

Title

Comparison of enteral nutrition with combined enteral and parenteral nutrition in post-pancreaticoduodenectomy patients: A pilot study.

Running title

Postoperative nutrition after pancreatoduodenectomy.

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Keyword

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Abstract

Background: Many clinical studies have demonstrated that early postoperative enteral nutrition (EN) improved the postoperative course. Post-pancreaticoduodenectomy (PD), patients tend to suffer from postoperative nausea, abdominal distention, and diarrhoea, causing difficulty in introduction of EN. This pilot study investigated the appropriate nutritional mode post-pancreatic surgery.

Methods: Between October 2006 and March 2007, the 2 postoperative nutritional methods were implemented with 17 patients in a prospective single-center study. Eight patients received only enteral nutrition (EN group) and 9 patients received enteral nutrition combined with parenteral nutrition (EN + PN group).

Results: There was no difference in patient characteristics and postoperative morbidity between the 2 groups. The rate of discontinuance of enteral feeding was significantly high in the EN group, and the duration of enteral feeding was significantly longer in the EN + PN group. The central venous line was retained for a significantly longer period in the EN + PN group, but there was no difference in the frequency of catheter-related infection between the 2 groups.

Conclusion: EN combined with PN is more adequate for patients after pancreatic surgery.

Background

In current digestive surgical practice, the benefits of enteral nutritional support, compared with parenteral nutrition, are widely recognised. Recent experiences have shown that early postoperative enteral nutrition (EN) enhanced immunocompetence, reduced clinical infection rates, and maintained gut structure and function, and it can potentially attenuate catabolic stress responses in patients after surgery [1-5]. Although many studies have reported that total parenteral nutrition (TPN) elicits infective complications associated with the catheter more frequently, some have reported that the cause of infection was hyperglycemia and caloric overload, and that insulin therapy could alleviate it [6,7]. In addition, enteral nutrition is believed to be safer and less expensive than parenteral nutrition. However, postoperative enteral feeding is associated with complications such as diarrhoea, abdominal distention, and abdominal cramps. On the basis of our experience and the findings of previous studies [8,9], it can be said that these symptoms worsen with increasing caloric intake and finally lead to discontinuance of enteral feeding.

Pancreaticoduodenectomy (PD) is associated with a high incidence of postoperative complications, even when performed at high-volume centres. An overall morbidity rate of 48% can be anticipated at major centres, whereas the mortality rate in these centres is less than 4%. The high rate of complications could delay postoperative resumption of adequate oral food intake. Moreover, cancer or chronic pancreatitis patients who are candidates for PD often have an associated comorbidity such as diabetes, jaundice, and protein-energy malnutrition [9,10]. Taken together, these issues

present the case for artificial nutritional support. Clinical experience focusing on postoperative feeding after major pancreatic resections is very limited [8-10]. Therefore, we believe that the optimal nutritional method after surgery is still unclear.

In our institution, which is a high-volume centre for pancreatic surgery, the patients who underwent PD, including pylorus-preserved PD (PpPD), routinely received enteral feeding from the early postsurgical period. However, there was no clinical regimen for enteral nutrition and the menu for enteral feeding, which was prescribed by the doctors, was unique for each patient. We retrospectively examined 30 patients who underwent PD and PpPD in the 18 months prior to this study. It was observed that enteral feeding was discontinued and changed to TPN in many of these patients because of diarrhoea and abdominal distention.

In this prospective pilot study, we aimed to ascertain which mode of nutrition was better after PD and compared the clinical outcomes, nutritional status, and immunological status of the 2 modes of postoperative nutrition, namely, enteral nutrition and enteral nutrition combined with parenteral nutrition.

Materials and Methods

Patients

We prospectively investigated 17 patients who had undergone PD or PpPD for peri-ampullary tumors from October 2006 to March 2007 at the Oita Red Cross Hospital, including 12 men and 5 women (mean age, 68.3 years; 43–86 years). Among these 17 patients, there were 10 cases of pancreatic invasive ductal carcinoma, 5 of

cholangiocarcinoma, and 2 of chronic pancreatitis with inflammatory mass (Table 3). Exclusion criteria included clinically relevant organ failure, ongoing infections, and inflammatory bowel diseases. Fully informed consent was obtained from all patients. After surgery, randomization was performed using sealed envelopes. Patients were divided into 2 groups: those who received only enteral nutrition (EN group, n = 8) and those who received both enteral and parenteral nutrition (EN + PN group, n = 9).

Surgical Procedure

The standard PD consisted of distal gastrectomy with complete of the duodenum and common bile duct, the gallbladder, the head, neck, and uncinate process of the pancreas, and lymphadenectomy. Standard lymph node dissection was performed according to the definition of Pedrazzoli et al. [11]. In PpPD, the duodenum was divided at a point 2 cm away from the pylorus. The passage was reconstructed by pancreatogastrostomy, end-to-side hepaticojejunostomy, end-to-end gastrojejunostomy in PD or pylorojejunostomy in PpPD, and an end-to-side jejunojejunostomy in Roux-en-Y-technique (30 cm aborally from the gastrojejunal anastomosis). All patients received needle-catheter jejunostomy at the end of the operation for postoperative nutritional support. 8 Fr silicone jejunal tubes were inserted from the proximal portion of the jejunojejunostomy and fixed by the modified Witzel technique. The opposite tip was induced extracorporeally via an abdominal wall at the left flank.

Postoperative Nutrition

All patients in both the groups received enteral feeding with/without parenteral nutrition as per the schedule outlined in Fig. 1. Briefly, the infusion of 500 ml of 5% glucose

commenced within 12 h after surgery and enteral feeding was started on postoperative day (POD) 2 in both the groups. All patients in 2 groups reached the maximum value of total caloric intake (obtained by Harris-Benedict equation) on POD 4. In the EN group, total caloric intake was 600 kcal/day on POD 2 and 1000 kcal/day on POD 3, supplemented with peripheral parenteral nutrition (PPN). In the EN + PN group, EN was started at 200 kcal/day and increased every 2 days to a maximum value of 600 kcal/day. The patients in the EN + PN group received parenteral nutrition by PPN and TPN to compensate for the caloric shortage. Parenteral nutrition was preferentially decreased. Oral intake was started on POD 7. TPN was stopped when the oral intake was over 500 kcal/day and EN was stopped when the oral intake was over 1000 kcal/day. A unified enteral diet (Isocal; Mead Johnson, Evansville, IN) containing 1000 kcal, 33 g protein, 123 g carbohydrates, and 42 g lipids per liter was administered to the patients. Possible adverse reactions to enteral nutrition were recorded daily. Enteral feeding was reduced or discontinued in case of intolerable emesis, abdominal distention/cramps, or diarrhoea.

Catheter Regimen

A central venous catheter was preoperatively inserted in all patients; Gabexate mesilate 1.5 g/24 h (FOY; Ono, Osaka, Japan) was administered through the catheter for 3 days after the operation. During the operation, all the patients received intra-abdominal drainage and urinary catheter. These catheters were removed as soon as possible except in 1 case that had serious complications.

Laboratory and clinical investigations

The operation time, blood-loss volume, and amount of blood transfusion during and after surgery were carefully recorded. Samples for laboratory investigations were taken on POD 1, 3, 5, 7, and 14. The laboratory parameters assessed included serum levels of total protein, albumin, pre-albumin, and transferrin (as nutritional parameters), lymphocyte counts, T-cell subpopulation (the ratio of CD4 T cells to CD8 T cells, i.e., CD4/CD8), and serum levels of IgG, IgM, and IgA (as immunological parameters), serum levels of total bilirubin, cholinesterase, alanine transaminase, aspartate transaminase, lactate dehydrogenase, alkaline phosphatase, gamma-glutamyl transpeptidase, amylase, urea nitrogen, and creatinine. Body weight was periodically measured before and after surgery. Postoperative complications, including surgical-site infection, leakage from anastomosis, pancreatic fistula, cholangitis, small bowel obstruction, delayed gastric emptying (a surgery-related complication), abdominal cramps, distention, diarrhoea, and vomiting (an enteral feeding-related complication) were carefully monitored every day.

Statistical analysis

The data are expressed as mean \pm SEM. The statistical significance of the data was determined by unpaired and paired student's t tests or the chi-square test. P value < 0.05 was considered to be statistically significant. Statistical calculations were made using Prism Version 4.0 (GraphPad Software Inc.).

Results

Seventeen patients were enrolled in this study. The median age of the entire study groups was 68 years (range, 43–86 years). Eight patients were provided postoperative nutritional support mainly by enteral nutrition (EN group), and 9 patients received enteral feeding combined with parenteral nutrition after surgery (EN + PN group). Both groups were comparable with respect to patient characteristics, preoperative factors, and preoperative laboratory findings (Table 1). With respect to intraoperative factors, there were no significant differences between the 2 groups in all parameters, including operation time, blood loss, the number of patients who received blood transfusion, surgical procedure, and histopathological diagnosis (Table 2).

The overall postoperative morbidity across all study groups was 53% and did not differ between the 2 groups (Table 3). One patient in the EN + PN group reported with minor pancreatic leakage. Another patient in the EN group reported with minor leakage of the gastrojejunal anastomosis. They conservatively recovered without any treatment. Another patient in the EN group died as a result of acute respiratory distress syndrome caused by infection. There was no difference in other complications, including ileus, anastomotic ulcer, and surgical-site infection between the 2 groups. The overall mortality was 5.8%.

Although the method of postoperative nutrition was different in each group, the total caloric intake including enteral plus parenteral nutrition was similar (Fig. 1).

With respect to factors related to postoperative nutrition, enteral feeding was well tolerated in the patients of the EN + PN group, few patients exhibited symptoms. Only 1 of 9 patients (11.1%) in the EN + PN group discontinued enteral feeding due to

diarrhoea before resuming oral intake. In contrast, 5 of the 8 patients (62.5%) in the EN group discontinued enteral feeding primarily due to diarrhoea and abdominal distention before resuming oral intake or sufficient oral intake (Table 4). Further, the duration of enteral feeding in the EN group was significantly shorter than that in the EN + PN group (10.6 ± 2.3 vs. 23.5 ± 4.4 days, $p = 0.0255$). On the other hand, the duration of retention of the central venous line in the EN + PN group was significantly longer than in the EN group (7.7 ± 1.1 vs. 12.0 ± 1.5 days, $p = 0.0418$). However, there were no significant differences in the frequency of catheter-related infection between the 2 groups (Table 4). No aspiration episodes or intestinal ischemia associated with enteral feeding were observed. Percentages of weight loss on POD 21, and the length of postoperative stay were not different between the 2 groups.

The subanalysis comprised 14 patients (EN group, 6; EN + PN group, 8) after excluding the 2 EN patients and 1 EN + PN patients, in whom enteral feeding could not be continued until POD 5. Among the nutritional parameters, serum albumin, total protein, albumin, and rapid-turn-over proteins such as pre-albumin and transferrin decreased until POD 3 and increased gradually thereafter, but there was no significant difference between the 2 groups (Fig. 2). Among immunological parameters, there was no significant difference in lymphocyte counts, and T-cell subpopulation, i.e., CD4/CD8, between the 2 groups (data not shown). The level of immunoglobulin decreased in the early postoperative days and gradually increased in the late postoperative days, especially in the EN + PN group, with significant differences between the groups in the levels of IgA and IgM on POD 14 (Fig. 3). Among other biochemical parameters, the

levels of ALT were significantly reduced in the EN group on PODs 7 and 14 (Fig. 4). The levels of ChE decreased in the early PODs, especially in the EN + PN group, with significant differences on PODs 1, 3, and 5 (Fig. 4). The levels of lactate on PODs 5 and 7 were significantly low in the EN + PN group (Fig. 4).

Discussion

PD is associated with a high incidence of postoperative complications even when performed at a high-volume centre. While the mortality rate can be reduced to less than 4%, the incidence of postoperative complications continues to range from 35% to 50% in most series. Most patients with pancreatic tumors present with significant weight loss due to anorexia and malabsorption, and they are expected to undergo a period of inadequate oral intake for up to 10 days after surgery [9,10].

In the last decade, several clinical and experimental studies have reported on the beneficial effects of perioperative enteral nutrition, especially early postoperative enteral feeding, over parenteral and delayed enteral nutrition under critical conditions [1-5]. The precise mechanisms through which early enteral feeding exerts its positive actions on the outcome are still unclear, but the preservation of the integrity of gut structure/function, balanced intestinal microflora, and the maintenance of an effective local and systemic immunocompetence, have been strongly implicated [1-5,8]. Despite these theoretical and clinical advantages, many surgeons remain committed to a postoperative period of 'bowel rest', which has long been hypothesised, but never demonstrated to reduce the risk of anastomotic leak. The role of artificial nutrition in

affecting morbidity after major pancreatic resection has been markedly neglected. In 1994, Brennan et al. published the first trial on postoperative nutritional support in patients undergoing PD and reported that routine postoperative TPN could not be recommended [12]. Since then, many reports have indicated the effect of postoperative enteral nutrition after PD [9,10].

In our unit, which is a high-volume centre of pancreatic surgery, all patients received enteral feeding after surgery. However, there was no guideline for postoperative nutritional support in our unit. Before performing this study, we retrospectively examined 30 patients who underwent PD, including PpPD, for nutritional aspects and postoperative complications (not published). In this data, the ratio of enteral nutrition drop-outs was high (34.6%) mainly due to diarrhoea in the early postoperative period irrespective of the volume of enteral feeding, although previous studies reported that approximately 90% of the enterally-fed patients reached the full nutritional regimen within 4 days of digestive surgeries, such as esophageal resection and gastrointestinal resection [1-5]. We considered it affected that PD contains lymph node and/or ganglion dissection around the celiac artery and the superior mesenteric artery, post-PD, diarrhoea is a frequent complication. In addition, there was no significant difference in the nutritional and immunological parameters and the clinical outcomes due to the volume of enteral feeding. Since the volume of enteral feeding was unstable and insufficient, almost all patients tended to undergo prolonged central venous line replacement (median, 14.0 days; range, 5–21 days); this resulted in 30.8% occurrence of catheter fever. In a recent investigation, it was revealed that the

high occurrence of infection-related complications did not result from the route of nutrition (total parenteral nutrition), but was caused by hyperglycemia [6]. Strict blood glucose control with insulin could lead to the prevention of infectious complications [7]. On the basis of these findings, we considered enteral nutrition combined with parenteral nutrition as a better mode of postoperative nutritional support.

In this clinical pilot study, we examined the procedure of postoperative nutritional support for patients who underwent PD, by which the patients would receive sufficient caloric intake without dropping out. Methods of reporting the tolerance to feedings have also varied considerably, but clinically significant intolerance is described in several recent series of elective surgical patients. In a recent study, feeding was considered to have been established successfully in 75% of the patients. Twenty-two (79%) of 28 patients in another report received >600 kcal/day from a standard enteral diet. Eighteen (72%) of the 25 patients achieved a feeding rate of >40 ml/hour in a third series. However, gastrointestinal complications were observed in 15 (83%) of the 18 patients receiving a standard enteral preparation; these most commonly consisted of nausea, vomiting, abdominal distension, and diarrhoea. On the basis of these data, we set 600 kcal/day as the maximal dose of enteral feeding in the EN + PN group, and we selected Isocal, which contains sufficient dietary fiber and medium chain fatty acids and that contribute to reduction in the occurrence of diarrhoea as the enteral diet in this study.

We divided the 17 patients into 2 groups according to the mode of postoperative nutritional support: the EN and EN + PN groups. There was no significant

difference in the baseline profiles between the 2 groups. Although the routes of administration of the diet were different, the patients of both groups had a similar total caloric intake and there was no significant difference between the 2 groups in nutritional analysis. Consistent with these findings, there was no difference between the 2 groups in terms of weight-loss on POD 21.

In tests of immunological function, there was no significant difference in cellular immunity, i.e., leukocytes and lymphocytes counts and T cell subpopulation. Serum immunoglobulin plays an important role in host humoral immunity. Although the serum levels of IgA and IgM dropped remarkably in all the patients after the operation, they recovered quickly in the EN + PN group and were significantly higher than those in the EN group. Our study suggested that the postoperative immunological function of the patients in the EN + PN group was significantly better than those in the EN group.

Clinically, more patients of the EN group dropped out of enteral feeding, mainly due to diarrhoea and abdominal distention, than those of the EN + PN group. The patients of the EN + PN group received parenteral nutrition longer than the EN group (7.7 ± 1.1 vs. 12.0 ± 1.5 days, $p = 0.0418$), but it was also demonstrated that there was no significant difference in occurrence of catheter-associated infection (3/8 in the EN group vs. 2/9 in the EN + PN group, $p = 0.4902$) under conditions where the central venous route was removed as early as possible.

In conclusion, we suggested that enteral feeding combined with parenteral nutrition may be as safe as standard enteral nutrition and further, it could be a suitable

mode of postoperative nutrition for patients who have undergone PD. In addition, enteral feeding combined with parenteral nutrition may improve early postoperative immunological status. However, further examination is required because of the small number of patients in this pilot study.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

SN conceived the study, participated in its design and coordination, and drafted the manuscript. All other author has contributed substantially to the study design and coordinated the study. All authors have read and approved the final manuscript.

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Table 1. Preoperative patient characteristics

Characteristic	EN group (n = 8)	EN+PN group (n = 9)
Age (yr)	66.5 ± 4.8	69.8 ± 3.3
Sex (Male/female)	6/2	6/3
Body weight (kg)	61.3 ± 2.9	55.8 ± 2.2
Body mass index (m ²)	24.2 ± 1.2	21.9 ± 0.5
Patients with jaundice (%)	25.0	33.3
Patients with diabetes (%)	25.0	11.1
Patients with preoperative PTCD (%)	25.0	22.2
Preoperative laboratory values		
Hemoglobin (g/L)	12.9 ± 0.6	11.7 ± 0.6
Albumin (g/L)	3.6 ± 0.1	3.5 ± 0.1
Bilirubin (mg/dL)	0.9 ± 0.1	0.8 ± 0.1
No significant differences noted.		

Table 2. Intraoperative factors and histopathology

Characteristic	EN group (n = 8)	EN+PN group (n = 9)
Duration of surgery (min)	457.4 ± 18.6	564.6 ± 56.6
Operative blood loss (mL)	954.3 ± 155.5	954.4 ± 271.3
Blood transfusion (%)	62.5	77.7
Surgical Procedures (PD/PpPD)	2/6	6/3
Histopathologic finding		
Pancreatic carcinoma	6	7
Cholangio cellular carcinoma	1	1
Chronic pancreatitis	1	1
No significant differences noted.		

Table 3. Postoperative complications

Complication	EN group (n = 8)	EN+PN group (n = 9)
Surgery related complications		
Pancreatic leakage (minor leakage)	0	1
Anastomotic leakage (minor leakage)	1	0
Ileus	1	0
Ulcer at anastomotic portion	0	1
Wound infection	3	1
General complications		
Pulmonary	1	0
Total number of patients with complications	5	4
Mortality	1	0
No significant differences noted.		

Table 4. Factors related postoperative nutrition

	EN group (n = 8)	EN+PN group (n = 9)	P value
Nutrition related complications			
Dirrhea	6	4	0.2014
Abdominal distention	7	1	0.0016
Nausea	2	3	0.7066
Removal day of central venous catheter (POD)	7.7 ± 1.1	12.0 ± 1.5	0.0418
Frequency of catheter fever (%)	37.5	22.2	0.4902
Duration of Enteral nutrition (days)	10.6 ± 2.3	23.5 ± 4.4	0.0255
Drop-out rate of EN (%)	62.5	11.1	0.0269
First day of oral intake (POD)	8.8 ± 0.9	8.4 ± 1.2	0.8068
Weght loss ratio on POD 21 (%)	12.9 ± 2.2	12.3 ± 1.7	0.8393
Hospital stay (days)	40.4 ± 5.9	57.2 ± 4.0	0.0826

Figure legends

Figure 1. Schedules of postoperative nutrition.

The infusion of 500 ml of 5% liquid glucose commenced within 12 h of surgery and enteral feeding was started on POD 2 in both groups. All patients in both groups reached the maximum volume of total caloric intake (derived using Harris-Benedict equation), on POD 4. In the EN group, the total volume of EN was 600 kcal/day on POD 2 and 1000 kcal/day on POD 3 with PPN. In the EN + PN group, EN started at 200 kcal/day and was increased every 2 days to a maximum volume of 600 kcal/day from POD 6. The patients received PPN until POD 3 or TPN from POD 4 to compensate for the caloric shortage. Oral intake started on POD 7. TPN was stopped when oral intake was over 500 kcal/day and enteral nutrition was stopped when oral intake was over 1000 kcal/day. EN: enteral nutrition, PPN: peripheral parenteral nutrition, TPN: total parenteral nutrition, OI: oral intake.

Figure 2. Comparison of nutritional parameters.

Mean values of prealbumin and transferrin in the EN (square) and EN + PN (triangle) groups. The error bars represent the standard error of the mean (SEM).

Figure 3. Comparison of immunological parameters.

Mean values of IgG, IgM, and IgA in the EN (square) and EN + PN (triangle) groups. The error bars represent the SEM; * signifies $p < 0.05$.

Figure 4. Comparison of biochemical parameters.

Mean values of ALT, lactate, and ChE in the EN (square) and EN + PN (triangle) groups. The error bars represent the SEM; * signifies $p < 0.05$.

Fig. 1

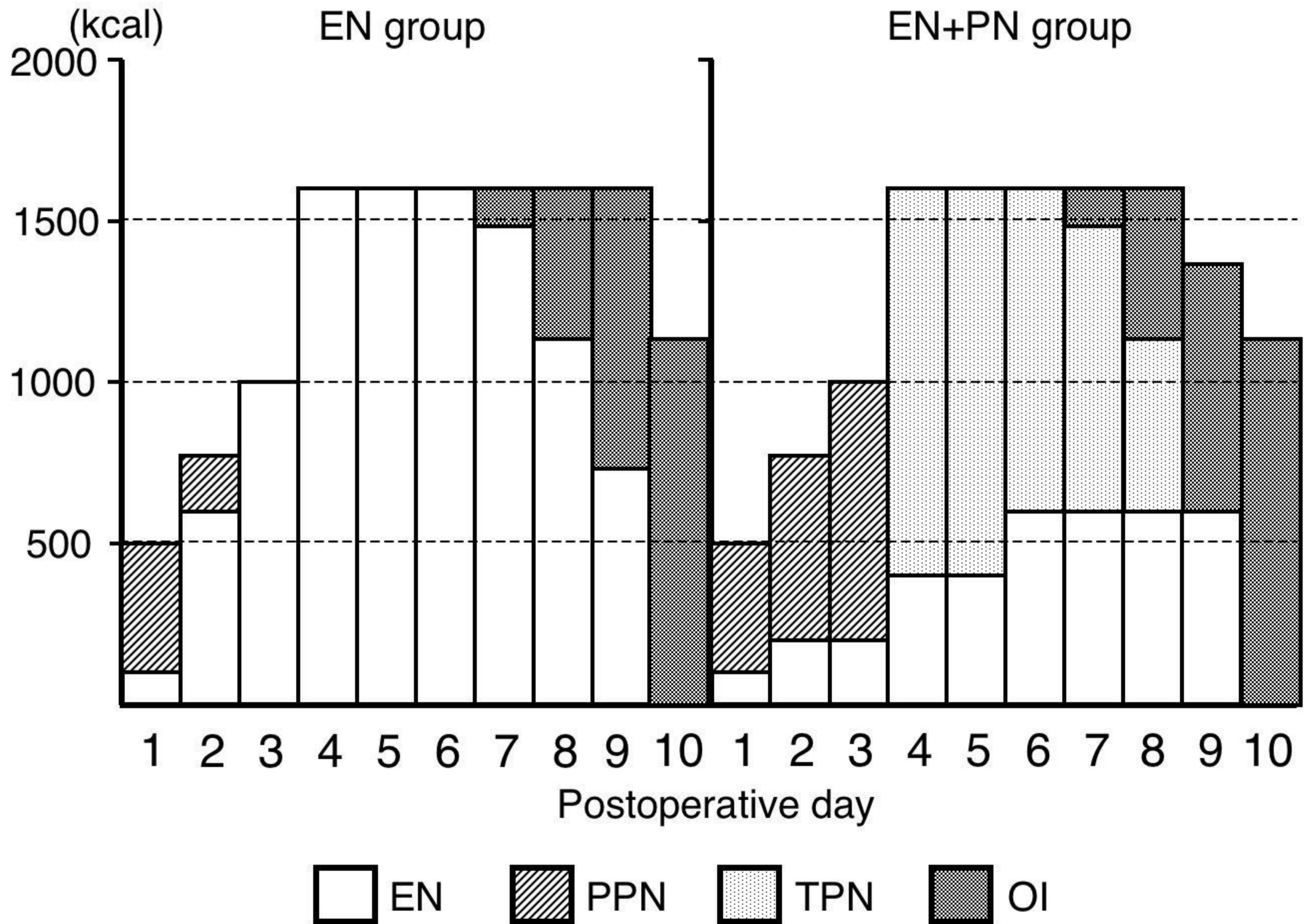


Fig. 2

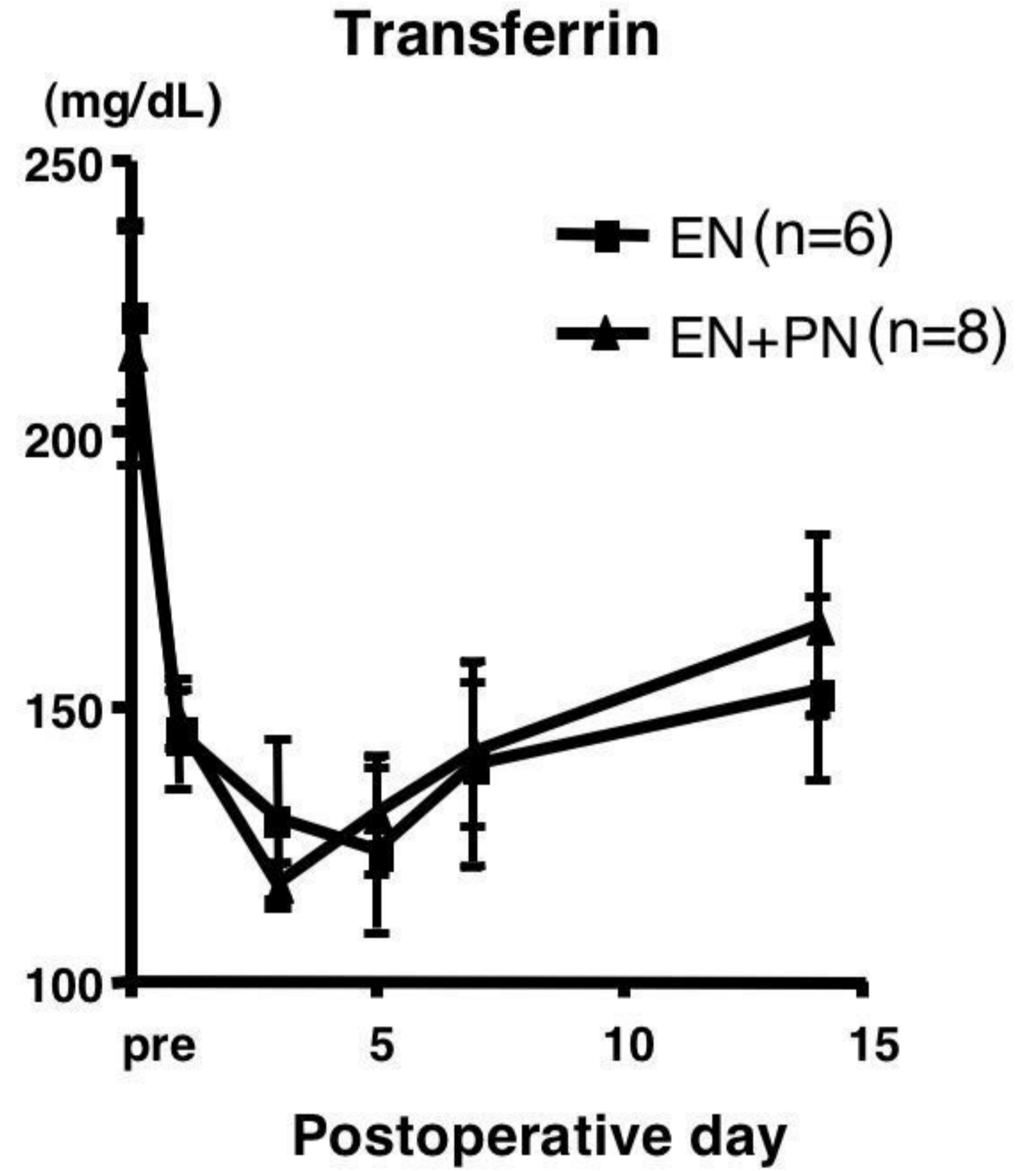
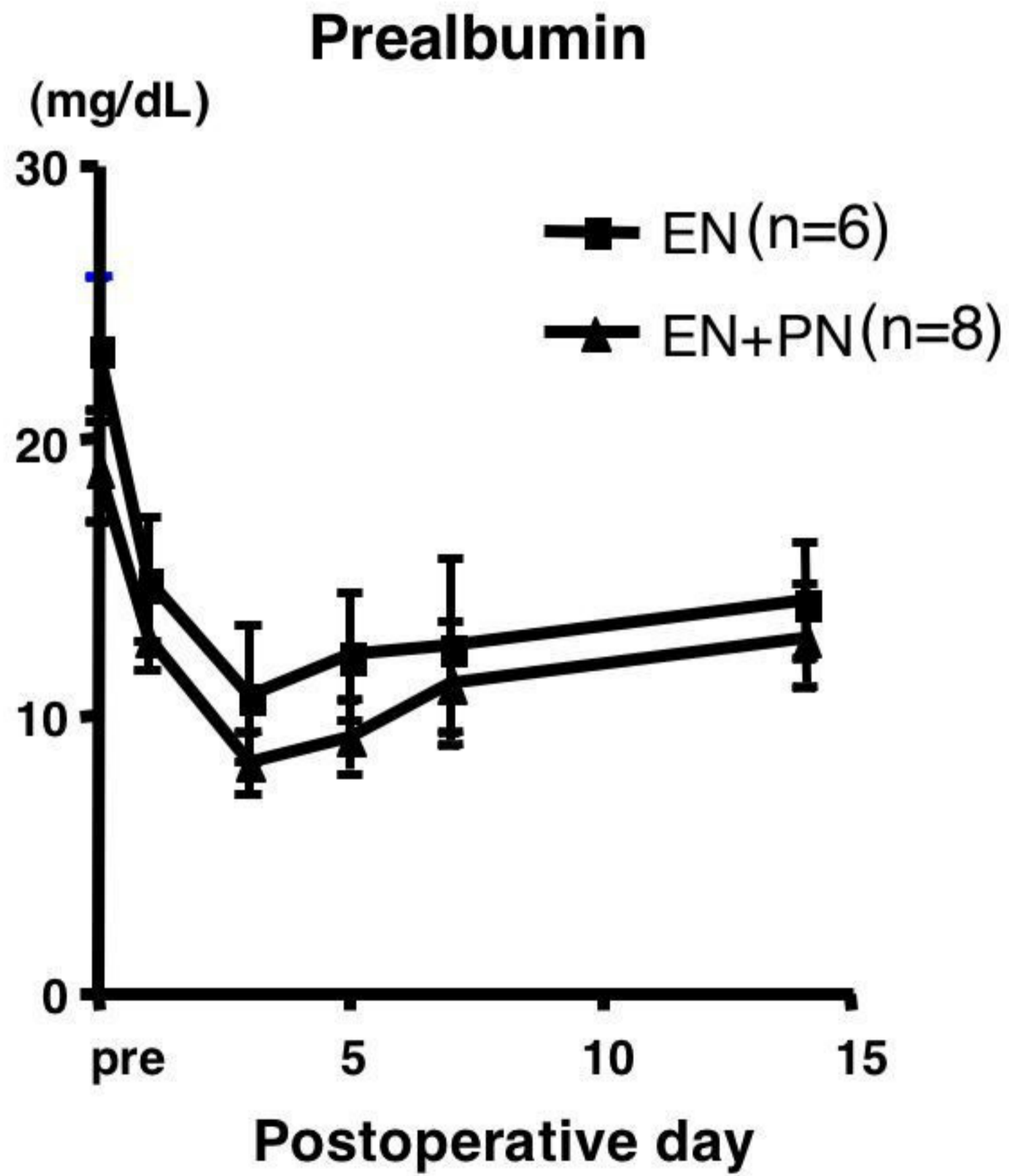


Fig. 3

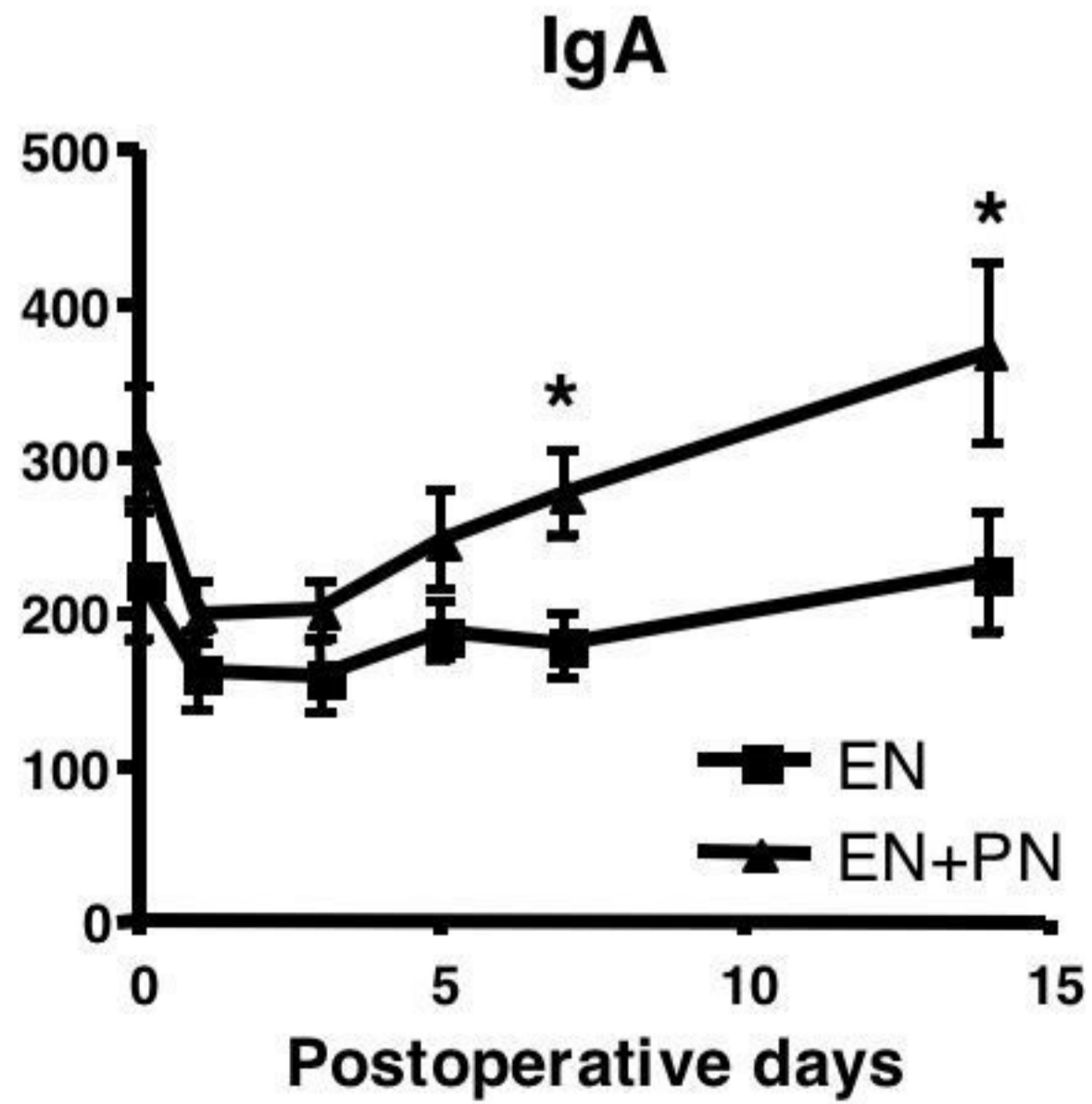
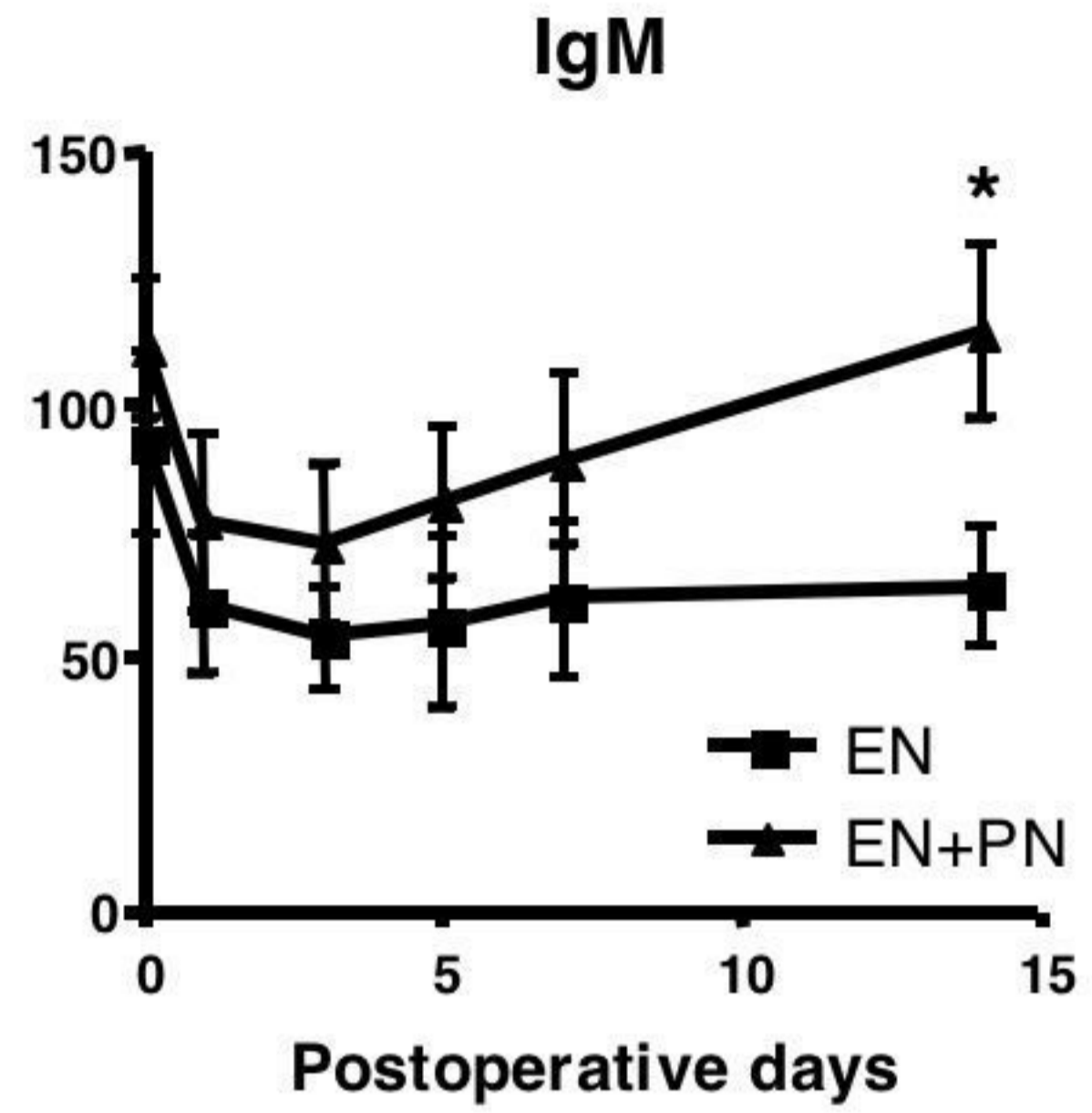
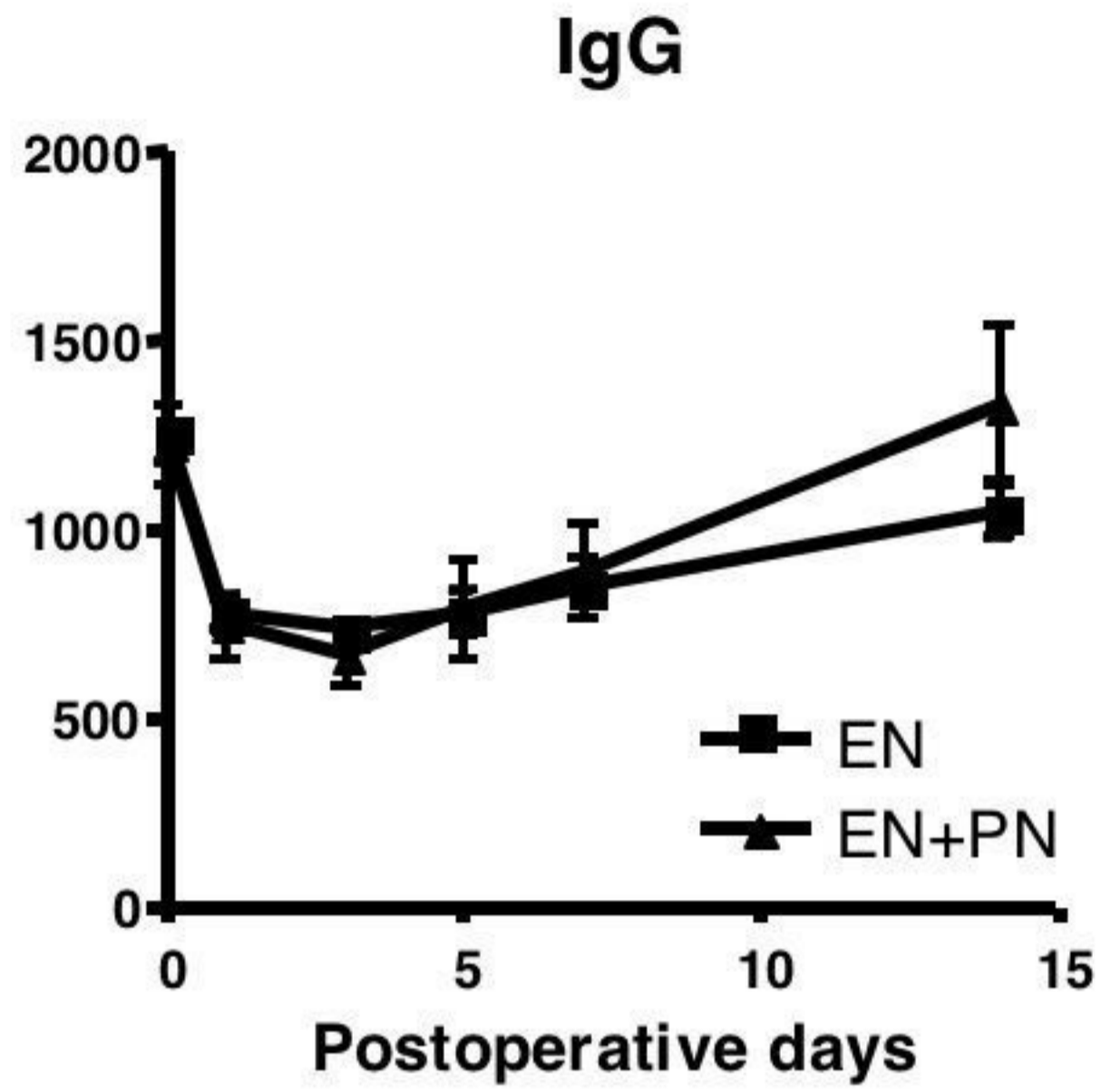
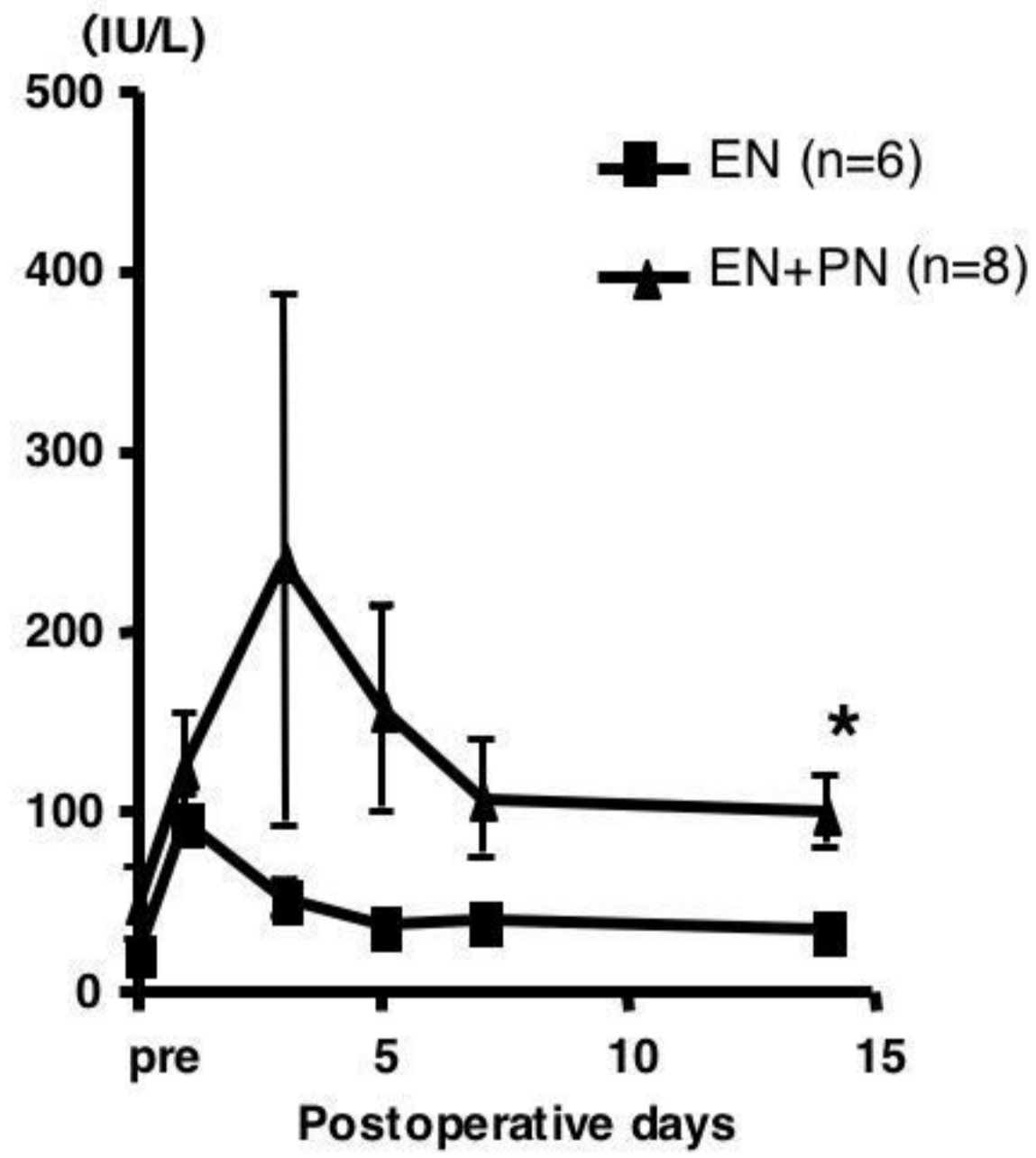
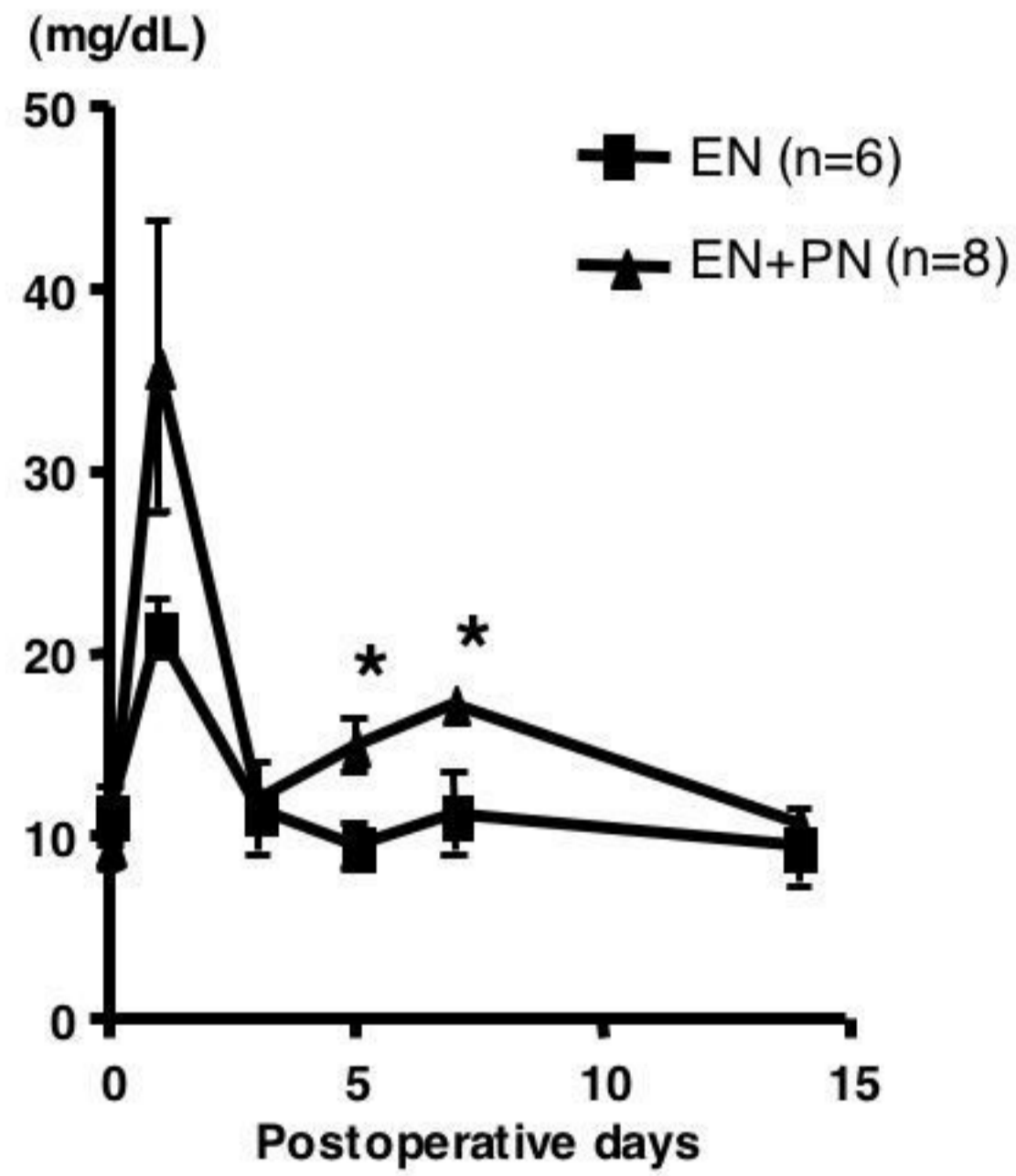


Fig. 4

ALT



Lactate



ChE

