

The therapeutic efficacy of ranolazine in comparison with conventional therapy in diabetic individuals with ischemic heart disease; a randomized clinical trial

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ABSTRACT

Introduction: Patients with diabetes mellitus (DM) have higher risk of coronary artery disease (CAD) and angina than the general population.

Objectives: We sought to assess the impact of ranolazine as an antianginal agent to diminish hemoglobin A1c (Hb A1c) level in diabetic individuals under treatment with metformin and gliclazide.

Patients and Methods: This study was a randomized parallel-group clinical trial to compare the therapeutic effects of ranolazine versus conventional treatment in patients with concomitant T2DM and stable angina. TERISA (type 2 diabetes mellitus evaluation of ranolazine in subjects with chronic stable angina) was employed to assess the efficiency of ranolazine in lowering the frequency of angina attacks. The study was performed on diabetic patients with symptomatic angina under treatment with either sublingual nitroglycerin or up to two types of antianginal agents. The patients in the intervention group received 1000 mg ranolazine twice a day while patients in the control group were administered with conventional treatment. Reduction in baseline Hb A1c level was determined at 4 and 8 weeks after the interventions.

Results: Ranolazine therapy resulted in up to 15% absolute reduction in Hb A1c level in diabetic patients who had baseline HbA1c level >7%. Ranolazine was more efficient in reducing Hb A1c in patients with poorly controlled disease (i.e. HbA1c>8%, $P=0.017$). Ranolazine did not affect the glycemic status of patients concomitantly treated with antidiabetic therapy ($P=0.560$).

Conclusion: Concurrent administration of ranolazine along with anti-diabetic treatments (i.e. metformin and gliclazide) was safe to reduce the level of HbA1c in patients with poorly controlled diabetes and stable angina.

Trial Registration: The protocol was approved in Iranian Registry of Clinical Trials under the number of IRCT20161026030511N3; <https://www.irct.ir/trial/24223>, Ethical code; R.SBMU.PHNM.1394.308.

Implication for health policy/practice/research/medical education:

Ranolazine can improve quality of life and exercise tolerance and reduce angina frequency. Ranolazine can also improve HbA1c level in individuals with concomitant type 2 diabetes mellitus and chronic stable angina without imposing any adverse effects on kidneys.

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Introduction

Type 2 diabetes (T2DM) is a global health problem particularly in developed countries. Diabetes mellitus (DM) increases the risk of coronary artery disease (CAD) and angina (1, 2) and is a significant predictor of mortality and comorbidity in patients with cardiovascular diseases and angina (3,4). Hyperglycemia may accelerate the risk of

atherosclerosis, a chronic inflammatory process which is known as the main contributor to cardiac complications. According to these, it is highly desirable to develop drugs to concurrently treat both T2DM and CAD.

Ranolazine is the first line antianginal drug with cardioprotective effects and no impacts on cardiac function, heart rate or blood pressure (5). Ranolazine

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decreased the need for administration of sublingual nitroglycerin and the frequency of angina (6,7) and also improved glycemic control and quality of life in diabetic patients (8). Ranolazine is believed to reduce myocardial ischemia and angina incidence through inhibiting cardiac slow sodium currents and reducing intracellular sodium and calcium overload as the main contributor to myocardial ischemia (9). The exact mechanism of action of ranolazine to modulate HbA1c level is still unknown. Ranolazine can regulate late sodium currents channels which are increased in hyperglycemia and promote glucose-stimulated insulin secretion (10-12). HbA1c is a clinically important biomarker for screening long-term glycemic control (13,14).

Objectives

Since the HbA1c-lowering effects of ranolazine have been reported in previous studies (3,15), clinical trials on this issue are rare. In the current clinical trial, we intended to assess the impacts of ranolazine on HbA1c level and clinical outcomes in patients with DM and stable angina. Our diabetic patients with stable angina were categorized into either intervention (i.e. ranolazine treatment) or control (i.e. conventional treatment) group. All the patients continued to receive conventional anti-diabetic treatments (i.e. metformin and gliclazide). The outcomes included angina frequency and glycemic level.

Patients and Methods

Study design

This was a parallel-group randomized clinical trial comparing the effects of ranolazine versus conventional therapy in patients with concurrent T2DM and stable angina. The patients who had been diagnosed with these conditions for at least 10 weeks were initially observed for 2 weeks to monitor their health status. Then nitroglycerin was replaced with ranolazine in the intervention group for 8 weeks.

Overall, 60 patients were recruited and divided into either the intervention or control group. The patients were recruited from the diabetes clinic of the Shahid Rajaie Heart Center from June 2015 to January 2016. Patients fulfilling inclusion criteria were randomly selected and allocated into intervention and control groups using the balanced block randomization method.

All the patients were asked to sign an informed consent form. Patients who developed any complication during the study were excluded. After entering the study, the patients were monitored for two weeks to assess their health condition (i.e. phase 1). During this period, the patients received their routine diabetic care (i.e. 500 mg metformin three times a day and 80 mg gliclazide twice a day). They also received 2.6 mg nitroglycerin daily to treat stable angina.

History of daily chest pain or angina and using

sublingual nitroglycerin was determined by questionnaire. The patients who received more than two types of antianginal medications had to spend a 2-week wash-out period before entering the study. No patients had been administered with more than two antianginal drugs or verapamil and/or diltiazem therapeutic diet. The patients who had been treated with either verapamil or diltiazem underwent dosage adjustment by administration of 500 mg maintenance dose of ranolazine twice a day. All the subjects were under observation for two weeks to examine their health status. After 2 weeks of observation, nitroglycerin was replaced with ranolazine in the intervention group while routine treatment continued in the control group.

Study population

Overall, 60 patients including 29 men and 31 women with mean age of 64 ± 5 years old were enrolled in this study. Based on standardized difference (difference/SD) of 0.75, power of 80% and an alpha value of 0.05, the sample size was calculated as 60 ($n=30$ per each group) using G-power software.

Inclusion criteria

Diabetic patients with HbA1c $> 6.5\%$, age > 50 years old, and chronic stable angina (i.e. persisted angina for more than three months, triggered by physical efforts, and relieved by rest and/or sublingual nitroglycerin) were included. Other inclusion criteria were angiographic evidence of $\geq 50\%$ stenosis, history of myocardial infarction (MI), CAD diagnosed by cardiac imaging or exercise test, and more than two weeks of treatment with at least two types of antianginal drugs. Patients should have had at least one angina attack per week to enter the study. Patients with T2DM treated with metformin and gliclazide who had systolic blood pressure of 120-160 mm Hg and presented with dyspnea were also included.

Exclusion criteria

New York heart association (NYHA) class III and IV patients were excluded from the study (16). Furthermore, patients with the history of acute coronary syndrome during the past two months, those planned for coronary revascularization, and patients who had history of cardiac infraction or transient ischemic attack within the past six months were excluded. Other exclusion criteria were as QTc of less than 500 ms, diastolic blood pressure of more than 110 mm Hg, and histories of liver cirrhosis, previous treatment with ranolazine, hypersensitivity or intolerance to ranolazine, as well as participation in experiments other than the current study. In addition, patients who were under treatment with trimetazidine, ivabradine or nicorandil, patients undergoing dialysis, and those, who received more than two types of antianginal medications were excluded.

Exercise test and laboratory investigations to determine HbA1c, fasting blood sugar (FBS) and 2-hours postprandial glucose (2HPP), serum creatinine and lipid profile were performed at baseline, as well as at 4 and 8 weeks after starting the study. Complete clinical data including histories of hypertension, received medications (e.g. antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and ARBs (angiotensin-receptor blockers), anti-diabetic drugs, calcium channel blockers (CCBs), beta-blockers and nitrates, anti-platelet agents, and antianginal drugs), smoking status, history of MI or coronary artery bypass graft (CABG), and the number of angina episodes were recorded using a standard questionnaire.

The number of angina attacks was recorded during a 24-hour period (i.e. from the evening of one day to the evening of the next day). The number of consumed sublingual nitroglycerin pills per day was also obtained using a self-reported questionnaire. After randomization, the patients in the intervention group were administered with 500 mg ranolazine for 1 week (i.e. loading dose) which was increased to 1000 mg twice a day (i.e. maintenance dose). In case of tolerance, the maintenance dose was administered for seven weeks. In the control group, the

patients continued their conventional therapy (i.e. 2.6 mg nitroglycerin for angina and metformin and gliclazide for diabetes).

Efficacy assessments

The primary endpoint of this study was the reduction of HbA1c in diabetic patients who received either ranolazine or conventional therapy after 8 weeks of the study. The other outcomes were improved treadmill exercise time, reduction in the number of administered sublingual nitroglycerin pills, and finally reduction in angina episodes per week.

Safety analysis

Adverse events were self-reported by patients using pre-prepared forms.

Laboratory measurements

Blood samples were withdrawn after overnight fasting in the laboratory of the Shahid Rajaie Heart Center. Plasma FBS and 2HPP levels were determined by the plasma glucose oxidase method. Plasma HbA1c was measured by high-pressure liquid chromatography (Hitachi 911 automatic analyzer). Figure 1 shows the CONSORT

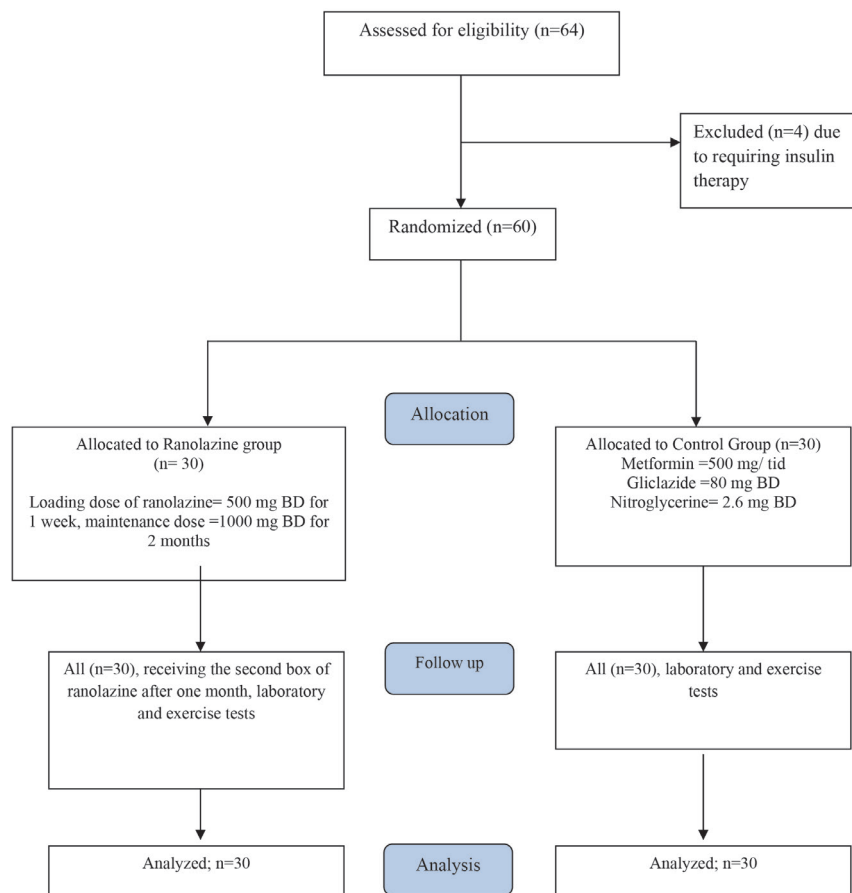


Figure 1. The CONSORT diagram of the study.

diagram of the study.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. All study protocols were approved by the institutional ethical committee at Shahid-Rajaei Heart center and Iran University of Medical Sciences. The study was also registered in the Iranian Registry of Clinical Trials (identifier: IRCT20161026030511N3, <https://www.irct.ir/trial/24223>; Ethical code; R.SBMU.PHNM.1394.308). Written informed consent was obtained from all the participants before any intervention.

Statistical analysis

Statistical analyses were performed using SPSS software for Windows version 23.0 (SPSS Inc., IL, USA). Descriptive statistics were used to present the data as mean \pm standard deviation (SD) and frequencies. Kolmogorov-Smirnov test was used to assess normal distribution of the variables. Independent samples student *t* test was used as the parametric test for normally distributed data, and Mann-Whitney U test was applied as non-parametric test for non-normally distributed variables. Chi-square test was used to compare qualitative variables. The significance level was considered as *P* value < 0.05 .

Results

The baseline and clinical characteristics of the studied patients have been shown in Tables 1 and 2 respectively.

Efficacy

The changes in the levels of HbA1c, FBS and 2HPP in both groups during the study described in Figures 2-5.

Effects of ranolazine on serum creatinine levels in diabetic patients

Ranolazine (1000 mg twice a day) did not affect creatinine level during 8 weeks post-treatment (Figure 6, *P*=0.182).

Adverse events

No serious adverse effects and no mortalities were noted during the study in neither of the groups. Mild adverse events have been reported in Table 3.

Discussion

For the first time, we here compared the therapeutic effects of ranolazine and conventional treatment in Iranian diabetic patients who suffered from stable angina. There were no significant differences comparing baseline clinical and demographic variables including gender, age, history of MI, history of heart surgery, smoking frequency, and duration of DM between the ranolazine and control groups indicating balanced distribution of these parameters. The primary therapeutic goals in diabetic patients are to maintain the HbA1c level below 7% and to reduce angina frequency. Our results revealed

Table 1. Baseline characteristics of patients

	Control group n = 30	Ranolazine group, n = 30	<i>P</i> value
Male	15	14	0.529
Female	15	16	0.529
Age (y)	64 (60.75-67.25)	65 (58-70)	0.058
History of MI	46.7%	43.5%	0.817
History of heart surgery	52.3%	78.3%	0.061
Years of smoking	7.5 years	7 years	0.767
Number of smokes per day	20	12	0.197
Duration of DM (y)	8.5	6	0.382

Abbreviations: MI, myocardial infarction; DM, diabetes mellitus.

Table 2. Clinical characteristics of the recruited patients following the start of the treatments

	Ranolazine group	Control group	<i>P</i> value
HbA1c baseline (%)	8.3 \pm 1.47	7.85 \pm 0.97	0.035
First month HbA1c (%)	7.4 \pm 1.15	7.7 \pm 0.96	0.85
Second month HbA1c (%)	7 \pm 0.96	7.8 \pm 0.96	0.072
FBS baseline (mg/dL)	161 \pm 51.59	128 \pm 54.81	0.002
FBS First month (mg/dL)	145 \pm 35.69	134.5 \pm 36.1	0.092
FBS Second month (mg/dL)	131 \pm 33.77	130.5 \pm 26.12	0.467
2HPP baseline (mg/dL)	291 \pm 80.56	199.5 \pm 58.94	0.011
2HPP First month (mg/dL)	250 \pm 59.25	195.5 \pm 44.65	0.011
2HPP Second month (mg/dL)	196 \pm 44.42	192.5 \pm 38.37	0.560
ET baseline	3.69 \pm 2.97	5 \pm 2.69	0.689
ET First month	5 \pm 3.52	5.2 \pm 2.97	0.613
ET Second month	5.5 \pm 3.32	4.65 \pm 2.79	0.353
Angina frequency w_1	7	6	0.251
Angina frequency w_2	6	6	0.585
Angina frequency w_3	5	6	0.046
Angina frequency w_4	5	6	0.001
Angina frequency w_5	4	6	0.003
Angina frequency w_6	4	6	0.001 \leq
Angina frequency w_7	4	5	0.001
Angina frequency w_8	3	5	0.001
Serum creatinine	1.024 \pm 0.214	0.974 \pm 0.174	0.399
Serum creatinine w_4	0.986 \pm 0.156	0.996 \pm 0.158	0.835
Serum creatinine w_8	1.062 \pm 0.196	0.978 \pm 0.211	0.182

Abbreviations: HbA1c; glycated hemoglobin A (HbA1c), FBS; Fasting blood sugar (mg/dL), 2HPP; 2-hours postprandial plasma glucose (mg/dL).

significant reductions in FBS level and angina frequency in the ranolazine group at 4- and 8-week post-intervention. Nevertheless, no significant alternations were seen in these parameters in the control group (*P*=0.134). On the other hand, the duration of the exercise test (*P*=0.353) and serum creatinine (*P*=0.182) were similar in both groups.

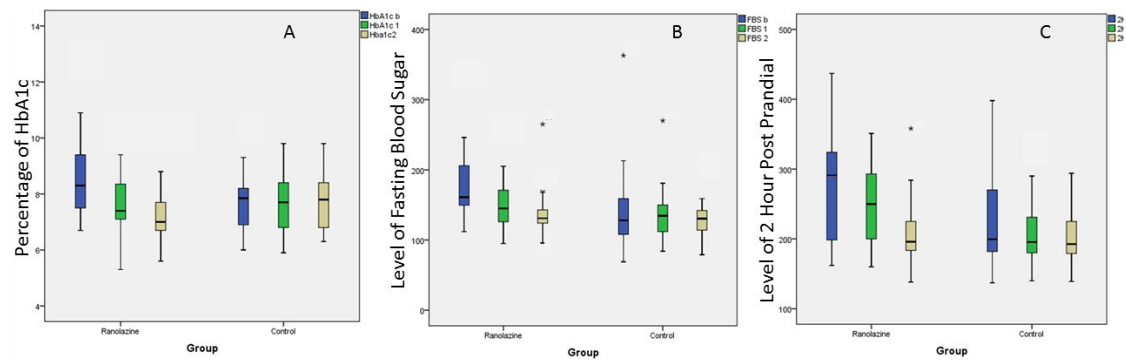


Figure 2. Alterations of Hb A1c, FBS, and 2HPP levels in the studied groups. (A) HbA1c percentage reduced in ranolazine treated group over the time while no significant change was observed in the conventional therapy group during the 8 weeks of study ($P = 0.072$). (B) FBS level reduced in both groups during the study with more pronounced reduction in the ranolazine group ($P = 0.011$). (C) The 2HPP levels showed a significant reduction in both ranolazine and control groups compared to the baseline ($P = 0.011$).

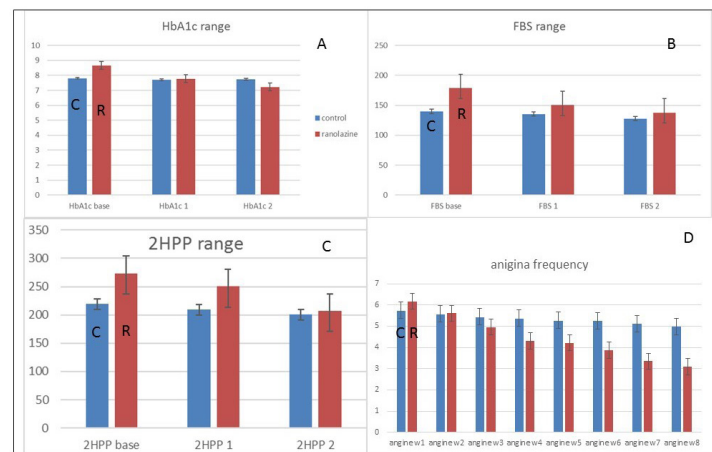


Figure 3. The changes in Hb A1c, FBS, 2HPP, and angina frequency in the studied groups. A) HbA1c significantly reduced in ranolazine following 8 weeks of treatment. B) FBS level significantly reduced in ranolazine group. C) While a decreasing trend was seen in the level of 2HPP in the ranolazine group, there was no significant difference comparing the mean difference of 2HPP between ranolazine and control groups after two months of intervention ($P = 0.56$). D) the number of angina attacks per week significantly reduced in both ranolazine and conventional therapy groups.

This indicates that ranolazine therapy can decrease HbA1c level in patients with concurrent T2DM and angina treated with conventional anti-diabetes therapies without increasing the risk of hypoglycemia. Nevertheless, there is insufficient data to conclusively conclude that ranolazine does not exaggerate the risk of hypoglycemia.

DM is a risk factor of CAD and angina (1, 2). Although there have been significant improvements in the management of heart diseases, the burden of mortality and morbidity due to heart disease still remains high (17). Recently, the beneficial roles of drugs modulating the energy metabolism and mitochondrial function of myocardial cells have been shown. These agents enhance the ability of myocardium to effectively metabolize glucose and to increase the overall ATP production (18, 20). Ranolazine, an approved antianginal drug, is capable of inhibiting cardiac late sodium currents (21). In patients

with T2DM, however, ranolazine administration reduced HbA1c percentage (3, 22) which was in accordance with our study.

HbA1c measurement is the gold standard indicator of glycemic status and is widely used as a diagnostic and prognostic marker in diabetes (23). In addition, increased HbA1c is considered an independent risk factor for cardiovascular diseases. Nevertheless, HbA1c level is influenced by fluctuations of hemoglobin, administration of medications, and the ethnicity of patients. Another limitation of HbA1c is that, it can only reflect the mean blood glucose level during the recent two to three months. Furthermore, HbA1c measurement cannot accurately reflect short-term glycemic variability in patients. Finally, HbA1c alternations are delayed limiting its application for monitoring the therapeutic effects of glucose-reducing agents.

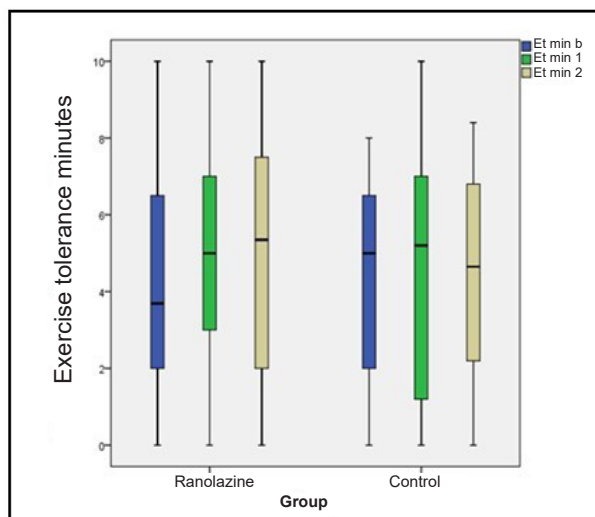


Figure 4. The exercise tolerance test in both studied groups at the baseline, and after 4 and 8 weeks of intervention. No significant change was observed in the exercise tolerance duration comparing the two groups ($P = 0.353$).

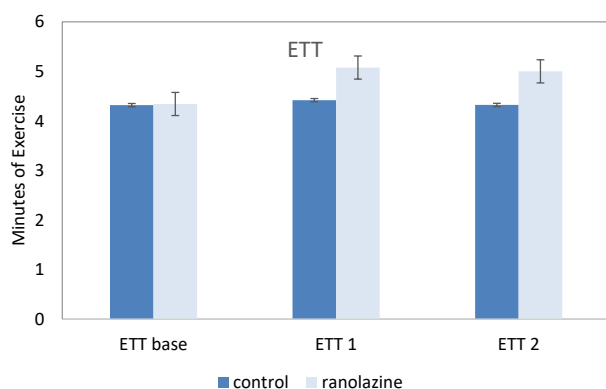


Figure 5. The exercise tolerance test (ETT) in both studied groups. Ranolazine significantly increased the capability of patients to perform the exercise test while no improvement was observed in patients that received conventional therapy.

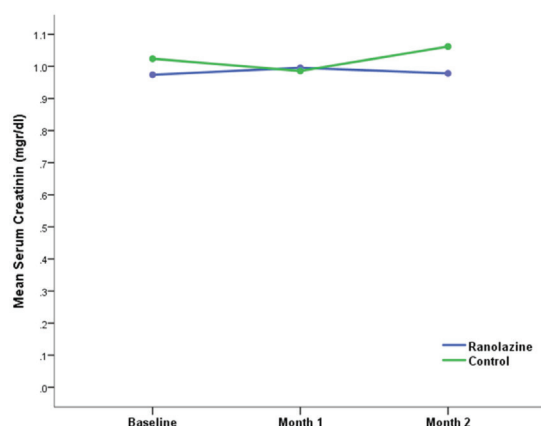


Figure 6. Serum creatinine levels at baseline and after 4 and 8 weeks of intervention.

Table 3. The incidence of adverse events (AE) in diabetic patients with angina received either ranolazine or conventional therapy

Adverse event	Diabetic patients with angina	
	Control group ^a	Intervention group ^b
Patients with AE	6	8
Discontinuation due to AE	0	0
Constipation	2	4
Dizziness	1	1
Nausea	1	1
Asthenia	2	2
Hypoglycemia	0	0
Other Adverse Events	0	0

^a 500 mg metformin TDS, 80 mg gliclazide BID, 2.6 mg nitroglycerin daily.

^b 500 mg metformin TDS, 80 mg gliclazide BID, 1000 mg ranolazine BID.

Ranolazine is an antianginal drug with cardioprotective features without any undesirable impacts on cardiac hemodynamic features such as heart rate and blood pressure. Ranolazine has been effective in the treatment of chronic angina both as monotherapy and in combination with commonly prescribed cardiovascular drugs (24, 25). The type 2 diabetes mellitus evaluation of ranolazine in subjects with chronic stable angina (TERISA) clinical trial was the first study to highlight the efficiency of ranolazine in reducing the frequency of angina episodes in diabetic patients who had high baseline HbA1c levels (8). Similarly, other studies have revealed the anti-hyperglycemic effects of ranolazine either alone or in combination with other agents (5,26,27). However, more studies are required to determine the optimal ranolazine-based pharmaceutical regimens to augment its therapeutic effects. Our patients who received ranolazine had improved exercise tolerance time which is in line with previous studies expressing that ranolazine significantly improved exercise duration compared with placebo (3,28). We also demonstrated that higher doses of ranolazine and longer durations of treatment can dose-dependently enhance the therapeutic effects of the drug in reducing HbA1c and FBS levels.

One of our objectives was to ascertain whether ranolazine could reduce the frequency of angina attacks in our patients. In this regard, the patients in both groups experienced chest pain every day at the beginning of the study. After receiving ranolazine; however, the patients in the intervention group mentioned a significant reduction in chest pain while patients in the control group expressed no alternation. According to our findings, it can be estimated that longer periods of ranolazine therapy (for instance 12 weeks) may result in disappearance of angina attacks in diabetic patients.

Conclusion

Ranolazine treatment can reduce the occurrence of angina attacks and improve quality of life and exercise tolerance

time in patients with concurrent T2DM and chronic stable angina. In addition, ranolazine was shown as a well-tolerated therapy reducing HbA1c level in these patients without causing renal dysfunction or imposing serious adverse events such as hypoglycemia.

Limitations of the study

The major limitation of our study was that elderly patients had difficulties to perform exercise test as most of them complained about physical limitations such as knee problems. Secondly, uneducated patients had difficulties in filling out their forms.

Authors' contribution

BFF and GG conducted the research. FF, ZG and SMA conducted the first edition. Accordingly, AZM and HB conducted the second edition and revised the manuscript. All authors read and signed the final manuscript.

Conflicts of interest

Authors declare no potential conflicts of interest. Ranolazine was provided to the patients free of any charge.

Ethical considerations

Ethical issues (including plagiarism, double publication) were completely observed by the authors. A part of this study was presented as an abstract in ISCOMS; the International Student Congress of (bio)Medical Sciences (www.iscoms.com).

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