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Research Article

Effects of a single preoperative dose of N(2)-L-alanyl-L-glutamine on insulin resistance and plasma glutathione levels in the early postoperative period

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KEYWORDS

Alanyl-glutamine;
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Abstract *Background:* Anesthesia and surgery starts a series of stress responses in the body. Subsequently, loss of normal anabolic actions of insulin and development of insulin resistance occur. Resulting hyperglycemia has been considered by an evidence based study as a risk factor for perioperative morbidity and mortality. We tested whether a single preoperative dose of alanyl-glutamine would prevent such responses in addition to maintaining glutathione level; an important factor for maintaining cellular redox potential.

Methods: A total of 40 cancer patients were enrolled in this study who received an infusions of 500 ml of Normal Saline started an hour before surgery and continued throughout the surgery. The Dipeptiven® group (20 patients): 2 ml Dipeptiven®/kg were added to saline, while the control group (20 patients): nothing was added to saline. Blood samples were taken a preoperative sample and two postoperative samples (immediately after immergence from anesthesia and 24 h after surgery). These samples were analyzed for plasma glucose, plasma insulin to calculate insulin resistance by HOMA test. Plasma reduced glutathione level was also analyzed in the same time points.

Results: We found that insulin resistance and glucose level were less in the tested time points in the Dipeptiven® group of patients when compared with the control group. Furthermore, plasma glutathione level was higher in the Dipeptiven® group than the control group.

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Conclusion: Preoperative alanyl-glutamine is helpful in amelioration of insulin resistance and improvement of plasma glutathione levels in the early postoperative period.

1. Introduction

Achieving ideal perioperative glycemic control is a challenging task, and it is considered an important goal in all enhanced recovery after surgery programs (ERAS) [1]. Perioperative hyperglycemia has been identified by evidence base as a risk factor for perioperative morbidity and mortality [2]. Preoperative fasting [3], preoperative mechanical bowel preparation (MBP) [4], surgery and anesthesia start a series of stress responses [5]. Non-diabetic cancer patients often have disturbed glucose metabolism. It was shown that every fourth patient coming for colorectal surgery without known diabetes had an elevated HbA1c [6].

All those together result in loss of normal anabolic actions of insulin and the development of insulin resistance which is a state of decreased biological effect to any given concentration of insulin [7]. There will be also a state of catabolism with continuous breakdown of muscle tissue and loss of energy stores that prolongs the time to recovery [8].

Intensive Insulin Therapy (IIT) protocols and tight glycemic control still have no evidence to support its routine use in the operating room. Maintaining blood glucose less than 150 mg/dL and reducing its variability may be both safe and effective. However, still intraoperative insulin therapy research is lacking and focused mainly on the cardiac surgery population [2]. A closed-loop artificial endocrine pancreas system has also been tried in the perioperative period [9]. Insulin regulated diurnal rhythm of metabolism is also lost due to prolonged preoperative fasting. Patients present to surgery after overnight fast in a state of catabolism mainly by effect of glucagon and cortisol [3]. So, preventing the development of insulin resistance by putting the patient in a balanced metabolic state to be able to take care of glucose control with endogenous insulin release is an ideal solution [1]. This is clinically important since intravenous insulin with the entailing need for continual adjustments is usually difficult to manage on regular surgical wards.

Our primary end point is to prove that a single preoperative dose of alanyl-glutamine may decrease insulin resistance and hyperglycemia commonly encountered in the early postoperative period. Glutamine, traditionally considered as a nonessential amino acid under normal physiological conditions, has received considerable attention in becoming ''conditionally indispensable'' during catabolic states such as major surgery [10]. Glutamine is one of the immunonutritions or pharmaconutritions currently under investigation [11]. Recently, there has been a trend to consider glutamine as a drug and not as a nutrient [12]. Glutamine has been found to preserve insulin sensitivity in animal studies [10]. Moreover, glutamine (via glutamate), cysteine, and glycine are the precursor amino acids for glutathione [13]. So increased insulin resistance results in glucose influx into cells not accustomed to excess glucose like endothelial cells. The only metabolic pathway for glucose in such cells is glycolysis. Massive glucose inflow to the mitochondria will eventually overrun the oxidative capacity, and oxygen free radicals are produced [14]. So proving that GSH, as an important antioxidant, is preserved in the treated group is our secondary end point.

2. Patients and Methods

2.1. Patients

Patients scheduled for elective abdominal surgery for neoplastic conditions were enrolled in our study. Inclusion criteria were patients scheduled for open laparotomy, over 18 years and less than 65 years of age. Patients with known diabetes mellitus performing surgery for pancreatic neoplasm and patients on corticosteroids were excluded. Also, patients with severe renal insufficiency, severe hepatic insufficiency, severe metabolic acidosis, or known hypersensitivity to any of the used medications were excluded.

The study design was reviewed and approved by the institutional ethics committee. Written informed consents from patients were given before inclusion.

2.2. Study design

Forty patients were randomized in our study, where twenty patients were studied per protocol.

2.2.1. Preoperative Protocol

The nutritional status of all patients was evaluated by BMI. The day before scheduled operation, only oral fluids were allowed. Both mechanical and chemical bowel preparation have been done for all patients while in the surgical ward. All patients underwent at least a standard 8-h preoperative fast.

Patients were randomized to:

1. *Control group*: All patients in this group received an infusion of 500 ml normal saline. The infusions were started an hour before surgery and continued through surgery to be finished over 3 h.
2. *Glutamine group*: All patients in this group received an infusion of 2 mL of Dipeptiven/kg body weight (equivalent to 0.4 g N(2)-L-alanyl-L-glutamine/kg body weight). The total calculated dose of Dipeptiven was added to 500 ml Normal saline. The rate of infusion was adjusted to be finished within 3 h. The infusions were started an hour before surgery and continued through surgery.

At the day of surgery, the patients arrived to the preoperative holding area at 8:00 am. Two 14-gauge IV catheters were inserted in two upper extremity veins. One IV catheter was used for Dipeptiven® or saline infusion and the other for anesthetic drug administration. The patients received morphine (0.1 mg/kg) IV and Midazolam (2–3 mg IV) as premedication. In addition, all patients received a single dose of intravenous antibiotic.

2.2.2. Intraoperative and Postoperative Protocol

General anesthesia was induced with intravenous injection of propofol (2–2.5 mg/kg) and fentanyl (1–2 mcg/kg) and maintained with Sevoflurane. Atracurium (0.3–0.6 mg/kg) was used for muscle relaxation. Standard intraoperative monitors were used. As per protocol data for circulation, O_2 saturation, blood losses, blood transfusion, and time of surgery were closely monitored. Crystalloids (Ringer-Acetate) and colloids (Hydroxyethyl-starch, Voluven) were given as intraoperative fluid replacement. Blood loss during surgery was replaced with crystalloids, colloids, and/or blood products. All surgeries were performed by surgeons with considerable surgical experience.

After surgery, the patients were transferred to the PACU, and then, all patients were discharged to the surgical ward. After emergence from anesthesia, 1000–1500 mL of a 5% glucose solution was administered in all patients until the next morning. Postoperative NPO was maintained for varying duration according to the type and extent of the surgical procedure.

Postoperative analgesia was provided with IV morphine via PCA pump (loading bolus 40 μg/kg, PCA bolus 25 μg/kg; lockout 5 min, background infusion 15 μg/kg/h) and paracetamol (Perfalgan 500 mg t.d.s.).

2.3. Analysis

Blood samples were taken, after an overnight fast, in the preoperative setting. Two samples were also collected: the first was immediately after emergence from anesthesia and the second 24 h after surgery before any oral liquid meal was allowed. The following estimations were done:

2.3.1. Plasma glucose estimation

Blood was collected by venipuncture into tubes containing fluoride. Plasma samples were separated by centrifugation at 3000 rpm for 10 min. Plasma glucose was measured by the glucose oxidase method using a commercially available kit supplied by Diamond, Egypt [15].

2.3.2. Plasma insulin estimation

Blood was collected by venipuncture into tubes containing EDTA. Plasma samples were separated by centrifugation at 3000 rpm for 10 min. Plasma was stored at −20 °C until analysis. Plasma insulin was assayed by a commercially available Enzyme-linked immunosorbent assay (ELISA) kit supplied by DRG Diagnostics (GmbH, Germany) [16].

2.3.3. HOMA-IR was calculated as

Insulin (μU/mL by the ELISA technique) × blood glucose (mg/dL by enzymatic assay)/405 proposed by Matthews et al. [17].

2.3.4. Reduced glutathione estimation

Plasma glutathione was measured by the Glutathione Assay Kit supplied by Bio-diagnostic (Egypt, Giza) according to the manufacturer's recommendations [18].

Serum ALT, AST, albumin, Na+ and K+ levels were assessed using conventional available kit.

2.4. Statistical analysis

Data were computerized and analyzed using the Statistical Package for the Social Science (SPSS) Version 13. Normality of the distribution of data was assessed by the Kolmogorov–Smirnov test. Demographic and hematological data from the two groups were compared using two-tailed *t*-test and Chi-square test as appropriate. Inter- and intra-group differences among the variables were recorded over time and were analyzed by using two-way analysis of variance for repeated measures and paired and unpaired *t*-tests with Bonferroni post-test analysis as appropriate. To present the results, mean ± SD was used and a $P < 0.05$ was considered statistically significant.

3. Results

This was a prospective randomized controlled clinical study that was conducted in National Cancer Institute of Egypt (NCI) between May 2012 and December 2012. Among the 40 patients initially enrolled, only two cases in the control group were excluded from the study because of massive blood loss and post operative arrest and were replaced with another two patients. The forty patients completed the study and had an uneventful postoperative period.

Data were normally distributed. Demographic characteristics, ASA distribution, and liver function tests are summarized in Table 1. There were no statistically significant differences as regard age, sex, BMI, and liver function tests (ALT and AST).

There was an increase in the plasma glucose level in the immediate postoperative period and in the 24 h postoperative results in both groups (P value < 0.05) as compared with the preoperative values. But there was more increase in the plasma glucose level in the control group compared to the glutamine group (P value < 0.05). However, as regard the plasma insulin level, there was no significant difference in each group or between the two groups (Table 2).

There was an increase in insulin resistance as indicated by increased HOMA-IR test in both groups in the immediate and in the 24 h postoperative samples (P value < 0.05) as compared with the preoperative value. But there was a significant increase in HOMA-IR test values in the control group as compared to the glutamine group in both postoperative samples (P value < 0.05) (Table 2, Fig. 1).

There were no significant differences in preoperative plasma glutathione levels between the two groups. However, immedi-

Table 1 Demographics characteristics of the patients.

	Control group	Glutamine group	*P* value
Age (year)	52.7 ± 1.2	51.9 ± 1.8	0.106
Sex (M/F)	10/10	12/8	0.751
BMI (kg/m^2)	26.1 ± 3.1	27.3 ± 2.2	0.166
ASA (I/II)	8/12	7/13	1.000
AST U/L	18.5 ± 3.4	17.4 ± 3.3	0.306
ALT U/L	17.2 ± 2.2	16.6 ± 3.1	0.485

Data presented as mean ± SD.

Table 2 Plasma glucose and insulin levels in the two groups.

	Control group			Glutamine group		
	Preoperative	Immediately postoperative	24 h Postoperative	Preoperative	Immediately postoperative	24 h Postoperative
Glucose (mg/dL)	80.00 ± 4.99	95.10 ± 9.34*	108.95 ± 8.38*	81.80 ± 5.74	89.15 ± 7.27*,†	97.70 ± 6.51*,†
Insulin (IU/mL)	10.20 ± 0.72	10.19 ± 0.88	9.92 ± 0.43	9.93 ± 0.48	9.89 ± 0.37	9.90 ± 0.50
HOMA-IR	2.01 ± 0.18	2.40 ± 0.34*	2.67 ± 0.24*	2.00 ± 0.01	2.17 ± 0.16*,†	2.39 ± 0.18,†

Data presented as mean ± SD.
HOMA-IR, homeostasis model assessment – insulin resistance.
† P value < 0.05 is considered significant as regard to control group.
* P value < 0.05 is considered significant as regard to preoperative value within the same group.

ate postoperative and 24 h postoperative, plasma glutathione levels were significantly higher ($P = 0.047$ and 0.003, respectively) in the glutamine group compared to the control group. But there was no significance difference within each group (Table 3).

Serum albumin at induction of anesthesia was normal in the two groups and declined non significantly in the immediate postoperative period, but 24 h postoperatively the serum albumin declined significantly in control group ($P = 0.00$) (Table 3).

There was a slightly increasing trend of AST and ALT in both groups postoperatively but not statistically significant. There were no statistically significant changes in the plasma sodium and potassium levels in both groups at any tested time points postoperatively (Table 4).

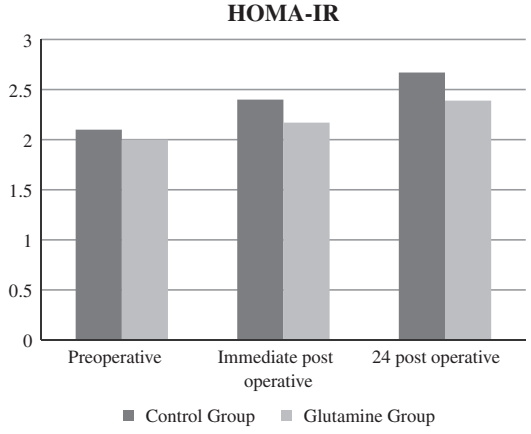

Figure 1 HOMA-IR in the two groups.

4. Discussion

We have tested the influence of preoperative IV alanyl-glutamine on insulin resistant state and hyperglycemia in the early postoperative patients. We found that in cancer patients presented for abdominal or pelvic surgery; insulin resistance and glucose level were less in two tested postoperative time points in the treated group. Furthermore, an important finding of our study was the preservation of glutathione serum level in the glutamine group of patients as compared to the control group.

We hypothesized that the preserved insulin sensitivity in glutamine group in our study might be due to interruption of the preoperative fasting state by glutamine in addition to the inherent effects of glutamine in this regards. Preoperative intake of a standardized nutrients through enteral or parenteral routes in order to break the overnight fasted catabolic state and set daytime anabolic metabolism before surgical stress has been tried [3,19]. The basal rate of insulin secretion is 0.4–0.7 U/h, increasing rapidly by 4- to 5-fold after ingestion of food [8]. Preoperative Carbohydrate Therapy (PCT) has been tried. PCT improved postoperative insulin sensitivity due to better preservation of the insulin signaling pathways for the major anabolic effects in muscle cells. A more recent explanation is preventing excessive incomplete mitochondrial β-oxidation, characterized by perturbed carnitine metabolism [20].

It is not known exactly how does glutamine act on insulin sensitivity, and it is currently under investigation. Glutamine has been found to preserve insulin sensitivity in animal studies. In canines, it has been shown that glutamine decreased insulin's action on glucose production and increased its effect on glucose utilization [21]. In rats, glutamine improved liver and peripheral insulin sensitivity. It was suggested that glutamine influences glucose and fat metabolism by reducing proinflammatory pathways through the observed decreased TNF-α production [22].

Table 3 Plasma glutathione and albumin levels in the two groups.

	Control group			Glutamine group		
	Preoperative	Immediately postoperative	24 h Postoperative	Preoperative	Immediately postoperative	24 h Postoperative
Glutathione (μmol/L)	6.44 ± 2.10	4.70 ± 1.50	4.80 ± 1.45	6.50 ± 1.80	5.64 ± 1.39†	6.30 ± 1.50†
Albumin (g/dL)	3.5 ± 0.10	3.4 ± 0.90	3.3 ± 0.05*	3.5 ± 0.08	3.5 ± 0.01	3.4 ± 0.90

Data presented as mean ± SD.
† P value < 0.05 is considered significant as regard to control group.
* P value < 0.05 is considered significant as regard to preoperative value within the same group.

Table 4 Other biochemical reading.

	Control group			Glutamine group		
	Preoperative	Immediately postoperative	24 h Postoperative	Preoperative	Immediately postoperative	24 h Postoperative
AST U/L	18.5 ± 3.4	18.6 ± 2.4	18.9 ± 3.5	17.4 ± 3.3	18.3 ± 3.1	18.5 ± 3.3
ALT U/L	17.2 ± 2.2	17.5 ± 2.3	17.6 ± 3.1	16.6 ± 3.1	16.9 ± 2.2	17.2 ± 2.5
Na mEq/L	130 ± 12	128 ± 11	129 ± 10	132 ± 12	130 ± 15	129 ± 12
K mEq/L	3.3 ± 0.2	3.3 ± 0.1	3.2 ± 0.2	3.4 ± 0.2	3.3 ± 0.3	3.3 ± 0.1

Data presented as mean ± SD.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; Na, sodium; K, potassium.
*P value < 0.05 is considered significant.

Adding to the risks of surgical stress and hyperglycemia is the oxidative stress which contributes to tissue injury. During surgical stress, plasma glutathione levels normally decrease [23]. Our current study proved that glutathione levels were higher in the glutamine treated group than control. Glutathione is normally present within the cell in a reduced (GSH) and an oxidized form (GSSG). The ratio of GSH:GSSG is the most important regulator of the cellular redox potential [13]. It is also a potent anti-oxidant as well. The redox potential influences the cellular capability to scavenge free radicals derived from oxygen and also influences several intracellular mechanisms [23].

Only few studies used pharmaconutrition concept or glutamine in this context. Bakalar and colleagues examined the influence of parenteral nutrition enriched with alanyl-glutamine in a dosage of 0.4 g/kg/day on insulin resistance in multiple-trauma patients. They showed that insulin resistance worsens with standard nutritional formula during the first week of critical illness, but glutamine supplementation was able to prevent this worsening [24]. Hissa et al. tried to identify the effects of alanyl-glutamine infusion during the operative period, upon blood lactate and glucose concentrations in cardiac surgery patients. They observed a significant decrease in glucose level during the intraoperative period in alanyl-glutamine treated patients compared with saline-treated patients. They proposed this difference to be due to the ability of glutamine to reduce insulin resistance without actually measuring insulin resistance [25]. Similarly, Cunha Filho and colleagues used alanyl-glutamine infusion in children submitted to elective cleft lip and palate repair. They compared the following variables at five different time points: glutathione, thiobarbituric acid reactive substances, glucose, insulin, C-reactive protein, and interleukin-6. They observed a better glycemic control in alanyl-glutamine group as compared with the control group [26]. In a recent study, Dock-Nascimento et al. found that a shortened preoperative fast with glutamine plus a carbohydrate based beverage improved insulin resistance and antioxidant defenses and decreases the inflammatory response after video-cholecystectomy [27].

We concluded that preoperative IV alanyl-glutamine is helpful in amelioration of insulin resistance and improvement of plasma glutathione levels in the early postoperative period. Our results support the use of alanyl-glutamine as a preoperative metabolic preconditioning medication. Further larger researches with different concentrations of glutamine are needed to elucidate and confirm our findings. More frequent intraoperative and postoperative measurements may be more informative. Also, late measurement of glycosylated hemoglobin may provide us with valuable results.

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