

The Effect of the Door to Needle Time of Streptokinase Administration on the Left Ventricular Function and Thrombolysis in Myocardial Infarction (TIMI) Flow Grade in Patients With Anterior Myocardial Infarction: A Single-Center, Prospective Follow-up Study

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Abstract- Early administration of thrombolytic agents is the standard treatment and crucial for the outcome for patients presenting with acute myocardial infarction (MI). This study was conducted to evaluate the door to needle time of streptokinase administration and the left ventricular function in patients with anterior MI. This study was a prospective, single-center study on participants with anterior MI who were received streptokinase and non-streptokinase groups. After administration of streptokinase, QTc was measured in hyper-acute, acute, and recent phases of anterior MI in the case group and compared with acute and recent phases in the control group. The left ventricular function in 5 and 42 days after emergency department arrival was measured and compared in two groups. The data were analyzed by descriptive statistics method and variance analysis in the SPSS software, version 22. The level of significance was considered to be 0.05. Among 87 participants (45 streptokinases, 42 non-streptokinase), there was a significant relationship between the door to needle time in patients who received streptokinase in 1 hour ($P=0.000$), 3 hours ($P=0.007$), and 6 hours ($P=0.016$) after onset the chest pain and an ejection fraction of the patients in 5 days after hospitalization. Also, there was a significant relationship between ejection fraction in 5 days ($P=0.000$) and 42 days ($P=0.000$) of administration streptokinase and door to needle time. Reduction of the door to needle time after anterior MI has significant effects on QTc and incidence of threatening arrhythmia.

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Introduction

The prevalence of cardiovascular disease (CVD) in the 20th century was increased, such that this disease is known as the main cause of mortality in the world (1).

Close to 2020, ischemic heart disease will become the commonest cause of death in the world, and it is considered the first cause of mortality in middle ages people in Iran. As coronary artery disease (CAD) accounts for a high percentage of CVD, early diagnosis and treatment will lead to a good prognosis of the patients

and fewer deaths (2). In the world, most research has been done on the pathophysiologic process, risk factors, and effective treatment of this disease, which has led to the invention of alternative caring methods and using special drugs (3).

One of the drug strategies that are very frequent is using streptokinase and tissue plasminogen activators. Among them, streptokinase, due to the several years of use in Iran, is better known and used more for acute ST-elevation myocardial infarction, results in recanalization of the infarct-related artery, save the left ventricular

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function, and finally, reduction of mortality (4).

Early administration of streptokinase is a crucial prognostic factor in the outcome of patients with acute myocardial infarction that affected infarct size, left ventricular salvage, and survival (5).

Also, several studies (6-7) indicate that low left ventricular ejection fraction after myocardial infarction is correlated with higher morbidity and mortality. Herein, streptokinase can have maximal benefit when it is administered in the first hour after symptoms appeared (8-9).

But, among them, any study cannot show the effect of early administration of streptokinase in patients with anterior myocardial infarction (MI), as a very dangerous type of MI, on left ventricular function follow up those patients. So, we evaluated the effect of the door to needle time on the left ventricular function and TIMI flow grade after streptokinase administration.

Materials and Methods

This is prospective, single-center study was performed among all patients with anterior myocardial infarction referred to the emergency department from January to November 2017.

Inclusion criteria were included all of the patients that diagnosed with anterior myocardial infarction based on the electrocardiographic changes (such as ST-T segment elevation or more than 1 mm in two or more consecutive ECG leads that presented anterior wall of the heart), increase in Biochemical marker (cardiac troponin greater than 0.50 ng/ml and creatinine phosphokinase greater than 25 U/L) and minimal duration of chest pain duration equal and greater than 30 minutes after chest pain onset.

The exclusion criteria include prior myocardial infarction, history of coronary artery bypass graft (CABG) surgery, pacemaker implantation, Incidence of cardiogenic shock, Killip class 3 or 4, contraindication of streptokinase administration; except the patients that referred after 6 hours from chest pain incidence.

The sample size of the study was determined 45 patients in each group by considering means space and the hypothesis of the same study (4).

The demographic variables such as age, gender, and cardiovascular disease risk factors (Smoking, the history of diabetes mellitus, hypertension, and dyslipidemia) were recorded.

The streptokinase group encompasses those patients who passed lower than 6 hours of their chest pain onset according to electrocardiographic changes, clinical signs and symptoms, primary history, and estimated distances

from the origin to the emergency department. The patients when arrived at the emergency department had suffering chest pain. These patients instantly received streptokinase 1,500,000/U (Farmsya-Belgium) in 1 hour within the antecubital vein in the left hand. For each of them, streptokinase dissolved with 50 ml of normal saline. Based on the door to needle time, the case group was categorized into 4 groups that include: group 1: 30 minutes, group2: 1 hour, group 3: 3 hours, and group 4: 6 hours.

For each patient, according to door to needle time, standard 12-lead-electrocardiograms (ECG) (paper speed of 25 mm/s, standardization of 10 mm/1 mV) were recorded using MAC 5500 machines (GE Medical system, Milwaukee, WI, USA). Then they were re-categorized in hyperacute, acute, and recent phases, based on ECG characteristics. Patients in the non-streptokinase group were assessed for QTc changes in acute and recent phases of MI. For each ECG, the QT was measured in all leads from the onset of the QRS to the end of the T-wave on the isoelectric baseline. The isoelectric baseline was defined by the reference line between two P-Q intervals. The end of the T-wave was defined as the return to the isoelectric baseline. When the U-wave followed the T-wave, QT was measured to the nadir of the curve between the T and U-waves. The QTc was obtained using Bazett's formula: $QTc = QT / \sqrt{RR}$.

The incidence of ventricular tachycardia/ fibrillation in different phases was recorded.

All the patients that were referred to the emergency department more than 6 hours after the onset of chest pain were in the non-streptokinase group. This group has not taken any dose of streptokinase. These patients are closely monitored.

The patients in both groups were transferred to the cardiac care unit and hospitalized for 5 days. During this time, they had received ASA, β -blockers, ACE inhibitors, statins, nitrates, and non-fractionated heparin, if they had no probability contraindications.

In 5 days after hospitalization, all the patients were transferred to percutaneous coronary intervention (PCI), and if angioplasty was successful, the patients remained in the study. During angiography, visual estimation of coronary artery diameter and coronary perfusion was evaluated using thrombolysis in myocardial infarction (TIMI) flow grade, and two cardiologists confirmed scoring. These cardiologists did not know about the study process. TIMI flow grade was defined as:

- grade 0=no perfusion,
- grade 1=penetration with minimal perfusion,
- grade 2=partial perfusion

grade 3=complete perfusion. "Patent artery or normal flow" was defined as TIMI flow III.

All the patients in both groups, 42 days after hospitalization, were referred to the echocardiography unit, and reconsideration left the ventricular function and left ventricular ejection fraction. The ejection fraction in 5 and 42 days after hospitalization was compared in both groups.

The aim of the study was explained to the patients, and their written informed consent was obtained according to the Declaration of Helsinki. Furthermore, it was explained that the patients could withdraw from the study at any time.

Variables are expressed as mean±SD and percentage. Differences in the frequency of characteristics were assessed by independent sample Student's t-test for continuous variables. The *Chi*-square test (or Fisher exact test if applicable) was used for categorical variables. Two-tailed $P < 0.05$ was considered significant. SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for data storage and analysis.

Results

In the final of this study, 87 patients participated. Of these patients, the majority of them (70.1%) were males and 26 (29.9%) were females. For all of the subjects, the mean age was 61.98 ± 12.80 years. Among demographic characteristics, there was a significant relationship between the type of groups (streptokinase and non-streptokinase) and gender ($P=0.002$), and age ($P=0.043$).

There is no dramatic correlation between coronary artery disease risk factors such as; hypertension ($P=0.37$),

diabetes mellitus ($P=0.11$), dyslipidemia ($P=0.09$), and smoking ($P=0.58$) and groups of the patients.

Out of 87 patients, 45 (51.7%) of them were in the case group with the mean of age 62.34 ± 13.25 years and received a therapeutic regimen of streptokinase. Among them, 8 (17.7%) patients were referred to the emergency department in 30 minutes after the onset of the chest pain symptoms, 9 (20%) patients in 60 minutes, 14 (31.1%) patients in 3 hours, and finally 14 (31.1%) patients after 6 hours.

There was a significant relationship between the door to needle time in a patient who received streptokinase in 1 hour ($P=0.000$), 3 hours ($P=0.007$), and 6 hours ($P=0.016$) after onset the chest pain and an ejection fraction of the patients in 5 days after hospitalization. This relationship was a negative correlation between the door to needle time and the ejection fraction of patients (Figure 1).

Also, paired T-test showed a significant relationship between ejection fraction in 5 days ($P=0.000$) and 42 days ($P=0.000$) of administration streptokinase and door to needle time, as a negative correlation.

Analysis of variance showed that there was a significant correlation between the ejection fraction of the patients who received streptokinase in 5 days ($P=0.000$) and 42 days ($P=0.000$) after hospitalization and TIMI flow grade.

In our study, 42 patients were in the non-streptokinase group. Statistical analysis showed that significant relationship between ejection fraction of patients in streptokinase and non-streptokinase groups in 5 days ($P=0.000$) (Figure 2) and 42 days ($P=0.041$) (Figure 3) after hospitalization.

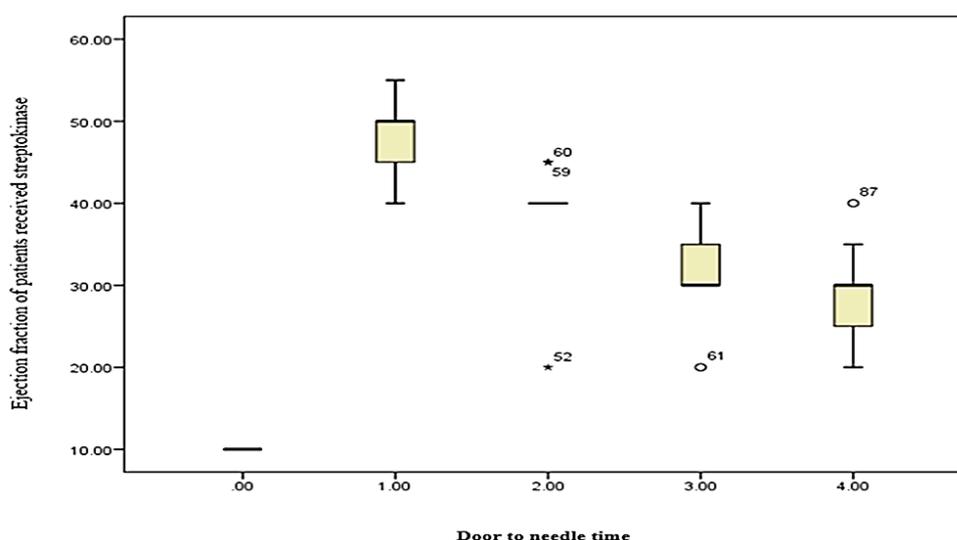


Figure 1. Door to needle time and an ejection fraction of patients who received streptokinase showed that the increase of the time in administration streptokinase correlated with decreasing of EF in 5 days after hospitalization. (1=30 minutes, 2=1 hour, 3=3 hours, 4=6 hours)

Door to needle time of streptokinase administration and the left ventricular function

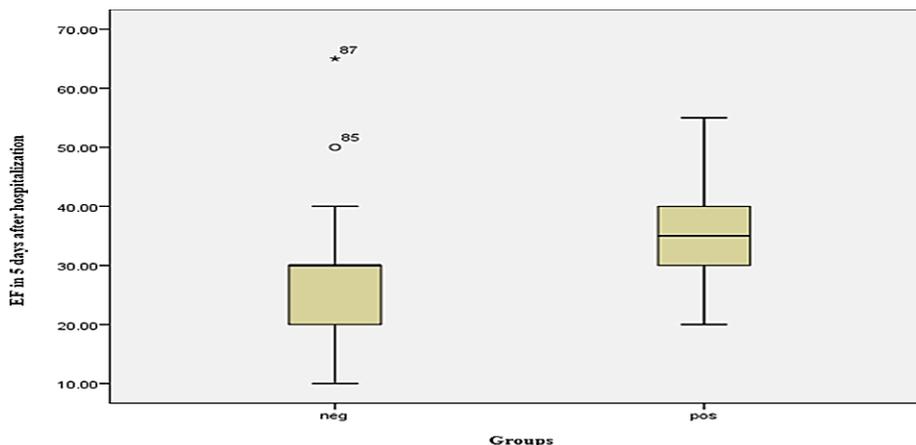


Figure 2. Relationship between ejection fraction in 5 days after between streptokinase and non-streptokinase groups. (neg= non-streptokinase group. Pos=streptokinase group)

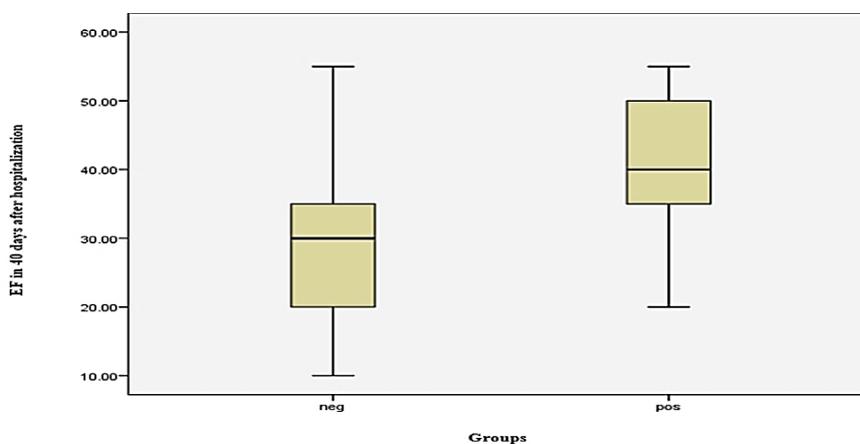


Figure 3. Relationship between ejection fraction in 42 days after between streptokinase and non-streptokinase groups. (neg= non-streptokinase group. Pos=streptokinase group)

Discussion

The endpoint of our investigation was determining the effect of the door to needle time of streptokinase administration the left ventricular function and Thrombolysis in Myocardial Infarction (TIMI) flow grade in different phases patients with anterior myocardial infarction.

The major findings of this study were the dramatically negative relationship between the door to needle time in a patient who received streptokinase and ejection fraction in 5 and 42 days after hospitalization.

Improvement of ejection fraction rate after fibrinolytic therapy in patients with MI was shown in Taheri et al. study (3). Also, our results were in parallel with other studies (10,11) that show the short time from symptom onset to thrombolytic therapy cause improvement of EF. But, the results of another study (12) revealed that streptokinase administration has no effect

on left ventricular ejection fraction rate in the first 24 hours and one month after discharge.

One of the reasons for the differences in results may be due to a small sample size of that study that affects the results of the study. Another possible factor that may affect this contradicts is the low dose of streptokinase for the patients that cause the fibrinolysis quality of the coronary arteries and then salvage of the left ventricular.

Some studies (13-15). showed that adherence to the American Heart Association (AHA) guidelines (16) has enhanced the quality of care of patients with myocardial infarction and is associated with dramatic reductions in in-hospital mortality rates. In the Boersma and *et al.*, study (8) showed that the explicit increase the survival with the use of fibrinolytic therapy compared with placebo and it was greatest among patients who taken fibrinolytic within 1 hour after symptom onset. Also, some investigation (13,17) showed that early administration of streptokinase in patients with acute MI,

cause the enhancement of survival.

Another important and novel finding of our study was the significant relationship between TIMI flow grade and door to needle time. This result indicated that when the door to needle time is less than 1 hour after symptoms onset, the chance of successful treatment of occluded coronary arteries after percutaneous coronary interventions (PCI) is greater than late administration of streptokinase. Although, in one study (18), TIMI flow after PCI in patients who received streptokinase showed a weak correlation with left ventricular function recovery one week after administration.

Also, Sheiban *et al.*, (19) showed that TIMI flow grade <3 at 24 hours after streptokinase administration was not associated with any significant change in left ventricular function during the six-month follow-up period. Moreover, this study indicated that between the door to needle time of fibrinolytic administration and TIMI flow grade, there is not any correlation.

Based on our investigation, the differences between our results and other studies may be due to the lack of determination of the TIMI flow grade in other studies in various phases of MI, which influences the final results. Also, those studies did not consider the door to needle time of thrombolytic administration in standard timing that was proposed with AHA (16) for thrombolytic therapy.

Based on the American Heart Association (AHA) and European Society of Cardiology recommendation that optimal door to needle time for fibrinolytic therapy is 30 minutes, so suggested that administration of streptokinase should be started earlier for patients with MI diagnosis with professional emergency medical technicians.

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