JMSCR Vol||06||Issue||01||Page 32363-32369||January 2018

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i1.151

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Clinical evaluation of effects of Intravenous Induction agents: propofol, ketamine and etomidate on blood sugar level

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Abstract

Background: *Hyperglycaemia is one of the stress responses to surgery and anaesthesia. Studies reported that volatile anaesthetics mainly sevoflurane impaired glucose use, suggesting a possible contribution to intraoperative hyperglycaemia.*

Aim: *To establish an effect if any on blood sugar by IV induction agents.*

Methods: *It is a prospective observational study. We selected 90 patients of either sex, ages between 18-55 yrs, ASA grade I /II undergoing elective minor surgical procedures with expected duration of 10-15 mins. All patients were divided into three groups (n =30 each);Group –A : received propofol 2 mg/kg, Group-B : received ketamine 2 mg/kg, Group – C : received etomidate 0.3 mg/kg. Blood sugar levels were measured before giving induction agents (at 0 min , taken as baseline) then at 5 mins,15 mins, 30 mins, 60 mins,90 mins and 120 mins interval. Hemodynamic parameters like heart rate (HR), mean arterial pressure (MAP) were also measured at similar time interval as blood glucose level. The values of each time interval was compared with respect to baseline value within a group by independent sample t-test.*

Results: *There were no significant differences between groups with respect to age, weight, gender distribution and duration of surgery. There was no significant change in blood glucose level in propofol. Ketamine increased blood sugar level which was statistically significant ($p < 0.05$) after 30 mins and 60 minutes from its administration but did not produce clinically significant hyperglycemia (> 180 mg/dl) at any of the study interval. Etomidate decreased blood glucose level which was significant ($p < 0.05$) after 2 hrs but was within the physiological range. Blood sugar level never decreased to < 60mg/dl. Propofol showed significant decrease in HR and MAP after 5 mins of giving induction agent. Ketamine showed significant increase ($p < 0.05$) in HR at 5 mins and 15 mins after giving induction agent. Etomidate showed no significant changes in HR & MAP.*

Conclusion: *Intravenous induction agents also result in impaired glucose response, though the changes are within physiological limits. Hyperglycemia occured with ketamine.*

Keywords: *Blood sugar level, etomidate, hyperglycemia, induction agent, ketamine, propofol.*

Introduction

Surgery under general anaesthesia exaggerates endocrine metabolic responses. Insulin secretion is impaired, resulting in decreased glucose use. Blood concentrations of catabolic hormones, such as cortisol, growth hormone and nor-epinephrine

are increased, resulting in enhancement of glucose production.[1,2] Because of the changes in glucose metabolism, hyperglycaemia occurs during surgery. Several studies reported that intraoperative hyperglycaemia is an independent risk factor for mortality and morbidity related to surgery. Hyperglycemias can potentiate brain, spinal cord and renal damage by ischemia .It blights WBC function and delayed wound healing. It also decreases gastric emptying time.[3,4]

Surgical procedures evoke an endocrine response and changes metabolism towards catabolism and it has been suggested that the endocrine response to anaesthesia is less than that to major surgical procedures.[5] The same authors suggested that blood sugar rises during surgery to an extent depending much more on the degree of stress than the type of anaesthesia. Despite the multitude of observations opinion vary widely on the hyperglycaemic responses of anaesthetic agents and anaesthetic techniques.

In other words patients suffering from diabetes if require surgery should be given a suitable IV anaesthesia, which will not hamper their disturbed metabolism. It is therefore that we considered to study the effect of propofol, ketamine and etomidate, the commonly used intravenous induction agents , on blood sugar levels.

Objective

Primary objective of this clinical study was to identify the effect of three anaesthetic agents like propofol, ketamine and etomidate with induction dose, on blood glucose levels in healthy non diabetic patients. Secondary objectives were to find out changes in hemodynamic parameters at similar time intervals.

Material and method

This was a prospective observational, single blinded study. After obtaining Institutional Ethics Committee clearance and written informed consent from each patient, 90 patients of either sex in the age group 18 to 55 years were included in this study. All the patients were with ASA physical status score I or II. They underwent different elective minor surgical procedures under general anaesthesia with expected duration of 10-15 mins.This study was conducted from July 2012 to July 2013 duration.Most of the patients were posted for fracture reduction, D & C, S & E, fibro adenoma , SSG and other minor surgical procedures. The exclusion criteria were as follows: Patients with ASA score III or IV, Mallampati grade III or IV, known suspected allergy to eggs or soya Products, Emergency surgeries, patient with DM, impaired glucose tolerance test and metabolic disorders, patient on drugs that cause hyper/hypoglycaemia.

The patients were kept NPO for 6 hours before surgery. Tablet ranitidine 150mg and tablet Alprazolam 0.5mg were given orally on the night before operation. On the day of surgery the patients were randomly divided into three groups of 30 patients each by sealed envelope technique. All cases were premedicated with inj glycopyrrolate 0.2 mg, inj midazolam 0.05mg/kg and inj fentanyl 1.5µg/kg i.v. Five mins after giving premedication, first blood sugar level was measured which was considered as at 0 min. Capillary Blood sample was collected from finger tip aseptically. Blood sugar level was measured using one touch select simple glucometer. At 0 min the heart rate and the mean arterial blood pressure were also recorded. Then Group-A was induced by propofol 2mg/kg, Group-B was induced by ketamine 2mg/kg and Group-C was induced by etomidate 0.3mg/kg. I-gel was inserted to all the three groups. Anesthesia was maintained with nitrous oxide and oxygen. Intravenous infusion of glucose and glucose containing saline was avoided. Normal saline was given to all for fluid replacement.

Blood glucose levels were measured at 5mins, 15 mins, 30 mins, 60mins , 90mins and 120 mins after giving induction agents. Heart rate and Mean arterial blood pressure were measured at similar time interval as blood glucose. The observations at 0 min for all the parameters of each group were

taken as baseline, and then it was compared with respect to other time intervals within a group. Patients in all the three groups were monitored in the recovery room for 2 hrs post-operatively and then shifted to their respective wards.

Statistical Analysis

Numerical data were presented as mean ± SE and categorical data as proportions (%). The standard deviation of mean is standard error (SE). Standard error = $\sigma/\sqrt{n}$; σ =standard deviation, n=sample size. The patient's characteristics like age, weight, duration of surgery were analysed by one way analysis of variance (ANOVA). Categorical data (e.g. sex distribution) was analysed using chi – square test. Significance of changes in blood glucose levels, heart rate and mean arterial pressure within a group at different point of time with respect to baseline (zero min) were done using independent sample t-test. All the raw data were subsequently entered into a Microsoft excel spread sheet and analysed using IBM SPSS software version 19. P Value ≤ 0.05 was taken as statistically significant.

Result

In the three groups of patients included in the study, female patients outnumbered the male patients but the difference was not statistically significant. Age, weight and duration of surgery in all the three groups were statistically compared by One way ANOVA .There were no significant difference in age, weight and mean duration of surgery. [Table-1]

In propofol group the blood sugar level did not change significantly at any of the time interval when compared with baseline value (with respect to 0 min) by independent sample t test [Figure-1]. In this study the mean baseline blood sugar level of ketamine was 91.60 ± 1.438 .At 5 mins , 15 mins , 30 mins , 60 mins , 90 mins and 120 mins the blood sugar level were 92.23 ± 1.467 , 94.0 ± 1.164 , 97.43 ± 1.218 , 95.7 ± 1.187 , 93.63 ± 1.266 , 90.66 ± 1.308. But the increase in blood glucose level were statistically significant at 30 mins ($p < .05$) and 60 mins ($p < .05$) .It did not show clinically significant hyperglycaemia which is considered as >180 mg/dl at any of the time interval. In ETOMIDATE group, there was a statistically significant decrease ($p < 0.05$) in blood glucose level after 2 hour [figure-1]. It did not cause clinically significant hypoglycaemia which is taken as less than 60 mg/dl.

The mean heart rate at 0 min, value taken before giving induction agent was taken as base line and compared with respect to other time interval after giving induction agents by independent sample t-test. The mean base line HR in propofol group was 87.13 ± 1.072 and after 5 mins it was decreased to 82.70 ±1.077, which was statistically significant ($p < .05$). [Fig -3] The MAP also showed a statistically significant decrease 5 mins after giving induction agent as compared to pre-induction value (94.06 ± .585 to 90.80 ± .586, $p<0.05$). [Fig-4] There were no significant changes in HR and MAP at other time intervals.

In ketamine group the HR at 0 min was 84.66 ± 1.756 , after 5 and 15 mins it increased to 92.36 ± 1.850, 90.7 ± 1.24 respectively which was statistically significant ($p< .05$).The MAP at 0 min was 88.76 ± 1.121(mm of Hg) , it increased to 94.03 ± 1.114 and 95.26 ± 1.060 after 5 and 15 minutes respectively (fig-3,4) which showed statistically significant ($p < .05$) rise .In etomidate group there were no changes in heart rate and mean arterial pressure at any of the time interval when compared to baseline value.

None of the patients in three groups developed significant hyperglycaemia or hypoglycaemia that required treatment at any time during the study period.

Discussion

Glucose metabolism can be modified by several factors during the perioperative period. It has been suggested that the hyperglycaemic response to surgery was related to the duration of the surgical operation and the extent of its stress.[6] Thus we have selected minor elective surgical procedures, average duration of surgery being 8-10 minutes to

avoid stress response. There are some animal studies regarding effects of induction agents on blood sugar level. Very few data are available related to human study .Here we did a clinical observation study to show changes in blood glucose level by intravenous induction agents.

We found that Propofol has no statistically significant changes in blood sugar level at any of the time interval. The effect of Propofol on glucose metabolism is not clearly understood. Propofol enhances insulin secretion; possibly by inhibiting k_{ATP} channels in ß-islet cells of pancrease. Propofol significantly impairs insulin sensitivity.[7,8] Propofol, a lipid formulation causes acute lipid load which exaggerates insulin resistance. It has no effect on glucose utilization.[9,10] Propofol decreases sympathetic nerve activity thereby reducing plasma concentrations of catecholamines .[11,12] Propofol after a single dose or a prolonged infusion does not affect corticosteroid synthesis or alter the normal response to adreno-corticotropic hormone (ACTH) stimulation. High dose propofol (60 mg/kg.hr) in animal has been shown to suppress glucose metabolism in the brain and possess neuroprotective properties in cerebral ischemia.[13] Here we have not measured plasma cortisol level. The stable glycaemic response of propofol in this study may be due to its effect on insulin secretion and insulin sensitivity.It also blunts sympathetic effect on glucose metabolism.

In this study ketamine increased blood sugar after 30 min and 60 min of giving induction dose of 2mg/kg. This result closely resembles with use of ketamine in children,rats and ketamine-xylazine anaesthesia in rabbits.[14,15] The acute hyperglycemic effect of Ketamine in part reflects α_2-adreno receptor-dependent changes of glucoregulatory hormones such as insulin, corticosterone, GH, and ACTH as shown by Joy K. Saha et al. After ketamine doses of 2mg/kg, causes significant increase in total plasma catecholamines (about 50% above the resting level) Takki et al .The apparent rise in blood sugar level in this study is probably because of rise in plasma catecholamine resulting from sympathetic stimulation. As the glycogenesis and neogluconeogenesis are intimately related with the sympathetic stimulation, it is expected that ketamine will have a significant effect on glucose metabolism. [16] However Suleiman I. et al showed dual effect of ketamine on blood sugar in an animal study. They observed low dose ketamine (166.6µg/kg) produced hyperglycemia which was significant at 15 mins & 30 mins following its administration. While higher doses of ketamine (1and 2mg/kg) produced hypoglycemia, even further higher doses (4mg/kg) did not influence on blood sugar upto one hour,but significantly raised at 2 hour.[17] Ketamine, like cocaine possesses dual properties of neuronal nor-adrenaline uptake blockade and local anaesthetic type depression of synaptic transmission. Cocaine has former property at low doses and the later at high doses. They suggest that ketamine may act on two sites with different activation threshold and mediate opposite effect.[18] They established that ketamine induced hyperglycemia may be mediated via α_2 adrenoreceptors.They also showed that selective α_2 receptor antagonists inhibit the hyperglycemic effect of ketamine in a dose dependent manner. Further clinical studies in humans are needed to establish the effect of ketamine on blood glucose level.

Etomidate shows statistically significant decrease in blood sugar at 120 mins ($p< 0.05$). This result closely resembles the observation of Karunia Ayu et al.Etomidate after induction dose of 0.2 mg/kg significantly decreases blood glucose level at two hour. The blood cortisol levels were significantly lower after 1 hr and 2 hr post induction. The hypoglycemic effect of etomidate is related to adrenocortical suppression inhibiting cortisol synthesis. Single dose etomidate inhibits 11-β-hydroxylase for 5-8 h post-operatively; the enzyme level is fully restored after 20 h.[19] The synthesis of both aldosterone and cortisol is blocked. A single induction dose of the etomidate suppress hormone production for 6-12 hr, while infusion for 1-2 hr blocks cortisol synthesis for up

to 24 hr. [20] In healthy patients there were no adverse cardiovascular effects from such an infusion during pelvic surgery and the only metabolic result of cortisol inhibition was a decrease in the expected glycaemic response .[21]

Both HR and MAP decreased significantly after 5 mins of giving induction dose of propofol. It is correlated with study of Larsen et al, propofol on induction dose of 2 to 2.5 mg/kg produces a 25% to 40% reduction of systolic blood pressure. Similar changes are seen in mean and diastolic blood pressure.[22,23] The decrease in arterial pressure is associated with a decrease in cardiac output/cardiac index, stroke volume index and systemic vascular resistance. Left ventricular stroke work index also decreased.[24]

Ketamine increased HR and MAP after 5 mins & 15 mins of its administration .The haemodynamic effect of ketamine is due to centrally mediated sympathetic responses which override the direct depressant effects of ketamine. Ketamine inhibits intraneuronal uptake of catecholamines, also inhibits extra neuronal nor epinephrine uptake.[25, 26]

In our study etomidate shows no changes in HR and MAP at any of the time interval. Gooding JM & Paris et al showed that an induction dose of 0.3 mg/kg of etomidate given to cardiac patients for non cardiac surgery results in almost no change in heart rate, MAP, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, stroke volume, cardiac index, pulmonary and systemic vascular resistance.[27] It is more cardio stable than other intravenous induction agents.Etomidate has lack of effect on sympathetic nervous system.[28]

The study could not be blinded properly due to different colour of ketamine than other induction agents. Large sample size is needed to extrapolate this data to common population.

The effect of IV induction agents on blood sugar level can be studied further in patient with impaired glucose tolerance test patients and in patient with diabetes.

Conclusion

Our study demonstrated that there was no significant changes in blood glucose level with propofol.ketamine increased blood sugar level which was statistically significant after 30 mins and 60 minutes from its administration but did not produce clinically significant hyperglycemia (> 180 mg/dl) at any of the study interval. Etomidate decreased blood glucose level which was significant after 2 hrs but within the physiological range. Blood sugar level never decreased to < 60 mg/dl.

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