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The Effects of Intravenous Propofol and Intravenous Etomidate as Induction Agents on Blood Glucose in Elective Surgeries Under General Anaesthesia: A Randomized Control Trail

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Abstract

*Introduction***:** Acute hyperglycemia is known to occur during major surgeries, its occurrence even for a brief period may lead to immune suppression. Surgeries which require general anesthesia are more susceptible for stress mediated immune response and intraop rise in blood glucose levels. Drugs used during induction and maintenance of anesthesia are also known to cause plasma glucose derangement along with surgical stress response, which can lead to adverse postoperative morbidity. *Aim:* To study the effect of blood glucose level at specified time intervals with intravenous Propofol and Etomidate. *Materials and Methods:* Sixty cases requiring general anesthesia, belonging to class 1 and 2 of American Society of Anesthesiology were selected. Patients were preoxygenated and premedication drugs were given and induced with either Propofol 2 mg/kg or Etomidate 0.3 mg/kg. Blood glucose was measured before premedication, at 5^{th} minute and at 15^{th} minute respectively. Statistical analysis done using Student *t*-test for parameters on continuous scale and Chi-square test for parameters on categorical scale. *p* - value of less than 0.05 was considered statistically significant. *Results:* The blood glucose in Etomidate Group increased compared to premedication value (84.7 ± 15.37 to 92.5 ± 17.09) and was statistically significant (*p - value 0.0167*). In Propofol Group, variation in blood glucose level was not significant (88.26 ± 15.47 to 87.0.5 ± 12.84). There was no significant increase in Heart rate, SBP, DBP & MAP at T5 & T15 in both the groups. *Conclusion:* In the current study, increase in blood glucose in nondiabetic patients following induction was found to be significantly high with Etomidate when compared with Propofol.

Keywords: Blood Glucose; Nondiabetic patients; Diabetes mellitus; Hemodynamic parameters.

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Introduction

The induction of anesthesia in patients undergoing any surgery has concerns including hemodynamic stability and attenuation of stress response. Of many metabolic reactions by the body during surgery the most important is resistance to insulin and hyperglycemia.[1] Hyperglycemia in the perioperative period is due to stress leading to release of many hormones such as epinephrine,

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cortisol and other inflammatory mediators. The immediate perioperative problems faced by the diabetic patients are: (i) Surgical induction of the stress response with catabolic hormone secretion; (ii) Interruption of food intake, which may be prolonged following gastrointestinal procedures; (iii) Altered conscious masks the symptoms of hypoglycemia and necessitates frequent blood glucose estimations; and (iv) circulatory disturbances associated with anesthesia and surgery, which may alter the absorption of subcutaneous insulin and is associated with significantly increased infectious complications associated with patient mortality.[2] Acute hyperglycemia in the perioperative period is associated with significantly increased complications and worsens prognosis even in the patients who had normal glucose tolerance test.[3,4] Hyperglycemia provokes numerous deleterious effects even on myocardium subjected to ischemia–reperfusion process. High blood glucose concentration abolishes ischemic preconditioning and amplifies reperfusion injuries and intraoperative glycemic control may be rendered difficult despite insulin therapy.[5]

The ADA specified that the diagnosis of diabetes mellitus should be made if a random plasma glucose value in an asymptomatic individual is > 11.1 mmol litre^{-1}. If a fasting plasma glucose is > 7.0 mmol litre^{-1} (6.1 mmol litre^{-1} blood glucose) in an asymptomatic individual, the test should be repeated on a different day and a diagnosis to be made if the value remains above this limit.[6] The ADA defines fasting plasma glucose concentrations between 6.1 and 7.0 mmol litre^{-1} (5.6–6.1 mmol litre^{-1} blood glucose) to represent 'impaired fasting glycemia.[6] WHO has also recommends the diagnosis of diabetes mellitus would be made if a random plasma glucose concentration is > 11.1 mmol litre^{-1} (venous whole blood > 10.0 mmol litre^{-1}).[6] It can also be diagnosed with a fasting plasma glucose concentration of > 7.0 mmol litre^{-1} and a second similar test or an oral glucose tolerance test producing a result in the diabetic range.

Lattermann R et al.[7] inferred that Combined spinal epidural technique can prevent hyperglycemia compared to GA in the patients undergoing any surgery, but surgeries which mandates the use of General anesthesia including Head and neck surgeries, Cardio-thoracic surgeries etc. requires intense monitoring of blood glucose and more so in diabetic individuals. Several intravenous anesthetic agents are used during induction including Ketamine which is associated with change in blood glucose levels and hemodynamics.

Propofol is an alkyl phenol, substituted with two isopropyl groups. The induction dose of propofol in healthy adults is 1.5 to 2.5 mg/kg, with blood levels of 2 to 6 μg/ml producing unconsciousness depending on the concomitant medications (e.g., opioid analgesics), patient's age, physical status and surgical stimulation.[8] It has been reported to inhibit phagocytosis and to reduce proliferative response of lymphocytes in critically ill.[9] Because fat emulsions are known to support the growth of micro-organisms, contamination can occur with long-term use of propofol.[10] Diabetic patients show a reduced ability to clear lipids from the circulation but with usage of propofol as an induction agent or during short anesthetic procedures for maintenance lipid accumulation is not seen.

Etomidate is a carboxylated imidazole which penetrates brain rapidly, reaching peak level within 1 min after intravenous injection. Etomidate transiently depresses adrenocortical function by dose dependent inhibition of conversion of cholesterol to cortisol. Etomidate blocks adrenal steroidogenesis and hence cortisol synthesis, by its action on 11 β-hydroxylase and cholesterol cleavage enzymes, and consequently decreases the hyperglycemic response to surgery by approximately 1 mmol litre^{-1} in nondiabetic subjects.[11]

There are several studies which have compared the effect of blood glucose using Propofol and other inhalational agents.[12–15] In current literature, there are no studies which have compared the effect of Propofol and Etomidate as induction agentson blood glucose in elective surgeries on nondiabetic patients. Hence, this study was conducted to compare the effect of Propofol and Etomidate as induction agents on blood glucose and hemodynamic parameters at specified time intervals.

Materials and Methods

This study was a double blind, prospective, randomized comparative study. The study was conducted at Adichunchanagiri Institute of Medical Science between 08.08.2018 and 25.02.2019. An approval by the Institutional Ethical Committee (AIMS/IEC/2197/2018–19) was obtained. Oral and informed consent was taken from all patients included in the study group.

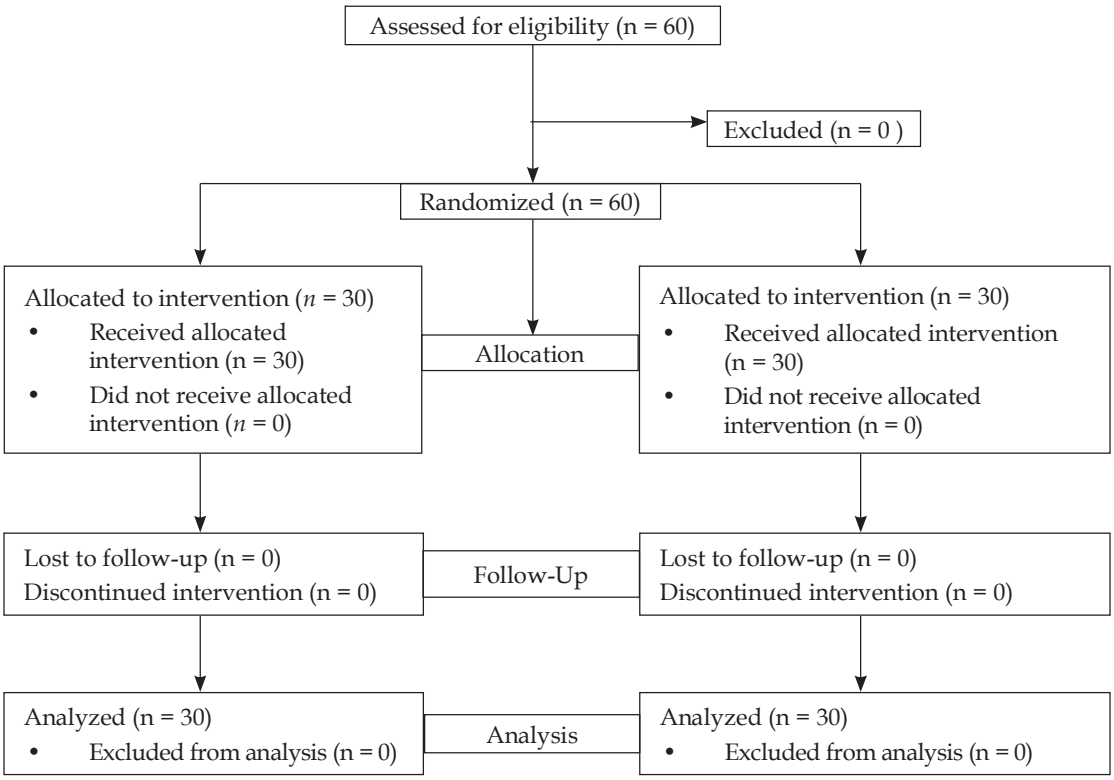

Fig. 1: Data-flow Diagram (DFD)

The necessary sample size was calculated to detect a 25% change in blood glucose level. Minimum number of patients required in each group was 30 and there were no dropouts in the study group. All patients between the age of 20 and 60 years with no associated comorbidities posted for elective surgeries were included in the study group. Standard deviation of the study was 33% of the mean, power of study was 80% with Alpha error being 0.005.

Patients with associated comorbidities, belonging to ASA Grade of more than II, cases posted for Emergency surgeries, patients with previously diagnosed Diabetes, patients with psychiatric illnesses, metabolic diseases, endocrine dysfunction, known allergy to study drugs, impaired coagulation profile and on medications which affects blood glucose at least one week before surgery like steroids, β blockers etc. were excluded from the study. Randomization was done according to random number table and study sample were divided into 2 Groups:

Group P: Where Propofol 2 mg/kg was used as induction dose (n = 30);

Group E; Where Etomidate 0.3 mg/kg was used as induction dose (n = 30).

A thorough preanesthetic check-up was done and all relevant investigations including complete hemogram, Renal function test, Serum Electrolytes, Bleeding time and Clotting time, Electrocardiogram and Random blood glucose assessment was done for all patients. Those patients who were accepted under ASA 1 and ASA 2 were included in the study. Patients were kept nil per oral for 8 hours prior to surgery. On arrival to the operating room monitors including ECG, NIBP, Pulse oximeter were connected for continuous monitoring of Pulse, Saturation, Systolic BP, Diastolic BP and Mean Arterial Pressure. All patients were premedicated with Inj. Midazolam 1 mg intravenously and preoxygenated with 100% oxygen for 5 minutes. Blood glucoses checked prior to induction, at 5 minutes and 15 minutes following induction with study drug. Group P patients were induced with Inj. Propofol 2 mg/kg and Group E patients with Inj. Etomidate 0.3 mg/kg. After administration of induction agent succinylcholine of 1.5 mg/kg was administered. Direct laryngoscopy done and tracheal intubation was performed by the senior

faulty to reduce the intubation response. Blood glucose levels with Pulse, Heart rate, Systolic Blood Pressure, Diastolic Blood Pressure were measured continuously and noted down at 5th and 15th minute after giving study drug. Blood glucose checked by glucometer - Optimum Exceed. With the data collected Blood glucose levels were compared between 2 Groups.

Stastistical Analysis:

Student *t*-test was used for parameters on continuous scale. Chi-square test was used for parameters on categorical scale. P - value of less than 0.05 was considered significant. Statistical software: SAS 9.2, SPSS 15.0, stata 10.1, Medcalc 9.0.1, Systat 12.0 & R environment ver. 2.11.1 was used.

Results

The demographic data showing age, sex, weight and ASA grading of the study groups has been shown in Table 1. The average age group in our study is 33.36 ± 14.33 for Group P and 34.36 ± 11.85 for Group E which is statistically comparable. Similarly the weight among the patients in two groups were comparable where the average weight in group P was 55.88 ± 9 and in group E was 57 ± 10.52.

There was no significant increase in Heart rate at different time intervals when compared to premedication value among the Groups P (*p* - value 0.73) and E (*p* - value 0.05). Change in MAP values were comparable and statistically insignificant when compared to premedication value among the Groups P (*p* - value 0.73) and E (*p* - value 0.05), as shown in Table 2.

The blood glucose in Group E was increased compared to premedication value & was statistically significant (*p* - value 0.0167), whereas in Group P the blood glucose variation at 5th and 15th minute was not statistically significant (*p* - value 0.7470) as compared to premedication value which is shown in Table 3. There were no major adverse effects seen during the study.

Discussion

On the basis of the collected evidence regarding ASA I–II status of the cases posted for surgeries requiring general anesthesia in nondiabetic patients, it is statistically significant that use of Etomidate as induction agent caused an increase in blood glucose level (*p* - value 0.0167), while the

Table 1: The demographic data showing age, sex, weight and ASA grading of the study groups

Variable	Group P	Group E	*p* - value
Age (years)	33.36 ± 14.33	34.36 ± 11.85	0.76
Sex (male/female)	14/16	19/11	-
Weight (kgs)	55.88 ± 9	57 ± 10.52	0.65
ASA I	14	17	-
ASA II	16	13	-

Table 2: Tabular column showing Hear Rate (HR) variation and Mean BP (Blood Pressure) variation in Group P and Group E before premedication, at 5th minute (T5) and at 15th minute (T15) respectively with its *p* - value. P-Propofol, E-Etomidate.

Group	Hr variation in Group P	Hr variation in Group E	Group	Mean BP variation in Group P	Mean BP variation in Group E
Premeds	88.92± 12.06	95.2 ±16.78	Premeds	88.92 ± 12.06	95.2 ± 16.78
T 5	91.66± 16.29	95 ± 13.92	T 5	91.66 ± 16.29	95 ±13.92
T 15	90.07± 13.72	87.53±12.62	T 15	90.07 ±13.72	87.53±12.62
p - value	0.73	0.05	*p* - value	0.73	0.05

Table 3: Blood glucose values which were measured following usage of Propofol and Etomidate at different time intervals. P-Propofol, E-Etomidate.

Group	Group P	Group E
Premedication value	88.26 ± 15.47	84.7 ± 15.37
5 Minutes	83.61 ± 14.55	88.13 ± 15.29
15 Minutes	87.05 ± 12.84	92.5 ± 17.09
p - value	0.7470	0.0167

same did not occur with the use of Propofol as induction agent (*p* - value 0.7470).

The reason for hyperglycemia during surgery may be surgical pain and metabolic response to surgical stress that even deeper plane of anesthesia cannot block the response. But with enough analgesia we can maintain blood glucose in normal limits and prevent hyperglycemia.

Jeong JS et al.[12] studied on the effects of propofol and enflurane on blood glucose. This study showed that propofol maintains normal glycemia during surgery compared to enflurane which supports our study.

Shekoufeh Behdad et al.[13] studied the effects of Propofol and Isoflurane on Blood glucose during Abdominal Hysterectomy in Diabetic patients in a study group of 30 women undergoing Abdominal hysterectomy. Blood glucose was measured during 60^{th} and 90^{th} minute of surgery and they concluded that Isoflurane caused an increase in blood glucose during maintenance of anesthesia as compared with Propofol where there was no rise in blood glucose levels which is similar to our study.

In the study by Diltoer M and Camu[14] the effect of isoflurane anesthesia on glucose tolerance test was evaluated with or without surgical stress. This study concluded that growth hormone and norepinephrine concentrations increases during surgical stress in turn causing insulin secretion in response to hyperglycemia impaired during isoflurane anesthesia without surgical stress, but during surgery under isoflurane anesthesia cortisol, growth hormone, norepinephrine, and epinephrine concentrations increases and due to insulin resistance and/or increased production of glucose, glucose tolerance impaired further[14] the effect of propofol or etomidate in our study for maintenance was not assessed and further research is required for the same.

Kitamura T et al.[15] in their study on Comparison of the changes in blood glucose levels during anesthetic management using sevoflurane and propofol implied that the effect on glucose metabolism of propofol was significantly less than that of sevoflurane. This study was performed on a study group of about 154 for Sevoflurane and 63 for Propofol. The study size is comparably larger than our study but the inference in the study is similar to ours showing the beneficial effects of propofol in glucose metabolism.

Zhu M et al.[16] study showed that propofol protects endothelial cells against hyperglycaemia induced insult. Kaushal RP et al.[17] in their study on the effect of etomidate and propofol as induction agent on hemodynamic andendocrine response in patients undergoing major cardiac surgeries including coronary artery bypass grafting, mitral valve and aortic valve replacement surgery on cardiopulmonary bypass showed that etomidate provided morestable hemodynamic response as compared to Propofol while Propofol caused vasodilation and resulted in fall of systematic BP. Thus, they concluded saying Etomidate could therefore be safely used for induction in patients with good LV functionfor CABG/MVR/AVR on CPB without serious cortisol suppression whose effect lasted for more than twenty-four hours. The hemodynamic stability has been similarly shown in our study as well where the Heart rate and Blood pressure did not alter for the induction dose in both the inducing agents as shown in Table 2.

Limitations

This study was conducted in nondiabetic patients and further studies are required to analyze the effects of the induction agents on blood glucose level in diabetic patients. Also, this study has considered the blood glucose variation only during induction of anesthesia while it has not taken into consideration the blood glucose variation during maintenance of anesthesia.

Conclusion

From the observations & results of the study we conclude that intravenous propofol prevents hyperglycemia compared to intravenous etomidate when values were compared to basal readings. Hemodynamic parameters were not statistically significant in both the groups. There were no significant adverse effects during the study.

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