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A Prospective Randomised Control Study to Compare Hyperglycemic Stress Response to General Anaesthesia in Non Diabetics and Controlled Diabetics Posted for Elective Surgical Procedures

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Abstract

Diabetic patients presenting for elective surgical procedures will place an increasing burden on anaesthetic services. The effects of surgical stress and anesthesia result in a a hypermetabolic stress response, referred to as "stress hyperglycemia". The aim of the study is to compare stress response to general anaesthesia by measuring the rise in blood glucose levels in controlled diabetics posted for elective surgical procedures in comparision with non-diabetic patients .Study was conducted in Department of Anaesthesiology, Osmania Medical College/Hospital, Hyderabad during 2010-2012 in Fifty ASA Grade I & Grade II patients. Institutional Ethics Committee has approved the study, written and informe consent was obtained from the patients. The study population were in the age group of 35-55 years, of either sex divided into two groups scheduled for elective surgical procedures of 2 hours of duration *(viz., laporatomy, thyroidectomy)*. A Opiod (Fentanyl) and Propofol based balanced general anaesthesia technique adequately attenuates Hyperglycemic Stress Response in Controlled Diabetics.

Keywords: Stress Response; Chronic Hyperglycemia; General Anaesthesia; Opioids; Cortisol; Hypothalamo-Pituatory Adrenal Axis (HPAA Axis); Diabetes Mellitus.

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Introduction

Diabetes Mellitus is a group of multisystem metabolic disease known to mankind since ancient times, first reported in Egyptian manuscript [1] with increased incidence in surgical patients in recent years [1]. It is characterized by presence of chronic hyperglycemia due to impaired insulin secretion or decreased tissue response leading to impaired *metabolism* of carbohydrates, lipids and proteins. The chronic hyperglycemia results in long term multiorgan dysfunction especially eyes, kidneys heart and blood vessels .The distinction between type 1 and type 2 DM was made in 1936 [3] and Type 2 DM was first described as a component of metabolic syndrome (1988) [4]. Incidence of diabetes in surgical patients is about 2% to 4%[5].

Under anaesthesia Stress Hyperglycemia in diabetics could lead to increased incidence of acute diabetic complications resulting in postoperative morbidity and mortality [6,7]. Therefore, discussing the effects of general anaesthesia in diabetic patients posted for elective surgeries were necessary.

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Diabetus Mellitus

Diabetes is a group of metabolic diseases mellitus is a state of relative or absolute insulin deficiency. American Diabetes Association (ADA) and World Health Organization (WHO) published new recommendations for diagnosis of diabetes mellitus [8, 9 ,10] and advise a reduction in the threshold limit for fasting plasma glucose concentrations. ADA recommendations focus on Fasting Plasma Glucose (FPG) and WHO focuses on Oral Glucose Tolerance Test (OGTT) for diagnosis.

Classification of Diabetes Mellitus

WHO and ADA recommend a more aetiologically based nomenclature for Classification of Diabetes Mellitus [8] and this system identifies four types. Type I (pancreatic B cell destruction) , Type II (defective insulin secretion/insulin resistance), "other specific types" and gestational diabetes [9,10]. Diabetes may be diagnosed based on the plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-goral glucose tolerance test (OGTT) or the A1C criteria [11,12,13].

Criteria for the Diagnosis of Diabetes [14]

FPG ≥ 126 mg/dL (7.0mmol/L). Fasting is defined as no calorie intake for at least 8hrs*

Or

2-hrs PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, glucose load equivalent of 75 g anhydrous glucose dissolved in water.*

Or

HbA1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

Or

Classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Diagnostic Tests for Diabetes

The diagnostic test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial reference assay. HbA1C is a stable glycosylated form of haemoglobin represents the average glucose level over time can be used an index of glycemic control . 5.7% is normal, >6.5 diabetes. The HbA1c test is currently considered the best measure of overall blood glucose control and of the risk of developing diabetic complications in the future. The test measures the percentage of hemoglobin molecules in the blood that have glucose attached to them. *Estimated Average Glucose (eAG)* – From HbA1c value average plasma glucose level over previous 3 months may be calculated approximately using *the ADAG linear regression formula*, eAG: 28.7 x HbA1c − 46.7 = eAG (in mg/dl). Stress response to anaesthesia and surgery is a physiological response characterized by hormonal and metabolic changes . The components of stress response are :

1. Endocrine response with pituitary hormone secretion and insulin resistance,
2. Sympathetic nervous system activation and
3. Immunologic and Hematologic changes.

The net metabolic effect of stress response (Neuro- Endocrinal outflow) is increased blood glucose levels. Diabetics have higher morbidity and mortality as surgical patients. Hyperglycemia during surgery presents unique challenges and produces deleterious effects on immune system and on the response to endotoxin. An understanding of physiological changes of stress response and its effects along with knowledge of precipitating factors and applying modulatory therapeutic methods in time allows even major procedures to be performed safely in Diabetic patients [15–17] . The development of these adverse effects is likely related to the numerous adverse cellular and biochemical events that occur as a result of hyperglycemia [18, 19]. Blood coagulation is activated by hyperglycemia, as circulating prothrombin fragments and D-dimers are increased, and platelet aggregation and thrombosis occur [20]. Inflammation and activation of proinflammatory cytokines is also induced by hyperglycemia. Hyperglycemia also abolishes intrinsic myocardial protective mechanisms, such as ischemic preconditioning [21].

Thus, hyperglycemia interacts at cellular and biochemical level in numerous ways, which may be responsible for the adverse effects associated with hyperglycemia.

This study analyses and compares hyperglycemic response during anaesthesia and surgical stress environment in a well controlled diabetes and non diabetic patients scheduled for elective surgeries.

Materials and Methods

The present study was conducted in Department of Anaesthesiology, Osmania Medical College/ Hospital during 2009-2012, to evaluate and compare the stress response to general anaesthesia and surgery in controlled diabetics and non diabetics posted for elective surgeries under General anaesthesia. A Fifty ASA Grade I & Grade II patients belonging to either sex in the age group 35-55yrs age group were selected randomly for the study. Patients were scheduled for elective surgical procedures of 1-2 hours of duration *(viz., laporatomy, thyroidectomy,*) and were divided into two groups Group D (Controlled Diabetics) and Group N (Non Diabetics) of 25 patients each. The rise in blood glucose was taken as a measure of stress response to surgery and anaesthesia in both the study groups for the following reasons (i) Simple test (ii) Cost effective (iii) Reliable (iv) Easy to perform and (v) Results are obtained with in the shortest possible time (5–10 seconds).

All surgeries were performed under general anaesthesia and intraoperatively blood glucose levels were estimated from finger prick capillary blood samples with glucometer. The study had approval from Institutional ethical committee and written, informed consent of all patients. Pre-operative assessment was done a day before and other systemic diseases were excluded. Standard NPO guidelines were advised, in diabetics insulin and oral anti diabetic drugs were precluded from night before operation. On day of surgery patients were wheeled into operating room and preoperative blood sugar levels were measured by Glucometer and noted, an i.v. access was secured and 0.9% normal saline infusion started @ 100 ml/hr as a part of no glucose protocol. A standard general anaesthesia technique (opioid+propofol + muscle relaxant) technique was adopted in both study groups– Premedication: Glycopyrrolate-0.2mg, Ondansetron-4mg, Fentanyl 2mcg/kg i.v. Induction & intubation: Propofol 2mg/kg+ Vecuronum 4mg, Maintenance: O_2: N_2O 2:2 lit/min, Vecuronium, Isoflurane 1% conc., Closed circuit with CO_2 absorber, Controlled Ventilation (Datex Ohmeda Aestiva anaesthesia workstation). At end of surgery neuromuscular block was reversed with neostigmine 0.05mg/kg and glycopyrrolate 10μg/kg and trachea extubated after pharyngeal suction. Intraoperatively vital signs were monitored with Philips Multichannel monitor and following parameters were recorded ECG, NIBP, SpO_2 & HR, rise in Blood Glucose levels was measured using glucometer utilizing glucose oxidase - reagent strip test method. Estimation was done at specified intervals intraoperatively as follows:

- Pre operatively fasting blood sugar
- 5 mins after intubation
- 30 mins after intubation
- Post operatively 5 min after extubation

Inclusion Criteria

1. ASA Gr I & Gr II
2. Age 35-55yrs
3. HbA1c level 5-7%
4. Elective surgeries of < 2hrs

Exclusion Criteria

1. ASA Gr.III & Gr IV
2. Blood Glucose ≤ 60mg%
3. HbA1c ≥ 7%
4. Uncontrolled Diabetes
5. Surgeries > 2hrs duration

Observations and Results

In the present study, Blood sugar levels were measured in both study groups at predetermined time intervals as mentioned and results were compared and analysed statistically Demographic data showing Age, Weight, Sex in both study groups were comparable without any statistical significance (p >0.05). Pre-operative Blood Sugar levels in both study groups: Group N - 88.16 (±9.55), Group D- 89.44(±16.83) were comparable and statistically insignificant (p value – 0.077). The trends of blood sugar levels at various time intervals in comparable between study groups at 5mins:: Group N 86.92(±10.77), Group D 89.96(±6.4); 30mins:: Group N 103.44(±14.09) Group D 108.44(±9.01) , and at 5mins after extubation Group N 117.60(±16.61) Group D 124.76 (±11.65, p values - 5min (after intubation): 0.23, 30min(after intubation) : 0.14 , 5min (after extubation): 0.08— statistically insignificant, percentage rise in blood sugar levels in both study groups at various time intervals were compared and analysed , intubation response showed a decrease of 1.064% in non diabetics.and a 0.63% increase in controlled diabetics. At the end of 30 mins and 5mins after extubation, blood sugar levels in Controlled diabetics showed a 3.57% increasewhen compared with non-diabetics at both time intervals. Blood

Table 1: Demographic data of study population

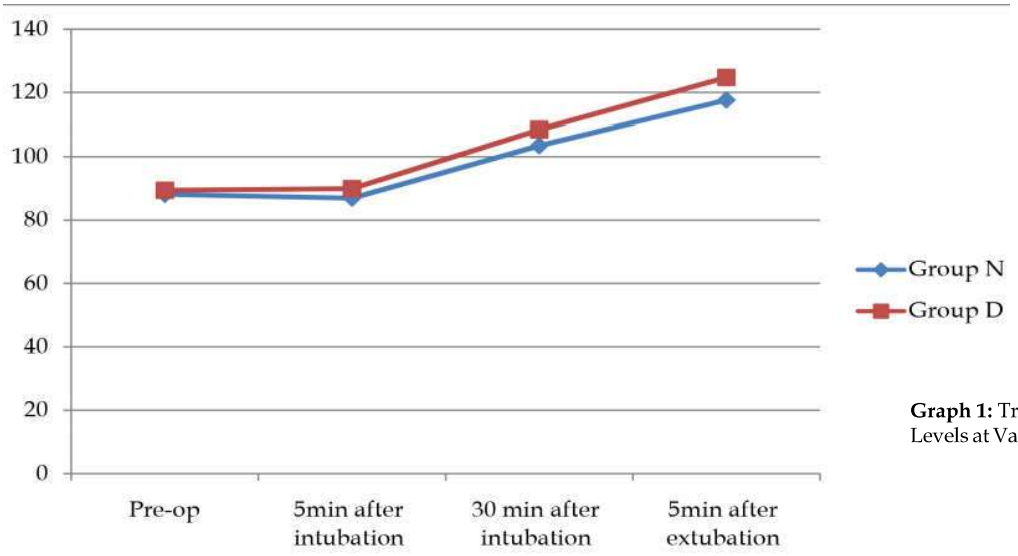
	Demographic Data Group N	Group D	'P' value
Age in yrs (Mean) (S. D.)	42.96 yrs (5.70)	45.48yrs (4.64)	(0.092)
Wt in kgs (Mean) (S. D.)	49.36 (4.16)	52.44yrs (7.97)	(0.093)
M : F Ratio	10: 15	13.12	

Table 2: Trends of Blood Sugar Levels at Various Time Intervals

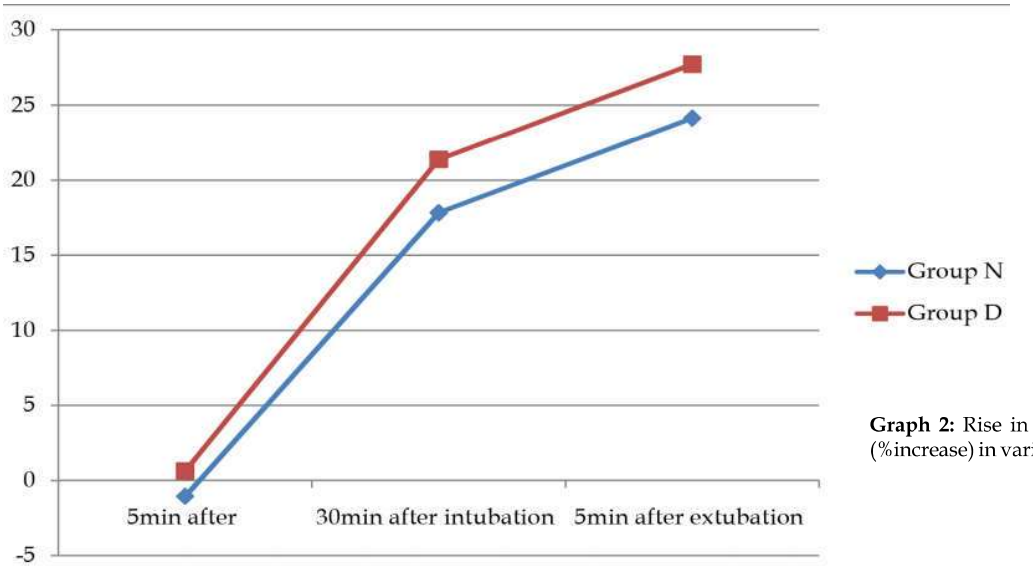
Group	Pre-Operative	5min after Intubation	30min after Intubation	5min after Extubation
Group N	88.16(9.56)	86.92(10.77)	103.44(14.09)	117.6(16.61)
Group D	89.44(16.83)	89.96(6.4)	108.44(9.01)	124.76(11.65)

Table 3: Rise in Blood Sugar levels (% increase) at various intervals

Group	5min after Intubation	30min after Intubation	5min after Extubation
Group N	-1.06% (10.16)	17.82% (14.16)	24.15% (9.5)
Group C	0.63% (7.3)	21.39% (11.01)	27.72% (11.65)



Graph 1: Trends of Blood Sugars Levels at Various Time Intervals



Graph 2: Rise in Blood sugar levels (%increase) in various time intervals

glucose values in both study groups during study were in the range of 63-151 mg%, the minimum and maximum mean blood glucose values were 88-125mg/dl, both values are in the physiological range. The average mean value of HbA1c in diabetic group was 6.24±0.64.

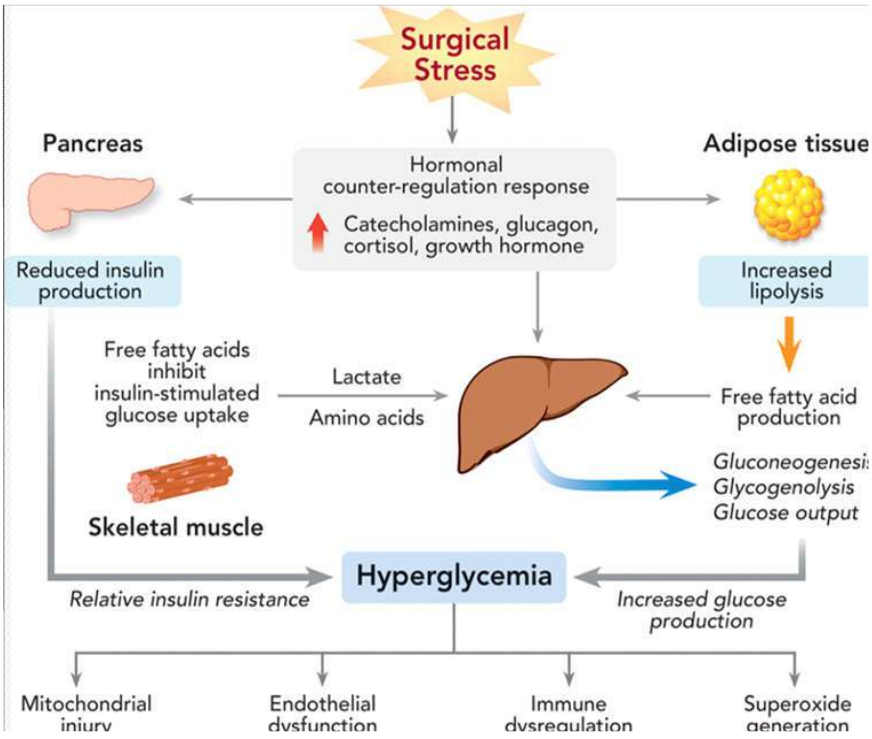
Discussion

Surgeries are considered a combination of multiple factors including tissue damage, fasting, blood-loss, effects of medication and temperature changes giving rise to stress response [22]. HPAA activation initiates the sympatho-adrenal stress response to surgery & anaesthesia [23,24]. Leading to increased pituatory hormone secretion, in specific, increase in Cortisol and Catecholamines [25,26]. Stress response is a state of relative insulin deficiency–reduced insulin secretion and increased insulin resistance [27] Increased cortisol and catecholamines reduce insulin sensitivity , GH has an anti-insulin effect [28,29]. Net effect of stress response is increased secretion of catabolic hormones lead to– neoglucogenesis & hyperglycemia. Thus stress response may be quantified by hyperglycemia. The metabolic changes are proportional to severity of surgical trauma and major intraabdominal operations produce significant changes in cortisol and blood glucose levels [30]. Hyperglycemic response to surgery and anaesthesia is in relation to duration and extent of stress (Clark RJ 10968, 1970). Hyperglycemia in the perioperative period can cause dehydration, fluid shifts, electrolyte abnormalities, a predisposition to infection, impaired wound healing, as well as ketoacidosis and hyperosmolar states [1]. Blood levels of ACTH, cortisol, epinephrine, norepinephrine and PRL has been used for evaluating stress [31]. Hormonal and Metabolic changes result in marked glucose intolerance and high incidence of stress hyperglycemia (Allison,Tomlin, Chamberlain 1968, Clareal,1970) and ketosis [32].

Metabolic responses to surgery and anaesthesia

Hormonal	Metabolic
Secretion of stress hormones	Increased
Cortisol	gluconeogenesis and
Catecholamines	glycogenolysis
Glucagon	Hyoerglycemia
Growth Hormone	Lipolysis
Cytokines	Protein breakdown
Relative decrease in insulin secretion	
Peripheral insulin resistance	

In diabetics changes described above result in increased insulin demand and risk of postoperative hyperglycemia which has a significant impact on occurrence of postoperative complications. [33,34,35, 36,37,38,39], Anesthetic drugs, have a variable effect on glycemic control , large doses of sedatives and hypnotics cause an abnormal blood sugar response (1954 hunter and Greenberg). pre-medicants act on neural mechanism controlling ACTH secretion and increase or inhibit the secretion.



Dexmedetomidine reduces serum cortisol levels which was not different statistically [40]. Most of drugs used, including neuroleptic drugs, opioids, thiopentone, propofol and sevoflurane have been found to stimulate PRL release during anesthesia [41,42,43]. Morphine and other opioids (fentanyl, sufentanil and alfentanil)

abolished ACTH and cortisol secretion at clinically used doses.[41]. Intravenous induction agent etomidate decrease steroidogenesis mediated by reversible blockade of 11-beta-hydroxylase activity and suppress adrenocortical function [44]. The literature reports a standard induction dose of etomidate can cause acute adrenocortical insufficiency and crisis [45] and subsequent decrease in hyperglycemic response to surgery [46]. Benzodiazepines in high doses (midazolam 0.2-0.4 mg 30 kg^{-1} and infusion of 0.9-0.125 mg kg^{-1} h^{-1}) inhibit steroid production at Hypothalamo pituatory level and decrease ACTH secretion and stimulate GH release [47], Effects of propofol on the synpathoadrenal system are well documented [48,49]. Propofol significantly suppresses circulating cortisol and abolished the cortisol response to surgery (Tetsuchiro sakai, David O' Flaaharty et al. (1995). Opiates influence centrally mediated neuro endocrine responses - modulate nociception at different levels of neuraxis and block sympathetic nervous system activity and HPAA [50]. Volatile anesthetic agents (in vitro)inhibit insulin production triggered by glucose, result in a hyperglycemic response [51,52], sevoflurane significantly decreased plasma concentrations of ACTH, cortisol and GH when compared to isoflurane [48]. Fentanyl abolishes the hyperglycemic stress response and reduce cortisol and GH responses better than halothane. The response to neuromuscular blocking agents is normal in diabetic patients and choice of depends on renal function and anesthetics selection is according to severity of various systemic diseases (such as DM , HTN & CAD). Further studies must be completed in order to understand the full clinical effects of this response in diabetic patients undergoing surgery. To insure proper perioperative management of diabetics, clinicians should be aware of anesthetic agents tend to cause hyperglycemia [53]. In the present study both groups were premedicated with glycopyrrolate 0.2mg , Ondansetron 4mg and fentanyl 2mcg/kg , induction with propofol 2 mg/kg. In this study propofol and fentanyl anaesthesia adequately attenuated the stress respone to intubation in both groups non-diabeticpatients showed 1.064% decrease and diabetics an increase by 0.63% rise in blood sugar levels. At the end of 30 min and after extubation the rise of blood glucose level showed a difference of only 3.57% between both study groups and the rise is statistically insignificant . The results of the above study show that hyperglycemic stress response is mild in both groups, diabetic group showed a slightly higher values but with in normal physiological range. The mean values of blood glucose in the study groups were within normal physiological range of 88-125mg/dl. In present study Propofol significantly suppressed circulating cortisol results of this study adhere to work of Tetsuhiro Sakai, David'O Flaherty (1995), which showed propofol completely abolished cortisol response to surgery intraoperatively and subsequent rise in blood sugar levels. Propofol/sufentanil anaesthesia effectively and significantly attenuates rise in intra operative glucose levels. In our study a balanced anaesthesia technique using a combination of Fentanyl and propofol effectively attenuated the rise in intraoperative blood glucose levels in both groups (Thomas Schrickar 2000). This study gives us an opportunity in understanding attenuation of hyperglycemic stress response to anaesthesia and surgery, and this knowledge also allows devising a balanced general anaesthesia technique by choosing a combination of various anaestheti drugs. This knowledge allows us to insure proper perioperative management of surgical stress in diabetic patients, minimize intraoperative use of insulin regimens, and importance of preoperative glycemic control in decreasing morbidity and mortality. This study attempts to determine levels of pre-operative HbA1c in Diabetic patients to ensure smooth and uneventful perioperative course and a value of <6, 5% can be recommended as a guideline.

Conclusion

Diabetic patients may require surgery as a consequence of their disease process or otherwise, optimal anesthesiologic management of these patients is challenging and crucial. It is essential to blunt the stress hormones secretion in order to prevent postoperative complications. Hyperglycemic stress response to anaesthesia and surgery in diabetic patients can be minimized by a well planned and well conducted balanced general anaesthesia technique. Intraoperatively propofol and opioids completely abolished ACTH and cortisol secretion which resulted in lesser degree of rise in blood sugar levels during surgery which is statistically not significant when compared to non-diabetics . Thus a meticulous glycemic control prior to elective surgery is required; if possible, HbA1c should be brought to normal levels before elective surgeries and is an essential part of perioperative care of diabetic patients.

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