Official Title: Safety and feasibility of Early Oral Nutrition after Endoscopic Treatment for Patients with Liver Cirrhosis: A Historical-prospective, Comparative Effectiveness study

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Study protocol

The purpose of the study was to compare safety and effectiveness of different feeding time in the real-world clinical practice. Detailed history-taking and physical examination were carried out on all recruited patients and basic information were recorded including liver function by Child-Pugh's scores and MELD scores, endoscopic features. EVL was performed after confirmation of esophageal varices and cyanoacrylate was injected if gastric varices were diagnosed. Further, the octreotide was given for 24 hours postop routinely. All the therapeutic endoscopies were performed by a technically proficient gastrointestinal endoscopist. The endoscopist, data collectors and statisticians were blinded to the follow-up dietary intervention tasks.

Eligible patients in the EN group were required to fast for 4 hours following endoscopic treatment and peptisorb produced by Milupa Nutricia GmbH was used for enteral nutrition at the beginning. The initial recommended dose of peptisorb is 60 g dissolved in 250ml water, which can provide 250 kcal energy (protein9.8 g, fat 2.45 g, carbohydrate 46.5 g). Transition to soft diet such as chicken custard could be carried out after 2 to 3 times of giving peptisorb emulsion if there were no adverse reactions. Further, it is recommended that the diet of patients should obey the principle of multiple-meal-with-small-amount-for-each and the daily meals could up to between 4 and 5 times. The time and amount of diet was recorded specifically and the total energy intake through enteral nutrition were calculated. Extra energies were supplemented by parenteral nutrition. All patients required fasting for at least 48 hours in the control group and parenteral nutrition was provided through intravenous infusion, then transit gradually from liquid diet to soft diet. All nutritional supports were provided based on the standard recommended by ESPEN guideline on clinical nutrition in liver disease that calorie requirement for 30 ~ 35 $kcal \cdot kg^{-1} \cdot d^{-1}$[22].

In addition, the prospectively enrolled patients in interventional group were divided into three subgroups according to dietary time. The early enteral nutrition (EEN) in the current study was defined as starting enteral nutrition between 4 and 12 hours after endoscopic therapy and delayed enteral nutrition (DEN) was defined as between 12 and 48 hours. The dietary time after 48 hours was defined as parenteral nutrition (PN).

Outcomes and definitions

The primary endpoint of this study was variceal re-bleeding following endoscopic treatment. The secondary endpoints were mortality whereas the adverse events during the 42-day follow-up. The days and expenses of hospitalization were also compared between the two groups in this study. Besides, inflammatory factor, serum albumin level, defecation time and the satisfaction with nutritional support of patients were also evaluated in the three subgroups.

Variceal Re-bleeding includes very early rebleeding and early rebleeding. In this study, very early rebleeding was defined as rebleeding within 5 days after endoscopic treatment whereas early rebleeding was defined as within 5 and 42 days after endoscopic treatment. Rebleeding within 48 hours was considered as failure treatment. Whatever anytime, once the rebleeding occurred, the patients would receive pharmacotherapy or endoscopic treatment again.

Satisfaction of the patients with nutritional support was assessed based on 5 - point Likert scale of very satisfied (5 points), satisfied (4 points), neither satisfied nor dissatisfied (3 points), dissatisfied (2 points) and very dissatisfied (1 point). The satisfaction rate was regarded as the proportion of very satisfied and satisfied.

Statistical analysis

Statistical analyses were performed using statistical software IBM SPSS Statistical 26.0 (SPSS, Chicago, IL). The baseline data of control group and intervention group were matched using propensity score analysis (PSM) in a ratio fashion of 1:1 using the nearest neighbor technique. Quantitative variables conforming to normal distribution were expressed as mean ± standard deviation (M±SD) whereas the variables not conforming to normal distribution were presented as median (interquartile range (IQR), (P25, P75)). Qualitative variables were expressed as percentages. Quantitative variables were compared using Student's *t*-test, Mann–Whitney nonparametric test or variance analysis, and x^2 test. On the other hand the Fisher's exact tests were used to compare qualitative variables in this study. Linear regression analysis was performed to find the significant factors influencing diet time after endoscopic treatment. The analysis of outcomes between the two groups was conducted based on intention-to-treat

(ITT) and per-protocol (PP) analysis. $P<0.05$ was considered statistically significant.