

EFFECT OF DEXMEDETOMIDINE INFUSION ON STRESS INDUCED BLOOD GLUCOSE LEVELS IN GENERAL ANAESTHESIA

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Abstract

Background: It is well known that stress has a substantial influence on metabolic function. Psychological and physical stress may serve as triggers for the onset of type 2 diabetes. The aim is to demonstrate the effect of intravenous Dexmedetomidine administration on stress induced blood glucose levels. **Materials and Methods:** Following the patients' agreement, 60 samples were randomly chosen and split into two major groups, each including 30 samples. Patients were administered a loading dose of Inj. Dexmedetomidine at a concentration of 1µg/kg diluted in 50ml of Normal Saline, delivered over a period of 10 minutes, prior to the start of the operation. This was followed by a maintenance dosage of 0.5µg/kg/hour until the completion of the procedure. Blood glucose levels were assessed in the patient's fresh capillary whole blood using a glucose strip test at the specified intervals: Baseline measurements were taken before to administering the Dexmedetomidine bolus. Additional measurements were taken after 30 minutes following intubation, as well as throughout the first and second hour after the operation. The duration of tracheal extubation, measured from the cessation of anaesthetic drugs and Dexmedetomidine to the moment when the patient was extubated, was documented. The Ramsay sedation score was measured at 0 and 60 minutes after extubation. The duration of the surgical procedure and the administration of anaesthetic were documented. **Result:** The age distribution of study participants (38.87 ± 12.29 Vs 42.47 ± 12.18 , $P > 0.05$) and the BMI distribution (25.34 ± 4.28 Vs 24.78 ± 3.28 , $P > 0.05$) were not substantially different between the two groups, indicating that the groups are similar. The blood glucose level exhibited a statistically significant decrease ($p < 0.05$) in patients as compared to controls. **Conclusion:** The use of dexmedetomidine as a preanesthetic drug and intraoperative infusion effectively mitigated the metabolic stress response to major operations, as seen by the maintenance of steady blood glucose levels.

INTRODUCTION

The human body is inherently equipped to perceive stress and respond to it. Stress reactions facilitate our body's adaptation to novel circumstances. Stress may enhance our vigilance, motivation, and preparedness to evade harm. Stress cannot be quantified accurately via tests. The existence and strength of these sensations can only be perceived by the person experiencing them. It often induces restlessness, apprehension, fatigue, and annoyance. One may encounter physical fatigue, lethargy, and an incapacity to handle situations. Stress, a biological response, may be activated by several internal or

external events.^[1] Stress may manifest as either acute or chronic. Both stress and chronic stress may induce a diverse array of adverse effects, but, chronic stress can have detrimental long-term consequences on an individual's health. Glucocorticoids (GC) and catecholamines are the primary endocrine reactions to stress. While these hormones may not induce immediate negative effects, prolonged exposure to them may disrupt the regulation of glucose levels in the body. The disruption of glucose regulation may result in persistent high blood sugar levels, which in turn can cause resistance to insulin and the development of type II diabetes.^[2]

Dexmedetomidine (DEX) is a potent alpha₂ adrenergic receptor agonist that is being used more often in the perioperative phase. It produces drowsiness, analgesia, anxiolysis, and suppression of sympathetic tone.^[3,4] Dexmedetomidine is sometimes referred to as a "Wonder Drug" because of its numerous use in the field of anaesthesia. Clonidine, the first member of the alpha₂ adrenergic group, was initially developed in 1960 as a nasal decongestant. However, it was subsequently repurposed as an adjuvant for both general and regional anaesthesia.^[5] The initial purpose of marketing dexmedetomidine was to provide sedation in the Intensive Care Unit (ICU) by using its highly specific adrenergic alpha-2 receptor agonist action. Dexmedetomidine, unlike regularly used sedatives like Propofol or Midazolam, induces a unique sort of drowsiness characterised by interactivity. This means that patients may be quickly awakened with stimulation and once awakened, they are cooperative. Dexmedetomidine was designed as an anaesthetic premedication to reduce the sympathetic response to perioperative stressors, such as laryngoscopy and intubation, due to its sympatholytic effects.

Empirical research has shown that DEX has the ability to inhibit postoperative stress and inflammation, while also maintaining the immune function of individuals undergoing surgery.^[6,7] The stress reaction to surgery and anaesthesia is characterised not only by alterations in pulse rate and blood pressure, but also by metabolic, neurohormonal, and immunological changes. Consequently, many markers such as blood glucose, serum cortisol, Interleukin-6, and plasma nor-epinephrine levels have been used to measure the stress response. The reduction of these markers by dexmedetomidine has been shown.

The hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal system play a crucial role in facilitating the stress response. To ensure the survival of the host during times of intense stress, the body generates evolutionarily conserved reactions such as insulin resistance and stress-induced hyperglycemia.^[8] Stimulation of hypothalamus, during stress, responds by causing ACTH release, resulting in sudden increase in cortisol.^[9] This rapidly mobilises the amino acids, fat; to form glucose, causes insulin resistance; thereby increasing blood glucose upto 50% above normal, making glucose available for energy and synthesis of other compounds needed by different tissues.^[10] Hence, estimation of blood glucose serves to be a reliable indicator for indirect assessment of stress response and its modulation by pharmacological agents like alpha-2 agonists.^[11] While the stress response is typically seen as a defence mechanism that helps the body adapt and build resistance to harmful stimuli, the ongoing hyper metabolic state can lead to the depletion of vital bodily components, resulting in fatigue, reduced resistance, delayed movement, and increased risk of illness and death.^[12] Patients with comorbidities such as obesity, hypertension, diabetes

mellitus, renal insufficiency, liver illness, and those in the senior age group may face life-threatening risks.

Multiple investigations have shown that intravenous administration of Dexmedetomidine during general anaesthesia may reduce the minimum alveolar anaesthetic concentration (MAC) of Sevoflurane. The primary purpose is to illustrate the impact of intravenous administration of Dexmedetomidine on stress-induced blood glucose levels. The secondary objective is to evaluate perioperative hemodynamic stability, the duration of tracheal extubation, and postoperative sedation levels.

MATERIALS AND METHODS

After obtaining institutional ethical and scientific research committee approval, a comparative observational study was conducted in tertiary care hospital -Velammal medical college hospital and research institute, Madurai, Tamilnadu. Study includes the patients undergoing elective surgeries requiring general anaesthesia.

Inclusion Criteria

Age group 18 to 60 years of age either sex
American Society of Anaesthesiologists (ASA) grade I and II

Patients undergoing elective surgery of duration 1-2 Hours requiring general anesthesia

Exclusion Criteria

Patients on α -2 agonists or antagonists, β blockers, calcium channel blockers, digoxin or any other anti-hypertensive agent, psycho active medications

Patients with diabetes

Pregnant and breast-feeding mothers

ASA grade III or IV patients

Those unwilling to participate in the study were excluded

After thorough pre anaesthetic check up and routine investigations, selected patients were informed about the motto of our study in local language and a written informed consent was taken after ensuring their willingness to participate in the study. Institutional ethical and scientific research committee approval. The study was done for the duration of 3 months.

Total sample selected were 60. The patients undergoing elective surgery requiring general anesthesia were divided into 2 groups each 30:-

Group A: patients were receive loading dose of Inj. Dexmedetomidine 1 μ g/kg diluted to 50ml with Normal Saline given over 10mins, given before induction, followed by maintenance dose 0.5 μ g/kg/hour till the end of surgery.

Group B: control group-patients will receive normal saline in a similar manner.

After ensuring adequate fasting, patient was shifted to operation theatre, multipara monitor was attached to note the baseline pulse rate, blood pressure, spo₂. 18G IV cannula was secured and Ringer Lactate at 5ml/kg/hour was started. All patients received premedication Inj. Glycopyrrolate 0.2 mg/i.m before

surgery; and before induction, Inj. Fentanyl 2mcg/kg/i.v given. Patients were pre oxygenated for 3 minutes with 100% oxygen, Propofol 1.5mg/kg given as boluses of 20-30mg till loss of eyelash reflex response and BIS dropped to 50, Inj. Succinyl choline 1.5 mg/kg/i.v and once fasciculation disappeared from toes, patients were intubated with appropriate size cuffed portex endotracheal tube. Anaesthesia was maintained with nitrous oxide in oxygen (50:50), at 3Litres/minute, with Inj. Vecuronium bromide 0.1mg/kg as loading dose and 0.025mg/kg as top-up when required and Sevoflurane was used. At the end of surgery nitrous oxide, Sevoflurane, Inj. Dexmedetomidine infusion was stopped. Patient was ventilated with 100% oxygen till onset of respiratory efforts, after which reversal of residual neuro muscularblockade was done with Inj. Neostigmine 50mcg/kg i.v and Inj. Glycopyrrolate 10mcg/kg i.v. Extubation was done after ensuring adequate response to verbal commands, breathing effort and muscle tone.

Parameters Under Study

Blood glucose levels were measured from patient's fresh capillary whole blood using glucose strip test at following intervals: Baseline (before Dexmedetomidine bolus), 30 minutes after intubation, 1st and 2nd hour post operatively. The time for tracheal extubation(taken from stoppage of anaesthetic agents and Dexmedetomidine to the time when patient was extubated) was recorded. Ramsay sedation score at 0 and 60th minute post extubation was recorded. Duration of surgery and anaesthesia were recorded.

Ramsay Sedation Score

Table 1: shows Ramsay Sedation Score

Score	Response
1	Anxious or restless or both
2	Co operative, oriented and tranquil
3	Responding to commands only
4	Brisk response to light glabellar tap or loud auditory stimulus
5	Sluggish response to light glabellar tap or loud auditory stimulus.
6	Patient exhibits no response.

The age, gender, body weight, duration of surgery (minutes), duration of anesthesia (minutes) were recorded. Serial blood glucose levels from fresh capillary whole blood using glucose test strips were estimated at following points – before induction (basal), 30 min after intubation and at one and 6 h after recovery from anesthesia. The total and hourly Sevoflurane requirements were measured at the end of every hour. The usage of Sevoflurane during anesthesia can be calculated as follows.^[13]

Dion's Formula

Usage of volatile anesthetic (mL) = [Dialed concentration × Total fresh gas flow × Duration at that concentration × Molecular weight]/[2412 × Density].

Table 2: Demographic data

Parameter	Group A	Group B	P value
Age	28.27±1.15	25.53±1.18	>0.05
Weight	60.1±5.50	58.37±6.25	>0.05

Statistical Analysis: The approach used for simple random sampling was the envelope method. The data was inputted into a Microsoft Excel spreadsheet and analysed using SPSS 23. The continuous variable (Height, Weight, BMI, Hemodynamic parameters) was described using the Mean ± SD, with all measurements taken into account. The categorical variables (Sex, ASA, comorbidity, Complications) were represented using frequency and percentage values. The chi-square test was used to assess the correlation between two groups in relation to categorical variables. The independent sample t-test was used to assess the correlation between the two groups in relation to continuous variables. A significance level of P<0.05 was used to determine statistical significance.

RESULTS

The research consisted of 30 individuals in each group. The distribution of men and females was statistically equivalent in each group (P>0.05). Both groups had similar demographic characteristics, including age, body weight, duration of operation, and duration of anaesthesia.

[Table 2] displays the distribution of study participants in terms of age (28.27 ± 1.15 Vs 25.53 ± 1.18, P>0.05), weight (60.1 ± 5.50 Vs 58.37 ± 6.25, P>0.05), duration of surgery (72.13 ± 4.21 Vs 69.23 ± 2.03, P>0.05), duration of anaesthesia (91.76 ± 3.06 Vs 99.06 ± 2.01, P>0.05), and BMI (25.34 ± 2.28 Vs 24.78 ± 1.28, P>0.05). These variables were not significantly different between the two groups, indicating that the groups are comparable.

[Table 3] displays the average blood glucose levels before intubation, 30 minutes after intubation, 60 minutes after the operation, and 120 minutes after the operation. For group A, the mean blood glucose levels are 106.4 mm/dl, 119.87 mm/dl, 106.63 mm/dl, and 97.87 mm/dl, respectively. For group B, the mean blood glucose levels are 97.87 mm/dl, 134.83 mm/dl, 131.47 mm/dl, and 119.63 mm/dl, respectively. The blood glucose level exhibited a statistically significant decrease (p<0.05) in patients as compared to controls. At the conclusion of 30 minutes, 10% of the individuals in the case group observed a decrease in blood glucose levels. The percentage reached 43.33% after 60 minutes and increased to 76.66% after 120 minutes. None of the individuals in the control group exhibited a decrease in blood glucose levels.

[Table 4] shows mean for RSS level immediately post extubation mean for study group A is 2.77 and control group B is 2.87 whereas RSS 60 mins post extubation for group A is 2.1 and mean for control group is 2.4.

Duration of surgery	72.13±4.21	69.23±2.03	>0.05
Duration of anaesthesia	91.76±3.06	99.06±2.01	>0.05
BMI	25.34 ± 2.28	24.78 ± 1.28	>0.05

Table 3: Blood Glucose level

Blood Glucose level	Group A	Group B
Mean (mm/dl)		
Blood glucose before intubation	106.4	97.87
Blood glucose 30 minutes intubation	119.87	134.83
Blood glucose 60 minutes post. op	106.63	131.47
Blood glucose 120 minutes post. op	97.87	119.63

Table 4: Ramsay Sedation Score (RSS) Level

RSS Level	Group A	Group B
RSS immediately post extubation	2.77	2.87
RSS 60 mins post extubation	2.1	2.4

DISCUSSION

Dexmedetomidine, a potent α_2 -adrenergic receptor agonist, has attracted significant attention due to its sedative, analgesic, perioperative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing effects. It has a comparatively high α_2/α_1 activity ratio.^[14] The analgesic effects of Dexmedetomidine are caused by its ability to suppress neuronal activation in the locus coeruleus, a brain region. This leads to a decrease in the production and activity of norepinephrine in the descending medullo-spinal noradrenergic pathway.^[15] The inhibition of inhibitory control causes a reduction in the release of histamine, leading to a state of hypnosis that resembles natural sleep, without any negative effects on breathing.^[16] Dexmedetomidine effectively reduces stress-induced blood glucose levels by its action as a postsynaptic α_2 agonist, leading to a considerable decrease in the release of norepinephrine and thus lowering blood glucose levels. The administration of this treatment leads to decreased levels of stress response indicators, including glucose, cortisol, and interleukins. Administration of anaesthesia and performance of surgical procedures such as laryngoscopy, intubation, and extubation elicit a stress reaction. Post-surgical incision leads to a rise in blood glucose levels. Cortisol and catecholamines promote glucose synthesis by stimulating hepatic glycogenolysis and gluconeogenesis. Furthermore, there is a reduction in the utilisation of glucose in peripheral tissues as a result of insulin resistance. This leads to the activation of neuroendocrine pathways, resulting in the production of cytokines. This, in turn, causes an elevation in levels of catecholamines and steroids, leading to a rise in blood glucose levels by up to 50% over the normal range. Therefore, measuring blood glucose levels is a dependable method for indirectly evaluating the body's stress reaction. The stress reaction may lead to weariness, reduced resistance, delayed walking, and higher rates of illness and death. Patients with comorbidities such as obesity, hypertension, diabetes mellitus, renal insufficiency, liver illness, or in the senior age range may potentially face life-threatening risks. The stress

response is clinically and metabolically evident via various endocrine, immune, and haematological impacts. These include the activation of the sympathetic nervous system, the development of insulin resistance and hyperglycemia, the creation of cytokines, and other alterations in the immune and blood systems. Surgical trauma initiates a cascade of stress responses through direct activation of the sympathetic nervous system (SNS).^[17] The magnitude of surgical stress is contingent upon the extent and length of tissue damage, and may be indicated by an augmented release of pituitary hormones and the stimulation of the sympathetic nervous system (SNS).

Higher doses of Dexmedetomidine have been found to produce adverse biphasic cardiac response i.e. hypertension followed by hypotension,^[18] while very low doses fail to attenuate stress response to critical events.^[19] Dexmedetomidine has been used as single bolus dose as well as bolus followed by infusion.^[20,21] In a study conducted by Keniya VM et al in 2011, it was shown that administering Dexmedetomidine via an infusion at a dosage of 1mcg/kg over a period of 10 minutes, followed by a continuous infusion of 0.2-0.7 mcg/kg/hr, may reduce the sympathetic and adrenal response to tracheal intubation. In their study, Gupta K et al 2013 administered a single bolus dose of intravenous dexmedetomidine over a period of 10 minutes before the induction of anaesthesia. On the other hand, Harsoor SS et al 2014 and Yacout AG et al 2012 employed a loading dosage of 1mcg/kg of dexmedetomidine over 10 minutes before the induction, followed by a continuous infusion of 0.5 mcg/kg/hr till the completion of the procedure. Due to the Dexmedetomidine's distribution half-life of around 9 minutes and the need to prevent the biphasic reaction, we used a dosage regimen similar to that utilised by Harsoor S S et al in 2014 and Yacout A G et al in 2012.^[22] Additional indicators of the physiological reaction to anaesthesia and surgery, such as Interleukin-6 and Nor-epinephrine, were unable to be assessed due to the unavailability of the necessary equipment at the institution. Furthermore, these inquiries are very costly.

CONCLUSION

Multiple studies have shown a correlation between the presence of stress, including both physiological and psychological factors, and the onset of type II diabetes. Stress has become an inherent aspect of everyday life, leading to many disruptions in the body's metabolic processes. Hyperglycemia resulting from stress is an adaptive mechanism that enables the body to cope with acute stressors. This phenomenon has been extensively shown in many research, particularly those involving animals. The stress-induced alterations might be quite advantageous in a sudden condition. However, in terms of long-term consequences, it might result in diverse adverse impacts on the body's metabolic processes. Chronic stress triggers hyperglycemia, which, in combination with other factors, induces insulin resistance at the tissue level. This ultimately results in the development of type II diabetes in individuals experiencing chronic stress. This gives rise to many complexities inside the body and might sometimes pose a risk to one's life. It is advisable to use and promote stress management treatments as a means of preventive action. The use of dexmedetomidine as a preanesthetic drug and intraoperative infusion effectively reduced the metabolic stress response to major operations, as seen by the maintenance of stable blood glucose levels.

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