Original Article

Influence of early enteral nutrition (EEN) on insulin resistance in gastric cancer patients after surgery

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Objective: To evaluate the benefits of reducing insulin resistance by early enteral nutrition (EEN) in gastric cancer patients after surgery. Methods: Gastric cancer patients were managed to randomly accept traditional total parenteral nutrition (group A) or EEN (group B) after surgical treatment. The patients in group B were fed by tubes with 250-500 mL 5% sodium chloride and glucose injection at 24 h post-surgery, and were fed enteral nutritional emulsion with constant infusion by pump slowly increasing from 20 mL/h to 100 mL/h from 48 h, and then transiting to total enteral nutrition. Insulin sensitivity of patients was detected by Quicki method before operation and at 24 h, 48 h, 72 h, 120 h and 168 h post-surgery. Results: A total of 77 patients were enrolled, with 42 patients in group A, and 35 patients in group B. Baseline characteristics, biochemical indexes and operational characteristics were well balanced between two groups. The time-insulin sensitivity curves of the two groups indicated that IR was present early (day 1 to day 7) in gastric cancer patients and was significantly different between patients who had undergone surgical treatment and those who had not. Insulin sensitivity (SI) of patients in group B were higher than patients in group A with adjusting BMI, age and SI preoperative at 72 h, 120 h and 168 h post-surgery. Conclusions: The management of EEN can alleviate insulin resistance in gastric cancer patients with surgical treatment.

Key Words: early enteral nutritional, gastric cancer, insulin resistance, insulin sensitivity, Glucose tolerance

INTRODUCTION

Although gastric cancer has greatly decreased in the United States, on a worldwide scale its incidence is still high, and it is the second leading cause of cancer death worldwide, behind lung cancer. Its highest incidence is in East Asia, presumably because of a diet consisting of heavily smoked, salted, and pickled foods. In China, gastric cancer has the highest mortality among all the malignant tumors. Most patients with gastric cancer suffer from different degrees of malnutrition and immunodeficiency before surgery.[1,2] And surgical stress can increase catabolism, leading to negative nitrogen balance. Therefore, nutritional support is important in the postoperative treatment for patients with gastric cancer. Insulin resistance (IR), one of the key factors affecting postoperative rehabilitation, occurs after surgery, which can lower the patient's immunity and tissue reparative ability, limiting wound healing and increasing the complication and mortality.

A large randomized trial shows that when postoperative hyperglycemia was controlled by insulin infusion to maintain normoglycemia, morbidity and mortality was reduced by almost half in intensive care.[3] Donald *et al* conducted a systemic review included 14 trials and suggested that patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR=0.63, 95% CI: 0.44-0.91).[4] Early enteral nutrition (EEN) has been showed to reduce septic complications and has been suggested to reduce the rate of multiple organ failure when initiated within 24 h.[5] Base on the same benefit of EEN and insulin infusion for postoperative recovery, the correlations of EEN and insulin resistance are hypothesized. Our study was intended to observe the influence of EEN on insulin resistance in gastric cancer patients after operative treatment.

MATERIALS AND METHODS

Patient selection and study design

Gastric cancer patients without diabetes history undergoing selective operation were eligible. This study was conducted in Fengxian District Central Hospital, Shanghai, China. Exclusion criteria included were: surgical contraindication, cancer cell metastasis to liver or lung, abnormal fasting blood-glucose (FBG), intolerance of enteral nutrition, serious postoperative complication such as massive haemorrhage, cardiopulmonary failure, serious infection. FBG and fasting insulin (FINS) was tested before surgery and at 24 h, 72 h, 120 h, 168 h after surgery. Biochemical indexes, BMI and other indexes were recorded before surgery. The Physiological and Operative Severity Score for the enumeration of Mortality and morbidity

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(POSSUM) score,[6] including physiological score (PS) and operative severity score (OSS) were also recorded. POSSUM score method proposed by Copeland in 1991 to evaluate the postoperative prognosis of the inpatient and has been widely used in Europe and America in recent years. It has been reported that it can offer a more accurate estimation for major operative risk in vascular surgery and general surgery.[7,8] The PS resembles APACHE II score. The added OSS, has been related closely to postoperative complication and mortality, and is more valuable than APACHE II score in evaluating the influence of surgery on patients.[9] All cases were randomly divided into the control group (group A) or the experimental group (group B) according to the random number table. Patients in group A were treated with routine insertion of nasogastric tube before surgery and postoperative total parenteral nutrition (TPN). Patients in group B were treated with insertion of both nasogastric tube and Flocare® polyurethane nasogastric feeding tube before surgery, with the nasogastric tube exceeding the end of gastrointestinal anastomosis for at least 20 cm in the surgery, and EEN after surgery.

Nutritional support plan

At 24 h after surgery, the patients in experimental group were fed by tubes with 250-500 ml 5% sodium chloride and glucose injection. At 48 h, started to feed enteral nutritional emulsion with constant infusion by pump, slowly increasing from 20 ml/h to 100 ml/h, and transiting to total enteral nutrition, ie fed enteral nutritional emulsion with tube by 30 ml (about 40 kcal/kg) every day. The total amount of infusion fluid was required to be 2500-3000 ml in 24 h, and the uninfused was supplemented by the same tube, combined with enteral nutritional emulsion, or by vein. This continued for about 7 days. The control group was treated with total parenteral nutrition with total calories of about 40 kcal/kg, with glucose150-200 g/d, lipid emulsion 1-1.5 g/(kg.d), and amino acid 1.0 g/(kg.d). All-in-one nutrient solution was infused through peripheral vein or central vein. Other clinical cares in both groups were routinely managed.

The calculation of insulin sensitivity

QUICK method, such as Arie K.[10] was used to calculate insulin sensitivity (SI) in all cases. The formula

$$SI = 1/[\log(FINS) + \log(FBG)].$$

ΔSI is the change of SI after surgery.

$$\Delta SI = |SIpreoprative - SIx| / SIpreoprative \times 100\%.$$

The QUICK method was proposed by Arie K *et al* in 2000 to test IR. The test only needs a few drops of blood and a simple calculation to get the data. This convenient, accurate, and reliable method does not require expensive equipment or complicated skill, and is useful for great case analysis and highly correlated with the gold standard of testing SI-euglycemic insulin clamp technique.[11]

Statistical method

Descriptive statistics were used to summarize continuous variables, and frequency and percentages to summarize discrete variables. Categorical variables were compared using the chi-squared tests, *t*-tests were used for the comparison of quantitative basic variables. When comparing insulin sensitivity and its changes, analysis of covariance was performed adjusting for age, BMI and preoperative SI, repeated measures analysis of variance was also performed with defining time-repeated insulin sensitivity assessment. SAS v9.2 was used for statistics analysis. The p value <0.05 was considered statistics difference.

Table 1. Characteristic of patients

Variable	Total (n=77)	Group A (n=42)	Group B (n=35)	*p*-value
Gender (%)				0.442
Male	47 (61)	24 (57)	23 (66)	
Female	30 (39)	18 (43)	12 (34)	
Celiac pollution (%)				0.109
No	45 (58)	28(67)	17 (49)	
Mild	32 (42)	14 (33)	18 (51)	
Surgical method (%)				1
Gastrectomy	73 (95)	40 (95)	33 (96)	
Gastrectomy+splenectomy	4 (5)	2 (5)	2 (4)	
Malignancy (%)				0.654
No metastasis	22 (29)	13 (31)	9 (26)	
Lymphatic metastasis	32 (41)	15 (36)	17 (48)	
Primary lesion metastasis	16 (21)	9 (21)	7 (20)	
Distant metastasis	7 (9)	5 (12)	2 (6)	
Age (year)	56.5	57.3±9.4	55.5 ±10.4	0.425
Bun (mmol/L)	5.0±1.2	5.1±1.1	5.0±1.4	0.760
Na (mmol/L)	141±4.0	141±4.2	141±3.8	0.980
K (mmol/L)	4.2±0.5	4.2±0.6	4.1±0.9	0.399
Hb (g/L)	126±19.8	123±20.7	127±18.7	0.430
WBC (×10^9/L)	5.9±1.7	5.6±1.6	6.27±1.73	0.102
BMI	23.2±1.5	23.3±1.6	23.1±1.3	0.450
OSS score	13.0±3.8	13.0±3.5	13.0±3.8	0.950
Possum score	17.8±2.8	18.0±3.1	17.5±2.5	0.463
Blooding during operation	238±152	246±149	228±157	0.626

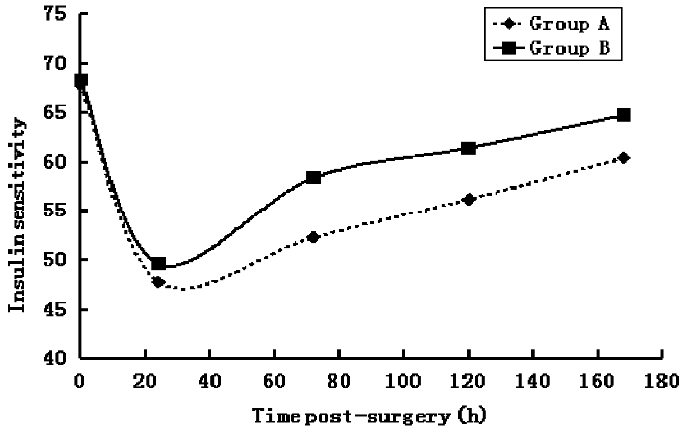

Figure 1. Curves of time-insulin sensitivity for patients of two groups

RESULTS

Patient characteristics

A total of 77 patients were enrolled and randomized to group A (42 patients) or group B (35 patients) between September 2007 and June 2010, with characteristics of patients as shown in Table 1. Baseline characteristics, biochemical indexes and operational characteristics were well balanced between the two groups (Table 1). The majority of surgical method used was gastrectomy (95%) with no or wild celiac pollution. The mean age in group A and group B was 57.3 and 55.5, respectively. Mean OSS and POSSUM score for all patients were 13.0 and 17.8, respectively.

Insulin sensitivity of patients

At 24h post-surgery, the insulin sensitivity of patients in the two groups sharply declined compared with preoperative level (47.8±5.6 and 49.6±5.3 vs 67.8±6.5 and 68.3±5.0, group A and group B, respectively), then it gradually increased during 72h to 168h post-surgery (Figure 1). The time-insulin sensitivity curve indicated that IR was present early (day 1 to day 7) in gastric cancer patients with surgical treatment. Curves of group A and group B were significantly different, the decreased degrees of insulin sensitivity of group B were less than group A when enteral nutrition at 24h post-surgery began, meanwhile, recovery of insulin sensitivity in group A was slower. Significant differences of insulin sensitivity were seen between two groups with adjusting BMI, age and SI at 72 h, 120 h and 168 h post-surgery (p<0.001) (Table 2). Differences for ΔSI2, ΔSI3 and ΔSI4 between two groups were also showed (p<0.001)(Table 3). When performing repeated measures analysis of variance, the two groups were different in insulin sensitivity and ΔSI by controlling repeated measures effect.

DISCUSSION

Postoperative enteral nutrition is considered to be the first choice.[12,13] For patients treated with abdominal surgery, especially gastrointestinal surgery, traditionally, enteral nutrition or food is offered usually after anal exhaust to avoid mechanical or chemical stimulation and pollution to the anatomosisi caused by food and digestive juice. According to previous study,[14] the recovery of gastric function and colonic function has been slow; small intestinal function usually returns to normal several hours (6-12 h) after surgery, which provides theoretical evidence for the application of early enteral nutrition. Many scholars at home and abroad have firmed the feasibility, safety and clinical meaning of giving EEN support to patients after gastrointestinal surgery.[15,16] EEN after surgery can provide enough calories and nitrogen source for the production of total protein and stress protein to correct negative nitrogen balance. In addition, it strengthens enteral mechanic and immune barrier function, and reduces enterogenic infection. It promotes intestinal peristalsis and activates endocrine system in the intestines to accelerate the production and release of intestinal hormone. Also regulates the secretion and excretion of gastric juice, bile and pancreatic juice.[17] Enteral nutrition not only meets the physiological needs, but also increases the absorption of nutrients, improves the quality of life of the patient and helps in rehabilitation.

Table 2. Insulin sensitivity of patients at pre and post-surgery

Time	Group A	Group B	p value
Preoperative	67.8±6.5	68.3±5.0	0.592*
24 h	47.8±5.6	49.6±5.3	0.070**
72 h	52.3±6.0	58.4±5.4	<0.001**
120 h	56.2±6.1	61.4±5.6	<0.001**
168 h	60.4±6.4	64.7±5.0	<0.001**
			<0.001***

*ANCOVA was performed to compare insulin sensitivity between group A and B adjusting for age, and BMI; **ANCOVA was performed to compare insulin sensitivity between group A and B adjusting for age, BMI, and SI; ***Comparison between group A and B using repeated measures ANOVA.

Table 3. The change of insulin sensitivity (ΔSI) of patients post-surgery (%)

Time	Group A	Group B	p value
24h	29.5±5.4	27.4±4.8	0.0818*
72h	22.8±6.1	14.5±4.3	<0.001*
120h	17.0±5.2	10.1±3.3	<0.001*
168h	10.9±4.6	5.3±2.3	<0.001*
			<0.001**

*ANCOVA was performed to compare insulin sensitivity of group A and B adjusting age, and BMI; **Comparison between group A and B using repeated measures ANOVA.

After surgery, raised blood glucose and lowered glucose tolerance in the patient will speed up catabolism and cause negative nitrogen balance, bad healing of wound, and higher infection rate, etc. This influences organic homeostasis, which is closely related to poor prognosis[18] causes postoperative insulin resistance.[19] Insulin resistance is a condition where the biological effect of insulin becomes lesser than normal. Organic sensitivity and response to insulin becomes weak and the biological reaction to insulin becomes weaker than the normal. Though the consistency of insulin raises, organic hyperglycemia cannot be corrected, which manifests in the resistance to all biological effects to lipid, protein, water-electrolyte balance, and sympathetic nerve, etc, especially in the regulation of glycometabolism. In addition it may cause hyperglycemia, hyperinsulinemia, and hyperlactacidemia, etc.[20] The IR is an abnormal pathophysiological condition and is a common risk factor in many diseases. It has become a hot topic and a common interest in many subjects in the field of medicine around the world. Among various causes of IR, perioperative and postoperative stress is the main cause during the surgery (mental, surgical trauma, nutrition status, etc). It's been revealed that the obstacle of signal transduction of insulin receptor and the increased insulin antagonistic hormone are both key links.[21] IR can be counted as a natural reaction to stress such as hungry or trauma, which can maintain blood glucose level to guarantee the uptake of glucose by brain and other important tissues and organs. Some researchers proved that hyperglycemia and IR are common in great abdominal surgeries; usually occurring at the start of anesthesia, reaching the peak within postoperative 24h, recovering fast in 2 to 5 days, and returning to normal within 2 to 3 weeks, if there are no complication.[22] But IR reduces the energy supplied through glycoxidation, leading to persistence of hyperglycemia and more decomposition of lipid and protein, which hinders the rehabilitation of patients after surgery.[23] Postoperative IR will make patients' immunity and reparative ability of tissues weaker; which limits wound healing and increases clinical complication and mortality. Thus lowering the degree of IR or its duration after surgery is beneficial for early rehabilitation of patients. In our study, we begin offered EEN for gastric cancer patients with operative treatment at 24 h post-surgery, the time-insulin sensitivity curve was significant higher than control arm, which directly indicated that postoperative IR was less serious with management of EEN. It should be noted that energy intake can affect insulin sensitivity, in our study we had to try to keep the balance of energy intake between two groups by controlling the unit weight energy, but comparison of insulin sensitivity did not adjust the energy intake and, this weakens the precision of our study.

Conclusion

Patients may be benefited from the management of EEN that can alleviate insulin resistance early in gastric cancer patients after surgical treatment.

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AUTHOR DISCLOSURES

All the authors claim that there is no conflict of interest.

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Original Article

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早期腸道營養對於術後胃癌病人胰島素抗性之影響

目的：評估早期腸道營養對於降低術後胃癌病人胰島素抗性之效益。方法：將術後的胃癌病人隨機分成接受傳統全靜脈營養(A 組)或早期腸道營養(B 組)。術後 24 小時，利用管灌給予 B 組病人 250-500 毫升 5%氯化鈉和葡萄糖；從 48 小時開始，利用幫浦以連續灌食方式給予腸道營養液，以每小時 20 毫升的流速緩慢增加至每小時 100 毫升，接著再轉換至完全腸道營養給予。在術前、術後 24、48、72、120 和 168 小時，利用 Quicki 法檢測病人之胰島素敏感性。結果：共有 77 位病人參與本試驗，A 組 42 人、B 組 35 人。兩組之基本特性、生化指標、以及手術性質大致相同。藉由兩組在不同時間點所測得的胰島素敏感性曲線指出，胃癌病人在術後早期(第 1 天到第 7 天)即出現胰島素抗性，且手術前後有顯著差異。在調整身體質量指數、年齡和術前 72、102 小時及術後 168 小時的胰島素敏感性，發現 B 組病人的胰島素敏感性顯著高於 A 組。結論：早期腸道營養的施行可減輕術後胃癌病人之胰島素抗性。

關鍵字：早期腸道營養、胃癌、胰島素抗性、胰島素敏感性、葡萄糖耐受性