce the incidence of adverse effects and complications associated with chemotherapy.

Leukaemia is one of the most common malignant tumours in children,[4] accounting for more than 30% of all malignant tumours in children, 95% of which are acute leukaemia (AL). Considering that among all AL cases, 75% are acute lymphoblastic leukaemia (ALL), so research on ALL is of great importance.

A few studies have assessed the effect of nutrition support on ALL. However, previous studies have only observed the effect of enteral nutrition on the clinical treatment or nutritional status of children. They did not focus on other advantages of enteral nutrition; for example, they did not determine whether it increased treatment tolerance, reduced complications, shortened length of hospital stay or reduced the costs of hospitalization. Therefore, this study focused on these indices in children to better reflect the advantages of enteral nutrition. In this study, we aimed to determine the effects of oral nutrition support specifically on the nutritional status, complications, hospital days, and medical costs in children with ALL receiving chemotherapy.

METHODS

Patients

From July 2013 and December 2015, paediatric patients diagnosed with ALL and undergoing chemotherapy in two paediatric wards at The First Affiliated Hospital of Zhengzhou University were enrolled in this study. We screened all the children in the two wards, and patients who met the inclusion criteria were enrolled in the study. According to the random-number method, one ward was chosen as the intervention group, and the other ward was

Corresponding Author: Rui Liang, Department of Nutrition, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China.
Tel: +86-371-66913051; Fax: +86-371-66295009
Email: ruiliang668@163.com; 872594651@qq.com
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considered the control group. Children in the two groups were matched for age and sex, to ensure the two groups had the same baseline data.

The study duration was 33 days. Inclusion criteria were as follows: (1) age, 1-14 years; (2) receiving therapy for inducing remission; (3) score for the Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP) ≥4; and (4) voluntary participation in the study. Further, children with severe infection, those in whom relevant indicators could not be detected, and those who needed fasting or parenteral nutrition were excluded from the study.

A total of 135 patients met inclusion criteria for the study. Eight patients were excluded due to incomplete records. Eventually, 127 patients were segregated into two groups: the ONS group comprising 60 patients and the control group comprising 67 patients. We reviewed and analysed clinical and nutritional data, complications, and costs in the two groups.

This study was approved by the Ethics Committee of Zhengzhou University (Scientific research No. 09 in 2014). Written informed consent was obtained from all participants.

Nutritional support

The ONS group was administered a conventional low-fat diet in addition to Peptamen® as the nutritional supplements. The oral supplements were prepared by adding 39.3 g Peptamen® to 150 mL water. The patients were fed 3-5 times per day. Children in the control group were administered a low-fat diet.

Physiological and biochemical indices

We collected data on weight, hemoglobin level, total protein level, and albumin level of children on the day before chemotherapy and day 30 of chemotherapy.

Complications

The incidence of hypoalbuminaemia, gastrointestinal reaction (such as nausea, vomiting, diarrhoea, and abdominal pain), pancreatitis, infection, and mouth ulcers was recorded.

Hospital time and costs

The use of human blood albumin and blood products, number of hospitalization days, and medical costs for both groups were recorded.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL). Measurement data are expressed as the mean±standard deviation. The Wilks-Shapiro normality test was used to analyse data distribution, an independent sample t-test was used for analysis of variables between groups. Count data was analysed by chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

Patient demographics

Data from the 127 patients with ALL were collected and analysed (Table 1). In general, there were no significant differences in the clinical and nutritional data in the two groups, and the baseline data were the same in the two groups (p>0.05).

Table 1. Baseline information of 127 children with acute lymphoblastic leukaemia

Characteristics	ONS group (n=60)	Control group (n=67)	p value
Sex			0.985
Men	42	47	
Women	18	20	
Age			0.854
1–5 years	35	38	
6–13 years	25	29	
Risk			0.139
Low	5	14	
Moderate	45	44	
High	10	9	
Weight (kg)	18.9±7.72	21.0±10.5	0.114

†Measurement data are expressed as the mean±standard deviation

Physiological and biochemical indices

Table 2 shows the differences in the physiological and biochemical indices between the two groups. During the observation period, the weight of children in the ONS group increased slightly, whereas the weight of children in the control group decreased after chemotherapy. The change in body weight between the two groups was statistically significant (p<0.05).

On days 0, and 15 of chemotherapy, there was no significant difference in the concentration of hemoglobin between the two groups (p>0.05). On day 30 of chemotherapy, the hemoglobin level in the ONS group was significantly higher than that in the control group (p<0.05).

Before chemotherapy, the levels of total protein, albumin, and prealbumin were not significantly different between the two groups (p>0.05); however, at the end of chemotherapy, the levels of these indices were significantly higher in the ONS group than in the control group (p<0.001).

Complications and costs

During the period of chemotherapy, no pancreatitis occurred in children in both groups. However, the incidences of hypoalbuminaemia, gastrointestinal complications, and infection were significantly lower in the ONS group than in the control group (p<0.05). The incidence of other complications such as mouth ulcers and nosebleeds did not differ between the groups (Table 3). We graded the gastrointestinal complications/infection according to the Common Terminology Criteria for Adverse Events (v4.03). The severity of the symptoms of the two groups was tested by Mann-Whitney U-test, and no statistical difference was noted between the two groups (p>0.05).

The control group had significantly higher mean units of blood transfused and albumin dosage than the ONS group (p<0.05). The mean duration of the patients' stay in the hospital was 37.5±6.82 days; there were no significant differences in the length of hospital stay (p>0.05), but the ONS group tended to have fewer hospital costs than the control group (p<0.05) (Table 3).

Table 2. Physiological and biochemical indices in the ONS and control groups

Variables	ONS group (n=60)	Control group (n=67)	*p* value
Weight loss(kg) †	-0.07±0.95	0.77±2.66	0.001
Hb (g/L)			
D0	79.3±20.4	79.8±17.3	0.873
D15	81.0±10.8	77.8±11.2	0.099
D30	86.1±11.2	79.9±10.7	0.002
TP (g/L)			
D0	63.0±5.8	63.4±6.3	0.744
D30	59.9±4.6	56.0±5.2	<0.001
ALB (g/L)			
D0	39.6±3.6	37.5±3.8	0.290
D30	39.4±3.3	34.7±4.8	<0.001
PA (g/L)			
D0	156±47.0	168±83.6	0.422
D30	232±57.8	148±77.1	<0.001

Hb: haemogoblin; TP: total protein; ALB: albumin; PA: prealbumin.
†Data for weight loss before and after intervention.

Table 3. The complications and costs in the ONS and control groups

Variables	ONS group (n=60)	Control group (n=67)	*p* value
Hypoproteinaemia†	9 (15.0%)	32 (47.8%)	<0.001
Gastrointestinal complication†	14 (23.3%)	28 (41.8%)	0.027
Infection†	21 (35%)	38 (56.7%)	0.014
Mouth ulcer†	4 (6.7%)	10 (14.9%)	0.138
Nosebleed†	2 (3.3%)	4 (6%)	0.484
Blood transfusion‡	4.71±4.36	8.87±7.33	<0.001
Albumin dosage‡	6.29±8.18	20.2±31.1	0.001
Dosage of amino acid‡	8.78±17.0	15.6±40.3	0.223
Length of hospital stay (d)‡	37.3±7.92	37.8±5.70	0.684
Costs of hospitalization (￥)‡	40109±8,608	53226 ±14,287	<0.001

†The data was n (%).
‡Measurement data are expressed as the mean±standard deviation.

DISCUSSION

Children with ALL who undergo treatment often experience nausea, vomiting, poor appetite, and reduced diet due to the effects of the chemotherapy drugs. In addition, a certain degree of damage occurs to the gastrointestinal tract in patients, which not only impairs digestion of food and declines absorption function of the gastrointestinal tract, but also makes patients prone to bloating after eating an ordinary diet, leading to further loss of appetite and secondary reduction in food intake.

L-asparaginase (L-asp) is an important drug widely used in chemotherapy of malignant tumours in the lymphatic system. However, L-asp is known to produce a variety of adverse reactions, of which acute pancreatitis is the most serious condition.[5] In addition to acute pancreatitis, abnormalities in the lipid profile are relatively common in children with ALL undergoing L-asparaginase therapy.[6] Cases of acute pancreatitis are very serious, but the incidence can be reduced by diet control.[7] Therefore, clinicians generally recommend that patients adopt a low-fat diet during the use of L-asp.[4] However, a low-fat diet increases the difficulty of achieving the normal amount of nutrients through dietary intake. Compared to the general diet, low-fat diets limit the intake of some food components such as fat, especially triglycerides and cholesterol, and protein, making children more prone to malnutrition. In addition, children have a high metabolic rate. Owing to their high nutritional needs for their growth and development as well as the nutritional needs of tumour cells, the risk of malnutrition increases further. Therefore, children with ALL are at a high risk of malnutrition during chemotherapy.

When dietary intake is inadequate or incomplete, oral nutritional supplements is the main means to supplement nutrition. As ONS is administered orally, which is similar to the patient's natural intake process, it has better compliance and is widely used in patients with chronic wasting diseases such as tumours.[8] A large number of studies have confirmed the clinical applications of ONS. Previous studies have also shown that oral nutritional interventions are effective in increasing the nutritional intake and improving some aspects of the quality or life in patients with cancer who are malnourished or at nutritional risk.[9] Phillipson et al found that ONS decreases the length of stay in the hospital, episode costs, and 30-day readmission risk in the inpatient population.[10] The European Society for Clinical Nutrition and Metabolism guidelines recommend ONS as the primary nutrition therapy for cancer patients undergoing radiotherapy.[11]

Similar to the result of Shan Zheng et al,[12] our study showed that children in the ONS group had significantly fewer gastrointestinal complications than those in the

control group. We also noted that when children with ALL undergoing chemotherapy were administered ONS, they were able to maintain gastrointestinal function and reduce the adverse reactions of chemotherapy and the occurrence of complications, which allowed continuation of treatment.

Change in weight is an objective indicator of nutritional status and has valuable clinical application. When food intake reduces or energy expenditure increases, the body experiences a negative energy balance and weight loss. Studies suggest that weight loss can accurately reflect malnutrition.[13] At the end of our intervention, the body weight of the control group was lower than that of ONS group, and the difference was statistically significant. This study showed that ONS can prevent the chemotherapy-induced weight loss.

In this study, the length of stay in the hospital was similar between the two groups, but the costs of hospitalization were significantly lower in the ONS group than in the control group. Compared with those in the control group, children in the ONS group had lower human blood albumin dosage, fewer blood-product infusions, and fewer complications, which contributed to the lower hospital costs in this group. Thus, our results are consistent with the findings of Phillipson TJ et al, who reported that ONS shortens the hospital stay and reduces medical expenses.[10]

The results of this study provide valuable evidence of the need for nutritional support in children receiving chemotherapy. However, there are a few limitations in this study that need to be addressed. First, this study only assessed the initial stage of ALL chemotherapy, and the nutritional supplements in all stages of chemotherapy needs to be studied further. Second, the relationship between nutritional status and chemotherapy outcome was not described in this study. In our further studies, we plan to extend the time of the intervention, increase nutritional supplements for the patients after chemotherapy, and conduct a follow-up. Third, we did not collect the outcome data of patients or conduct regression analysis for the relationship between nutrition and outcome. We plan to do this in our upcoming study.

Conclusion

In conclusion, ONS can improve the nutritional status of children, reduce the incidence of complications, and decrease the costs of hospitalization. Therefore, ONS is beneficial for children undergoing chemotherapy and is especially necessary when children are at risk of nutritional deficiency.

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AUTHOR DISCLOSURES

No competing interests are reported.

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