

Comparison of the effects of SGLT 2 inhibitors and sulfonylurea on electrocardiographic parameters

SGLT 2 inhibitörleri ve sülfonilürenin elektrokardiyografik parametreler üzerindeki etkilerinin karşılaştırılması

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SUMMARY





Objective: Tp-e, QT, and Tp-e / QT are parameters showing ventricular repolarization. The increase in these parameters causes an increase in cardiovascular mortality, mostly due to malignant arrhythmias. Our study aimed to compare the long-term changes in electrocardiographic parameters in patients with uncontrolled diabetes despite using metformin, with the addition of SGLT 2 inhibitor or sulfonylurea (SU) to the treatment.

Method: This retrospective study was enrolled in 133 type 2 DM patients with uncontrolled diabetes who applied to the internal medicine outpatient clinic, using single oral antidiabetic agents. The patients were divided into two groups as SU and SGLT 2 inhibitor additive. SU was added to the treatment of 69 patients, and SGLT 2 inhibitor was added to 64 patients. 12-lead superficial ECG records of participants who received combined therapy for at least six months were analyzed and compared. RR distance, QT interval, and Tp-e intervals were measured on the ECG. QTc was calculated using Bazett's formula. (QT/ \sqrt{RR}). Tp-e / QT and Tp-e / QTc ratios were calculated.

Results: Seventy-eight (58.6%) of the participants were female, and 55 (41.4) were male. The age and gender distribution of both groups were similar. The group to which SGLT 2 inhibitor was added, Tp-e, QT, and QTc distances were significantly lower than the SU group ($p < 0.001$ for each). Also, the Tp-e / QT and Tp-e / QTc ratios were significantly greater in the SU group (0.210 ± 0.029 vs 0.190 ± 0.03 ; $p < 0.001$ and 0.201 ± 0.051 vs 0.184 ± 0.032 ; $p = 0.022$ respectively).

Conclusions: In our study, we showed that the addition of SGLT2 inhibitors to monotherapy in people with diabetes with poor glycemic control has a positive effect on ECG parameters, which are indicators of repolarization, compared to other oral antidiabetics.

Keywords: SGLT 2 inhibitors, sulfonylurea, ventricular repolarization, Type 2 diabetes mellitus

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Amaç: Tp-e, QT ve Tp-e / QT ventriküler repolarizasyonu gösteren parametrelerdir. Bu parametrelerdeki artış, çoğunlukla malign aritmilere bağlı olarak kardiyovasküler mortalitede artışa neden olur. Çalışmamız, metformin kullanımına rağmen kontrolsüz diabetes mellituslu hastalarda tedaviye SGLT 2 inhibitörü veya sülfonilüre (SU) ilave edilmesiyle elektrokardiyografik parametrelerdeki uzun süreli değişiklikleri karşılaştırmayı amaçladı.

Yöntem: Bu retrospektif çalışma, iç hastalıkları polikliniğine başvuran tek oral antidiyabetik ajan kullanan, kontrolsüz diyabetli 133 tip 2 DM hastası üzerinde yapıldı. Hastalar tedaviye SU ve SGLT 2 inhibitörü eklenenler olarak iki gruba ayrıldı. 69 hastanın tedavisine SU, 64 hastaya SGLT 2 inhibitörü eklendi. En az altı ay boyunca kombine tedavi gören katılımcıların 12 derivasyonlu yüzeysel EKG kayıtları analiz edildi ve karşılaştırıldı. EKG'de RR mesafesi, QT aralığı ve Tp-e aralıkları ölçüldü. QTc, Bazzet formülü kullanılarak hesaplandı. (QT / \sqrt{RR}). Tp-e / QT ve Tp-e / QTc oranları hesaplandı.

Bulgular: Katılımcıların 78'i (% 58,6) kadın, 55'i (41,4) erkekti. Her iki grubun yaş ve cinsiyet dağılımı benzerdi. SGLT 2 inhibitörü eklenen grup, Tp-e, QT ve QTc mesafeleri SU grubuna göre anlamlı olarak daha düşüktü (her biri için $p < 0,001$). Ayrıca Tp-e / QT ve Tp-e / QTc oranları SU grubunda anlamlı olarak daha yüksekti (sırasıyla $0,210 \pm 0,029$ 'a karşı $0,190 \pm 0,03$; $p < 0,001$ ve $0,201 \pm 0,051$ 'e karşı $0,184 \pm 0,032$; $p = 0,022$).

Sonuç: Çalışmamızda glisemik kontrolü zayıf diyabetli kişilerde monoterapiye SGLT2 inhibitörlerinin eklenmesinin repolarizasyon göstergesi olan EKG parametreleri üzerinde diğer oral antidiyabetiklere göre olumlu etkisi olduğunu gösterdik.

Anahtar sözcükler: SGLT 2 inhibitörleri, sülfonilüre, ventriküler repolarizasyon, Tip 2 diyabetes mellitus.

INTRODUCTION

Diabetes Mellitus (DM) is an important health problem with an increasing prevalence worldwide. Although recently developed treatment methods are promising, it is a common cause of mortality and morbidity, primarily due to the complications it causes¹. Cardiac complications have an essential place among these. Empagliflozin and dapagliflozin are Sodium-Glucose Co-transporter (SGLT 2) inhibitor that acts independently of insulin and decreases blood glucose levels by increasing glucose excretion from urine². SGLT2 inhibitors can be used alone or in combination with other antidiabetics. Recently, its positive cardiac effects have been proven by large-scale studies. It has been reported that it decreases hospital stay and mortality, especially in heart failure with reduced ejection fraction and diastolic dysfunction³. However, its effects on ventricular arrhythmia are not clearly known. Clinical studies have reported that the Tp-e interval and Tp-e / QT ratio are helpful but straightforward parameters for predicting increased ventricular arrhythmias and cardiovascular events. It is more effective in showing ventricular repolarization because it is not affected by heart rate like QT and QT dispersion (QTd)⁴. Many studies have shown that prolonged TP-e interval is associated with increased cardiac mortality⁵⁻⁹.

Our study examined the effect of adding empagliflozin or dapagliflozin to treatment on Tp-e and Tp-e/QT, which are indicators of ventricular repolarization, in patients receiving monotherapy and with unregulated type 2 DM.

MATERIAL AND METHODS

One hundred thirty-three type 2 DM patients who applied to endocrinology and internal medicine outpatient clinics and had insufficient glycemic control were included in the study. These patients were switched from monotherapy to combination therapy with dual oral agents due to poor glycemic control. The patients were divided into two groups. The first group was the patients in whom sulfonylurea (SU) was added to the monotherapy, and the second group was the patients who had empagliflozin or dapagliflozin added. SU was added to 69 patients, and empagliflozin was added to 64 patients. Medical anamnesis of all patients participating in the study were taken, and a complete physical examination was performed. Drug use histories were questioned. Anthropometric measurements were taken and recorded. Electrocardiographic (ECG) records of the patients after combination therapy for a minimum of six months were reviewed.

12-lead ECG recording (50 mm / s, 10 mm / mV) was obtained using Nihon Kohden (Tokyo, Japan) brand ECG device. ECG papers were scanned and transferred to digital media, and measurements were made manually by magnifying 300 times in a computer environment. QT and Tp-e intervals and QRS duration were calculated. Corrected QT (cQT) was computed using Bazzet's formula (QT / \sqrt{RR} interval).

Those with known coronary artery disease, systolic heart failure, chronic renal failure, endocrine disorders, active infection, radiotherapy and chemotherapy treatment, those with left bundle branch block on ECG, atrial fibrillation, electrolyte disorder that may cause ECG changes (hypercalcemia, hypokalemia hypomagnesemia,

etc.), those with a history of cardioverter defibrillator and pacemaker implantation, antiarrhythmic drug use, patients using drugs that can change the QT interval (antidepressants, neuroleptics, hydroxychloroquine, etc.) were excluded from the study.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software (version 22.0; SPSS Inc., Chicago, IL, USA) was used to analyze the data. Categorical variables were expressed as percentage (%) and frequency. Continuous variables were expressed as mean \pm standard deviation. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for the normality test of the data. A comparison between groups was made using the Mann-Whitney U- or t-test

according to data distribution. The Chi-square test was used to evaluate the differences of categorical variables between groups. P-value <0.05 was considered significant.

RESULTS

The study group's mean age was 65.52 ± 13.72 years (78 female / 55 male). There was no significant difference in age and gender between the groups (66.11 ± 10.58 vs. 65.09 ± 12.16 , respectively, $p = 0.607$). There was no statistically significant difference between the groups regarding the number of hypertensive and hyperlipidemic patients. Table 1 shows the demographic and anthropometric measurements of the patients.

Table 1: Comparison of demographic and anthropometric measurements of the groups

Parameters	SGLT-2 inhibitor added group (64) (Mean \pm SD)	Sulfonylurea added group (69) (Mean \pm SD)	p-value
Age (years)	66.11 ± 10.58	65.09 ± 12.16	0.607
Gender (female /male)	38 / 26	40 / 29	
HT, n (%)	21 (32.8 %)	19 (27.5 %)	0.236
HL, n (%)	25 (%39.1)	29 (%42.1)	0.561
Smokers, n (%)	14 (%21.8)	16 (%23.2)	0.347
Duration of diabetes, years	7.4 ± 3.1	$7,8 \pm 3.5$	0.217
Body mass index (kg/ m ²)	30.49 ± 3.4	29.3 ± 4.6	0.630
Systolic BP (mmHg)	130.6 ± 11.3	132.2 ± 10.2	0.725
Diastolic BP (mmHg)	81.6 ± 5.7	81.5 ± 6.1	0.843
LVEF (%)	61.8 ± 3.2	62.3 ± 4.1	0.539

HT: Hypertension, HL: Hyperlipidemia, BP: blood pressure, LVEF: Left ventricular ejection fraction

When biochemical parameters were compared, fasting blood glucose levels and HbA1c were slightly lower in the SGLT 2 inhibitor group. However, this difference had no statistical

significance (128.2 ± 33.4 vs 132.8 ± 29.2 ; $p = 0.394$ and 6.9 ± 1.4 vs $7.1 \pm 1,9$; $p = 0.324$). There was no significant difference between both groups in terms of other parameters (Table 2).

Table 2: Comparison of laboratory findings

Parameters	SGLT-2 inhibitor added group (64) (Mean ± SD)	Sulfonylurea added group (69) (Mean ± SD)	p- value
FPG (mg/dL)	128.2 ± 33.4	132.8 ± 29.2	0.394
HbA1c (%)	6.9 ± 1.4	7.1 ± 1.9	0.324
Creatinine (mg/dL)	0.86 ± 0.22	0.87 ± 0.21	0.866
Uric acid	5.6 ± 2.9	5.8 ± 3.0	0.124
Na (mEq/L)	137.5 ± 6.1	137.1 ± 4.5	0.692
K (mEq/L)	4.6 ± 0.6	4.5 ± 0.8	0.217
Ca (mg/dL)	9.5 ± 0.7	9.6 ± 0.6	0.506
Total CHL	222.4 ± 49.3	218.4 ± 38.3	0.468
HDL-C (mg/dL)	44.5 ± 6.1	46.5 ± 5.6	0.648
LDL-C (mg/dL)	133.4 ± 38.5	132.2 ± 35.1	0.834
Triglyceride (mg/dL)	181.4 ± 71.5	174.7 ± 19.9	0.591
AST, IU/L	29.3 ± 14.4	32.1 ± 13.2	0.212
ALT, IU/L	28.3 ± 12.1	27.3 ± 10.6	0.654

FBG: Fasting plasma glucose, Na: Sodium, K: *Potassium*, Ca: *Calcium*, CHL: cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase

After six months of follow-up, there was a significant decrease in Tp-e interval in patients using empagliflozin or dapagliflozin as an add-on to metformin compared to SU (72.52 ± 10.93 ms vs. 83.65 ± 11.21 ms, $p < 0.001$). When the QT and QTc intervals were compared, there was a significant difference between the two groups (383.13 ± 31.17 vs 398.46 ± 25.62 and $398.19 \pm$

46.92 vs 439.08 ± 63.96 ; $p < 0.001$ for each). Also, the Tp-e / QT and Tp-e / QTc ratios were significantly lower in the empagliflozin group compared to the SU group (0.190 ± 0.030 vs 0.210 ± 0.029 ; $p < 0.001$ and 0.184 ± 0.032 vs 0.201 ± 0.051 ; $p = 0.022$). The comparison of ECG parameters of the groups is shown in Table 3.

Table 3: Electrocardiographic findings between groups

Parameters	SGLT2 inhibitor added group (64) (Mean ± SD)	Sulfonylurea added group (69) (Mean ± SD)	p value
QT interval (ms)	383.13 ± 31.17	398.46 ± 25.62	<0.001
QTc interval (ms)	398.19 ± 46.92	439.08 ± 63.96	<0.001
Heart rate (beats/min)	82.14 ± 18.52	77.68 ± 13.62	0.114
Tp-e interval (ms)	72.52 ± 10.93	83.65 ± 11.21	<0.001
TP-e / QT	0.190 ± 0.030	0.210 ± 0.029	<0.001
Tp-e / QTc	0.184 ± 0.032	0.201 ± 0.051	<0.022

Tp-e: T peak-to-end

DISCUSSION

As a result of the study, we showed that QT, QTc, Type, Tp-e / QT, and Tp-e / QTc show ventricular repolarization changed positively with the addition of SGLT 2 inhibitors to monotherapy.

Cardiovascular complications caused by DM are generally asymptomatic and silent. Therefore, early identification of complications and early

initiation of necessary measures may decrease mortality. Ventricular arrhythmia also takes an important place among these complications. The risk of sudden cardiac death due to arrhythmias is higher in diabetic patients than in the average population¹⁰. The reasons for this may include silent ischemic coronary artery disease, impaired ventricular function, impaired repolarization abnormalities, and changes in cardiac autonomic

activity. A possible cause in all these pathologies is the increased heterogeneity of ventricular repolarization. The Tp-e interval shows the transmural dispersion of ventricular repolarization¹¹. Many studies have shown that prolonged TP-e interval is associated with increased cardiovascular mortality⁵⁻⁹. However, the Tp-e / QTc ratio is also a sensitive index for showing ventricular repolarization⁴.

In a recent large trial, empagliflozin has been shown to reduce cardiovascular mortality in type 2 DM patients at high cardiovascular risk. It has also been shown to reduce hospitalizations and improve concomitant heart failure symptoms with reduced ejection fraction³. Although the possible pathogenesis of this is not known clearly, the underlying cause is thought to be due to arterial stiffness, cardiac oxygen demand, and a decrease in volume load. In animal experiments, empagliflozin has been shown to reduce left ventricular mass and fibrosis in mice with metabolic syndrome¹². In a study conducted in humans, it has been demonstrated that the 1-year use of SGLT 2 inhibitors in patients with coronary stents reduces the patency of coronary stents and the formation of new plaques¹³. Based on this study, we think that by providing plaque stabilization in coronary arteries, myocardial perfusion can continue well, and arrhythmia can be reduced in long rotation. In another experimental animal study, it was reported that dapagliflozin, an SGLT2 inhibitor, improves ventricular repolarization by increasing mitochondrial functions in mice with insulin resistance¹⁴.

We think that a treatment method that can improve electrocardiographic parameters such as Tp-e, Tp-e / QT in diabetic patients, that is, reduces the heterogeneity of ventricular repolarization, may decrease cardiovascular mortality. Our study showed that the addition of empagliflozin, an SGLT 2 inhibitor, to the treatment due to insufficient glycemic control despite taking metformin improved ECG parameters, which is an indicator of ventricular arrhythmia.

LIMITATIONS

The study's main limitation was that the number of patients was relatively small, and it was a single-center study. Another limitation was our analysis of two oral antidiabetic drugs in combination therapy. There is a need to investigate the benefits of SGLT2 inhibitors on arrhythmia with extensive population studies, including other antidiabetics.

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