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Original Article

Safety and efficacy of peripheral nutrition fluid (MG-TNA®) in patients undergoing surgery for hepatobiliary and pancreatic disease: Results of a phase 4 trial

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Backgrounds/Aims: Essential nutritional support and nutrition therapy for patients with hepatobiliary and pancreatic diseases undergoing surgery is critical, as it may improve clinical outcome. How to implement rational fluid therapy and nutritional support after surgery and effectively protect organ function is crucial for postoperative recovery. The aim this study was to examine the safety and efficacy of peripheral nutrition fluid (MG-TNA®) in patients undergoing surgery for hepatobiliary and pancreatic disease. **Methods:** All adult patients undergoing surgery for hepatobiliary and pancreatic disease received peripheral nutrition fluid (MG-TNA®) on the second postoperative day for 3 days. During administration of parenteral nutrition, patients were closely monitored for adverse effects (primary endpoint). Secondary endpoints included nutritional parameters such as serum prealbumin, transferrin, and creatine kinase (CK) levels. **Results:** Thirty patients completed the study and were included in the full analysis set. There was no evidence of metabolic complications such as hyperglycemia, azotemia, hypertriglyceridemia, metabolic acidosis and hypokalemia. In addition, there were no adverse effects. There was a significant decrease in serum prealbumin and CK on the third postoperative day ($p<0.0001$). Although not statistically significant, serum transferrin levels tended to decrease ($p=0.0519$). **Conclusions:** Administration of peripheral nutrition fluid (MG-TNA®) during postoperative period in patients undergoing surgery for hepatobiliary and pancreatic disease proved to be safe with improvement of the nutritional state of the patient. **(Ann Hepatobiliary Pancreat Surg 2019;23:133-137)**

Key Words: Nutritional support; Fluid therapy; Safety; Efficacy

INTRODUCTION

Hepatobiliary disease including hepatitis, pancreatitis, cholecystitis, alcoholic liver disease, cirrhosis, hepatocellular carcinoma and pancreatic cancer in East Asia is prevalent and accounts for half of the total global incidence. And 5-20% of them will undergo high risk hepatobiliary surgery each year for both benign and malignant disorders.[1]

The liver, gallbladder and pancreas are the main organs of nutritional metabolism, including protein synthesis, glycogen storage, fat digestion and detoxification. These functions become damaged to a greater or lesser extent in patients with diseases, resulting in various metabolic disorders, and their disturbed nutritional condition is associated with disease progression. Most patients present with significant weight loss due to anorexia and malabsorption, and are expected to have a period of inadequate oral intake up to 10 days after surgery.[2,3] Malnutrition of different degrees will occur in at least more than half of these patients.[4]

Therefore, essential nutritional support and nutrition therapy for patients with hepatobiliary and pancreatic diseases undergoing surgery is very important, as it may improve clinical outcome.[5,6] However, considering the nutrient metabolism abnormalities during the perioperative pe-

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riod, the nutritional support and fluid therapy could become complex. How to implement rational fluid therapy and nutritional support after surgery and effectively protect organ function is crucial for postoperative recovery.[7]

Perioperative nutrition is a well recognized aspect of care in recent years and has been shown to reduce the incidence of complications and to reduce hospital stay.[8] Although clinical research has shown that early delivery of nutrition via the gastrointestinal tract after severe injury can reduce septic morbidity and mortality in critically injured patients,[9,10] evidence suggests that routine post-operative enteral nutritional support may lead to increased incidence of gastric stasis.[11] Currently the effects of nutritional supplements given to initiate enteral nutrition (EN) or peripheral nutrition (PN) are still debated. The aim this study was to examine the safety and efficacy of parenteral nutrition fluid (MG-TNA®) in patients undergoing surgery for hepatobiliary and pancreatic disease.

MATERIALS AND METHODS

Patient selection

This study was approved by our Institutional Review Board. Written informed consent was obtained from all patients. All adult patients undergoing surgery for hepatobiliary and pancreatic disease were eligible. Patients with severe liver cirrhosis (above child class A) and renal failure were excluded. Also, patients with disorders of amino acid metabolism, coagulation deficiencies, uncontrolled diabetes, severe hypercholesterolemia, history of myocardial infarction and patients allergic to protein were excluded.

Study protocol

After screening prior to surgery, all patients who met the inclusion criteria received the peripheral nutrition fluid (MG-TNA®) starting on the second postoperative day for 3 days (Fig. 1). The maximum administration rate was 3.7 ml/kg/hr. During administration of parenteral nutrition, patients were closely monitored for adverse effects (primary endpoint). Secondary endpoints included nutritional parameters such as serum prealbumin, transferrin, creatine kinase (CK) levels. In addition, patients were evaluated for metabolic complications such as hyperglycemia, hypokalemia and metabolic acidosis.

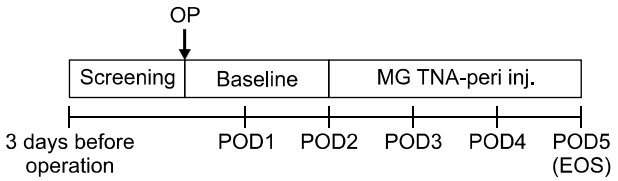

Fig. 1. Schematic diagram of study protocol. After screening prior to surgery, all patients who met the inclusion criteria received peripheral nutrition fluid (MG-TNA®) starting on the second postoperative day for 3 days. OP: Operation, POD: Postoperative day, EOS: End of study.

Sample size calculation and statistical analyses

Since this study was a single arm study to examine the safety and efficacy of a parenteral nutrition solution, a specific sample was not calculated. Instead, we decided to enroll at least 30 patients in reference to previous similar studies using similar parenteral solution. Continuous variables were analysed using the paired t-test or Wilcoxon signed rank test.

RESULTS

During a 5-month period, a total of 32 patients were enrolled. However, 2 patients failed to meet the inclusion criteria and failed the screening test as well. As a result, 30 patients completed the study and were included in the full analysis set. Mean age was 57.23±10.77 and male to female ratio was 2 to 1 (Table 1). Most patients underwent surgery due to malignant disease. Liver resection was the most common operation performed (43.3%) (Table 1). There was a significant decrease in serum prealbumin and CK on the third postoperative day ($p<0.0001$). Although not significant, serum transferrin levels tended to decrease ($p=0.0519$) (Fig. 2). During the study period, patient vital signs, physical examination and laboratory results revealed no adverse effects. Also, there was no mortality case.

DISCUSSION

Metabolic alterations of hepatobiliary disease are characterized by hyperdynamic changes, hypermetabolism, and catabolism. Hyperdynamic changes raise energy expenditure through increasing cardiac output and activation of the sympathetic nervous system, decreasing systemic vascular resistance, and so on.[12] Hypermetabolic defined

Table 1. Clinical characteristics of the study population

Variable	n=30
Age (yrs)	57.23±10.77
Sex (male to female)	2 to 1
Height (cm)	164.37±9.69
Weight (kg)	66.36±13.83
BMI (kg/m^2)	24.42±4.27
Social history	
alcohol	3 (10.0%)
smoking	13 (43.3%)
Past medical History	
DM	6 (20.0%)
HTN	7 (23.3%)
Hepatitis	7 (23.3%)
Diagnosis	
Malignant	24 (80.0%)
Hepatocellular carcinoma	9 (30.0%)
Gallbladder cancer	2 (6.7%)
Cholangiocarcinoma	6 (20.0%)
Metastatic adenocarcinoma*	4 (13.3%)
Pancreatic adenocarcinoma	3 (10.0%)
Benign	6 (20.0%)
Pancreatic cystic tumor	2 (6.7%)
Bile duct stone	2 (6.7%)
Gallbladder stone	1 (3.3%)
Chronic pancreatitis	1 (3.3%)
Operation	
Hepatectomy	13 (43.3%)
Pancreatectomy	6 (20.0%)
Cholecystectomy	7 (23.3%)
Splenectomy	1 (3.4%)
Others	3 (10.0%)

*Metastatic adenocarcinoma from colon or rectum
BMI, Body mass index; DM, Diabetes mellitus; HTN, Hypertension

as resting energy expenditure (REE) >120% compared with the expected value. Studies have reported 30% of patients with ascites, cirrhosis or hepatocellular carcinoma are considered hypermetabolic.[13] Catabolism is another significant metabolic alteration. Isotope techniques have been used to demonstrate that patients with hepatobiliary disease have a significantly higher urea production compared with controls, indicating both increased protein catabolism and diminished muscle protein synthesis. Abnormal metabolism of carbohydrate and fat also occur with hepatobiliary disease.[12] This may result from cortisol and catecholamine increased, while glucose clearance and oxidation diminished. In hepatobiliary disease, glucose intolerance occurs in 40-90% of cases, and insulin is required in as many as 80% of patients. Not only does hepatobiliary disease cause metabolism change occurred, hepatobiliary surgery transiently aggravated the changes.[12] After liver resection, patients appear to have increased level of aminotransferase, caused by surgical trauma, damage of liver cell and liver ultrastructure, and release of inflammatory mediators.[14]

A decreased level of nutrients can affect many systems and functions including respiratory failure, cardiac and neurological dysfunction, and insulin resistance. Hypo/hyperglycemia, hypocalcaemia and hypophoshataemia particularly after major resection should not be ignored and require correction.[12] Malnutrition adversely affects the prognosis of these hepatobiliary patients, and poor nutritional status in patients undergoing surgery is well known to increase postoperative morbidity by deteriorating various organ functions and the immune system of the patients.[15] If patients are unable to maintain adequate intake via the mouth, artificial nutrition is used to improve nutritional status.

Perioperative nutritional support composes with pre-operative and postoperative nutrition. At present, the view about pre-operative nutritional therapy is that the treatment should be provide to hepatobiliary patients with serious malnutrition or who prepare to have major surgical treatment with mild to moderate malnutrition. The main purpose is to improve the nutritional status of the patients, to improve their operation tolerance, reduce or avoid postoperative complications and mortality.[16,17] Postoperative nutrition should be provide to patients who have accepted with preoperative nutritional therapy, or who have severe malnutrition and/or complications after surgery. Patients fasting more than 1 week also need postoperative nutrition support.[12]

EN improves nutritional status and liver function, enhanced immunocompetence, decreased clinical infection rates, maintained gut structure and function, potentially attenuate catabolic stress responses in patients after surgery and prolongs survival.[17] However, postoperative total enteral feeding is associated with complications such as diarrhea, abdominal distention, and abdominal cramps. These symptoms worsen with increasing caloric intake and can lead to discontinuance of enteral feeding. Nutritional treatment strategy accepted by majority practitioners is that EN support should be actively applied, if the gastrointestinal anatomy and function allows. Otherwise

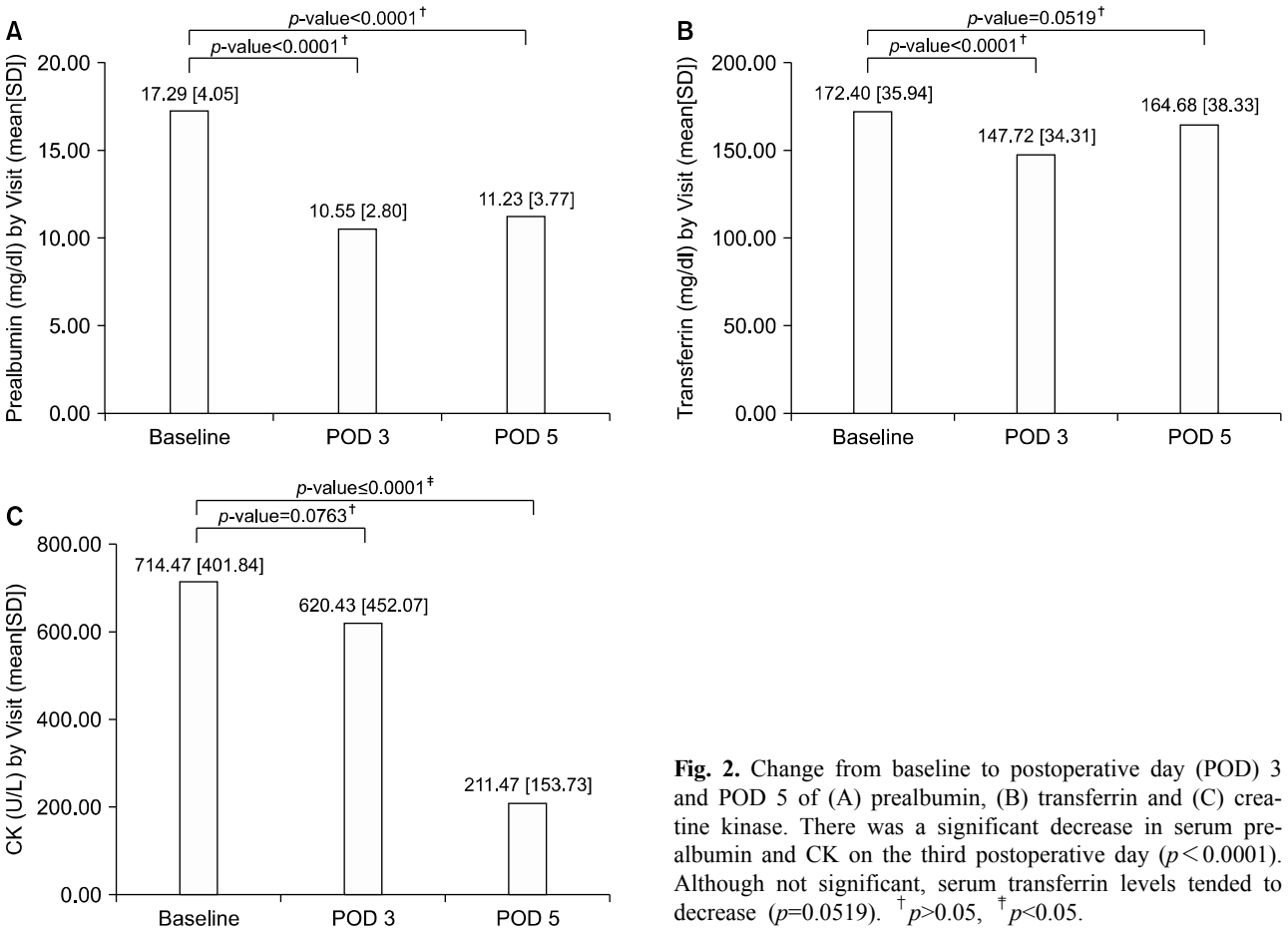

Fig. 2. Change from baseline to postoperative day (POD) 3 and POD 5 of (A) prealbumin, (B) transferrin and (C) creatine kinase. There was a significant decrease in serum prealbumin and CK on the third postoperative day ($p < 0.0001$). Although not significant, serum transferrin levels tended to decrease ($p=0.0519$). †$p>0.05$, ‡$p<0.05$.

PN should be applied until gastrointestinal function recovery.[18]

PN is an intravenous administration of nutrients delivered into a large-diameter vein or a peripheral vein.[2] If the patients enduring diffuse peritonitis, intestinal obstruction intractable vomiting, paralysis of intestine or intractable diarrhea, PN should be supply first until gastrointestinal function resume. PN offers the possibility of increasing or ensuring nutrient intake in patients in whom normal food intake is inadequate and EN is not feasible.[2,12]

However, parenteral nutrition can be complicated by many metabolic problems, which may arise from inadequate or excessive amounts, or from inappropriate composition of nutrients. The most severe complications are cholestatic liver disease and bone disease.[19] Also catheter-related and infectious complications can occur.[19] In our study, there were no complications in patients receiving PN partially because of peripheral administration of PN.

Demirer et al.[20] reported a potential beneficial effect of soybean oil/olive oil based lipid emulsions for use in PN regarding inflammatory response and oxidant capacity in the treatment of patients. In their study, decrease from baseline in serum prealbumin and transferrin levels was observed on the 4th postoperative day in all groups receiving PN which was similar to the results of our study.[20]

At present, most experts believe that PN combined with EN should be considered when EN cannot satisfy the energy needs for patients who has indications of nutritional support.[21] There is also some evidence that nutritional supplementation with immunonutrient formulas containing arginine, fish oil lipid emulsion with omega-3 fatty acids, dextrose, and structured triglyceride may offer a benefit in terms of preserved liver function and better clinical outcome leading to improved wound healing, decreased infectious morbidities and shorter hospital stay. Concomitant administration of glutamine-enriched early EN and PN proved to be a potent protectant against intestinal mucosal barrier injury after liver transplantation.[20,22,23]

However, there are limitations to this study. The small

size of the study cohort, the single arm nature of this study and short administration period of the peripheral nutrition fluid may have limited the results of this study. Future multi-arm studies with a larger cohort with longer administration of peripheral nutrition fluid are needed.

In conclusion, administration of peripheral nutrition fluid (MG-TNA®) during the postoperative period in patients undergoing surgery for hepatobiliary and pancreatic disease proved to be safe and may improve the nutritional state of the patient.

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REFERENCES

1. DuBray BJ Jr, Chapman WC, Anderson CD. Hepatocellular carcinoma: a review of the surgical approaches to management. Mo Med 2011;108:195-198.
2. Howard L, Ashley C. Nutrition in the perioperative patient. Annu Rev Nutr 2003;23:263-282.
3. Shiraki M, Nishiguchi S, Saito M, Fukuzawa Y, Mizuta T, Kaibori M, et al. Nutritional status and quality of life in current patients with liver cirrhosis as assessed in 2007-2011. Hepatol Res 2013;43:106-112.
4. Merli M, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O, et al. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. Liver Int 2010;30:208-214.
5. Merli M, Nicolini G, Angeloni S, Riggio O. Malnutrition is a risk factor in cirrhotic patients undergoing surgery. Nutrition 2002;18:978-986.
6. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med 1994;331:1547-1552.
7. Sun Y, Yang Z, Tan H. Perioperative nutritional support and fluid therapy in patients with liver diseases. Hepatobiliary Surg Nutr 2014;3:140-148.
8. Koretz RL, Avenell A, Lipman TO. Nutritional support for liver disease. Cochrane Database Syst Rev 2012;(5):CD008344.
9. Doig GS, Heighes PT, Simpson F, Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. Injury 2011; 42:50-56.
10. Yi F, Ge L, Zhao J, Lei Y, Zhou F, Chen Z, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. Intern Med 2012;51:523-530.
11. Traverso LW, Hashimoto Y. Delayed gastric emptying: the state of the highest level of evidence. J Hepatobiliary Pancreat Surg 2008;15:262-269.
12. Liu Y, Xue X. Systematic review of peri-operative nutritional support for patients undergoing hepatobiliary surgery. Hepatobiliary Surg Nutr 2015;4:304-312.
13. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol 2012; 10:117-125.
14. Facciorusso A, Barone M. Glucose intolerance and hepatocellular carcinoma: recent findings for old diseases. Hepatobiliary Surg Nutr 2014;3:91-92.
15. Martindale RG, McClave SA, Taylor B, Lawson CM. Perioperative nutrition: what is the current landscape? JPEN J Parenter Enteral Nutr 2013;37(5 Suppl):5S-20S.
16. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN guidelines on enteral nutrition: liver disease. Clin Nutr 2006;25:285-294.
17. Mouzaki M, Ng V, Kamath BM, Selzner N, Pencharz P, Ling SC. Enteral energy and macronutrients in end-stage liver disease. JPEN J Parenter Enteral Nutr 2014;38:673-681.
18. Cahill NE, Murch L, Jeejeebhoy K, McClave SA, Day AG, Wang M, et al. When early enteral feeding is not possible in critically ill patients: results of a multicenter observational study. JPEN J Parenter Enteral Nutr 2011;35:160-168.
19. Ghabril MS, Aranda-Michel J, Scolapio JS. Metabolic and catheter complications of parenteral nutrition. Curr Gastroenterol Rep 2004;6:327-334.
20. Demirer S, Sapmaz A, Karaca AS, Kepenekci I, Aydintug S, Balci D, et al. Effects of postoperative parenteral nutrition with different lipid emulsions in patients undergoing major abdominal surgery. Ann Surg Treat Res 2016;91:309-315.
21. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M; ESPEN. ESPEN guidelines on parenteral nutrition: non-surgical oncology. Clin Nutr 2009;28:445-454.
22. Zhu X, Wu Y, Qiu Y, Jiang C, Ding Y. Effect of parenteral fish oil lipid emulsion in parenteral nutrition supplementation combined with enteral nutrition support in patients undergoing pancreaticoduodenectomy. JPEN J Parenter Enteral Nutr 2013;37: 236-242.
23. Jiang JW, Ren ZG, Chen LY, Jiang L, Xie HY, Zhou L, et al. Enteral supplementation with glycyl-glutamine improves intestinal barrier function after liver transplantation in rats. Hepatobiliary Pancreat Dis Int 2011;10:380-385.