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Assessment of sensitivity to the anesthesia in a diabetic rat model

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Abstract. – OBJECTIVE: Diabetes mellitus and glucose regulation are important in deciding on surgical intervention in pre-surgical assessments. In our study, we aimed to investigate the correlations between the induction time of anesthesia, glucose level, and weight in a diabetic rat model.

MATERIALS AND METHODS: Weight-matched adult male Wistar rats were grouped as control (n=8) and diabetic (n=8). In the latter group, diabetes was induced with a single intraperitoneal injection of 50 mg/kg streptozotosin. 72 hours after the injection, animals possessing a blood glucose concentration above 300 mg/kg were considered diabetic. The weights and blood glucose levels were observed for 7 days. In the end, 80 mg/kg ketamine and 12 mg/kg xylazine were administered to both groups, and the induction time of anesthesia was recorded. The success of anesthesia was confirmed with toe pinching by using a clamp. The Student's *t*- and Pearson's correlation tests were used for statistical analyses.

RESULTS: The induction time of anesthesia was significantly reduced in the diabetic group compared to the controls ($p<0.01$). Diabetic animals weighed less than the control group ($p<0.01$). The correlation analysis in the diabetic group showed that the weight and blood glucose level of animals did not influence the induction time of anesthesia (respectively, $p=0.80$, r: 0.150; $p=0.68$, r: -0.300). A negative correlation between blood glucose concentration and weight was found in diabetics ($p<0.05$, r: -0.828).

CONCLUSIONS: The dosage of anesthetic agents is important in the effectiveness of anesthesia, and surgical complications. Since our results indicate the susceptibility of diabetics to anesthesia, we suggest that the dose of anesthetics should be finely adjusted considering the presence of diabetes.

Key Words:
Diabetes Mellitus, Rat, Anesthesia dose, Induction, Time.

Introduction

Diabetes mellitus (DM) is an endocrinological condition characterized by a circulating fasting blood glucose level of ≥126 mg/dL as a result of the lack/absolute deficiency of insulin secretion from ß-cells in the islets of Langerhangs of the pancreas or the low/absence of glucose transporters (GLUT) involved in the transport of glucose into the cell and metabolic disorder. Increased free oxygen radicals and lipid peroxidation play a role in the initiation and progression of DM[1]. It is thought[2] that the damage observed in β cells, which is one of the most sensitive structures to oxidative stress, is due to the toxic effects of hyperglycemia. It has been emphasized that hydrogen peroxide (H_2O_2) is effective on the insulin receptor signaling system after its conversion to the hydroxyl (OH.) radical, which is a highly reactive oxygen species (ROS) and may play an important role in the signal transduction pathways regulated by the insulin receptor[3]. DM causes undesirable biochemical, morphological and functional changes in tissues and organs by negatively affecting carbohydrate, lipid and protein metabolism[1]. Long-term hyperglycemic state can result in neuropathy, nephropathy, cardiovascular and cerebrovascular complications, capillary blood vessel, heart, nerve, kidney, eye, and ultimately organ failure and death[4-6].

Preoperative preparations are very important in orthopedic surgery, surgery for various traumas, or malignant tumors. In orthopedic operations, many factors, such as the success of the operation, the patient's age, general condition, the surgical success of the operator, as well as concomitant diseases affect the choice and dose of anesthesia applied. No matter how duly the surgical technique is performed in the interventions,

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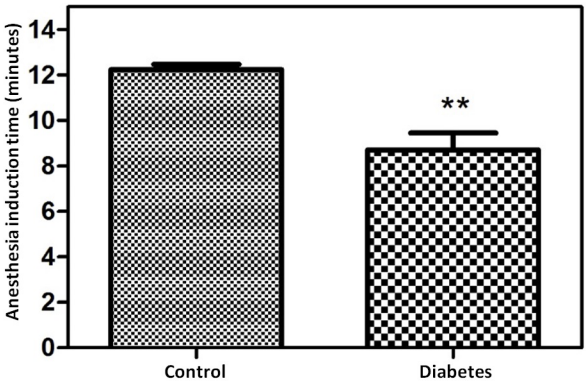

Figure 1. Comparison of anesthesia induction times. $^{**}p<0.01$.

this may not be sufficient for the success of the intervention. For this reason, the importance of the anesthesia technique applied, the systemic condition of the patient and postoperative follow-up cannot be denied[7-9].

Diabetes mellitus and glucose regulation in pre-surgical evaluations are important in deciding on surgical intervention. In our study, we aimed to investigate the correlation between anesthesia entry times, sugar levels and weight in a diabetic rat model.

Materials and Methods

In this study, male Wistar Albino rats (250-300 gr) were obtained from Mustafa Kemal University, Faculty of Medicine, Experimental Animal Center. The rats used in the experiment were kept under room temperature conditions in a dark and light environment for 12 hours. During the experiment, these rats were fed with normal mouse chow and water. Throughout the experiment, rats were provided with conditions according to the International Laboratory Animal Ethical Guidelines.

Animal Protocol

16 weight-matched adult male Wistar rats were grouped as control (n=8) and diabetic (n=8). At the beginning of the experiment, the blood glucose levels of all rats were measured with a glucometer and recorded. The rats in the whole group were given their normal feed and water throughout the experimental period. In the second group, diabetes was induced by 50 mg/kg single dose intraperitoneal streptozotocin injection. 72 hours after the injection, the urine of the rats in the diabetic group was examined with a strip and when the color change (turning from yellow to green) in the strip was observed, the blood sugar levels were measured with a glucometer, and the rats with a value of 300 mg/dl and above were considered as diabetic[10]. Weight and blood sugar levels were observed for 7 days. Ultimately, 80 mg/kg ketamine and 12 mg/kg xylasine were applied to both groups, and anesthesia induction time was recorded. Anesthesia success is confirmed by using a clamp.

Statistical Analysis

Graph-Path Prism 5 program (La Jolla, CA, USA) was used for statistical analysis. Student's *t* and Pearson's correlation tests were used to compare the weights and blood sugar levels of the rats in the group. A *p*-value below 0.05 was considered statistically significant.

Results

Comparison of glucose, weight and anesthesia induction times between groups is shown in Table I. Glucose level in the diabetic group (493.0±20.7 mg/dl) was statistically significantly higher than the control group (96.57±3.2 mg/dl) ($p<0.001$). Anesthesia induction time (8.70±0.74 minutes) was significantly decreased in the diabetic group compared to the control group (12.24±0.23 minutes) ($p<0.01$). The weight of the diabetic group (337.5±14.9 g) was lower than that of the control group (452.7±23.4 g) ($p<0.01$) (Table I, Figure 1).

The correlation of the anesthesia induction time to the other parameters studied in the diabetic group is shown in Table II. Correlation analysis of the animals in the diabetic group showed that weight and blood glucose levels did not affect

Table I. Comparison of glucose, weight and anesthesia induction times between groups (Mean±SD).

	Control	Diabetes Mellitus	*p*-value
Glucose (mg/dl)	96.57±3.2	493.0±20.7*	<0.001
Weight (gr)	452.7±23.4	337.5±14.9*	<0.01
Duration (minutes)	12.24±0.23	8.70±0.74*	<0.001

$^{*}p<0.01$.

the anesthesia induction time (p=0.80, r: 0.150; p=0.68, r: -0.300, respectively). There was a negative correlation between blood glucose concentration and weight in the diabetic group (p<0.05, r: -0.828) (Table II, Figure 2).

Discussion

There is no research in the literature on whether concomitant diabetes affects the duration of anesthesia in patients who will undergo surgery and how the dose of the anesthetic should be adjusted. In our rat study, we found that the anesthetic administered before the surgery caused the diabetic group to enter anesthesia more quickly. Therefore, we concluded that the dose of the anesthetic should be reduced in the diabetic group and possible complications caused by the anesthetic can be prevented.

Diabetes regulation is an important problem in patients who undergo surgery. Hormones that increase with the stress of surgery reduce insulin sensitivity and inhibit insulin secretion in patients with insulin deficiency. Ultimately, this can quickly lead to hyperglycemia and ketosis. Perioperative fasting and drugs given before the operation may cause hypoglycemia. It can have very serious consequences as the patient who has been anesthetized or sedated cannot feel the warning signs of hypoglycemia or seek help[11]. At least 3-4 days before the operation, the patient should be evaluated by measuring hemoglobin A1c and plasma glucose levels. Patients with insufficient glycemic control who undergo major surgical procedures

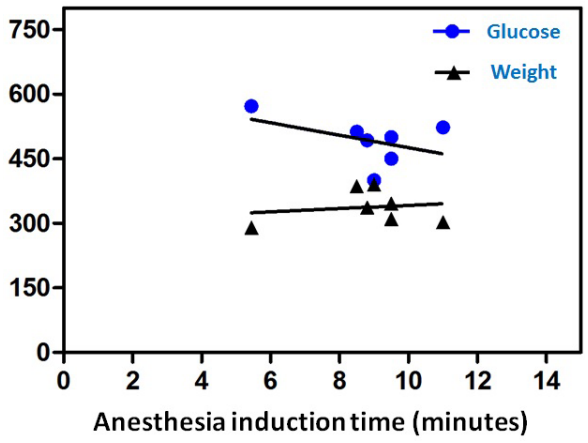

Figure 2. Correlation of the anesthesia induction time in diabetes group.

Table II. Correlation of the anesthesia induction time to the other parameters studied in the diabetes group.

Characteristic		R value	p-value
Weight	Duration	0.150	0.80
Glucose	Duration	-0.300	0.68
Glucose	Weight	-0.828*	**0.02**

*p<0.05.

should be hospitalized a few days before the operation for this purpose, if possible. The operation should be postponed in patients with plasma glucose levels>250 mg/dl against the risk of complications[12]. However, in our study, we concluded that the anesthetic dose would increase the surgical complication, as it caused the diabetic rats to enter anesthesia in a shorter time.

Surgical stress causes excessive release of proinflammatory cytokines and increases in catecholamine, cortisol, and glucagon and growth hormone levels due to increased sympathetic activation. The increase in these hormones leads to hyperglycemia by facilitating endogenous glucose production and insulin resistance in the liver and reducing glucose utilization in skeletal muscle. Even in the absence of surgical stress, anesthesia modulates the glycemic response by affecting the neuroendocrine response or directly altering pancreatic insulin release[13]. Perioperative hyperglycemia has been shown[14-16] to increase the risk of stroke and sepsis, length of stay in ventilation and intensive care unit, risk of acute kidney injury, wound infection and mortality. In our study, we concluded that the given anesthetic increased the glucose level even more and thus increased the risk of complications related to hyperglycemia.

There is a relationship between perioperative blood glucose levels and anesthetic technique. In some clinical studies[17], propofol anesthesia during surgery in patients without DM has been shown to result in lower blood glucose levels compared to volatile anesthetics. In a retrospective study[17] of 188 Type 2 DM patients who underwent major surgery, it was shown that propofol triggered lower blood glucose levels than sevoflurane during surgery in non-DM patients who had undergone different types of surgery, and anesthesia using sevoflurane or propofol resulted in a similar frequency of hyperglycemia in the perioperative period. It has been reported[18] that high-dose opioid use suppresses the hypothalamic-pituitary axis and sympathetic nervous system activation, thereby eliminating the hyperglycemic response to surgery. General anesthesia alone is not con-

traindicated in diabetic patients, but clinical examination should be performed preoperatively for dysautonomia and polyneuropathy[19]. Up to 10% of DM patients are symptomatic for diabetic neuropathy. Diabetes can affect response to nerve stimulation, blocks, and neuraxial techniques. There is a prolongation of the block time and an increased risk of infection when the catheter is placed[20]. Since there is no consensus for ideal blood glucose levels, perioperative management should be provided by evaluating the type of diabetes before surgery, the type and duration of surgery, anesthesia technique, comorbidities, and the expected fasting time after surgery. In the study of Leal et al[21], it was stated that in streptozotocin rats, modified and lower doses of propofol could be performed with lower doses of anesthesia induction in these rats. In our study, we found that anesthesia induction with ketamine was more rapid in diabetes. This can be considered as a complication of diabetes. It is probably due to the negative effects of diabetes on circulation and neurons. Therefore, we concluded that the dose of anesthesia should be reduced in the diabetic group in order to obtain balanced anesthesia.

Conclusions

The dose of anesthetic agents is important in terms of the effectiveness of anesthesia and surgical complications. Since our results show that diabetics are very sensitive to anesthesia, we think that the doses of anesthetics should be finely adjusted considering the presence of diabetes. Our study should be confirmed by clinical studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contributions

Concept: M.Y. and R.D.; Design: M.Y. and R.D..; Supervision: R.D.; Funding: M.Y.; Materials: M.Y. and R.D.; Data: M.Y. and R.D.; Analysis: M.Y. and R.D.; Literature search: M.Y. and R.D.; Writing: R.D.; Critical revision: M.Y.

Ethics Approval

The study protocol was approved by the Ethics Committee of Experimental Research Ethics Committee of Mustafa University Faculty of Medicine (Approval No.: 2020/1327).

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References

1) Black HS. A Synopsis of the Associations of Oxidative Stress, ROS, and Antioxidants with Diabetes Mellitus. Antioxidants (Basel) 2022; 11: 1-16.
2) Robertson RP. Nrf2 and Antioxidant Response in Animal Models of Type 2 Diabetes. Int J Mol Sci 2023; 24: 1-12.
3) Thomas DT, DelCimmuto NR, Flack KD, Stec DE, Hinds TD, Jr. Reactive Oxygen Species (ROS) and Antioxidants as Immunomodulators in Exercise: Implications for Heme Oxygenase and Bilirubin. Antioxidants (Basel) 2022; 11: 1-24.
4) Paul S, Ali A, Katare R. Molecular complexities underlying the vascular complications of diabetes mellitus - A comprehensive review. J Diabetes Complications 2020; 34: 107613.
5) Woloszyn-Durkiewicz A, Mysliwiec M. The prognostic value of inflammatory and vascular endothelial dysfunction biomarkers in microvascular and macrovascular complications in type 1 diabetes. Pediatr Endocrinol Diabetes Metab 2019; 25: 28-35.
6) Mishra RK, Alokam R, Sriram D, Yogeeswari P. Potential role of Rho kinase inhibitors in combating diabetes-related complications including diabetic neuropathy--a review. Curr Diabetes Rev 2013; 9: 249-266.
7) Atilgan N, Duman N, Colak TS, Korucu IH, Demiryurek M, Yilmaz M. Comparison of the results of percutaneous and open screw fixation in the treatment of scaphoid nonunion fractures. Eur Rev Med Pharmacol Sci 2022; 26: 9204-9211.
8) Atilgan N, Duman N, Colak TS, Korucu IH, Demiryurek M. Multidisciplinary treatment and functional outcome evaluation of combined injuries of nerves, vessels, and flexor tendons: spaghetti wrist. Eur Rev Med Pharmacol Sci 2022; 26: 8808-8815.
9) Koca I, Ucar M, Arik HO, Yilmaz M, Dokuyucu R. Alpha-lipoic acid could be a promising treatment in steroid-induced osteonecrosis. Eur Rev Med Pharmacol Sci 2022; 26: 7404-7412.
10) Gulturk S DA, Kosar İ, Cetin A, Dökmetas H, Demir T. Effect of Exposure to 50 Hz Magnetic Field With or Without Insulin on Blood^Brain Barrier Permeability in Streptozotocin-Induced Diabetic Rats. Bioelectromagnetics 2010; 31: 262-269.
11) Moningi S, Nikhar S, Ramachandran G. Autonomic disturbances in diabetes: Assessment and anaesthetic implications. Indian J Anaesth 2018; 62: 575-583.
12) Diabetes Canada Clinical Practice Guidelines Expert C, Malcolm J, Halperin I, Miller DB, Moore S, Nerenberg KA, Woo V, Yu CH. In-Hospital Management of Diabetes. Can J Diabetes 2018; 42: 115-123.

13) Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000; 85: 109-117.

14) McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. Diabetes Care 2005; 28: 810-815.

15) Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, Hudson M, Mendoza J, Johnson R, Lin E, Umpierrez GE. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 2010; 33: 1783-1788.

16) American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020; 43: 14-31.

17) Kitamura T, Kawamura G, Ogawa M, Yamada Y. [Comparison of the changes in blood glucose levels during anesthetic management using sevoflurane and propofol]. Masui 2009; 58: 81-84.

18) Kim H, Han J, Jung SM, Park SJ, Kwon NK. Comparison of sevoflurane and propofol anesthesia on the incidence of hyperglycemia in patients with type 2 diabetes undergoing lung surgery. Yeungnam Univ J Med 2018; 35: 54-62.

19) Gebhard RE, Nielsen KC, Pietrobon R, Missair A, Williams BA. Diabetes mellitus, independent of body mass index, is associated with a "higher success" rate for supraclavicular brachial plexus blocks. Reg Anesth Pain Med 2009; 34: 404-407.

20) Ten Hoope W, Looije M, Lirk P. Regional anesthesia in diabetic peripheral neuropathy. Curr Opin Anaesthesiol 2017; 30: 627-631.

21) Leal N, Calvo R, Agrad FZ, Lukas JC, de la Fuente L, Suarez E. Altered dose-to-effect of propofol due to pharmacokinetics in rats with experimental diabetes mellitus. J Pharm Pharmacol 2005; 57: 317-325.