Investigation of the Effects of Sevoflurane and Desflurane on Erythrocyte Deformability in Transient Hyperglycemia

Geçici Hiperglisemi anında Sevofluran ve Desfluranın Eritrosit Deformabilitesi Üzerine Etkilerinin Araştırılması

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ABSTRACT

Aim: Micro and macrovascular complications due to long-term hyperglycemia are associated with increased mortality and morbidity. Erythrocytes exposed to hyperglycemia for a long time may cause morphological changes in erythrocytes such as decreased deformability and development of aggregation. As a result, complications such as shortening life span of erythrocytes, impairment of oxygen carrying capacity, tissue hypoxia may occur. In our study, we would like to investigate the effects of Sevoflurane and Desflurane on erythrocyte deformability during transient hyperglycemia.
Materials and Methods: In this study, 30 male Wistar albino rats were used. The animals were randomly divided into five groups, each contained 6 rats: Diabetic control (group DC), diabetic hyperglycemia group (group DH), diabetic hyperglycemia group with desflurane (group DH-D), and diabetic hyperglycemia group with sevoflurane (group DH-S) groups. Another 6 rats without diabetes were assigned as control group (group C). Streptozotocin-induced diabetic rats were kept 6 weeks, then transient hyperglycemia was created, and the administration of sevoflurane and desflurane were performed. After 24 hours blood samples were obtained and deformability measurements were performed in erythrocyte suspensions containing Htc 5% in a PBS buffer.
Results: Diabetes mellitus was found to increase relative resistance in the control group ($p < 0.0001$). Acute hyperglycemia increased relative resistance in diabetes control, relatively. Group DH, Group DH-D and Group DH-S deformability index were significantly different when compared to Group DC ($p=0.007$, $p=0.025$, $p=0.016$, respectively). It was found that administration of desflurane or sevoflurane did not alter erythrocyte deformability during acute hyperglycemia ($p = 0.591$, $p = 0.739$).
Conclusion: As a consequence, we think that we can safely use inhalation anesthetics such as Desflurane and Sevoflurane during acute hyperglycemia attacks. But, it needs further investigation as both experimental and clinical

Key Words: Transient hyperglycemia, Desflurane, Sevoflurane, erythrocyte deformability

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ÖZET

Amaç: Uzun süreli hipergliseminin oluşturduğu mikro ve makrovasküler komplikasyonlar mortalite ve morbidite artışı ile birliktedir. Eritrositlerin ise yaşam süreleri boyunca uzun süre hiperglisemiye maruz kalmaları morfolojik olarak eritrositlerde deformabilitede azalma ve agregasyon gelişmesi gibi bir takım değişikliklere neden olmaktadır. Bunun sonucunda eritrositlerin yaşam sürelerinde kısalma, oksijen taşıma kapasitesinde bozukluk, doku hipoksisi gibi komplikasyonlar meydana gelmektedir. Sevofluran ve desfluranın ise eritrosit deformabilitesi üzerine etkileri ile ilgili çeşitli çalışmalar mevcuttur. Biz de bu çalışmamızda geçici olarak oluşturulan hiperglisemi sırasında sevofluran ve desfluranın eritrosit deformabilitesi üzerine etkilerini araştırmayı amaçladık.
Yöntem: Çalışma Gazi Üniversitesi Deneysel ve Klinik Araştırma Merkezi'nde Gazi Üniversitesi Deney Hayvanları Etik Kurulu onayı ile yapıldı. Çalışmaya 30 rat dahil edildi. Ratlar; kontrol grubu, diyabetik-kontrol, diyabetik hiperglisemi, diyabetik–hiperglisemi-sevofluran, diyabetik-hiperglisemi-desfluran olmak üzere 5 gruba ayrıldı. Streptozosin ile diyabet oluşturulan ratlar 6 hafta yaşatıldıktan sonra geçici hipergilisemi oluşturuldu ve sevofluran ve desfluran anestezisi uygulandı. 24 saat sonra kan örnekleri alındı ve santrifüj edildi. Eritrosit deformabilitesi sabit akım filtrometre sistemleri kullanılarak ölçüldü. Rölatif rezistansının artması eritrosit deformabilitesinin azalması olarak yorumlandı.
Bulgular: Diyabet oluşturulmasının kontrol grubuna göre rölatif rezistansı arttırdığı bulundu ($p<0.0001$). Akut hiperglisemi, diyabet kontrol grubuna göre rölatif rezistansı arttırdı. Grup DH, Grup DH-D ve Grup DH-S deformabilite indeksi Grup DK ile karşılaştırıldığında anlamlı olarak farklı bulundu ($p=0.007$, $p=0.025$, $p=0.016$). Akut hiperglisemi sırasında Desfluran veya Sevofluran uygulanmasının ise eritrosit deformabilitesini değiştirmediği tespit edildi ($p=0.591$, $p=0.739$).
Sonuç: Sevofluran ve Desfluran gibi inhalasyon ajanların akut hiperglisemi sırasında güvenle kullanılabileceğini düşünmekteyiz. Ancak bu bulguların daha detaylı ve geniş serilerde yapılacak klinik ve deneysel çalışmalarla desteklenmesi gerekmektedir.

Anahtar Sözcükler: Geçici hiperglisemi, Desfluran, Sevofluran, eritrosit deformabilitesi

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INTRODUCTION

Glucose is a main energy source of body cells for their process. With an increase in blood glucose level, Insulin, which is secreted by pancreas, directs glucose toward cells and reduces the sugar level in blood. Insulin is effective in regulating glucose metabolism. But, an inadequacy of insulin release from pancreas, insulin resistance or both may cause increased glucose level in blood. The ratio of Diabetes Mellitus has increased gradually all over the world. It is expected that almost 300.000 people will have suffered from this disease by 2025 (1,2). Although many improvements and advances in medical treatments may extend lifespan, long term complications affect quality of life badly. During the diabetes, biochemical changes in blood, metabolic last products, and the interaction with each other may cause some changes in hematologic parameters such as hematocrit, aggregation, and erythrocyte deformities. The increase in glucose level primarily affects erythrocytes and vascular endothelial cells. Chronic hyperglycemia causes the increase of reactive oxygen molecules, carbonyl compounds, and enzymatic protein glycosylation in erythrocyte (3,4). Also, calcium, sorbitol, and glycerol are observed to increase (5,6). These changes cause the decrease of erythrocyte lifespan due to membrane lipids imbalance and decrease of membrane permeability (3,7). As a consequence of these events due to hyperglycemia, reduction of erythrocyte deformability occurs. General anesthetic agents are known to have an effect on cardiovascular functions and microcirculation (8). The effects of anesthetic agents are associated with impairment of tissue and organ perfusion during an anesthesia (9,10). In this study, we aimed to observe the effect of desflurane and sevoflurane on erythrocyte deformability in diabetic rats with acute hyperglycemia.

MATERIAL and METHOD

Animals and Experimental Protocol

The study was conducted after the approval of Gazi University Experimental Animals Ethics Committee in Gazi University Experimental and Clinical Research Center (GUDAM). In this study, all of the procedures were used to obey the rules and standards of the Guide for The Care and Use of Laboratory Animals.

In this study, 30 male Wistar albino rats were used, weighing between 200 and 250 g, raised under the same environmental conditions. The temperature of environment was under 20-21 ^{0}C at cycles of 12-hour daylight and 12-hour darkness and had free access to food until 2 hours before the anesthesia procedure.

The animals were randomly divided into five groups, each contained 6 rats: diabetic control (group DC), diabetic hyperglycemia group (group DH), diabetic hyperglycemia group with desflurane (group DH-D), and diabetic hyperglycemia group with sevoflurane (group DH-S) groups. Another 6 rats without diabetes were assigned as control group (group C).

STZ (Sigma Chemicals, St. Louis, MO, USA) was dissolved with saline solution (0.9% NaCl) to be prepared. STZ was prepared freshly just before the treatment at a dose of 55 mg.kg^{-1} body weight. 3 days after the administration, blood glucose levels of diabetic rats were examined and recorded with glucometer (mg/dl). In case fasting glucose levels of rats were higher than 250 mg.dl^{-1}, rats were accepted as diabetic and they were included in the diabetic groups (diabetes only, diabetes hyperglycemia, diabetes hyperglycemia plus sevoflurane and diabetes hyperglycemia plus desflurane). The rats were kept alive 6 weeks after streptozotocin administration for chronic diabetes before sevoflurane and desflurane were given to them.

Hyperglycemia

Hyperglycemia was provided throughout implementing of intraperitoneal glucose injection as 2.5g.kg^{-1}. Saline was given to normoglycemic groups as the same amount.

Before the initiation of study, calibrations of anesthetic gas vaporisers were checked. 6% Desflurane and 2% sevoflurane were administered as a minimum alveolar concentration (MAC). Transparent plastic container (40x40x70 cm) was used for anesthesia procedure. The observation of the rats was possible by the container, which was connected to a half open anesthesia machine with static hoses. The anesthetic gases were given into the container with 100% O_2.

The rats were classified as five groups (n=6). The control, DC and DH groups were not subjected to any application. Desflurane (Suprane, Eczacıbaşı, İstanbul, Türkiye) was administered at 6% inspiratory concentration, 6 L.min^{-1} in 100% O_2 for 2 hours, and sevoflurane (Sevorane, Abbot, İstanbul, Türkiye) was administered at 2% inspiratory concentration, 6 L.min^{-1} in 100% O_2 for 4 hours.

Twenty-four hours after the anesthesia procedure, ketamine 100 mg.kg^{-1} intraperitoneally was used for sacrification of the rats. All rats were sacrificed under anesthesia and after then heparinized total blood samples were used to prepare erythrocyte packs. Deformability measurements were observed by using erythrocyte suspensions with 5% hematocrit in a phosphate buffered saline (PBS) buffer.

Deformability Measurements

Blood samples were carefully collected and the measurement process was performed as fast as possible to avoid hemolysis of erythrocytes. The centrifugation at 1000 rpm for ten minutes was performed for the collected blood samples. An isotonic PBS buffer was used for the collapsing erythrocytes and this was centrifuged at 1000 rpm for ten minutes. Liquid located on the upper surface was taken away. After three times of washing processes, isolated red cell packs were obtained.

Erythrocyte packs and PBS buffer were mixed to generate a suspension with a value of 5% Htc. They were used to measure deformability. We performed these procedures at 22ºC. The constant-current filtrometer system was used to measure the deformability, 10 ml of erythrocyte suspension and PBS were used to prepare samples to be measured. The flow rate was 1.5 ml/min with an infusion pump, continuously. It was preferred to use a 28 mm nucleoporin polycarbonate filter with a 5-µm pore diameter.

The pressure transducer was used to be observed pressure changes during erythrocytes' passing through the filter, and the data was transferred to the computer via a software, which was MP30 data equation system (Biopac Systems Inc, Commat, USA). Computer programs were used to measure the pressure changes at various times for necessary calculations. For every sample measurement, system calibration was checked. The filtration system was used to allow buffer (P_T) and the erythrocytes (P_E) to pass through the filtration system and the changes in pressure were measured. The calculation of the relative refractory period value (Rrel) by relating the pressure value of the erythrocyte suspension to the pressure value of buffer was performed. Increasing Rrel in the deformability index was interpreted to adversely affect the erythrocytes' deformability.

Statistical Analyses

Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) 17.0 program was used for statistical analysis. Kolmogorov–Smirnov test was used for the comparisons to determine the distribution of all variable groups. Using Kruskal-Wallis test assessed variations in erythrocytes deformability. Bonferroni adjusted Mann-Whitney U test was used after significant Kruskal-Wallis to determine which group differs from the other. Results were expressed as mean± standard deviation (Mean ± SD). Statistical significance was set at a p value <0.05.

RESULTS

Diabetes mellitus was found to make relative resistance increase in the control group (p <0.0001). Acute hyperglycemia increased relative resistance in diabetes control, relatively. Group DH, Group DH-D and Group DH-S deformability index were significantly different when compared to Group DC (p=0.007, p=0.025, p=0.016, respectively). It was found that administration of desflurane or sevoflurane did not alter erythrocyte deformability during acute hyperglycemia (p = 0.591, p = 0.739)(Figure 1).

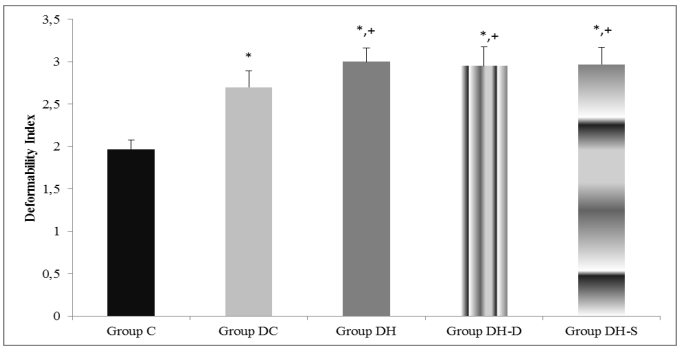

Figure 1: Erythrocyte deformability values of the groups. Each bar represents the mean ± SE.
* p<0.05 compared to Group C; + p< 0.05 compared to Group DC

DISCUSSION

Diabetes mellitus is a metabolic disorder diagnosed increasingly all over the world, which is characterized by high glucose level along with low insulin levels. In these patients, cardiovascular complications, mortality rate, and length of hospital stay are observed to increase (11-13). In patients with diabetes, hematologic changes, endothelial dysfunction, and platelet hyperactivity are observed. These changes contribute to etiology of vascular complications due to diabetes (14,15).

Released hormones as a response to surgical stress cause increased insulin resistance, the impairment of using glucose in peripheral tissues, and hyperglycemia. In a previous study, hyperglycemia results in increased erythrocyte aggregation, and changes the nature of hemoglobin, serum proteins, and erythrocyte membrane proteins (16). The shape of erythrocyte is biconcave, which is a necessary feature of it. This feature provides erythrocyte with extra surface area and the ability of deformability. In end organ capillaries, erythrocytes have an ability to change their shapes to carry Oxygen and vital molecules, and remove waste materials. This feature is called deformability (17). Thanks to deformability, erythrocytes can change their shapes while flowing in big vessels in the direction of flow (bigger than 3 mm) or in very tinny capillaries. The deformability of erythrocytes is determined by the following three properties: Visco-elastic properties of membrane, cytoplasmic viscosity, and surface-volume ratio. The structure provides erythrocytes to change their shapes when passing capillaries, also change into previous anatomic shape after the passing, which is called membrane Skeleton. It is located just beneath the cell membrane and consists of various proteins. Protein Kinase C plays a key role for membrane protein stabilization and deformability (18-21). This skeleton provides changes of erythrocyte shape without changing surface area, so erythrocytes changing their shapes may pass capillaries easily. Erythrocytes with lessen changing abilities will cause circulatory system disorders as well. Some of genetic abnormalities, diabetes, hypertension, cardiovascular disorders, aging, tumors, anemia, malaria, impaired tissue perfusion, oxidative stress, some drugs, and other factors increasing blood viscosity may result in decreased erythrocyte deformability (22-25). Erythrocyte deformability gains more importance during the microcirculation. Impaired perfusion in tissue level is blamed on reduced erythrocyte deformability in diabetes (26,27). Prat et al. cited that poor glycemic control was related to increased rate of complications such as nephropathies, neuropathies or retinopathies (28). Sufficient blood volume in microcirculation is needed for sufficient tissue perfusion. General anesthetic agents are known to have an effect on cardiovascular functions and microcirculation (8). Anesthetic agents change the diameter of arteriole and venules related to their dose. According to an experimental previous study, halogens agents such as halothane and sevoflurane were shown to have more negative inotropic effect in diabetes (29). After the surgery with general anesthesia, it is possible to observe reduced erythrocyte deformability and increased aggregation(30).

According to Aydogan et al. shown that deformability due to sevoflurane reduced in elderly rats (31). Also, Desflurane was shown to reduce deformability in elderly rats (32). In another study, Sevoflurane was shown to reduce deformability in male rats, while Desflurane was shown to reduce deformability in both female and male rats (33).

Acute hyperglycemia is a prognostic factor for various disorders. There is a correlation between acute hyperglycemia and high mortality rates for patients with acute myocardial infarction, stroke and operated for cardiovascular disorders (34-38). According to a study in 2012, it was shown that even only 5 minutes exposure to hyperglycemia might change erythrocyte deformability (39). Riquelme et al. (40) showed that 2 hours exposure to hyperglycemia changed viscoelastic feature of erythrocyte membrane dramatically, Shin et al. showed that erythrocyte deformability was depended on dose and time as well (41). Diltoer and Camu showed that isoflurane caused glucose intolerance (42). In previous studies, halothane, enflurane and isoflurane were shown to repress insulin response to glucose as dose-dependently and reversibly (42-44). Etrafi et al. shown that hyperglycemia occurred during 60 minutes after Halothane induction and continued 120 minutes (45). Dikmen et al. used Sevoflurane and Desflurane in diabetic rats after acute hyperglycemia and found that increased glucose level stayed until 24 hours postoperatively, but this finding was not statistically significant (46). In this study, we aimed to investigate the effects of sevoflurane and desflurane on erythrocyte deformability during the hyperglycemia which was created temporarily, and we found that implementation of Desflurane and Sevoflurane did not change the erythrocyte deformability in hyperglycemia. As a consequence, we think that we can safely use inhalation anesthetics such as Desflurane and Sevoflurane during acute hyperglycemia attacks. But, it needs further investigation as both experimental and clinical.

Conflict of interest

No conflict of interest was declared by the authors.

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