Short term nasogastric versus oral feeding in hospitalised patients with advanced cirrhosis: A randomised trial

Mei-Ling Sharon Tai, Hamizah Razlan, Khean-Lee Goh, Siti Hawa Mohd Taib, Abdul Halim Mohd Huzaimi, Sanjay Rampal, Sanjiv Mahadeva

Keywords: Liver cirrhosis, Enteral nutrition, Nutrition intervention nasogastric feeding, Chronic liver disease

1. Introduction

 Decompensated liver cirrhosis is a significant burden to healthcare resources and represents one of the commonest causes of hospital admissions to gastroenterology units worldwide. Hospitalization rates for liver cirrhosis have not only increased over time, but also have associated morbidity and mortality. Malnutrition, a well recognized association with hospitalized cirrhotics, has been reported to be a significant contributing factor towards the poor prognosis of the disease. Causes of malnutrition in liver cirrhosis are multi-factorial, but generally include a reduction in oral intake, increased protein catabolism and insufficient synthesis, and malabsorption associated with portal hypertension.

 As most patients with decompensated cirrhosis do not satisfy their nutritional requirements, intervention in the form of enteral supplementation is now recommended as the standard of care. Long term (up to 12 months) oral feeding in patients with cirrhosis has been shown to result in an increased caloric intake, improvements in liver function and even a reduction in the incidence of hepatic encephalopathy. Although oral feeding is the preferred route of enteral supplementation, many patients with advanced cirrhosis, particularly those who have been hospitalised, are known to have an insufficient dietary intake.

 In cirrhotic patients with an inadequate oral intake, it is suggested that tube feeding, usually with a nasogastric (NG) tube, should be used to deliver enteral nutrition. A single centre study previously compared in-patient enteral feeding via an NG tube to oral supplementation in 35 patients with advanced cirrhosis over a 6 week period. 6 weeks of NG feeding in patients with cirrhosis, in
contrast to orally fed patients, resulted in an increase in serum albumin, Child-Pugh score and in-hospital survival. Although this study demonstrated a clear advantage of NG over oral feeding, the clinical relevance of this finding is somewhat questionable. Most patients who get admitted for decompensated cirrhosis do not stay in hospital for more than a month. Furthermore, it is uncertain if patients with cirrhosis are willing to continue with NG feeding in the community for prolonged periods of time. From a practical perspective, it is of greater relevance to determine if short-term NG feeding, i.e. while the patient is still in hospital, has any advantages over oral supplementation. We designed a randomized clinical trial in an attempt to answer this query.

2. Methods

2.1. Study design

A prospective, randomized study was conducted in 2 large teaching institutions. Local institutional ethics committee approval was obtained before commencement of the study and the study was registered with Clinical Trials. Gov, an international registry of clinical trials. Randomisation was performed according to a computer-generated numbering system. Sequential numbers with random generation of either NG feeding or oral feeding, done by an independent investigator (SR) blinded to the patients, were sealed in an envelope. Following informed consent, consecutive patients recruited for the study would then be allocated to either NG feeding group or the oral feeding group after removing the sealed envelope. The process of recruitment and allocation were conducted by two of the main principal investigators, MLST and HR.

The period of nutritional intervention was decided for two weeks, as this was the maximum practical period most patients could remain as in-patients and the minimum period for any nutritional benefit. Patients would subsequently be assessed after another four weeks (i.e. week six) to determine any lasting effects from the initial intervention. Nutritional and clinical parameters (see below) were obtained at baseline (day 0), two weeks after and at week six — see study protocol flow chart (Fig. 1). The total calorie intake of patients in each group was assessed during the period of nutritional intervention. The primary outcome for this study was to compare the mean changes of nutritional parameters at 2 and 6 weeks between the NG and orally fed groups of patients. A secondary outcome was to assess for changes in liver function and subsequent complication rates between the 2 groups.

2.2. Patients

Patients were recruited from the adult gastroenterology wards in both institutions between August 2007 and May 2010. All patients with decompensated liver cirrhosis admitted to the ward for any reason during the period of study were screened for eligibility. The diagnosis of cirrhosis was based on a combination of clinical features, blood profile and radiological imaging results. Clinical features were those of portal hypertension, particularly abdominal ascites and/or gastro-esophageal varices. Blood profile included evidence of thrombocythemia and/or coagulopathy.

![Flow of patients in the study](image-url)
Radiological features, either with ultrasound or computerised tomography, had to demonstrate a shrunken liver with or without features of portal hypertension. Cirrhotic patients with the following features were excluded from the study: hepatic encephalopathy Grade 3–4, hepatocellular carcinoma, serum creatinine > 300 μmol/l and acute upper gastrointestinal haemorrhage.

2.3. Nutritional assessment

Nutritional assessment was based on anthropometry, biochemical markers and subjective global assessment (SGA). Anthropometric measurement consisted of triceps skinfold thickness (TST), midarm circumference (MAC) and midarm muscle circumference (MAMC). TST and MAC were measured using standard methods.15 Midarm muscle circumference (MAMC) was calculated using the formula: MAMC = MAC – (3.1415 × TST).15

Serum albumin and transferrin were utilized as biochemical nutritional markers. Although nonspecific, serum albumin has been used to assess change in nutritional status and stratifying risk of malnutrition.16 Good correlation between transferrin levels with the Child-Pugh score have been demonstrated before and a reduced level of serum transferrin is additionally indicative of decreased caloric intake.18 In this study, we were only able to measure serum transferrin levels at baseline and week 2, but not at 6 weeks due to financial constraints.

The SGA is a simple evaluation tool that allows physicians to incorporate clinical findings and subjective patient history into a nutritional assessment.15 Based on history taking and physical examination, nutritional ratings of patients are obtained as follows: well-nourished-A, moderately malnourished-B and severely malnourished-C. Both the SGA and anthropometry tools have been shown to be reliable and valid measures of nutritional status among local patients with advanced cirrhosis.5

2.4. Nutritional support

The requirement for enteral nutrition and caloric assessment of dietary intake in both NG and oral feeding groups were performed by 2 hospital-based dietitians (SHMT and MH). Patients in the NG group received supplements to achieve an energy intake of 35–40 kcal/kg/day and protein intake of 1.2–1.5 g/kg/day. In non-diabetic patients, Osmolite® (Abbott Lab., USA) enteral supplementation was utilized in the NG group whilst Ensure® (Abbott Lab., USA) supplements were provided in addition to the standard hospital diet in the oral group. Each 237 ml of Osmolite® provided 350 kCal of energy with a 14% protein, 29% fat and 57% carbohydrate distribution, together with 24 essential minerals and vitamins. 237 ml of Ensure® (i.e. one serving) provided 355 kCal of energy with 16.7% protein, 54.3% carbohydrate, 29.0% fat distribution together with essential minerals and vitamins as well. In both groups, Nutren Diabetik® (Nestle Nutrition, Vevey, Switzerland), which contained low carbohydrate with <0.2% sucrose, a fibre blend (soluble, insoluble and inulin) and high quality protein (50% whey, 50% casein) was administered to diabetic patients. All patients in the NG group additionally received standard concentrations of branched chain amino acids, Falkamin® (Dr. Falk GmbH & Co, Germany) in view of the beneficial effect of these supplements in chronic liver disease.18 Each sachet of Falkamin (25 g per sachet) contained 13.1 g of protein, 0.3 g of fat and 9.6 g of carbohydrate. Patients in the NG group were additionally allowed to ingest orally if they so desired.

A fine-bore feeding tube (12G Enteryflex, Tyco Healthcare, Ireland) was inserted into all NG patients and tube positions were confirmed by chest X-ray prior to commencement of enteral feeding. Enteral feeding was continuously infused with the aid of a peristaltic feeding pump at a flow of 30 ml/h and increased according to patient’s tolerance to a maximum rate of 50–80 ml/h (depending on patients’ body weight). Due to the perceived poor tolerance of NG tube placement in most of our local patients, we decided to assess the level of discomfort to NG tube during the study. An inverse 100 mm Visual Analogue Scale (VAS), with a score ranging from 0 (poor tolerance/extreme discomfort) to 100 (good tolerance/no discomfort at all) was administered to all NG patients at the end of 2 weeks of feeding or beforehand if patients withdrew from the intervention arm for any reason. This scale has previously been used in our local population to assess tolerance/level of discomfort associated with colonoscopy.19

Assessment of calorie intake during hospitalization was determined by the dietary recall method done every three days for two weeks in the oral group, and a simple summation of total enteral supplements in the NG group. The objective was to determine the adequacy of caloric intake per patient with minimum reporting bias. Calculation of calories of food and drinks intake (composition of the diet) was based on local reference data.20

2.5. Clinical parameters

Assessment of liver function, determined by the Child-Pugh score,21 was conducted at baseline (day 0), 2 weeks after intervention and at week 6 of the study. In addition, the development of any complications, namely, upper gastrointestinal bleeding, sepsis, hepatic encephalopathy, recurrent ascites and mortality (any cause) was documented during the study period.

2.6. Statistical analysis

Sample size calculation was based on the primary outcome, using a standard sample size calculation software.22 Based on an expected difference of 3.5 g/l (estimated standard deviation 5.8) serum albumin between the NG and oral group,14 we estimated that 22 patients in each treatment arm would have an 80%
power to detect a significant difference at 2 weeks at an α level of 0.05.

Analysis was performed on an intention-to-treat basis. All data was entered into Statistical Packages for the Social Sciences (SPSS) version 16.0 (Chicago, Illinois, USA) software for analysis. Continuous variables between the NG and Oral feeding group at baseline were expressed as means whilst categorical data were reported in proportions. Analysis was performed with Mann–Whitney U test, Chi-square test or Fisher’s exact test where appropriate. Statistical significance was assumed at a p value of <0.05.

3. Results

67 eligible patients with decompensated cirrhosis were invited to participate in the trial between August 2007 and May 2010 in both institutions. 13 patients refused to participate and 54 (80%) patients consented to be randomized to NG (n = 30) and oral (n = 24) feeding. 2 patients in the NG group were unable to tolerate placement of the NG tube and withdrew the tubes the same day after placement. Hence, complete data was available for 28 (NG group) and 24 patients (oral group) in Table 1 highlights the demographics, clinical characteristics and nutritional status of both groups of patients. The mean age was similar in both groups (59.6 years in NG group, 58.2 years in oral group) and there were no significant differences in gender nor ethnic distribution. The common cause of cirrhosis was viral hepatitis (42.8% in NG group, 54.2% in oral group) and both groups of patients had advanced liver disease, with the mean Child-Pugh scores of 10.8 and 10.1 in the NG and oral groups respectively. In terms of nutritional status, both NG and oral groups had a similar proportion of SGA grade B patients (64.3% in NG group, 70.8% in oral group), whilst TST, MAMC and serum Albumin values were not different (Table 1). The mean serum transferrin was lower in the NG compared to the oral group (1.3 ± 0.4 vs 1.7 ± 0.7, p = 0.011). This appears to correlate with a higher proportion of infections (25% NG vs 20.8% oral) and hepatic encephalopathy (14.3% vs 8.3% oral) in the NG group.

Figure 1 outlines the details of recruitment and follow up during the period of study. In the NG group, two patients required early termination from the study due to complications, namely acute pancreatitis and variceal bleeding. A total of 24/28 patients completed NG feeding for two weeks. Prior to the 6 week follow up, among the 24 patients, four patients died as a result of septicemia (n = 2), upper gastrointestinal bleeding (n = 1) and acute coronary syndrome (n = 1). A further three patients failed to return for follow up at 6 weeks. In the oral group, two patients died as a result of septicemia within 2 weeks. Prior to follow up at 6 weeks, a further three patients suffered mortality due to hepatic encephalopathy (n = 1) and septicemia (n = 2). Two patients in the oral group failed to attend for the 6 week follow up. All patients in both groups who failed to attend the 6 week follow up visit were not resident nearby and cited logistic reasons for failing to return when we contacted them.

3.1. Nutritional and clinical parameters at 2 weeks

Table 2 highlights the mean changes in nutritional and Child-Pugh scores after 2 weeks of intervention. NG feeding resulted in a significantly higher calorie intake in patients compared to oral feeding (1721 ± 599 vs 1346 ± 448, p = 0.015). NG feeding for 2 weeks resulted in an increase in MAMC compared to oral feeding, but this failed to reach statistical significance. No significant differences in other nutritional parameters nor the Child-Pugh scores were noted between both groups at 2 weeks.

The average VAS score (range from 0 mm indicating complete intolerance to 100 mm indicating complete acceptance) for tolerance to the NG tube was 42.9 ± 20.5 mm. Using a pre-defined VAS score of <50 mm as an indication of poor tolerance to NG tube placement, we identified that 12/28 (42.9%) patients had poor tolerance to NG tube placement in this study.

3.2. Follow up data at 6 weeks

18/28 (64.3%) patients in the NG group and 17/24 (70.8%) patients in the oral group were assessed at 6 weeks (Fig. 1). Table 2 illustrates the data that was analysed on an intention-to-treat basis and no significant differences were noted in both groups.

Figure 2 illustrates the mortality rates in both groups of patients with advanced cirrhosis in this study. No differences were noted at 2 weeks, but a slightly lower mortality rate was observed in the NG group after 6 weeks (14.3% NG vs 20.8% oral, p = NS).

4. Discussion

This study represents one of the largest clinical trials to have been conducted comparing NG against oral supplementation in patients with advanced cirrhosis. Patients in both NG and oral treatment arms had moderately severe malnutrition, evident by >60% of SGA grade B cases in both groups and <5th percentile mean values of the TST and MAMC. Although baseline calorie intake was not documented, we previously reported that patients with advanced cirrhosis had a significantly inadequate calorie intake with their normal diet and we did not expect this group of patients to be any different. Feeding for 2 weeks via the NG route provided a higher calorie intake but did not translate into improvements in nutritional or clinical parameters over oral feeding. Furthermore, almost half of the patients had a poor tolerance to NG tube placement and early withdrawal from the NG group was as high as 15%. It is possible that tolerance to NG tubes may have been enhanced if it was only left overnight, whilst enabling normal oral feeding during the day. However, this would
have necessitated repeated NG tube insertions on a daily basis, which would have reduced tolerance and compliance as well.

This study has failed to demonstrate any significant benefit of short term NG over oral supplementation on nutritional status and liver function in patients with advanced liver cirrhosis. Increases in serum albumin levels seen in both groups during follow up were artificially high, most likely a result of intravenous albumin administration during paracentesis rather than a result of nutritional supplementation. These findings are in contrast to early randomized trials of NG versus oral feeding, which appeared to indicate an advantage for NG feeding. In a study which randomized 16 and 19 patients with advanced cirrhosis to NG and oral for almost 4 weeks respectively, Cabre et al demonstrated a significant improvement in serum albumin and reduction in mortality in patients who had received NG feeding. \cite{14} In a similar study consisting of patients with only alcoholic liver cirrhosis, Kearns et al had reported significantly greater improvements in liver function and encephalopathy after 4 weeks of NG feeding in 16 patients compared to 15 patients with oral feeding only. \cite{24} In both of these studies, patients on an oral diet only received a standardized low-sodium hospital diet, whilst the NG group received highly fortified calorie supplements, which may have accounted for the observed differences. Although well designed, both of these studies suffered from small sample sizes, limiting the validity of the data.

A possible explanation for the lack of benefit of NG feeding in this study may relate to the underlying aetiology of cirrhosis. In previous trials and other non-randomised studies that have shown an advantage for NG feeding, \cite{14,24,25} the majority of patients had alcoholic liver disease. Alcoholic patients are known to develop malnutrition for other reasons apart from liver damage per se\cite{26} and the prevalence of malnutrition has been shown to be higher in alcohol compared to non-alcohol induced liver cirrhosis. \cite{27} In Asia, viral hepatitis (predominantly Hepatitis B) remains the predominant cause of chronic liver disease,\cite{28} and differences in severity of malnutrition have been reported in Asian patients with viral and alcoholic cirrhosis.\cite{2,29}

The safety of NG tube placement and feeding in patients with advanced cirrhosis has been of some concern. The potential to provoke gastrointestinal bleeding from upper gastrointestinal varices has been suggested in a previous study which demonstrated higher rates of re-bleeding varices in patients with NG compared to oral feeding.\cite{10} In our study, 1/28 (3.6%) patient in the NG arm developed variceal bleeding and subsequently died following the bleed. In contrast, no patients in the oral feeding group developed gastrointestinal bleeding. The small number (ie $n = 1$) in this study is insufficient to prove that NG insertion provoked bleeding. Furthermore, septic complications between both groups of patients appear comparable and there was a trend towards a lower mortality rate in the NG group after 6 weeks, indicating that NG feeding did not have a more deleterious effect compared to oral intake alone in this study.

The benefits of an ultra-short duration of NG feeding ($<7$ days) was explored in a randomized trial of cirrhotic patients following an episode of variceal bleeding.\cite{30} In this study, NG feeding ($n = 12$), when compared to oral feeding ($n = 10$) with a standard low-sodium hospital diet, did not demonstrate any advantage of early enteral feeding after a variceal bleed. However, the small sample size, the ultra-short duration of enteral feeding and the specialized group of patients in this study (i.e. only variceal bleeding) limits the applicability of this data to the decompensated patient with cirrhosis without variceal bleeding. In a recent non-randomised, evaluation of nutritional practices in patients with advanced cirrhosis in France, investigators explored the benefits of NG feeding in a group of 24 patients with an inadequate oral intake.\cite{13} When compared to the majority of patients with oral supplementation, patients with NG feeding had a higher mortality rate and no differences in septic complications were observed.

There are several limitations to this study. The principal investigators were not blinded to the allocation of nutritional intervention and this may have introduced some bias in data collection. A sham trial with NG insertion into the control group, i.e. oral supplementation, may have been one method of reducing this bias, but it was felt not to be ethically viable in view of the discomfort caused by NG tube placement. Another limitation was the poor follow up at 6 weeks’ duration in this study. Although not the primary outcome, more complete data collection at this stage would have strengthened the conclusions drawn from the study. Nevertheless, the total number of patients at 6 weeks’ follow up remains one of the largest sample sizes to date and intention-to-treat analysis was performed as well.

This study aimed to determine the role of NG feeding in advanced cirrhotic patients who were admitted briefly to hospital for decompensation. Recent guidelines have advocated the use of NG feeding in patients with advanced cirrhosis when they are unable to maintain an adequate oral intake from normal food.\cite{19} Whilst a longer period of NG feeding may confer advantages in clinical improvement, this prospective randomized trial has demonstrated that short term NG feeding of up to 2 weeks duration confers little benefit over a pure oral intake. Furthermore, as NG tube placement appears to be poorly tolerated in our patients, oral supplementation should be preferred in patients who are admitted for a brief episode of decompensation.

**Statement of authorship**

MLST — Data collection, data analysis, initial draft of manuscript
HR — Data collection
KLG — administrative support, critical revision of manuscript
SHMT — technical assistance, data collection
MHAA — technical assistance, data collection
SK — statistical analysis
SM — study design, data analysis, final drafting of manuscript

All authors have read and approved the final version of the manuscript.

**Conflict of interest statement**

All the authors in this study declare no conflict of interest with regards to the conduct of this study and the publication of any material derived from the study.
Acknowledgement

Funding disclosure:
This work was funded by a research grant from the following:

i) Long-Term Research fund (Vote F), University of Malaya (Vote no: FQ020/2007A)

ii) Educational grant from the Malaysian Society of Gastroenterology and Hepatology

The study sponsors have not played any role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; nor in the decision to submit the manuscript for publication.

References