Section: Surgical Gastroenterology

Original Research Article

EFFECT OF IMMUNO-NUTRITION ON NUTRITIONAL STATUS OF LIVER TRANSPLANT WAITING PATIENTS – RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: End stage liver disease (ESLD) patients are found to be at great probability of emerging malnourishment due to metabolic changes, liver disease pathology and associated nausea, anorexia, cirrhosis, etc. The patients awaiting or referred for liver transplantation (LT) have to be managed with proper nutritional planning and supplementation in order to avoid waiting period complications and to plan for a better post operative outcome. **Materials and Methods:** Patients with ESLD (n=141) were randomly assigned to control (CON, n=72) and intervention (INT, n=69) groups after obtaining informed consent. The CON group has given supervised diet advice and INT group received oral immunonutrient (100g) per day for one month. Nutritional status was monitored by subjective global assessment (SGA) and standard anthropometry before and after therapy. **Result:** Association of immunonutrition with Child-Pugh class (CPC) in the pre and post therapy after one month reported a statistically significant ($p<0.05$) reduction in liver disease severity. The average nutritional score was found to be lesser in the intervention group after one month of immunonutrient therapy, 11.2 (2.2) compared to the control group, 14.3 (3.4) and this result was found to be statistically significant, $p<0.001$. This indicated that the immunonutrient therapy was effective in improving the nutritional status. However, no significant difference was observed in the weight, body mass index (BMI), MUAC, MAMC and TST between the two groups both at baseline and at one month, $p>0.05$. **Conclusion:** Immunonutrienttherapy was found to be beneficial in augmenting the nutritional status of liver disease patients during the LT waiting period.

INTRODUCTION

Nutrition plays a significant role in health maintenance in all disease conditions. The main role of liver is the nutrient metabolism and the hepatic metabolic changes in cirrhotics leads to insulin resistance and sensitivity to hepatic tissues results in muscle depletion and loss of subcutaneous fat and can be manifested before the development of obvious malnutrition.[1,2] In the early stages of cirrhosis, protein catabolism will be higher and protein deficiency will be at peak as disease advances, leads to sarcopenia and low muscle strength and muscle mass depletion is quiet common in CLD patients awaiting LT.[3,4]

Malnutrition is quite common in CLD patients without cirrhosis too and undernutrition is always concealed by overweight.[5] Many complications are associated with undernutrition in cirrhotic patients namely, sarcopenia, frailty and the prognosis of patients will be further impaired if the patient has sarcopenia.[6-14]The deficiency of arachidonic acid substantially increases the mortality risk in patients with advanced liver cirrhosis.[15]Malnutrition is significantly linked with high rate of morbidity and mortalityand the LT cost are high.[16-20] Hence, early and routine nutritional assessment are significant in

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the management of hepatic cirrhosis by using SGA, bioelectric impedance analysis (BIA), and standard anthropometric measurements.[21,22]

ESLD patients have less tolerance for protein and PEM is correlated with deficiency of vitamin A, zinc and magnesium.[23] Malnourished ESLDs are at high risk of infectious issues, increased duration of stay in hospitals, and higher mortality in pre and post LT.[24,25]

MATERIALSANDMETHODS

144ESLD patients attending gastroenterology clinic of JIPMER, Puducherry were enrolled into the study after obtaining informed consent and randomized into control and intervention groups. The study was registered in clinical Trials Registry-India (CTRI/2019/08/020973).Institutional ethical committee (Human studies) approval (JIP/IEC/2018/502) was obtained from JIPMER, Puducherry.After the patient recruitment, socio-demographic data and nutritional status were assessed during the first visit (enrolling). The control group (CON) were advised to follow supervised diet advice for 1month and provided nutritional counselling. Immunonutrient 100g was provided to the patients to ensure the compliance rate of 75% and to be taken orally in a day for 1 month for the intervention group (INT) along with supervised diet advice and nutritional counselling.100g of FresubinOnco powder provides 415 kcal, 28g of protein, 11g of fat, ω-3/ ω-6 fatty acids (2g/0.70g), L-arginine 425mg, glutamine 500mg with other essential vitamins and minerals. Nutritional status was assessed before and after therapy using "subjective global assessment (SGA)" and other "standard anthropometric measurements".Patients were categorized as "well nourished,being grade A (score 7–14), moderately malnourished as grade B (score 15–28), and severely malnourished as grade C (score 29–35)".Anthropometric measurements, including body weight (kg), height (cm), body mass index (BMI) in Kg/m2, mid upper arm circumference (MUAC) in cm, mid arm muscle (MAMC)in cm, (TST) in mm were estimated.

Sample size was estimated at 5% level of significance and 80% of power. The estimated sample size was 64 in each group and it is further inflated to 72 in each group with an expected drop out of 10%. Computer-generated random number sequence, block randomization of varying size generated through the computer was used to randomize the patients. The sequence was generated by a staff in the liver clinic who was not a part of the study. The random sequence was concealed before allocation by SNOSE technique (Serially numbered opaque sealed envelope). The principal investigator allocated the participants to the corresponding arm. Because of the nature of the intervention (difference in the intervention in both arms), blinding of the investigator and also the participant was not possible. Statistical analysis was computed using SPSS Statistics version 19 software. The comparison of the quantitative variables between two groups were conducted using the independent students' t-test, and the comparison between more than two groups were carried out using a one-way analysis of variance (ANOVA). The means of the difference was estimated using independent sample t-test.All statistical analyses were carried out at 5% level of significance, andp-value <0.05 was considered significant. Consort flow diagram for the study is shown below as [Figure1].

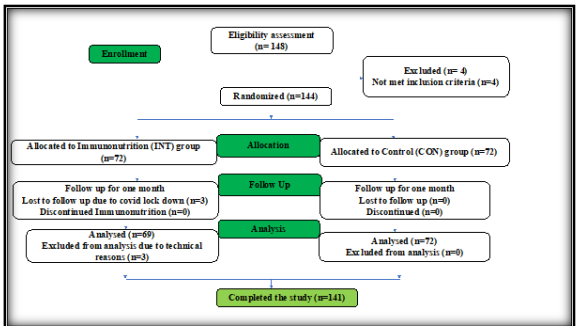

Figure 1: Consort Flow Diagram

RESULTS

ESLD patients were randomly allocated to control and intervention groups. The mean age and other clinical characteristics were similar in both groups and it showed that two groups were comparable and details are provided in [Table1].

The majority of patients with liver disease were having alcoholism as the major etiology in both groups. Occupation of the patients were mainly agricultural work and other jobs and were in low socioeconomic status. Other clinical factors like comorbidity, smoking, edema and food type were not associated with the intervention status.

Baseline nutritional status of ESLD patients in control and intervention groups didn't show any association between groups and showed that the groups were similar and comparable with respect to nutritional status and details are provided in [Table 2].

The comparison of clinical characteristics of ESLD patients in control and intervention groups at baseline and at one month is provided in [Table 3]. Association of intervention status with edema, ascites and Child-Pugh class were not found to be statistically significant (p>0.05). No significant difference was observed in the median MELD-Na score between the intervention 15 (9.8) and control 15 (10) groups, p >0.05. No significant difference was observed in the mean BMI in both groups at baseline and at one month.

The association of Child-Pugh class with pre and post therapy in control and immunonutrition groups as per analysis done by Stuart Maxwell test are provided in [Table 4]. Immunonutrient therapy has

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shifted some groups in late ESLD stage (CPC-B&C) to early ESLD stage (CPC-A). Association of immunonutrition with Child-Pugh class in the pre and post therapy after one month reported a statistically significant ($p<0.05$) reduction in liver disease severity.

Table 1: Baseline demographic and clinical characteristics of ESLD patients in control and intervention groups

Demographic/ Clinical characteristics	Category	Control (n=72) %	Immunonutrition (n=69) %	p-value
Age#		49.6 (11.4)	49.3 (9.3)	0.85
Height (cm)#		166.2 (7.2)	163.3 (8.3)	<0.05*
Gender	Males	60 (83.3)	53 (76.8)	0.33
	Females	12 (16.7)	16 (23.2)	
Occupation	Agriculture	13 (18.1)	19 (27.5)	0.06
	Shop	7 (9.7)	11 (15.9)	
	Driver	7 (9.7)	7 (10.1)	
	Govt. Job	3 (4.2)	3 (4.3)	
	Others	31 (43.1)	13 (18.8)	
	Housewife	11 (15.3)	16 (23.2)	
Marital status	Married	69 (95.8)	69 (100)	0.25
	Unmarried	3 (4.2)	0	
Etiology	Alcoholism	33 (45.8)	39 (56.5)	<0.05*
	Cryptogenic	13 (18.1)	17 (24.6)	
	Hepatitis (B&C)	17 (23.6)	13 (18.8)	
	Others	9 (12.5)	0	
Comorbidity	Yes	17 (23.6)	14 (20.3)	0.74
	No	55 (76.4)	51 (73.9)	
Alcoholism	Yes	36 (50)	39 (56.5)	0.4
	No	36 (50)	30 (43.5)	
Smoking	Yes	6 (8.3)	6 (8.7)	0.9
	No	66 (91.7)	63 (91.3)	
Edema	Yes	43 (59.7)	38 (55.1)	0.58
	No	29 (40.3)	31 (44.9)	
Food type	Vegetarian	4 (5.6)	6 (8.7)	0.53
	Non-Vegetarian	68 (94.4)	63 (91.3)	

*Statistically significant ($p<0.05$)

Table 2: Baseline nutritional status of ESLD patients in control and intervention groups

Nutritional status	Category	Control (n=72) %	Immunonutrition (n=69) %	p-value
Nutritional status, SGA	A	25 (34.7)	16 (23.2)	0.12
	B	47 (65.3)	53 (76.8)	

Table 3: Clinical characteristics of ESLD patients in control and intervention groups at baseline and at one month

Clinical characteristics	Category	Pre therapy (Baseline)			Post therapy (At one month)		
		Control (n=72) %	Immunonutrition (n=69) %	p-value	Control (n=72) %	Immunonutrition (n=69) %	p-value
Edema	Yes	43 (59.7)	38 (55.1)	0.58	28 (39.4)	30 (43.5)	
	No	29 (40.3)	31 (44.9)		43 (60.6)	39 (56.5)	0.63
Ascites	Yes	47 (66.2)	48 (69.6)	0.67	30 (41.7)	37 (53.6)	
	No	24 (33.8)	21 (30.4)		42 (58.3)	32 (46.4)	0.16
Child-Pugh class	A	23 (32.0)	25 (36.2)	0.86	23 (32.4)	30 (44.1)	
	B	35 (48.6)	31 (45.0)		36 (50.7)	28 (41.2)	
	C	14 (19.4)	13 (18.8)		12 (16.9)	10 (14.7)	0.36
Clinical characteristics		**Pre therapy (Baseline)**			**Post therapy (At one month)**		
		Control (n=72)	**Immunonutrition (n=69)**	**p-value**	**Control (n=72)**	**Immunonutrition (n=69)**	**p-value**
MELD-Na Score $		17 (10)	14 (9.5)	0.04	15 (10)	15 (9.8)	0.19
BMI#		23.9 (4.2)	25.1 (4.9)	0.12	23.8 (3.9)	24.7 (4.5)	0.18

$ Median (IQR) / #Mean (SD)

Table 4: Association of Child-Pugh class with pre and post therapy in CON and INT groups@

Clinical Characteristics	Category	Control (n=72)		Immunonutrition (INT) (n=69)		p-value
		Pre-CON	Post-CON	Pre-INT	Post- INT	
Child-Pugh Class	A	23	23	25	30	0.02*
	B	35	36	31	28	
	C	14	13	13	10	

*Statistically significant ($p<0.05$) @ Stuart Maxwell test

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Table 5: Comparison of nutritional screening parameters among ESLD patients in control and immunonutrition groups at baseline and at one month

Clinical characteristics#	Pre therapy(Baseline)			Post therapy(Atone month)		
	Pre- CON(n=72)	Pre-INT(n=69)	p-value	Post-CON (n=72)	Post-INT(n=69)	p-value
Weight (Kg)	65.9 (11.8)	67.6 (16.3)	0.51	65.2 (11.2)	66.4 (15.0)	0.59
BMI (Kg/m2)	23.9 (4.2)	25.1 ((4.9)	0.12	23.8 (3.9)	24.7 (4.5)	0.18
MUAC (cm)	24.8 (3.3)	25.5 (4.7)	0.29	24.5 (3.4)	25.3 (4.6)	0.25
MAMC (cm)	20.9 (2.6)	21.1 (3.2)	0.71	20.5 (2.7)	20.9 (3.1)	0.45
TST (mm)	12.5 (4.9)	14.1 (7.4)	0.12	12.7 (5.5)	14.3 (7.7)	0.18
Nutritional Score	15.8 (3.3)	16.3 (3.8)	0.46	14.3 (3.4)	11.2 (2.2)	<0.001*
SGA –A n (%)	25 (34.7)	16 (23.2)	0.12	36 (50.7)	63 (91.3)	<0.001*
B n (%)	47 (65.3)	53 (76.8)		35 (49.3)	6 (8.7)	

#Mean(SD)/ *statistically different from control group (p<0.001)

The comparison of nutritional screening parameters among ESLD patients in control and intervention groups at baseline and at one month are provided in [Table 5]. The average nutritional score was found to be lesser in the intervention group after one month of immunonutrition therapy, 11.2 (2.2) compared to the control group, 14.3 (3.4) and this result was found to be statisticallysignificant, p <0.001. This indicated that the immunonutrition therapy was effective in improving the nutritional status, [Figure 2]. However, no significant difference was observed in the weight, BMI, MUAC, MAMC and TST between the two groups both at baseline and at one month, p>0.05.

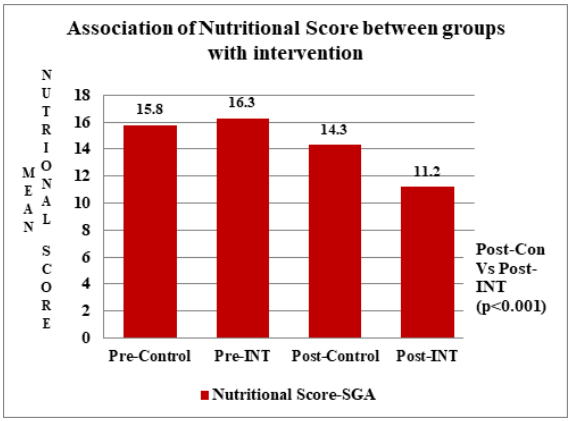

Figure 2: Association of nutritional score between groups with intervention

Immunonutrient therapy significantly improved the nutritional status of patients in the INT group compared to control and is illustrated in [Figure 3].

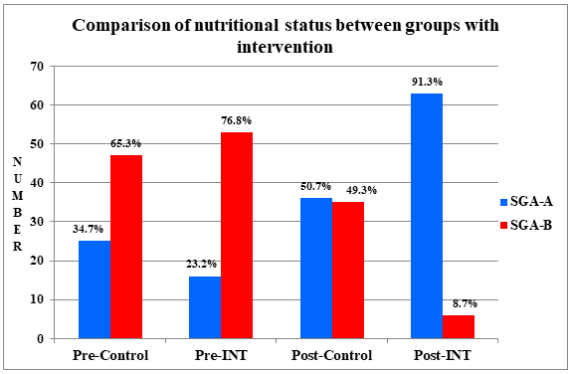

Figure 3: Comparison of nutritional status between groups with intervention

DISCUSSION

A total of 141 patients were enrolled in our study and all the baseline clinical and demographic characteristics in two groups didn't show any significant differences. In our study, the majority of patients with disease were males (83.3% in control Vs 76.8% in INT group), having alcoholism as the etiology in both groups with 45.8% in control and 56.5% in INT groups. These results were reinforced in a study, where 61% had alcoholismas the causative factor and majority (72%) were males.[26] No significant difference (p>0.05) was observed in the median MELD-Na score between the immunonutrition 15 (9.8) and control 15 (10) groups in our study, supporting the findings in another study.[27] No significant difference was observed in mean BMI in both the groups at baseline and at one month and this is supported by another study that BMI might be influenced by fluid retention leads to underestimation of malnutrition.[28] Regarding nutritional level status among our study patients, 65.3% in control and 76.8% in INT groups were moderately malnourished (SGA-B) which is higher compared to similar study, the reported rate of malnutrition among cirrhotics in Indian population were 47% and sarcopenia was 84%.[29,30]

The rate of malnutrition is directly proportional to the disease severity among liver patients as reported in our study.[29]Immunonutrition aids in shifting some patients in Child-Pugh class B and C to early stage of Child-Pugh class A in our study and showed a statistical significance, p<0.05. Studies related to immunonutrition and nutritional status among liver disease patients are very few. The average nutritional score by SGA was found to be lesser in the intervention group after one month of immunonutrition therapy, [11.2 (2.2)] compared to the control group, [14.3 (3.4)] and this result was found to be statistically significant, p <0.001. This indicates that the immunonutrition therapy was effective in improving the nutritional status in ESLD patients. A study on preoperative immunonutrition reported a contradictory finding that therapy didn't have major beneficial effects in improving the nutritional status and it might be due to very short period of preoperative immunonutrient therapy.[27] No significant difference was observed in the weight, BMI, MUAC, MAMC and TST between the

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two groups both at baseline and at one month with immunonutrition or supervised diet advice in control groups, p>0.05 in our study.

As of now, published studies supporting the effect of pre-operative immunonutrition on nutritional status among ESLD patients are scarce, but one trial on the same among colorectal patients are ongoing.[31] One meta-analysis suggested to use immunonutrition perioperatively for entire patients undergoing major gastrointestinal (abdominal) surgeries due to reduction in hospital stay.[32]Another study reported a reduction in post operative hospital stay with the use of preoperative immunonutrition among colon and rectum malignancy patients.[33] Most of the patients with GI diseases may get benefitted from immunonutrition as it supports our study finding of enhanced nutritional status.[34] ESLD patients underwent LT had reported an augmented nutritional status with immunonutrient therapy compared to control in another study.[27]

The tolerance of immunonutrition in our study patients were good without any adverse events assessed by "the presence or absence of any intolerance issues (vomiting, nausea, abdominal cramping, bloating)' and 5 clinical trials had reported regarding the tolerance levels of enteral immunonutrition and showed an analogous result for immunonutrition in the perioperative period.[35-39] To assess the compliance rate and any adverse events to immunonutrition, principal investigator made a phone call every week and the compliance rate were also good and found to be safe to administer in our study patients. It was supported by another study which reported that enteral immunonutrition was safe to administer in patients admitted for malignancy related gastrointestinal surgeries.[40]One more study showed no adverse events during preoperative immunonutrition therapy and few patients were reported vomiting and bloating post operatively, but tolerated the liquid supplement afterwards.[41]

The limitations of the study are that among our ESLD patients, 34.7% in control group were in SGA-A and 23.2% in intervention groups were in SGA-A even though it is small compared to moderate malnutrition percentage in two groups. Immunonutrition and supervised diet advice are significant in improving the nutritional status and clinical outcome by improving the functional status of ESLD patients as evidenced by our study findings. Hence it is essential to do nutritional assessment by SGA, as it is easy to use in clinical setting and to plan nutritional intervention along with nutritional counselling.

CONCLUSION

The effect of immunonutrition on nutritional status among ESLD patients was found to be beneficial in augmenting the nutritional status in the immunonutrient group compared to the control group. Marginal improvement in the nutritional status has been observed in the control group as expected, who received supervised diet advice. The findings emphasize the importance of early nutritional interventions among ESLD patients awaiting liver transplant.

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