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Original Research Article

Effect of sulfonylureas on attenuation of electrocardiographic ST-segment elevation during an acute myocardial infarction in diabetics

Bapugouda Sahebagouda Patil[1], Naser Ashraf Tadvi[2]*

[1]Department of Pharmacology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India
[2]Department of Basic Medical Sciences, College of Medicine, Majmaah University, Al Majmaah, 11952, Kingdom of Saudi Arabia

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***Correspondence to:**
Dr. Naser Ashraf Tadvi,
Email: n.tadvi@mu.edu.sa

ABSTRACT

Background: Sulfonylureas are primarily used in the treatment of diabetes mellitus act by inhibiting ATP sensitive potassium ATP (K-ATP) channels. Similar channels are also present are also present in heart venticular muscle. Previous studies reveal that these drugs are able to reduce the electrocardiographic ST- segment elevation changes during an acute myocardial infarction. Hence, the present study was designed to evaluate the attenuating effect of sulfonylureas on ST- segment elevation in diabetic patients presenting with acute myocardial infarction.
Methods: This cross sectional study included 73 diabetic patients presenting with the signs and symptoms of acute myocardial infarction of less than 24 hours duration along with CPK levels of more than 25 IU/L. Of them 5 were excluded from the study. The remaining 68 patients were included in the study, out of which 36 patients were in the study group (sulfonylurea group), and 32 patients were in the control group (non-sulfonylurea group).
Results: No statistically significant difference was seen in the demographic parameters like age, sex, duration of diabetes mellitus and CPK levels ($p>0.05$). Among 68 patients 38 patients were diagnosed as STEMI. The mean magnitude of ST-elevation in the study group (n=16) was 2.3±0.12 and in control group (n=22) patients it was 3.7±0.33. The percentage of NSTEMI was significantly higher in study group compared to control. Statistically significant difference ($p<0.05$) was seen only between CPK level of range 25 and 100IU/L and mean magnitude of ST-segment elevation in STEMI patients. Significant difference in the mean magnitude of ST-segment elevation was observed in case of females among the study and control groups ($p<0.05$).
Conclusions: Sulfonylureas drugs play a significant role in attenuation of ST-segment in diabetic patients presenting with acute myocardial infarction. Further, large multicentric studies are required to confirm the exact correlation between sulfonylureas and ST-segment.

Keywords: Acute myocardial infarction, Diabetes, Sulfonylureas, ST-segment elevation

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.[1]

The incidence of cardiovascular disease is increased in individuals with type 1 or type 2 diabetes mellitus. There is also marked increase in peripheral artery diseases, heart failure, coronary artery diseases, myocardial infarction,

and sudden death in patients with DM. The American Heart Association has designated DM as a coronary heart disease (CHD) risk equivalent.[1] With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.

Sulfonylureas (SUs) are advocated in the treatment of type 2 DM as a single drug or in combination with other anti-diabetic regimens. Sulfonylureas stimulate insulin release by binding to a specific site on the β cell KATP channel complex (the sulfonylurea receptor, SUR) and inhibiting its activity. KATP channel inhibition causes cell membrane depolarization and the cascade of events leading to insulin secretion.[2] These channels are widely distributed in various tissues and may be associated with diverse cellular functions. They are also involved in myocardial infarction (MI) which is the most common life threatening illness and is frequently associated with DM.[3] In the heart, the KATP channel appears to be activated during ischaemic or hypoxic conditions and may be responsible for the increase of K+ efflux and shortening of the action potential duration. Therefore, opening of this channel may result in cardio protective as well as proarrhythmic effects. Thus, these channels play an important regulatory role in the cardiovascular system. Furthermore, KATP channels are the targets of important classes of drugs, i.e., the anti-diabetic sulfonylureas, which block the channels.[4,5]

The present study was conducted with two objectives. The primary objective of the study was to assess the percentage of patients with non ST-elevation MI (NSTEMI) and ST-elevation MI (STEMI) in diabetic patients on sulfonylureas and on non-sulfonylureas presenting with acute MI and to compare the percentage of NSTEMI and STEMI in sulfonylureas with non-sulfonylureas groups.

The secondary objective of the study was to measure the magnitude of ST-elevation in diabetic patients on sulfonylureas and on non-sulfonylureas presenting with acute MI and to compare the magnitude of ST- elevation in sulfonylurea group with non-sulfonylurea group presenting with acute MI.

METHODS

This descriptive cross sectional study was conducted at Department of Pharmacology in collaboration with Department of General Medicine, Kamineni Institute of Medical Sciences, (KIMS) Narketpally, Nalgonda from September 2012 to October 2014.

After getting approval from institutional ethics committee, total of 73 diabetic patients presenting with the signs and symptoms of acute myocardial infarction of less than 24 hours duration along with CPK levels of more than 25 IU/L were selected for the study. These patients were included in the study or control group depending upon their antidiabetic regimen.

Inclusion criteria

Study groups

Diabetic patients of either sex, aged between 30 and 90 years on sulfonylureas or in combination with any other anti-diabetic drugs for any duration presenting with acute myocardial infarction of less than 24 hours with creatinine phosphokinase (CPK) levels more than 25 IU/L were included in the study.

Control groups

Diabetic patients of either sex, aged between 30 and 90 years on any anti diabetic drug other than sulfonylureas or on diet therapy and/or no medical therapy for any duration presenting with acute myocardial infarction of less than 24 hours with CPK levels more than 25 IU/L.

Exclusion criteria

Patients presenting with left/right bundle - branch block, with left ventricular hypertrophy with strain pattern (√) by ECG, with AMI with symptoms more than 24 hours duration and patients on meglitinide therapy were excluded from the study.

Out of 73, 5 patients had been excluded from the study. The remaining 68 patients were included in the study, out of which 36 patients were in the study group (sulfonylurea group), and 32 patients were in the control group (non-sulfonylurea group). The demographic data of these patients were collected and the first ECG charts of all these patients were selected for the ST-segment analysis.

The ECGs of these patients were analysed by the physician who was completely blind about the study and study groups. A baseline was traced horizontally in all leads and ST- segment elevation was measured at 20-40 ms after the J point in all the affected leads. The criteria for diagnosing the patients as STEMI are either more than 2 mm elevation in 2 contiguous chest leads, (V1-V6) or more than 1 mm elevation in 2 contiguous in limb leads (I, I, I, II, III, avR, avL, avF). 12 These ECGs were categorised into STEMI OR NSTEMI, and the magnitude of ST-segment elevation was noted down for all the STEMI patients.

Statistical analysis

All the data was collected and tabulated in MS excel sheet. Statistical analysis was done using SPSS version 19 software. The following tests were applied, and the p value of $p<0.05$ was considered as statistically significant. Chi-square test was applied to analyse the distribution of NSTEMI and STEMI in the study and control group, for sub group analysis related to sex and CPK levels Fisher exact test was applied to analyse the distribution of NSTEMI and STEMI in the study and control group. Unpaired 't' test was applied to compare the mean

magnitude of ST-segment elevation in STEMI patients in main group as well as subgroups.

RESULTS

The study included 36 patients in the study group (sulfonylurea group), and 32 patients were in the control group (non-sulfonylurea group). Table 1 presents the demographic data of the study population. The study group and control group are identical and comparable as there is no statistically significant difference in the demographic parameters like age, sex, duration of diabetes mellitus and CPK levels (p>0.05).

Table 2 presents the distribution of STEMI and NSTEMI in study and control group. In the study group 16 (44.5%) patients were diagnosed as STEMI and 20 (55.5%) patients as NSTEMI. In the control group 22 (68.7%) patients were diagnosed as STEMI and 10 (31.3%) patients were diagnosed as NSTEMI. On applying the Chi-square test the percentage of NSTEMI patients is statistically significant in the study group compared to control group (p<0.05).

Table 1: Demographic characteristics of study population.

Parameters	Study group (sulfonylurea group)	Control group (non-sulfonylurea group)
Age (in yrs) (Mean±SD)	63.2±11.0	60.6±12.1
Females	17 (47%)	13 (41%)
Males	19 (53%)	19 (59%)
Duration of diabetes (in yrs) (Mean±SD)	7.1±3.5	5.9±4.1
CPK (IU/L) (Mean±SD)	180.8±86.5	172.6±62.7

Table 2: Distribution of STEMI and NSTEMI in study and control group (N=68).

Groups	STEMI	NSTEMI
Study group (n=36)	16 (44.5%)	20* (55.5%)
Control group (n=32)	22 (68.7%)	10 (31.3%)

*p<0.05

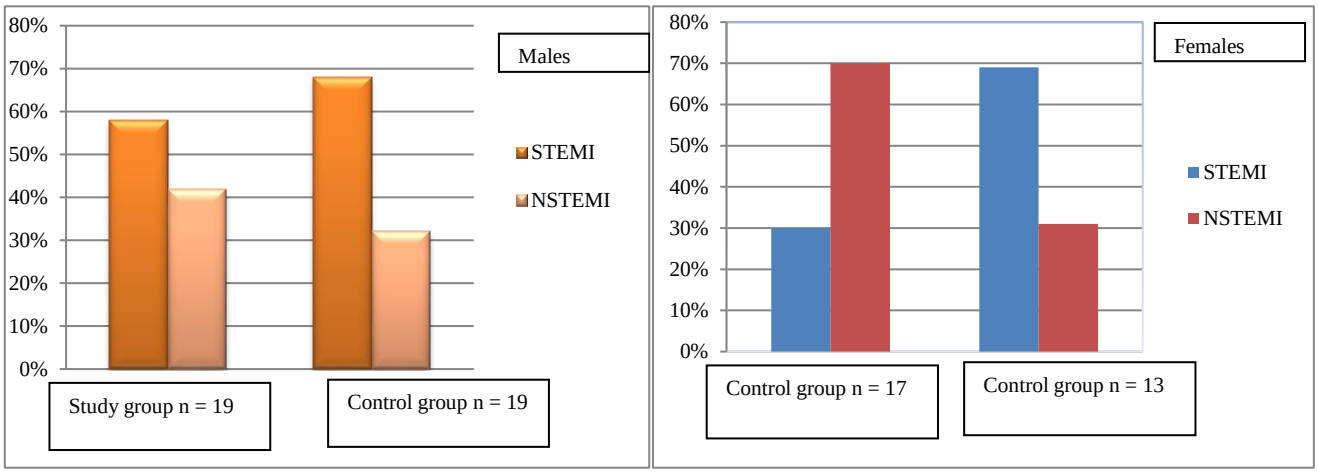

Figure 1: Sex wise distribution of proportion of STEMI and NSTEMI in study and control group.

Table 3: CPK level wise distribution STEMI and NSTEMI in study and control groups.

Category	CPK values					
	Between 25 and 100 IU/L		Between 101 and 200 IU/L		More than 200 IU/L	
	Study group (n=7)	Control group (n=4)	Study group (n=16)	Control group (n=16)	Study group (n=13)	Control group (n=12)
STEMI	5 (72%)	2 (50%)	6 (38%)	11 (69%)	5 (38%)	8 (69%)
NSTEMI	2 (28%)	2 (50%)	10 (62%)	5 (31%)	8 (62%)	4 (31%)

There were 38 male and 30 female patients in the present study. Their distribution in the study and control groups was given in Figure 1. Of total 38 males, 11 (58%) patients were diagnosed as STEMI and 8 (42%) patients were diagnosed as NSTEMI in the study group. In the control group 13(68%) patients were diagnosed as STEMI and 6 (32%) patients were diagnosed as NSTEMI. Out of 36 females, 5 (30%) patients were diagnosed as STEMI and

12 (70%) patients were diagnosed as NSTEMI in the study group. In the control group 9 (69%) patients were diagnosed as STEMI and 4(31%) patients were diagnosed as NSTEMI. On applying the Fisher exact test the percentage of NSTEMI patients is statistically significant in the study group compared to control group ($p<0.05$).

CPK level wise distribution of STEMI and NSTEMI in study and control group (N=68) were given in Table 3. There were 11 patients who had CPK values between 25 and 100 IU/L. Out of which 7 patients were in the study group and 4 patients were in the control group. In the study group 5 (72%) patients were diagnosed as STEMI and 2 (28%) patients were diagnosed as NSTEMI. In control group 2 (50%) patients were diagnosed as STEMI and 2 (50%) patients were diagnosed as NSTEMI.

There were 32 patients who had CPK values between 101 and 200 IU/L. Out of which 16 patients were in the study group and 16 patients were in the control group. In the study group 6 (38%) patients were diagnosed as STEMI and 10 (62%) patients were diagnosed as NSTEMI. In the control group 11 (69%) patients were diagnosed as STEMI and 5 (31%) patients were diagnosed as NSTEMI.

There were 25 patients who had CPK values more than 200 IU/L. Out of which 13 patients were in the study group and 12 patients were included in the control group. In the study group 5 (38%) patients were diagnosed as STEMI and 8 (62%) patients were diagnosed as NSTEMI. In the control group 8 (69%) patients were diagnosed as STEMI and 4 (31%) patients were diagnosed as NSTEMI.

On applying the Fisher exact test the percentage of NSTEMI patients is statistically not significant in the study group compared to control group ($P>0.05$).

Table 4: Mean magnitude of ST-segment elevation in STEMI patients (N=38).

Groups	Mean±SEM (in mm)
Study group (n = 16)	2.3±0.12*
Control group (n = 22)	3.7±0.33

*p<0.05

Among 68 patients 38 patients were diagnosed as STEMI, these were selected for measurement of magnitude of ST-segment elevation. The mean magnitude of ST-elevation in the study group (n=16) was 2.3±0.12 and in control group (n=22) patients it was 3.7±0.33 as given in Table 4. On applying student unpaired 't' test the difference in the mean magnitude of ST-segment elevation is statistically significant in the study group compared to control group ($p<0.05$).

Table 5 shows the sex wise distribution of mean magnitude of ST-segment elevation in STEMI patients. Out of 38 patients diagnosed as STEMI, there were 24 male and 14 female patients. No statistically significant difference in the mean magnitude of ST-segment elevation was observed among male patients in both study (n=11) and control groups (n=13) ($p>0.05$). Whereas in case of females the difference in the mean magnitude of ST-segment elevation was statistically significant between study (n=5) and control groups (n=9) ($p<0.05$).

Table 5: Sex wise distribution of mean magnitude of ST-segment elevation in STEMI patients (N=38).

Males		Females	
Groups	**Mean±SEM (in mm)**	**Groups**	**Mean±SEM (in mm)**
Study group (n=11)	2.45±0.15	Study group (n=5)	2.2±0.2*
Control group (n=13)	3.23±0.34	Control group (n=9)	4.4±0.6

*p<0.05

Table 6 presents the CPK level wise distribution of mean magnitude of ST-segment elevation in STEMI patients. Out of 38, 7 patients had presented with CPK values between 25 and 100 IU/L. Of them, 5 patients were in study group and 2 patients were in the control group with the mean magnitude of ST-segment elevation of 2.0±0.0 and 3.5±0.5 respectively and this difference was statistically significant ($p<0.05$). 18 patients had presented with CPK values between 101 and 200 IU/L. 18 patients had presented with CPK values between 101 and 200 IU/L. 6 patients were in study group with the mean magnitude of ST-segment elevation of 2.5±0.2 and 12 patients were in the control group with the mean magnitude of ST-segment elevation of 3.4±0.4 and the difference between two groups was not significant statistically ($p>0.05$).

Table 6: CPK level wise distribution of mean magnitude of ST-segment elevation in STEMI patients (N=38).

CPK values 25 to 100IU/L		CPK values 101 to 200IU/L		CPK values more than 200IU/L	
Groups	**Mean±SEM (in mm)**	**Groups**	**Mean±SEM (in mm)**	**Groups**	**Mean±SEM (in mm)**
Study group (n=5)	2.0±0.0*	Study group (n=6)	2.5±0.2	Study group (n=5)	2.6±0.2
Control group (n=2)	3.5±0.5	Control group (n=12)	3.4±0.4	Control group (n=8)	4.0±0.7

13 patients had presented with CPK values more than 200 IU/L. 5 patients were in study group with the mean magnitude of ST-segment elevation of 2.6±0.2 and 8 patients were in the control group with the mean magnitude of ST-segment elevation of 4.0±0.7 and no statistically significant difference was seen between them ($p>0.05$).

DISCUSSION

Sulfonylureas are the mainstay of treatment in type 2 diabetic patients. These drugs produce their effect by blocking KATP channels in the pancreas thereby causing insulin release.[2] However KATP channels are also present in the heart and are involved in myocardial infarction. These channels open up during ischemia of the cardiac tissue and are responsible for the ST-segment elevation in the electrocardiography.[6]

Sulfonylureas block these cardiac KATP channels also causing suppression of the ST-segment elevation during acute MI. The MI patients on sulfonylureas even though they have ST elevation MI, they are mis-diagnosed as to have non ST elevation MI because of this effect of sulfonylureas on KATP channels.[6] Therefore the present study is undertaken to evaluate the effect of sulfonylureas on S-T segment elevation in DM patients presenting with acute MI.

In the present study, a total of 73 diabetic patients presenting with acute myocardial infarction were reviewed. Out of these, five patients were excluded from the study as they could not meet the inclusion criteria. The remaining patients were divided into study group i.e. patients receiving sulfonylurea and control group i.e. patients receiving other therapies than sulfonylurea. The ECG of all these patients were analysed for the S-T changes during an acute MI.

The present study found that the percentage of NSTEMI is significantly more in the study group (55.5%) compared to control group (31.3%). The mean magnitude of elevation of ST-segment is significantly less in the study group (2.3±0.12) compared to control group (3.7±0.33). These results suggest that the sulfonylureas may have a role in attenuating the ST-segment in type 2 diabetic patients who are presenting with acute myocardial infarction. This was in agreement with the findings of Chen et al.[7] According to his report, glibenclamide initially blocked KATP channels and masked ECG change and after the drug elimination, elevation of delayed ST-segment was appeared.

In sex wise sub group analysis, among the female diabetic patients who presented with acute MI, the percentage of NSTEMI is significantly more in study group (70%) when compared with the control group (31%), whereas in male patients the percentage of NSTEMI is more in the study group (42%) as compared to control group (32%) but the difference was not statistically significant. This was in contrast to the findings of Huizar et al study in which a female preponderance (males 37.5% females 62.5 %) was observed.[8]

In the subgroup analysis of female diabetic patients presented with STEMI, the mean magnitude of ST-segment elevation was significantly less in study group (2.2±0.2) compared to control group (4.4±0.6). It is difficult to explain and conclude as the sample size in subgroup is very small. But among male patients the difference in the mean magnitude of ST-elevation in the study group compared to control group was not statistically significant.

In the sub group analysis for CPK values, the percentage of NSTEMI in study group is not significantly different as compared to control group. This may also be because of less sample size in each sub group. However, in the sub group analysis of 3 different CPK values, the patients who had CPK values between 25 and 100 IU/L, the mean magnitude of ST-segment elevation is less in study group (2.0±0.0) compared to control group (3.5±0.5) which was statistically significant. Whereas the patients who had CPK values between 101 and 200 IU/L and more than 200 IU/L the difference was not statistically significant between the two groups. This could be explained as follows, in patients who had CPK values more than 100 IU/L it is postulated that there is a greater extent of myocardial injury causing more KATP channels to open up which should lead to a greater increase in ST-segment elevation. So, the sulfonylureas failed to blunt the ST-segment completely. So, the attenuation effect of sulfonylureas on ST-segment is less.[8]

Studies of Huizar et al demonstrated that the control group had a greater percentage of AMI with CPK >500 mg/dl as compared with the sulfonylurea group (59% vs. 37%, $p=0.05$).[8] In his study, study group comprised of patients receiving only sulfonylureas. This was in contrast to our study group. He determined that the difference in percentage of AMI with CPK >500 mg/dl might be due to higher thrombolytic use in the control group with a subsequent rapid washout of cardiac enzymes.

From the present study it is found that the decrease in magnitude of ST-elevation in STEMI patients in the sulfonylurea group is statistically significant when compared with control group. This might be due to underlying mechanism i.e. sulphonylureas block the cardiac KATP channels that are located in the cytoplasmic and mitochondrial membrane.[9,10] This was in agreement with the findings of Fernández et al.[11] Similar conclusion was also drawn by Kubota et al by conducting an experimental study on animals.[12] He demonstrated that the opening of KATP channels plays an important role in the development of ST-segment elevation during myocardial injury and showed that ST-segment elevation during acute myocardial injury could be blunted by glyburide (KATP channel blocker), but potentiated by pinacidil (KATP channel opener) in non-ischemic tissue. By reducing the

ischemia-related accumulation of K^+ in the extracellular space, treatment with sulfonylureas may lead to less hyperpolarization of the resting membrane potential within the ischemic area and thus causes less ST-segment elevation in the ECG recordings.

CONCLUSION

The findings of the present study confirm that sulfonylurea drugs have a definite role in attenuation of ST-segment in diabetic patients presenting with acute myocardial infarction. Many patients on sulfonylureas are misdiagnosed as NSTEMI depending upon the ECG even though they have ST-segment elevation, and these patients do not receive thrombolytic therapy which may lead to higher mortality and morbidity in these patients. So the diabetic patients on sulfonylureas presenting with NSTEMI might be reconsidered for the thrombolytic therapy. Further large multicentric studies are required to confirm the correlation between sulfonylureas and ST-segment.

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