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Original Article

GLUCOSE, C-PEPTIDE AND CORTISOL RESPONSE TO SURGERY UNDER GENERAL ANESTHESIA IN DIABETIC SUBJECTS WITH TREATMENT VARIABILITY

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ABSTRACT

Diabetic patients are considered to be at increased risk of perioperative morbidity and mortality because of the involvement of their vital organs and the autonomic nervous system in the natural course of the disease. Various aspects of anesthesia and surgery cause stress induced hemodynamic, endocrine and metabolic changes in type 2 diabetic subjects. The present study was designed to investigate the surgical stress response difference between the patients groups those who are treated with only insulin and with insulin-oral hypoglycaemic drugs combination before surgery. Stress response was measured with the changes of blood glucose, C-peptide and cortisol.

A total number of 30 subjects who were admitted in BIRDEM hospital in fit physical condition (ASA Class I & II) were selected for the present study. Among them 15 patients were treated with only insulin and 15 patients were treated with insulin-OHA combination before surgery. All of the subjects were received total abdominal hysterectomy under general anesthesia. Three samples were collected from each subject. The first sample (control, PT_0) was collected just before anesthesia; second sample (PT_1) collected 10 minutes after incision and third sample (PT_2) collected 10 minutes after extubation. Plasma glucose was measured by glucose oxidase method, serum C-peptide and cortisol by chemiluminescent based ELISA technique.

The mean±SD age and BMI were 44±6 years and 24.4±3.0 kg/m^2 respectively. In insulin treated group, the plasma glucose level was significantly higher in PT_2 and it was about 147% whereas in insulin-OHA group, the plasma glucose level was significantly higher in both PT_1 (111%) and PT_2 (196%). The serum C-peptide values were decreasing tendency but not significant in both groups. The serum cortisol level was increased gradually and significantly higher in PT_2 in both groups.

The data suggest that a) insulin treatment alone is more effective than insulin-OHA combination to control blood glucose in type 2 diabetic subjects undergoing surgery under general anesthesia, b) lower abdominal surgery under general anesthesia in well controlled type 2 diabetic subjects is accompanied by a hyperglycemic response which results from rise of insulin antagonists like cortisol rather than fall of insulin secretion, but the two treatment modalities lead to similar cortisol response.

Key words: General anesthesia, Serum glucose, cortisol, Total abdominal hysterectomy

INTRODUCTION

Diabetes mellitus is one of the major chronic diseases affecting mankind all over the world and it has been declared as an epidemic in developing countries by both the World Health Organization and International Diabetes Federation. Epidemiological evidences suggest that fifty percent of all diabetic patients present for surgery during their life time[1]. Inevitably, diabetic patients presenting for incidental surgery, or surgery related to their disease, will place an increasing burden on anesthetic services. Perioperative morbidity and mortality are greater in diabetic than in nondiabetic patients[1]. This is due to the pathophysiology that is more and more complicated in diabetic than in nondiabetic subjects. Stress response to surgery and anesthesia, counter regulatory hormones, preoperative fasting states, dehydration and insulin deficiency complicate the

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situation. These lead to abnormal metabolism of carbohydrate, protein and fat as well as electrolyte imbalance. In response to stress during surgery and anesthesia- the biochemical parameters like stress hormone (cortisol, epinephrine, glucagon and growth hormone), plasma glucose, ketone bodies, blood urea nitrogen, lactate, free alanine, pyruvate, C-peptide and electrolytes being altered[2,3,4]. The stress response leads to secretion of many anabolic and catabolic hormones and if the stress response is prolonged, the continuous hypermetabolic state may result in exhaustion of essential components of the body e.g. glucose, fat, protein and minerals causing increased morbidity and mortality[5]. The stress response leads to secretion of many anabolic and catabolic hormones and if the stress response is prolonged, the continuous hypermetabolic state may result in exhaustion of essential components of the body e.g. glucose, fat, protein, minerals, causing loss of weight, fatigue, decreased resistance, delayed ambulation and increased morbidity and mortality[6]. The plasma concentration of insulin during stress has been noted to be biphasic, characterized by the suppression of insulin secretion followed by a normal secretion, which has been termed as the phase of physiologic insulin resistance. Insulin is short lived in comparison to C-peptide. It can be measured indirectly from C-peptide because, during the course of insulin synthesis, C-peptide is cleaved from proinsulin, stored in secretory granules, and eventually released into the bloodstream in amounts equimolar with those of insulin[7].

Diabetic patients are usually treated with three methods: diet control alone, diet control with oral hypoglycaemic agents and diet control with insulin[8]. According to recent guideline for management of diabetes, diabetologists of BIRDEM prescribe insulin and OHA combination for some patients.

The present study was designed to investigate the stress response difference between the patients groups those who are treated with only insulin and with insulin-oral hypoglycaemic drugs combination before surgery. Stress response was measured with the changes of blood glucose, C-peptide and cortisol.

SUBJECTS AND METHODS

Thirty subjects who were admitted in BIRDEM hospital in fit physical condition (ASA Class I & II) and received total abdominal hysterectomy under general anesthesia were studied. Among them 15 patients were treated with only insulin and 15 patients were treated with insulin-OHA combination before surgery. First blood sample of each subject were served as a control. Patients taking steroid or analgesics drugs, and obese or malnourish subjects were not included in the study.

DESIGN OF GENERAL ANESTHESIA

Thiopental, halothane, fentanyl, vecuronium, nitrous oxide with oxygen.

PREPARATION OF THE SUBJECTS

Patients were recruited 1 week before surgery while undergoing preoperative evaluation and testing in the hospital. First of all the purpose of the study was explained in details to each subjects. The evaluation consisted of nursing and anesthesia functional health evaluation, provision of information regarding the surgery and obtaining appropriate laboratory testing. After recruitment into the study, informed written consent and demographic data were obtained. Weight and height of individual were recorded accordingly. All the patients took 7.5 mg medazolam at bed time the night before surgery. Patients were fasted for 6-8 hours prior to surgery and morning dose of antidiabetic therapy was omitted.

CONDUCTION OF ANESTHESIA

On arrival at preoperative room an 18G vasofix intravenous cannula was inserted into right anticubital vein for obtaining blood sample and another one was inserted into the left cephalic vein near to wrist for administration of fluid and other medications. The patients were next brought to the operating room where they underwent anesthesia and surgery. The anesthetic protocol was strictly maintained in all patients and consisted of an intravenous induction using thiopental sodium 5 mg/kg body weight, vecuronium 0.1 mg/kg body weight and fentanyl 1.5 μg/kg body weight. Once intubated with an endotracheal tube, anesthesia was maintained with inhaled O_2/N_2O (1:2) and appropriate dialing of halothane. Anesthesia is maintained with halothane as required to ensure adequate depth of anesthesia assessed by pulse, BP, tearing and sweating. Vecuronium 0.02 mg/kg body weight every 20 minutes and fentanyl 0.5 μg/kg body weight every

30 minutes is continued until 20 minutes before the anticipated end of surgery. Pulse, BP, SpO_2, continuous ECG, temperature, sweating and tearing is monitored every 5 minutely and recorded with corresponding sample. Temperature was maintained within normal limit. The patients were received ringer's lactate solution with appropriate volume as per 4-2-1 rule. After operation the patients were extubated with intravenous Neostigmine 0.05 mg/kg body weight and Atropine 0.02 mg/kg body weight. The time of introduction of anesthesia, incision, end of surgery and extubation was recorded properly.

SAMPLE COLLECTION

Three samples (8-10 ml) were collected through right handed cannula with all precautions. The first blood sample was drawn just before anesthesia, 2nd sample 10 minutes after incision and 3rd sample 10 minutes after extubation. Two ml of blood from each sample was kept in a test tube containing sodium fluoride and potassium oxalate in 1:3 ratios to prevent glycolysis and coagulation and remaining blood was taken in a plain test tube. Both of them were immediately placed into iced water and brought to Research division, BIRDEM. The samples were centrifuged at 3000 rpm for 15 minutes immediately and serum was stored at -40^0C until further analysis.

ANALYTICAL METHOD

Plasma glucose was measured by glucose-oxidase method (Randox, UK). Serum creatinine, urea, SGPT, uric acid was measured by colorimetric method. Total Cholesterol and TG was measured by enzymatic method. Serum electrolytes were measured by Dry Chemistry method (DT-60, USA). Serum C-peptide was measured by chemiluminescence based EIA method (Immulite, USA).

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS (Statistical Package for Social Science) software for Windows version 10 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

All subjects were fit for general anesthesia in preoperative anesthetic assessment and values were within normal limit. The mean±SD age and BMI were 44±6 years and 24.4±3.0 kg/m^2 respectively, systolic and diastolic blood pressure were 140±15 mmHg and 85±10 mmHg respectively; pulse was 84±14 per minute and duration of surgery was 81±15 minutes (Table 1). The median (range), triglyceride and cholesterol were 131 (55-302) mg/dl and 190 (105-293) mg/dl respectively. The mean±SD, serum creatinine, SGPT, serum urea and uric acid were 1.0±0.12 mg/dl, 13.85±7.27 U/l, 20.42±6.50 mg/dl and 3.23±1.21mg/dl respectively. All the values within normal limit (Table 1).

Table-I

Clinical and biochemical characteristics of the study subjects (n=30)

Age (yrs)	44±6
BMI (kg/m^2)	24.4±3.0
Systolic BP (mmHg)	140±15
Diastolic BP (mmHg)	85±10
Pulse (per minute)	84±14
Duration of surgery (minutes)	81±15
TG (mg/dl)	131 (55-302)
Cholesterol (mg/dl)	190 (105-293)
Creatinine (mg/dl)	1.0±0.12
SGPT (U/l)	14±7
Urea (mg/dl)	20.4±6.5
Uric acid (mg/dl)	3.23±1.21

The mean±SD values of plasma glucose in PT_0, PT_1 and PT_2 were 6.38±2.62, 6.33±2.26 and 8.81±2.15 mmol/l and the serum C-peptide values were 1.73±0.90, 1.82±0.98 and 1.65±1.12 ng/ml respectively for insulin group. The plasma glucose level was significantly higher in PT_2 comparison to PT_0 (PT_0 vs PT_2, p=0.003)and PT_1 (PT_1 vs PT_2, p=0.003) whereas serum C-peptide values were almost similar in all samples (Table 2). The mean±SD values of plasma glucose in PT_0, PT_1 and PT_2 were 5.98±1.74, 6.66±1.78 and 11.16±2.70 mmol/l and the serum C-peptide values were 2.19±0.80, 1.92±0.85 and 1.85±0.75 ng/ml respectively for insulin-OHA combined group. The plasma glucose level was significantly higher in PT_1 (111%) than PT_0 it was also higher in PT_2 (196%) over PT_0 and PT_1 (PT_1 vs PT_2, p=0.0001) whereas serum C-peptide values were decreasing tendency but not significant (Table-II).

Table-II

Perioperative glycemic and insulinemic status of insulin and insulin-OHA treated subjects

Treatment group	Glucose (mmol/l)			C-Peptide(ng/ml)		
	PT_o	PT_1	PT_2	PT_o	PT_1	PT_2
Insulin	6.38±2.62^a	6.33±2.26^a	8.81±2.15^b	1.73±0.90	1.82±0.98	1.65±1.12
(n=15)	(100%)	(99%)	(147%)			
Insulin-OHA	5.98±1.74^a	6.66±1.78^b	11.16±2.70^c	2.19±0.80	1.92±0.85	1.85±0.75
(n=15)	(100%)	(111%)	(196%)			

Results are expressed as M±SD. PT_0= Preoperative (before anesthesia), PT_1= Peroperative (10 minutes after incision), PT_2= Postoperative (10 minutes after extubation). Values in rows with different superscripts are significantly different each other when using student paired 't' test.

Table-III

Perioperative serum cortisol status of insulin and insulin-OHA treated subjects

Treatment group	Cortisol (ng/ml)		
	PT_o	PT_1	PT_2
Insulin (n=15)	11.28±6.0$^{a100\%}$	12.77±7.17$^{a113.21\%}$	31.48±11.27$^{b279.08\%}$
Insulin-OHA (n=15)	11.91±3.30$^{a100\%}$	14.58±5.19$^{a122.42\%}$	34.84±5.87$^{b292.53\%}$

Results are expressed as M±SD. PT_0= Preoperative (before anesthesia), PT_1= Peroperative (10 minutes after incision), PT_2= Postoperative (10 minutes after extubation). Values in rows with different superscripts are significantly different each other when using student paired 't' test.

The mean±SD values of serum cortisol in PT_0, PT_1 and PT_2 were 11.28±6.00, 12.77±7.17 and 31.48±11.27 ng/ml respectively for insulin group. The serum cortisol level was increased gradually and significantly higher in PT_2 (Table 3). The mean±SD values of serum cortisol in PT_0, PT_1 and PT_2 were 11.91±3.30, 14.58±5.19 and 34.84±5.87 ng/ml respectively for combined group. The serum cortisol level was increased gradually and significantly higher in PT_2 (PT_0 vs PT_2, p=0.0001; PT_1 vs PT_2, p=0.0001) (Table 3).

DISCUSSION

Seshiah (2006) showed that surgery causes a considerable metabolic stress in the non-diabetic and more so in a diabetic subject[9]. The stress response to surgery is mediated by neuroendocrine system essentially by stimulating the adreno-medullary axis. The neuroendocrine system comes into play to maintain fuel requirements by glycogenolysis and gluconeogenesis through stress hormones like catecholamines, glucagon, cortisol and growth hormone. In a non-diabetic there is enough insulin secretion to utilize the fuel produced by the stress hormones and thus glucose homeostasis is maintained. This compensatory role of insulin is less possible in type 2 diabetic subjects.

Rothenberg and Loh-Trivedi (2006) documented that surgery elicits a stress response that is directly proportional to the degree of tissue trauma[10]. A recent study (Adams, 2000) suggests that the principal mechanism lies with the elevation of sympathetic tone with a consequent release of cortisol and catecholamines during surgery[11]. These hormones, in turn, lead to relative insulin hyposecretion, insulin resistance, and increased protein catabolism. Anesthesia also principally affects glucose metabolism through the modulation of sympathetic tone; however, *in vitro* evidence exists that insulin secretion is suppressed by inhalational agents with consequent increase in serum glucose level.

The perioperative stress response between insulin and combined insulin-OHA treated groups of type 2 diabetic patients are not well studied. The subjects those who are treated with insulin, only the PT_2 (147%) value of plasma glucose is significantly high. But those who are treated with insulin with OHA combination shows both PT_1 (111%) and PT_2 (196%) values are significantly high (Table 2). It indicates that the type 2 diabetic subjects those who are treated with only insulin show better glycemic control when they undergo surgery under general anesthesia.

The C-peptide concentration in insulin treated group is slightly increased in PT_1, then it decreases in PT_2; but the change is not significant. In combined insulin-OHA group, C-peptide values decrease gradually in PT_1 and PT_2, but the difference is not statistically significant. Demirbilek *et al*. (2004) demonstrated a similar effect of remifentanil and alfentanil based intravenous anesthesia on endocrine response during total abdominal hysterectomy[12]. Sing (2003) reported that the plasma concentration of insulin during stress is biphasic, characterized by suppression of insulin secretion followed by a normal secretion, which has been termed as the phase of physiologic insulin resistance[13].

Carli (1993) reported that total abdominal hysterectomy with halothane or isoflurane anesthesia leads to two fold reduction in serum cortisol level[14]. But with the onset of surgery, serum cortisol concentration increased rapidly. Mizutani *et al*. (1996) showed that cortisol concentration during medazolam/fentanyl/oxygen/air anesthesia combined with epidural anesthesia in patients undergoing total abdominal hysterectomy and also compared with another group of patients sevoflurane/nitrous oxide/oxygen anesthesia combined with epidural anesthesia[15]. Castillo *et al*. (1997) reported that serum cortisol and other hormonal levels are significantly higher during intravenous anesthesia than during balanced anesthesia[16].

The present study shows serum cortisol level that is significantly higher in PT_2 in both groups. These were in good agreement with published data. When the patients are treated with only insulin cortisol, level raised by 279% after operation. But when they are treated with insulin with OHA, cortisol raised by 293%. It indicates that only insulin treated group gives better result regarding cortisol but it is not studied well.

CONCLUSIONS

a) Insulin treatment alone is more effective than insulin-OHA combination to control blood glucose in type 2 diabetic subjects undergoing surgery under general anesthesia

b) Surgery under general anesthesia in well controlled type 2 diabetic subjects is accompanied by a hyperglycemic response which results from rise of insulin antagonists like cortisol rather than fall of insulin secretion.

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