Original Article

Early Postoperative Feeding Could Partially Replete Plasma Glutamine and Arginine Following Resection of Colorectal Cancer

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Key Words
Glutamine;
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Nasogastric feeding;
Nasojejunal feeding

The purpose of the study are: (1) To assess the relative changes of plasma glutamine and arginine levels following surgical stress, and (2) to compare the effects of early feeding methods on the restoration of glutamine and arginine.
One hundred and forty patients underwent colon resection for cancer entered the study. Group I patients were kept on nothing per os (NPO) for 6 days. Group II, III, IV were fed through a nasogastric (NG) tubes, and group V, VI, VII were fed through a nasojejunal (NJ) tubes from the second to the sixth postoperative day (POD) with low residual, high-fat and glutamine-containing enteral formulas. The patients had measurement of plasma glutamine and arginine preoperatively, on the first and the sixth postoperative day.
Both plasma glutamine and arginine decreased following surgery in all groups of patients. Glutamine and arginine were surprisingly higher than the preoperative level on the sixth POD in NPO group. Glutamine and arginine were relatively restored with early tube feeding.
In conclusion, the study suggested that plasma glutamine and arginine were decreased following surgery, but starvation will probably mobilize the glutamine and arginine reserve in the body. Early feeding could at least partially replete glutamine and arginine.
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Severe trauma, burns, and sepsis are characterized by a hypermetabolic response that rapidly depletes vital nutrient reserves.[1,2] The extraordinary demand for energy erodes lean body mass, depletes visceral protein stores, and compromises immune function, thereby setting the stage for postoperative complications, multiple organ failure, and death.[3-8] Decreased immunity following injury has been suspected of being associated with increased morbidity and mortality. Glutamine and arginine are two major amino acids associated with host immunity.[9-11] Additionally, lack of luminal nutrients leads to gut mucosal atrophy and immunological dysfunction of the intestinal immune system.[12,13] Nutritional support for the acutely stressed patient has long been recognized as a major component of surgical care.[14,15] Impairment of the gut barrier has been shown to result in the translocation of intraluminal bacteria and toxins into

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the intestinal lymphatics and blood stream. Therefore, it is of great importance that the intestinal barrier be preserved. Past studies suggested that early feeding following injury decreases morbidity and mortality.[16,17] The aim of the study is to (1) assess the relative change of serum glutamine and arginine levels following surgical stress, and (2) compare the effects of early feeding methods on the restoration of glutamine and arginine.

Materials and Methods

From October 2003 to April 2008, 140 patients who underwent elective colon resection for colorectal cancer by a single surgeon (T.-C.H) entered the study. Patients with previous gastric resection, previous vagotomy, and active peptic ulcer were excluded from the study. The patients' demographics and baseline characteristics such as age, sex, and location of tumor were noted. There were 78 males and 62 females. Ages ranged from 30 to 87 years old (average 61.7 years old). There were 55 colon and 85 rectal carcinomas. Cases were randomized into seven groups of 20 patients each. There was no significant difference in gender, age, preoperative albumin and BMI among groups. Group I patients were kept on nothing per os (NPO) for 6 days. Patients in groups II, III and IV were fed through nasogastric (NG) tubes from the second to the sixth postoperative day (POD) with low residual (Osmolite-HN; Abbott, USA), high-fat (Pulmocare; Abbott, USA) and glutamine-containing (AlitraQ; Abbott, USA) enteral formulas, respectively. Patients in groups V, VI and VII were fed through nasojejunal (NJ) tubes from the second to the sixth POD with Osmolite-HN, Pulmocare and AlitraQ enteral formulas, respectively. Patients receiving NJ feeding were also given simultaneous NG tube decompression by gravity. Pulmocare was diluted from 1.5 kcal/cc to 1 kcal/cc, and polycose was added to AlitraQ to make the formulas isonitrogenous and isocaloric before feeding (Table 1). Polycose (Abbott, USA) is a readily digestible carbohydrate and provides 3.8 cal/g of powder. An NG tube was inserted prior to surgery. A NJ tube was inserted during laparotomy in groups V, VI & VII. A standard colon resection was then performed for all the patients. Feeding began at 500 kcal/500 cc/day from the second POD. If the patient tolerated the formula well, feeding increased to 1500 kcal/1500 cc/day the following day and remained at this rate until the end of the study. Feeding mode was continuous with pump. Abdominal distension, repeated vomiting, and high gastric residual (Over 200 cc per shift) were considered signs of poor tolerance in patients receiving NG feeding. Abdominal distension, repeated vomiting, and high gastric drainage (> 1500 cc/day) were considered poor tolerance in patients receiving NJ feeding. At times, feeding was withheld for a few hours if the aforementioned symptoms were present.

All of the patients received nutritional assessment preoperatively, at the first and sixth POD. Nitrogen balance was calculated on the first and sixth POD. Five milliliter of blood was drawn and stored in heparinized tubes, which were centrifuged and stored at -70 °C. Ion exchange chromatography method (Beckman system 6300) was used to measure plasma amino acid including glutamine and arginine, preoperatively, and on the first and the sixth postoperative day. Student's t-test and the x^2 test was used for statistical analysis. $p < 0.05$ was considered statistically significant. The study was approved by the ethics committee of Mackay Memorial Hospital. Informed consent was obtained from the patient prior to initiation of the study.

Results

There were no perioperative mortalities or ana-

Table 1. Compositions of the three different formulas with their additions

Formulas	Osmolite HN	Pulmocare	AlitraQ
Protein (g/100 kcal)	4.2	4.2	4.2
Fat (g/100 kcal)	3.5	6.1	2.1
Carbohydrate (g/100 kcal)	13.4	7.0	18.2
Glutamine (g/L)	0	0	14.2
Osmolarity (mOsm/kg)	310.0	328.0	429.0
pH	6.6	6.7	6.8

* Pulmocare was diluted from 1.5 kcal/cc to 1 kcal/cc.
# Polycose was added to AlitraQ to make it 1 kcal/cc.

stomotic leakages related to early tube feeding. Poor tolerance, the most common complication seen in patients with early tube feeding, occurred in 14 patients (23%) with NG feeding and 18 patients (30%) with NJ feeding. The intolerance amongst the groups was not statistically significant ($p > 0.05$). Patients usually tolerated feeding after the rate of infusion was slowed for a day or withheld for a few hours. No patient needed to have feeding stopped completely. Daily energy requirement was calculated by multiplying basal energy expenditure (BEE), using the Harris-Bennedict Equation with stress factor and activity factor. The amount of energy received on the POD 5 was 78 ± 15% in group II, 71 ± 16% in group III, 74 ± 14% in group IV, 75 ± 14% in group V, 73 ± 15% in group VI, and 77 ± 12% in group VII. Aside from those in NPO group, all the patients had significantly less negative nitrogen balance on the sixth POD than on the first POD ($p < 0.05$) (Figs. 1 & 2).

In the NPO group, plasma glutamine was 347.1 ± 130.7 nmol/ml prior to the surgery and dropped significantly to 276.2 ± 121.8 nmol/ml on the first POD ($p = 0.019$), but was surprisingly higher than the preoperative level on the sixth POD (379.1 ± 147.9 nmol/ml). Plasma glutamine was also significantly decreased on the first postoperative day before the feeding was started in all groups [pre-op vs. first POD: 380.0 ± 154.3 nmol/ml vs. 291.6 ± 89.2 nmol/ml in group II ($p = 0.021$); 425.2 ± 148.9 nmol/ml vs 386.2 ± 159.8 nmol/ml in group III ($p = 0.30$); 350.7 ± 142.4 nmol/ml vs. 261.6 ± 109.9 nmol/ml in group IV ($p = 0.047$); 446.0 ± 163.2 nmol/ml vs. 325.3 ± 158.3 nmol/ml in group V ($p < 0.001$); 497.5 ± 129.6 nmol/ml vs. 379.7 ± 122.0 nmol/ml in group VI ($p < 0.001$); 462.7 ± 77.2 nmol/ml vs. 353.1 ± 66.1 nmol/ml in group VII ($p < 0.001$)]. Plasma glutamine then increased moderately to a level slightly lower than the preoperative level on the sixth POD following tube feeding [337.5 ± 129.0 nmol/ml in group II; 408.7 ± 165.0 nmol/ml in group III; 324.4 ± 160.7 nmol/ml in group IV; 383.5 ± 183.8 nmol/ml in group V; 431.0 ± 134.7 nmol/ml in group VI; 421.5 ± 110.8 nmol/ml in group VII (Table 2, Figs. 3 & 4).

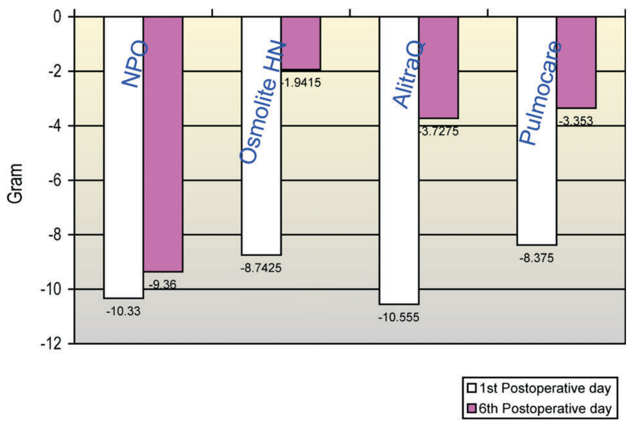

Fig. 1. Comparison of nitrogen balance in nasogastric feeding and NPO (Less nitrogen balance on the 6th POD than on the 1st POD in groups with NG feeding, $p < 0.05$).

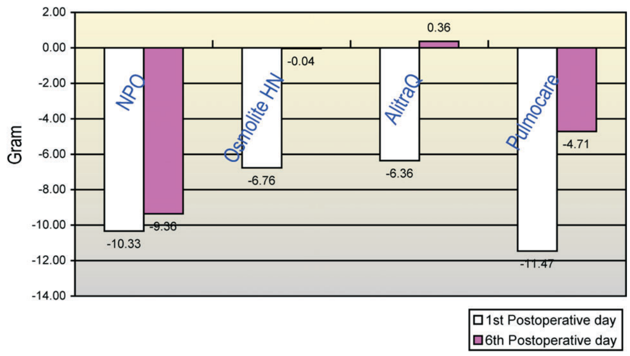

Fig. 2. Comparison of nitrogen balance in nasojejunal feeding and NPO (Less nitrogen balance on the 6th POD than on the 1st POD in groups with NJ feeding, $p < 0.05$).

Table 2. Comparison of change of glutamine among groups

	Preoperative	First POD	Sixth POD
Gr. I	347.1 ± 130.7*	276.2 ± 121.8*	379.1 ± 147.9
Gr. II	380.0 ± 154.3@	291.6 ± 89.2@	337.5 ± 129.0
Gr. III	425.2 ± 148.9#	386.2 ± 159.8#	408.7 ± 165.0
Gr. IV	350.7 ± 142.4&	261.6 ± 109.9&	324.4 ± 160.7
Gr. V	446.0 ± 163.2§	325.3 ± 158.3§	383.5 ± 183.8
Gr. VI	497.5 ± 129.6‡	379.7 ± 122.0‡	431.0 ± 134.7
Gr. VII	462.7 ± 77.2^	353.1 ± 66.1^	421.5 ± 110.8

* $p = 0.019$ between 1st POD and preoperative value in NPO group; @ $p = 0.021$ between 1st POD and preoperative value in NG feed Osmolite HN group; # $p = 0.30$ between 1st POD and preoperative value in NG feed Pulmocare group; & $p = 0.047$ between 1st POD and preoperative value in NG feed AlitraQ group; § $p < 0.001$ between 1st POD and preoperative value in NJ feed Osmolite group; ‡ $p < 0.001$ between 1st POD and preoperative value in NJ feed Pulmocare group; ^ $p < 0.001$ between 1st POD and preoperative value in NJ feed AlitraQ group.

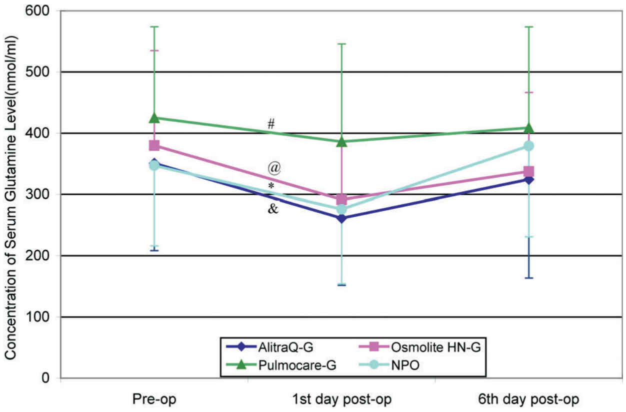

Fig. 3. Comparison of change of glutamine in patients with nasogastric feeding and NPO. *, $p = 0.019$ between 1^{st} POD and preoperative value in NPO group; @, $p = 0.021$ between 1^{st} POD and preoperative value in Osmolite HN group; #, $p = 0.30$ between 1^{st} POD and preoperative value in Pulmocare group; &, $p = 0.047$ between 1^{st} POD and preoperative value in AlitraQ group.

In the NPO group, plasma arginine was 54.6 ± 22.6 nmol/ml prior to the surgery and dropped to 34.7 ± 19.7 nmol/ml on the first POD ($p = 0.15$), but was surprisingly higher than the preoperative level on the sixth POD (76.1 ± 27.1 nmol/ml). Plasma arginine was also decreased significantly on the first POD before the feeding started, and then increased moderately to a level slightly lower than the preoperative level. Plasma arginine also decreased significantly following surgery in all groups of patients [pre-op vs. first POD: 61.8 ± 37.2 nmol/ml vs. 54.6 ± 66.9 nmol/ml in group II ($p = 0.65$); 68.1 ± 34.0 nmol/ml, vs. 39.7 ± 23.7 nmol/ml in group III ($p < 0.001$); 64.9 ± 31.4 nmol/ml vs. 40.6 ± 24.8 nmol/ml in group IV ($p = 0.017$); 64.9 ± 33.9 nmol/ml vs. 33.1 ± 19.4 nmol/ml in group V ($p = 0.004$); 89.3 ± 28.2 nmol/ml vs. 46.0 ± 15.0 nmol/ml in group VI ($p < 0.001$); 66.4 ± 26.0 nmol/ml vs. 41.2 ± 16.3 nmol/ml in group VII ($p < 0.001$)]. Plasma arginine was then increased moderately to a level slightly lower than the preoperative level on the sixth POD following tube feeding (59.2 ± 38.4 nmol/ml in group II; 71.1 ± 32.1 nmol/ml in group III; 99.4 ± 53.7 nmol/ml in group IV; 78.0 ± 25.9 nmol/ml in group V; 85.9 ± 23.5 nmol/ml in group VI; 104.2 ± 36.2 nmol/ml in group VII) (Figs. 5 & 6). It was demonstrated that feeding patients AlitraQ increased plasma arginine level more significantly than feeding the other two formulas on the sixth POD [99.4 ± 53.7 nmol/ml vs. pre-op 64.9 ± 25.9 nmol/ml in NG group ($p = 0.01$); 104.6 ± 37.4 nmol/ml vs. pre-op 68.1 ± 25.9 nmol/ml in NJ group ($p < 0.001$)] (Table 3, Figs. 5 & 6).

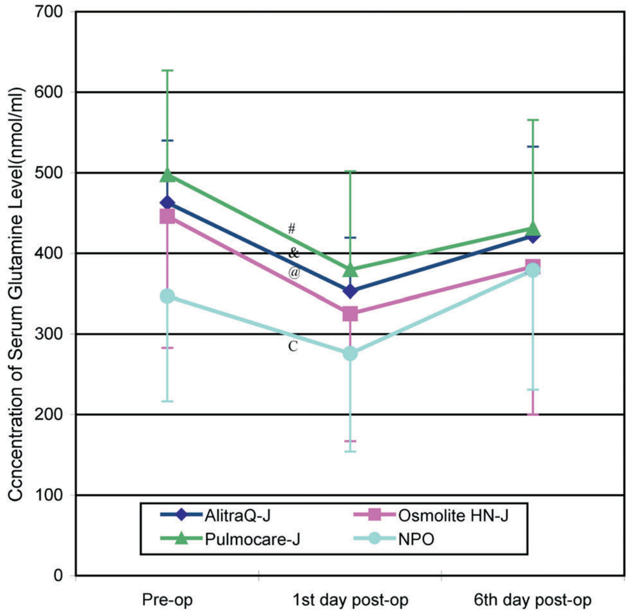

Fig. 4. Comparison of change of glutamine in patients with nasojejunal feeding and NPO. *, $p = 0.019$ between 1^{st} POD and preoperative value in NPO group; @, $p < 0.001$ between 1^{st} POD and preoperative value in Osmolite group; #, $p < 0.001$ between 1^{st} POD and preoperative value in Pulmocare group; &, $p < 0.001$ between 1^{st} POD and preoperative value in AlitraQ group.

Discussion

Traditional practice has been to delay enteral feeding for a few days following laparotomies until the patient is able to consume oral diet. Surgery is a stress per se, and starvation by NPO is an additional stress. Bacterial translocation is believed to be a major factor in the development of nosocomial sepsis, multiple organ dysfunction syndromes, and death.[3,4,18] Since the mucosal atrophy associated with NPO is believed to be one of the reasons for the bacterial translocation, past studies suggested that early feeding supplying nutrient intraluminally following injury is important in strengthening the mucosal barrier and decreasing morbidity and mortality.[19,20] Safety, conve-

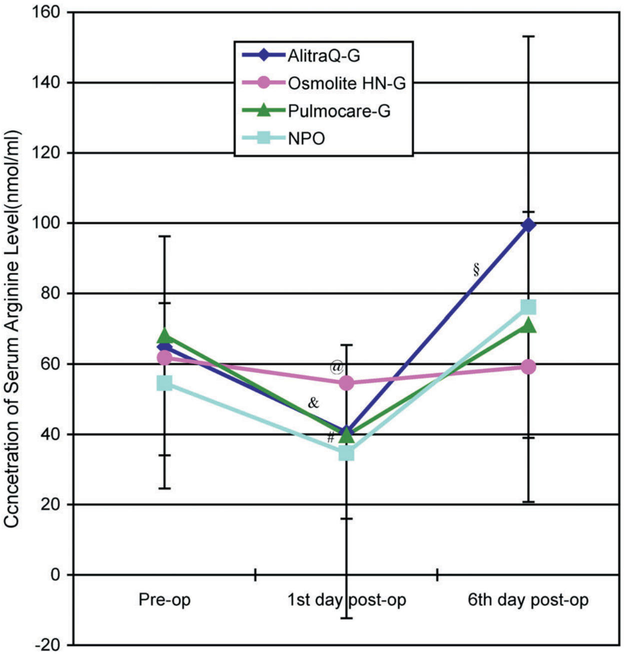

Fig. 5. Comparison of change of arginine in patients with nasogastric feeding and NPO. @, $p = 0.65$ between 1st POD and preoperative value in Osmolite group; #, $p < 0.001$ between 1st POD and preoperative value in Pulmocare group; &, $p = 0.017$ between 1st POD and preoperative value in AlitraQ group; §, $p = 0.01$ between 6th POD and preoperative value in AlitraQ group.

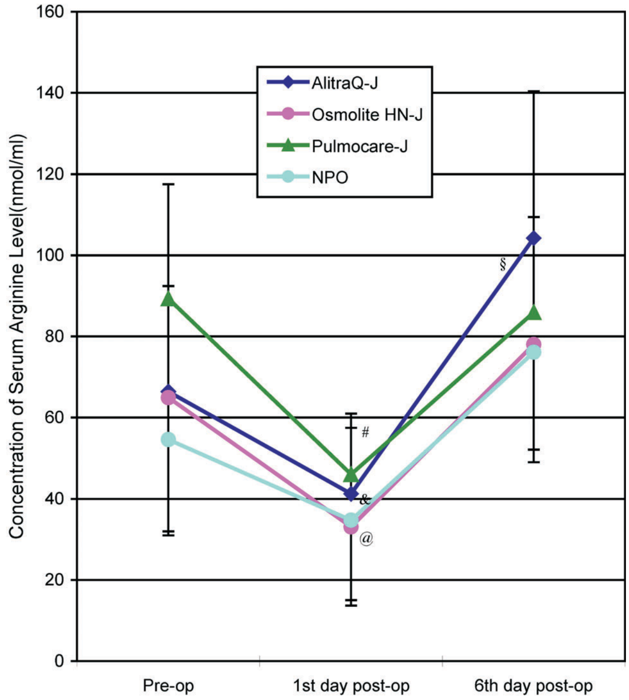

Fig. 6. Comparison of change of arginine in patients with nasojejunal feeding and NPO. @, $p = 0.004$ between 1st POD and preoperative value in Osmolite group; #, $p < 0.001$ between 1st POD and preoperative value in Pulmocare group; &, $p < 0.001$ between 1st POD and preoperative value in AlitraQ group; §, $p < 0.001$ between 6th POD and preoperative value in AlitraQ group.

nience, and reduced cost are the commonly cited advantages of enteral nutrition.[21,22] Gastric paresis occurs 24 to 48 hours following surgery. Despite laparotomy or acute stress, small bowel motility and absorption remain functionally intact. Thus early enteral feeding is preferred over gastric feeding in most series.[14,15] Physiologically, however, gastric feeding is more advantageous than enteral feeding. Whether the patients can really benefit from early feeding is still debatable. Even more controversial is whether certain components are more beneficial for the patient. Recently, several specific micronutrients have been shown to stimulate the immune system and therefore may decrease the incidence of bacterial translocation. Glutamine and arginine are two amino acids suggested to aid host immunity.[9-13] Glutamine has been shown to protect the gastrointestinal mucosa in a number of conditions and with certain treatment modalities, such as chemotherapy and radiotherapy. Glutamine serves multiple functions, including nitrogen

Table 3. Comparison of changes of arginine among groups

	Preoperative	First POD	Sixth POD
Gr. I	54.6 ± 22.6®	34.7 ± 19.7®	76.1 ± 27.1
Gr. II	61.8 ± 37.2@	54.6 ± 66.9@	59.2 ± 38.4
Gr. III	68.1 ± 34.0#	39.7 ± 23.7#	71.1 ± 32.1
Gr. IV	64.9 ± 31.4&,^	40.6 ± 24.8&	99.4 ± 53.7^
Gr. V	64.9 ± 33.9*	33.1 ± 19.4*	78.0 ± 25.9
Gr. VI	89.3 ± 28.2‡	46.0 ± 15.0‡	85.9 ± 23.5
Gr. VII	66.4 ± 26.0§,+	41.2 ± 16.3+	104.2 ± 36.2§

® $p = 0.15$ between 1st POD and preoperative value in NPO group; @ $p = 0.65$ between 1st POD and preoperative value in NG feed Osmolite group; # $p < 0.001$ between 1st POD and preoperative value in NG feed Pulmocare group; & $p = 0.017$ between 1st POD and preoperative value in NG feed AlitraQ group; ^ $p = 0.01$ between 6th POD and preoperative value in AlitraQ group; * $p = 0.004$ between 1st POD and preoperative value in NJ feed Osmolite group; ‡ $p < 0.001$ between 1st POD and preoperative value in NJ feed Pulmocare group; + $p < 0.001$ between 1st POD and preoperative value in NJ feed AlitraQ group; § $p < 0.001$ between 6th POD and preoperative value in NG feed AlitraQ group.

exchange between tissues, regulation of protein synthesis, and provision of a precursor in nucleotide synthesis. Its role as a preferred fuel source for the enterocyte has been well documented.[7,8] Several studies have shown that supplemental arginine improves host immune defenses.[6] Its ability to increase thymic weight and thymocyte immune response has been suggested. The authors hypothesized that surgical stress will decrease plasma glutamine and arginine, while early feeding through nasogastric tube may resplenish some of the glutamine and arginine stores.

In order to minimize bias, a single surgeon's experience of elective major surgery for a single disease, colon resection for colorectal cancer, was collected for the study. Patients who underwent surgical treatment for a gastroduodenal ulcer, such as gastric resection, vagotomy, or active ulcer disease, were excluded from the study. None of the patients were allowed to receive plasma or albumin transfusion throughout the study. Gastric paresis occurs 24-48 hour following surgery. Despite laparotomy or acute stress, small bowel motility and absorption remain functionally intact. Thus, intrajejunal feeding has been preferred over intragastric feeding due to earlier return of peristalsis following laparotomy. More controversial is whether certain nutrient components are more beneficial for the patient. In order to make the comparison more meaningful, besides the group of nothing by month, we purposely divided patients to groups with two different routes of feeding and receiving three different formulas containing different nutrient components. Not surprisingly, plasma glutamine and arginine decreased significantly on the first postoperative day. It was usually not possible for postoperative patients to receive an excess amount of feeding following surgery. Isocaloric, isonitrogenous nutritional support, such as parenteral nutrition, is most likely impossible. Therefore, 500 cc was given on the second POD after gastric paresis recovered, and increased to 1500 cc/day the following day. As different formulas have different components, three different formulas were tested. In order to make the formulas comparable, Pulmocare was diluted to 1 kcal/cc and Polycose was added to the AlitraQ resulting in 1 kcal/cc. Most of the patients tolerated this kind of feeding well. Although it was necessary to slow or even stop feeding for a few hours in some patients, all of the patients eventually tolerated the maximum rate of feeding. The higher osmolarity may explain the high frequency of intolerance in the AlitraQ group. High fat content in Pulmocare may result in slow digestion and stasis, which may be the reason for its poor tolerance compared with Osmolite HN. Other than those in the NPO group, all the patients had significantly less negative nitrogen balance on the sixth POD than the first POD. This finding sugggests that early NG feeding helps to preserve our lean body mass. Plasma glutamine and arginine level also improved on the sixth POD. Although the plasma glutamine and arginine did not return to the preoperative level, the improvement was promising. The study demonstrated that feeding patients AlitraQ with additional supply of glutamine and arginine increased plasma arginine level, but not glutamine level, more significantly than feeding with the other two formulas. Surprisingly, both the plasma glutamine and arginine values were higher on the sixth POD than the preoperative value. One speculation (or hypothesis) would be that the body responds to the life threatening crisis, causing the release of large amounts of tissue reserve of glutamine and arginine. If the plasma glutamine and arginine were measured at the later day, e.g. on the eight or tenth postoperative day, the value may be even lower than the preoperative value.

Conclusion

The present study suggested that plasma glutamine and arginine were decreased in the blood following surgery, but starvation will probably mobilize the glutamine and arginine reserve in the body. Early feeding could at least partially replete plasma glutamine and arginine.

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原　著

手術後早期鼻胃及鼻空腸灌食可以部分恢復血漿中麩胺酸及鮭卵酸

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本研究的目的為 (1) 評估外科手術抑壓對血漿中麩胺酸及鮭卵酸的改變。(2) 比較早期灌食對於麩胺酸及鮭卵酸恢復的效果。

接受大腸切除來治療大腸癌的一百四十位患者分為四組。第一組患者手術後禁食六天。第二、三、四組患者從手術後第二日至第六日分別由鼻胃管給予低渣、高脂肪或含麩胺酸的配方灌食。第五、六、七組患者則以鼻空腸管由第二日至第六日灌食了上述的三種配方。所有患者在手術前，手術後第一日及第六日測量了血漿中的麩胺酸及鮭卵酸。手術後，血漿中的麩胺酸及鮭卵酸在所有的患者均下降。很意外的在禁食組第六天時的血漿中的麩胺酸及鮭卵酸比手術前的數值來的高。而且在早期灌食的患者，灌食可以部分恢復血中的麩胺酸及鮭卵酸。

這一研究顯示手術後血漿中的麩胺酸及鮭卵酸會下降，但禁食可能可以動員身體內儲藏的麩胺酸及鮭卵酸。早期灌食至少可以部分恢復血漿中的麩胺酸及鮭卵酸。

關鍵詞　麩胺酸、鮭卵酸、鼻胃灌食、鼻空腸灌食。