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ORIGINAL ARTICLE

Does Tight Glucose Control During the First 24 hours of Hospitalization Reduce Scintigraphic Infarct Size in STEMI Patients?

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Abstract

Background: Hyperglycemia at the time of admission is related to increased mortality and poor prognosis in patients diagnosed with ST-segment elevation myocardial infarction (STEMI).

Objective: We aimed to investigate whether tight glucose control during the first 24 hours of STEMI decreases the scintigraphic infarct size.

Methods: The study population consisted of 56 out of 134 consecutive patients hospitalized with STEMI in a coronary care unit. Twenty-eight patients were treated with continuous insulin infusion during the first 24 hours of hospitalization, while the other 28 patients were treated with subcutaneous insulin on an as-needed basis. The final infarct size was evaluated with single-photon emission computed tomography (SPECT) in all patients on days 4 to 10 of hospitalization. The groups were compared and then predictors of final infarct size were analyzed with univariate and multivariate linear regression analysis. A p-value < 0.05 was considered statistically significant.

Results: The mean glucose level in the first 24 hours was 130 ± 20 mg/dL in the infusion group and 152 ± 31 mg/dL in the standard care group (p = 0.002), while the mean final infarct size was 20 ± 12% and 27 ± 15% (p = 0.06), respectively. The multivariate linear regression analysis demonstrated that the mean 24-hour glucose level was an independent predictor of the final infarct size (beta 0.29, p = 0.026).

Conclusion: Tight glucose control with continuous insulin infusion was not associated with smaller infarct size when compared to standard care in STEMI patients. (Int J Cardiovasc Sci. 2020; 33(5):497-505)

Keywords: ST-Elevation Myocardial Infarction/mortality/mortality; Hyperglycemia; Hospitalization; Insulin; Tomography, Emission Computed,Single Photon/methods; Myocardial Perfusion Imaging.

Introduction

Hyperglycemia has become a predictor of mortality and morbidity in patients with acute coronary syndrome (ACS).[1] High blood glucose levels cause increased mortality, larger infarct size, unsuccessful reperfusion, and prolonged hospitalization.[2,3] Glucose has direct harmful effects on the myocardial tissue by increasing the levels of oxygen radicals, free fatty acids, ketones, and lactate. Also, it enhances platelet aggregation and activates other mediators in the coagulation system, leading to unsuccessful reperfusion.[4]

Hyperglycemia is caused by increased sympathetic activity as a consequence of disease severity. It has been shown that mortality increases with glucose levels higher than 140 mg/dL both at the time of admission and in the

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first 24 hours.[5] Current guidelines recommend glucose-lowering therapy when admission glucose levels exceed 200 mg/dL[6] Guideline recommendations are based on this therapeutic threshold to avoid hypoglycemia, as shown in the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study.[7] However, the population of that study consisted of critically ill patients treated in intensive care units rather than patients with ST-segment elevation myocardial infarction (STEMI).

Previous studies have not comprehensively investigated whether intensive blood glucose control aiming for levels lower than 140 mg/dL in the first 24 hours of STEMI is beneficial in relatively low-risk patients. Evaluation of scintigraphic infarct size with single-photon emission computed tomography (SPECT) in STEMI patients is a valuable outcome for pilot studies aiming to search for new treatment modalities with a limited number of patients.[8] In our study, we aimed to investigate the effects of tight glucose control with continuous insulin infusion during the first 24 hours of hospitalization on final infarct size in STEMI patients.

Methods

Study population

Of 134 consecutive patients presenting with STEMI, 56 were included in the study. Their mean age was 55.1 ± 11 years, and 44 (78.6%) were male. They all had successful reperfusion demonstrated angiographically in the infarct-related artery during the first 6 hours of chest pain . Inclusion criteria were having admission glucose levels higher than 140 mg/dL (irrespective of having a prior diabetes diagnosis), being diagnosed with myocardial infarction (MI) for the first time, and being hemodynamically stable. Local ethics committee approval was obtained for the conduct of the study. Written informed consent was obtained from all patients included in the study. STEMI diagnosis was made as per the criteria stated in current guidelines. The success of reperfusion was defined in patients receiving thrombolytic therapy as 70% or more resolution of the ST-segment elevation on electrocardiography and relief of ischemic chest pain within 90 minutes of treatment. All patients underwent primary or rescue percutaneous coronary intervention (PCI) or an early invasive strategy. In patients treated with primary or rescue PCI, Thrombolysis in Myocardial Infarction grade 3 (TIMI-3) flow in the infarct-related artery was accepted as successful reperfusion. The patients in whom TIMI-3 flow and ST-segment resolution on ECG could not be achieved were excluded from the study. All study patients were treated with standard anti-ischemic therapy, including treatment with beta-blockers, renin-angiotensin converting enzyme inhibitors, statins, and dual antiplatelet agents.

Blood glucose regulation

In half of the study patients (n = 28), blood glucose levels were regulated with insulin infusion, targeting levels between 80-140 mg/dL. Insulin infusion was administered in line with the Yale University infusion protocol. The protocol has been described elsewhere and proven to be safe for avoiding hypoglycemia.[9,10] The Yale University infusion protocol allows nurses to adjust the infusion dose without a need for order. In the remaining 28 patients, short-acting insulin was administered subcutaneously on an as-needed basis upon the clinician's discretion. Blood glucose was measured every time with the same glucometer at the bedside. Enteral alimentation with a cardiac and diabetic diet started 4 hours after PCI provided that the patient was clinically stable. After the first 24 hours, blood glucose levels were checked 4 times a day in all patients. Subcutaneous insulin was administered when needed in all study patients according to the standards of care.

Myocardial perfusion scintigraphy

All study patients underwent myocardial perfusion scintigraphy with SPECT using 10 mCi of technetium-99m sestamibi on days 4 to 10 of hospitalization. Tomographic images were obtained using a dual-head gamma camera with a high-resolution collimator (Siemens Medical Solutions, Erlangen, Germany). After the standard view images were acquired, the percentage of the final infarct size was calculated automatically with a software (Emory Toolbox). All scintigraphic images and associated calculations were acquired and performed in the nuclear medicine laboratory of Istanbul University Institute of Cardiology. All estimations were conducted by a single experienced operator, who was blinded to the study patients.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median with 25–75 percentiles based on their distribution. Categorical variables were described as percentages and numbers. Kolmogorov-Smirnov test and/

or histogram was used to define the distribution of the data. Group comparisons were performed using a two-sample t-test or Mann-Whitney U test according to the distribution of the data, while a chi-square test was used for the categorical variables. We chose a large effect size (0.50, because of the small dataset), with α = 0.05, n = 56, and 7 predictors for linear regression models. Power was calculated as 0.87. The association between final infarct size (dependent variable) and predictors was evaluated with univariate and multivariate linear regression models. The assumptions of our linear regression model were the following: a near-normal linear relationship exists between the independent and dependent variables, which was assessed with a scatter plot. Little or no important collinearity was detected among the independent predictors, and no variable in the variance inflation factor (VIF) model was over 5. Residuals had a near-normal distribution, and no important autocorrelation was found in Q-Q plot among residuals. Potential pathophysiological and clinical predictors of the final infarct size were included based on the results of previous studies and the results of univariate linear regression analysis with data from the present study. In all statistical analyses, a p-value < 0.05 was considered statistically significant. R software with Hmisc and rms packages, version 3.2.2 (R Project, Vienna, Austria), was used for statistical analysis.

Results

In total, 56 out of 134 STEMI patients were included in the study. Their mean age was 55.1 ± 11, and 44 (78.6%) were male (Figure 1). Half of the participants (n = 28) were treated with insulin infusion. There were no statistically significant differences in demographic and clinical characteristics and biochemical results between the two groups (Table 1). The mean admission glucose levels were 192 ± 47 mg/dL in the insulin infusion group and 178 ± 49 mg/dL in the standard care group (p = 0.3). The mean blood glucose levels in the first 24 hours were 130 ± 20 mg/dL in the insulin infusion group and 152 ± 31 mg/dL in the standard care group (p = 0.002). The mean admission glucose level was 217 ± 57 mg/dL in the diabetic patients and 163 ± 21 mg/dL in the nondiabetic patients (p < 0.0001). The mean 24-hour glucose level was 153 ± 29 mg/dL and 133 ± 21 mg/dL in the diabetic and nondiabetic patients, respectively (p = 0.006). In the insulin infusion group, blood glucose levels lower than 60 mg/dL were detected twice; however, no patients manifested symptomatic hypoglycemia. Mean 24-hour glucose levels lower than 140 mg/dL were found in 20 out of 28 patients in the insulin infusion group and in 13 out of 28 patients in the standard care group (p = 0.05). The mean final infarct

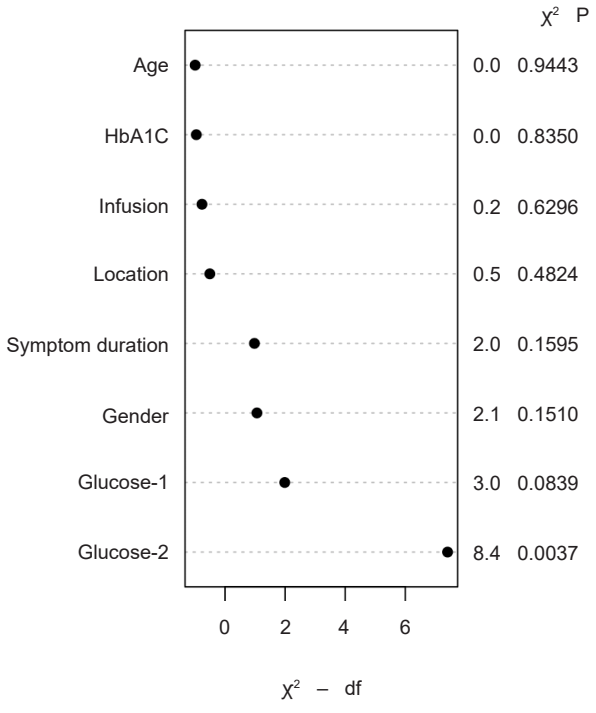

Figure 1 – Glucose-1: admission glucose; Glucose-24: mean 24-hour glucose; HbA1C: glycated hemoglobin.

Table 1. Characteristics of study patients according to blood glucose control regimen groups

	Insulin infusion	Standard care	p-value
Age (years)	55.4 ± 12.2	55 ± 11.7	0.885
Gender (female/total [%])	6/22	6/22	1
BMI (kg/m^2)	27.5 ± 3.9	27.4 ± 5.4	0.822
DM (n, %)	14/28	9/28	0.277
HT (n, %)	11/28	13/28	0.787
HL (n, %)	7/28	9/28	0.768
Smoking (n, %)	16/28	12/28	0.408
Pre-infarct angina (n, %)	12/28	15/28	0.422
Symptom duration (minutes) (median, IQR)	160 (112-240)	160 (120-180)	0.971
Systolic blood pressure (mm Hg)	129 ± 25	125 ± 28	0.529
Diastolic blood pressure (mm Hg)	79 ± 15	74 ± 14	0.288
Heart rate (beat/ minute)	74 ± 15	80 ± 16	0.137
STEMI location (anterior/total)	12/28	12/28	1
Admission glucose (mg/dL)	192 ± 47	178 ± 49	0.303
Mean 24-hour glucose (mg/dL)	130 ± 20	152 ± 31	0.002
Total cholesterol (mg/dL)	205 ± 50	191 ± 43	0.274
HDL cholesterol (mg/dL)	38 ± 8	39 ± 14	0.89
LDL cholesterol (mg/dL)	139 ± 38	124 ± 33	0.12
Triglycerides (mg/dL)	164 ± 48	174 ± 76	0.134
HbA1c (%)	6.9 ± 2.1	6.4 ± 1.9	0.434
Creatinine (mg/dL)	1.1 ± 0.5	0.9 ± 0.2	0.136
Hematocrit (%)	39 ± 7	39 ± 8	0.863
Creatine phosphokinase (peak) (mg/dL)	2390 ± 2156	2884 ± 2335	0.42
Creatine phosphokinase-MB (peak) (mg/dL)	263 ± 201	273 ± 183	0.84
Infarct size (%)	27.1 ± 15.2	20.0 ± 12.6	0.062

BMI: body mass index; DM: diabetes mellitus; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; STEMI: ST-segment elevation myocardial infarction; HT: Hypertension; HL: Hyperlipidemia.

size was 20 ± 12% in the insulin infusion group and 27 ± 15% in the standard care group (p = 0.06).

In the univariate linear regression analysis, anterior location of the infarct, symptom duration, and mean 24-hour glucose level were found to be predictors of the final infarct size (beta [β] 8.74, p = 0.022; β 0.027, p = 0.033; β 0.174, p = 0.014, respectively). Partial effect plot of 24-hour blood glucose and final infarct size is shown in Figure 2. In the multivariate linear regression analysis adjusted for age, gender, symptom duration, infarct location, admission glucose levels, 24-hour glucose levels, HbA1c levels, and glucose-lowering modality, only mean 24-hour glucose level independently predicted the final infarct size (Table 2).

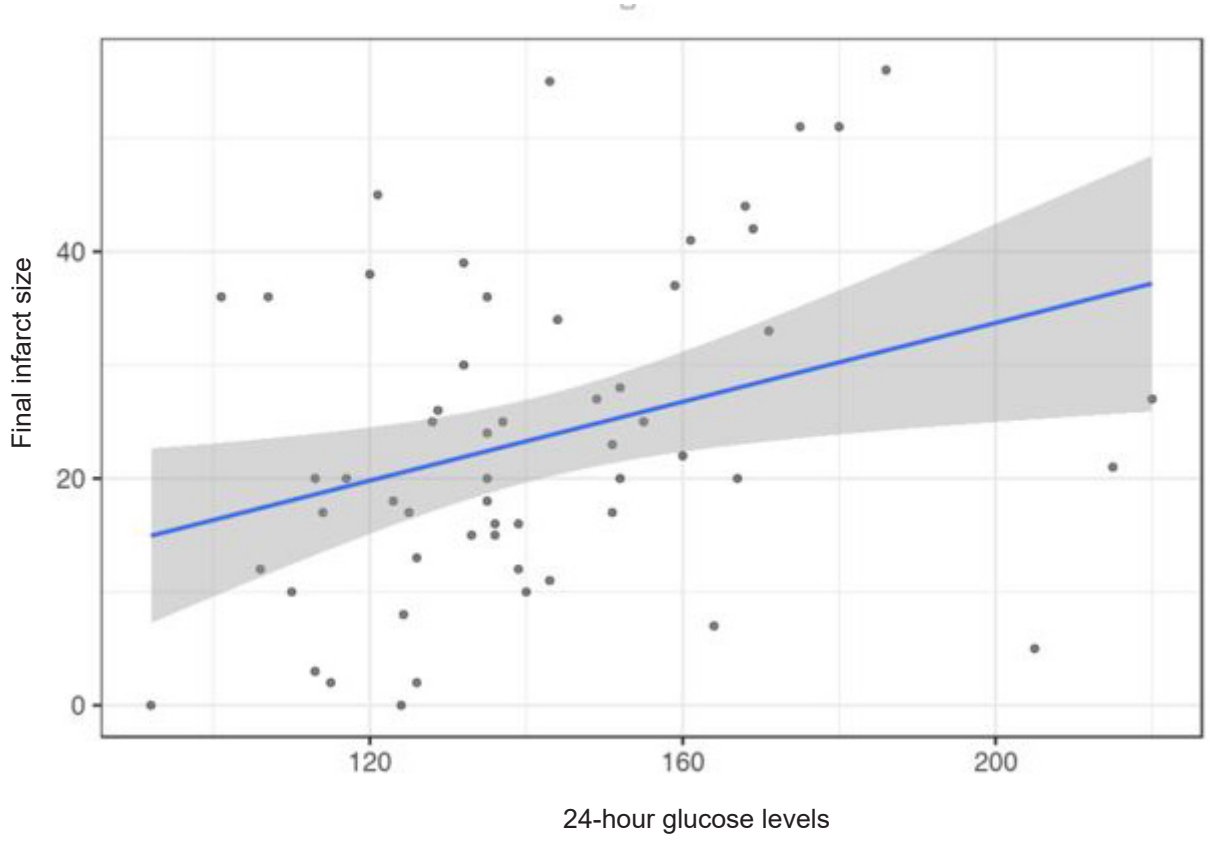

Figure 2 - Partial effect plot of 24-hour blood glucose and final infarct size.

Table 2 – Univariate and multivariate regression coefficients for predictors included in the model

	Univariate beta coefficient	Univariate p-value	Multivariate beta coefficient	Standard error	Multivariate p-value
Female gender	4.447	0.343	4.49	5.32	0.404
Age	0.251	0.124	0.12	0.194	0.527
Glucose-1	-0.03	0.933	-0.092	0.070	0.193
Glucose-24	0.174	0.014	0.290	0.125	0.026
HbA1c	0.260	0.806	-0.266	1.321	0.841
İnsulin infusion	-7.107	0.062	-2.867	4.846	0.558
Anterior location	8.74	0.022	4.246	4.608	0.363
Symptom duration	0.027	0.033	0.027	0.028	0.347

Glucose-1: admission glucose; Glucose-24: mean 24-hour glucose.

Relative effect of each predictor in the model is shown in Figure 3.

Discussion

The main finding of our study is the association of mean 24-hour glucose levels with a small infarct size in STEMI patients. Tight glucose control with insulin infusion did not reduce final infarct size when compared to standard glucose control regimen. Additionally, tight glucose control with a target level between 80-140 mg/dL during the first 24 hours of STEMI was defined as safe and feasible in our study population.

To the best of our knowledge, this is the first study that investigated the relationship between

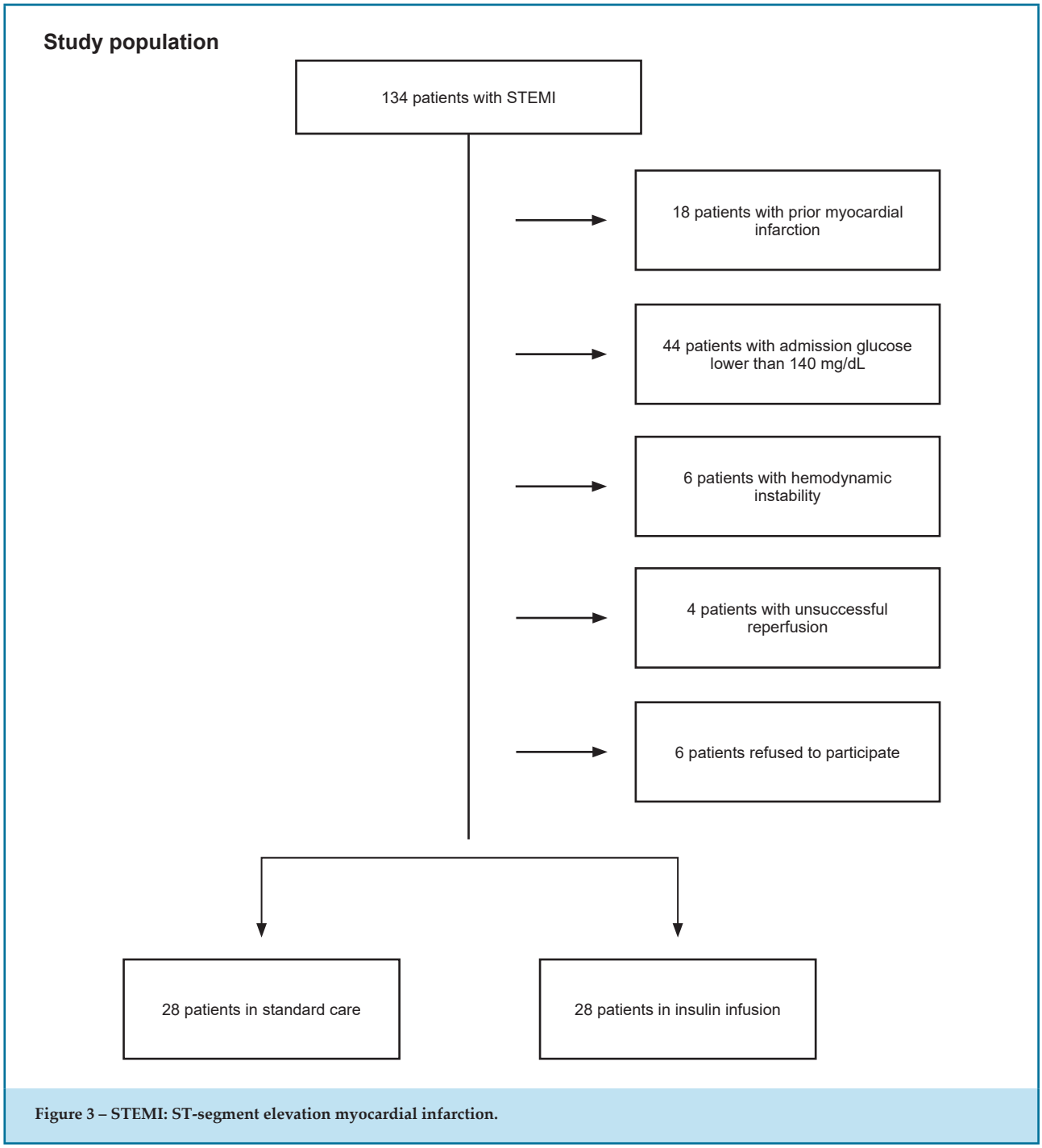

Figure 3 – STEMI: ST-segment elevation myocardial infarction.

tight glucose control with a target glucose level of 80-140 mg/dL and scintigraphic infarct size in STEMI patients. Stress-induced hyperglycemia is known to be related to longer hospital stays and increased mortality, especially in nondiabetic patients.[11] The American Heart Association reports that an admission glucose level higher than 140 mg/dL is considered hyperglycemia in ACS.[12] However, current STEMI guidelines recommend starting insulin therapy for glucose levels higher than 200 mg/dL.[6] Additionally, no detailed recommendations are provided by guidelines as to the modality of glucose level regulation to be used, whether insulin should be administered subcutaneously or via intravenous infusion. In most studies investigating the relationship between MI and glucose metabolism, a glucose-insulin-potassium (GIK) solution has been used.[13] The GIK infusion has in theory beneficial effects on the ischemic myocardium with the involvement of various mechanisms exhibiting a cardioprotective effect during the course of MI. Two of those mechanisms are noteworthy because one of them reduces free fatty acid (FFA) levels and the other one facilitates glycolysis. FFAs inhibit glycolysis, increase lactate levels, and facilitate the release of free hydrogen ions; thereby, they reduce contractility of the cardiac muscle, cause diastolic dysfunction, and lower the arrhythmia threshold.[14,15] Furthermore, insulin has anti-inflammatory, antioxidant, antiplatelet, and nitric oxide (NO)-mediated vasodilatation effects.[16,17]

In the DIGAMI-1 (Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction 1) study, patients were treated with glucose-insulin infusion during the first 24 hours of MI, and then subcutaneous insulin therapy was administered for the rest of the hospital stay. The mean glucose level was found to be lower in the infusion group, and the DIGAMI-1 study showed positive results with glucose-insulin therapy in a 1-year follow-up.[18] However, these findings were not confirmed in the DIGAMI-2 study because the study failed to achieve the target glucose levels.[19] In the HI-5 (Hyperglycemia: Intensive Insulin Infusion in Infarction) study on MI patients with admission glucose levels higher than 140 mg/dL, insulin-dextrose infusion therapy with target levels of 180 mg/dL was compared to placebo. However, the study failed to achieve the target levels and concluded that infusion therapy did not show any beneficial effects. A subgroup analysis of the study reported that patients with a mean 24-hour glucose level of less than 144 mg/dL (8 mmol/L) had lower mortality.[20] The CREATE-ECLA (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latinoamerica) trial is the largest-scale study within this context and reported neutral results for the GIK infusion therapy in STEMI patients.[21] However, the study reported that the mean 24-hour glucose level was higher in the GIK arm compared to usual care alone (155 mg/dL vs 135 mg/dL, respectively). A subanalysis of the CREATE-ECLA study found that during the first 24 hours of MI, every 10 mg/dL elevation in glucose levels caused an additional 8% rise in mortality. Investigators of the CREATE-ECLA study concluded that there is a need to ascertain whether lowering the serum glucose levels with a modified regimen will affect clinical outcomes. An overall evaluation of the study results regarding the effect of glucose-insulin or GIK infusion on MI patients reveals that these treatment modalities have neutral or harmful impacts on mortality. However, the subgroup analysis demonstrated reduced mortality when the target glucose levels were achieved with treatment. In the BIOMArCS-2 (Biomarker Study to Identify the Acute Risk of a Coronary Syndrome 2) study, the effect of intensive insulin therapy on enzymatic and scintigraphic infarct size in ACS patients was investigated.[22] However, intensive insulin therapy failed to reduce both the enzymatic and scintigraphic infarct sizes in that study. Regarding the limitations of the BIOMArCS-2 study, the patient population consisted of both STEMI and non-STEMI patients, patients with a history of previous MI were included, and scintigraphy was performed 6 weeks after the index event. In our study, patients with a history of previous MI were meticulously defined and excluded. Furthermore, patients failing to achieve successful reperfusion were excluded in order to minimize the factors that could potentially affect the final infarct size.

Infarct location is a major factor that affects final infarct size. In our study, infarct location predicted final infarct size in univariate linear regression analysis. However, in multivariate analysis, infarct location failed to predict final infarct size. This could be explained by the small sample size of the study. In addition, all participants achieved early reperfusion successfully, which may have reduced the effect of location on final infarct size.

Our results demonstrated that reduced blood glucose levels during the first 24 hours of STEMI was related to smaller infarct size. This finding is compatible with reports of increased mortality with elevated mean 24-hour glucose levels in STEMI patients. Conversely, it is a matter of debate whether lowering glucose levels to less than 140 mg/dL is safe and would increase mortality. The insulin infusion protocol we used in our study has been demonstrated to be safe for avoiding hypoglycemia. The final infarct size was not different between the two groups (20.0% vs 27%, p = 0.06). We believe that this lack of statistical significance was associated with a tendency for higher admission glucose levels in the insulin infusion group and an aggressive subcutaneous insulin treatment in the comparator group, rather than occurring as a usual consequence of patient selection and treatment bias. The insulin infusion protocol achieved the target blood glucose levels in 20 out of 28 patients (71%) (mean: 80-140 mg/dL). Of the remaining 8 patients, 6 had admission glucose levels higher than 250 mg/dL. It could be argued that the protocol is not successful at achieving the target levels when the admission glucose levels are higher than 250 mg/dL. In two tests, the blood glucose levels were lower than 60 mg/dL, but symptomatic hypoglycemia was not observed in any patients. The mean number of blood glucose measurements in 24 hours was 12 and the mean insulin infusion rate was 1:35/hour. This treatment protocol seems to be safe for avoiding hypoglycemia and appropriate for the treatment of MI patients; however, its effectiveness will be reduced if the baseline glucose level is higher than 250 mg/dL.

Study limitations

This study has several limitations. It is a single-center study, there is no blinding, and the study population consists of relatively low-risk patients. Therefore, the results may not be generalized to all MI patients. Lack of angiographic data is another limitation. To detect myocardial salvage index is a more powerful outcome than final infarct size in the studies investigating the effect of a new treatment modality in STEMI patients. Therefore, lack of data regarding myocardium at risk limited the results of this study. The participation of a small number of patients in the study limited the analytical power.

Conclusion

Tight glycemic control with continuous insulin infusion is not associated with smaller infarct size when compared to standard care in STEMI patients. Conversely, glycemic control in the first 24 hours of STEMI may reduce the final infarct size irrespective of the regimen used for controlling blood glucose levels. A target blood glucose level between 80-140 mg/dL can be achieved by using the Yale University insulin infusion protocol safely in MI patients with admission glucose levels higher than 140 mg/dL.

Author contributions

Conception and design of the research: Gulsen K, Okcun B, Ersanli MK. Acquisition of data: Gulsen K, Ayca B. The authors thank Ali Karagoz for the statistical analysis. Writing of the manuscript: Gulsen K. Critical revision of the manuscript for intellectual content: Baskurt M, Okcun B.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Istanbul University Cerrahpasa School of Medicine under the protocol number 13728/2009. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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