Original Article

Factors Associated with Delay in Thrombolytic Therapy in Patients with ST-Elevation Myocardial Infarction

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Abstract

Background: *Treatment delay in the management of ST-elevation myocardial infarction conversely correlates with prognosis and survival of the patients. This study aimed to investigate factors associated with delay in the thrombolytic therapy of these patients in Tehran.*

Methods: *Between 2007 and 2010, the interval between the self-reported time of the onset of symptoms and initiation of the thrombolytic agent in 513 patients with a diagnosis of acute ST-elevation myocardial infarction was recorded. Medical history and socio-demographic characteristics of the patients treated within two hours after the onset of symptoms and patients treated after two hours from the onset of symptoms were compared, and the odds ratios were calculated using logistic regression.*

Results: *The mean age of the patients was 61.2 (SD = 11.1) years, and 76% of the patients were male. The median time between the onset of symptoms and treatment was 158 (SD = 30.4) minutes. Mean for decision time was 61 (SD = 19), which was responsible for 83% of the entire treatment delay. The mean transportation time was 34 (SD = 12) minutes, and the median door-to-needle time was 44 minutes. Odds ratio for history of diabetes mellitus was 1.90 (95% CI: 1.26-2.87), for hypertension was 1.55 (95% CI: 1.08-2.23), and for prior coronary heart disease was 1.47 (95% CI: 1.17-1.84).*

Conclusion: *The most important factor associated with delay in treatment was decision time. Improving emergency medical services dispatch time, obtaining pre-hospital electrocardiograms for early diagnosis, and pre-hospital initiation of thrombolytic therapy may reduce the delay time.*

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Introduction

ST-elevation myocardial infarction (STEMI) is a major cardiovascular event, which may result in great mortality and morbidity. Myocardial damage caused by acute STEMI is a time-dependent process. Reperfusion therapy can alter the course of infarction, limit extent of damage, and improve subsequent prognosis.[1-3] Thrombolysis is still the most common reperfusion method used in myocardial infarction, and the greatest benefit is obtained when thrombolytic agents are administered within the first hour after myocardial infarction (MI).[4] The efficacy of reperfusion therapies is

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decreased with the prolongation of the time interval between the onset of symptoms and treatment.[5-7] It is estimated that the benefit is a reduction of 1% in death, for every hour saved when administering the drug within the first six hours after MI.[8] In addition, it has been demonstrated that 25% of patients treated with thrombolytic agents within the first hour leave the hospital with no evidence of myocardial necrosis, a concept termed aborted MI.[9] Treatment delays with either thrombolytic therapy or primary percutaneous coronary intervention (PPCI) are associated with higher six-month mortality in patients with STEMI receiving reperfusion therapy.[10] However, it has been observed that in many situations, thrombolytic therapy is carried out after a longer period than the recommended time period.[11] A number of factors determine the delay in starting thrombolytic therapy such as contacting emergency medical services (EMS), transporting the patient, admitting the patient in the emergency department, initial assessment of the patient including obtaining and interpreting the electrocardiogram (ECG), decision making, and delay in preparing the drug.[12]

Because the prevalence of MI has increased substantially in recent years, it is important that all avenues of treatment of the MI patient such as treatment delay factors be explored. Although timely initiation of reperfusion therapy in patients with STEMI is of great importance, in real practice still there are many factors leading to treatment delay. The International Registry Data shows that only 41% of patients who receive in-hospital thrombolytic agents present to hospital within two hours of symptom onset and only one third receive treatment within two hours.[13] Treatment delay variables differ in different countries according to cultural, economic, educational, and social backgrounds.[14, 15] In the scientific literature, there is very little evidence about the different components of treatment delay and their duration in the clinical setting of developing countries such as Iran.

This cross-sectional study was conducted to investigate factors associated with thrombolytic therapy delay in STEMI patients in Tehran (the Capital of Iran) with the ultimate goal of effecting a reduction in STEMI burden.

Methods

This cross-sectional study was performed in three random samples of Tehran's general teaching hospitals, namely Loghman Hakim Medical Center, Imam Hussein Hospital, and Taleghani Hospital, between October 2007 and January 2010. At the time of patient arrival in the emergency department, patients with acute coronary syndrome were screened via the ECG, physical examination, serum biochemical markers of necrosis, and history by well-trained physicians and nurses. Diagnosis of STEMI was based on typical symptoms, typical rise and gradual fall or a more rapid rise and fall of biochemical markers of myocardial necrosis, and concurrent ST-T changes. ST-T changes compatible with STEMI were defined as ST elevation of at least one millimeter in at least two contiguous or related ECG leads or new left bundle branch block according to the American Heart Association's guidelines. After the selection of patients with acute STEMI, contraindications of thrombolytic therapy in each patient were reviewed. Patients with a diagnosis of STEMI who were eligible for thrombolytic therapy were included in our study. The initial sample of this study consisted of 585 patients, and the following patients were excluded sequentially: patients who had been transferred from another medical center (n = 5), patients who developed symptoms for acute MI after hospital admission date and time (n = 3), uncooperative patients (n = 8), patients who did not use EMS (self transportation) (n = 28), patients who had an unknown time of symptom onset (n = 10), patients who did not have new or presumed new ST-segment elevation in two or more leads or left bundle branch block on the first ECG (n = 3), and patients who were visited by a physician before hospital arrival (n = 15). Finally, 513 patients (389 men and 124 women) with a diagnosis of acute STEMI fulfilled our inclusion criteria.

The physician completed case record forms at the time of admission. In all the patients, a detailed medical history of previous hospitalization for cardiovascular disease, presence or management of hypertension (blood pressure greater than or equal to 140/90 mmHg or use of antihypertensive drugs), hypercholesterolemia (total serum cholesterol greater than 200 mg/dl or use of lipid-lowering agents), renal failure (serum creatinine greater than 1.7 mg/dl), and diabetes mellitus (use of anti-diabetic medication or fasting blood glucose greater than 126 mg/dl) was recorded. Socio-demographic characteristics (e.g. age and sex) and current smoking status were also recorded.

Because occlusion may occur intermittently, myocardial demands may vary, and the presence and function of collateral circulation may play an important role, the timing of the onset of ischemic symptoms is only a crude measure for determining when the infarct-related artery occluded and myocyte necrosis began, thus self-reported time of the onset of symptoms as time of acute MI was recorded as accurately as possible. The time of contact with EMS was obtained from forms completed by the emergency medical technicians, the time when the patient arrived at the hospital was recorded from the admission form, the precise time of the initiation of the thrombolytic agent was obtained from the hospital records, and the interval between the self-reported time of the onset of symptoms and initiation of the thrombolytic agent was defined as treatment delay time. Based on treatment delay time, the patients were divided initially into two categories: patients treated within two hours after the onset of symptoms (early treatment) and patients treated after two hours from the onset of symptoms (late treatment). This two-hour time point was chosen because it has been shown that

the beneficial effect of thrombolytic therapy is substantially higher in patients presenting within two hours after symptom onset compared to those presenting later.[16]

The study was approved by the Medical Research Ethics Committee of Shahid Beheshti University of Medical Sciences and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Continuous variables are presented as mean values and standard deviation. The categorical variables are presented as absolute and relative frequencies. Differences in the distribution of characteristics in the patients, classified according to the extent of pre-hospital delay, were examined using the chi-square test for the discrete variables, while the t-test was employed to examine differences between the different delay groups for the continuous variables. Logistic regression analysis was utilized to determine which of the socio-demographic, clinical, and behavioral characteristics best distinguished between the two groups. The logistic regression analysis initially included the patients' age, sex, smoking habits, and medical history in conjunction with the use of lipid-lowering agents and anti-hypertensive and anti-diabetic drugs. Final models were constructed by using the stepwise regression procedure. All the statistical calculations were performed using SPSS software, version 19.0 (SPSS Inc, Chicago, Il, USA). The logistic regression analysis results are presented as calculated odds ratios with 95% confidence intervals. Significance level for analysis was defined as p value < 0.05.

Results

During the 3 years of the study period, 513 patients with STEMI were treated with thrombolytic agents. Of this total, 76% were male, 42% were smokers, 17% were known cases of diabetes mellitus, 35% had a history of hypertension, 46% were known cases of hypercholesterolemia, 5% were known cases of renal failure, and 43% had a history of prior coronary heart disease (CHD). The mean age of the patients was 61.2 (SD = 11.1) years, with 33% of them being older than 70 years. The baseline characteristics of the patients treated with thrombolytic agents with the extent of treatment delay are presented in Table 1. Amongst the patients with STEMI, those treated with thrombolytic agents after two hours of symptom onset were more likely not only to be male (p value = 0.033), elderly (p value < 0.001), and current smokers (p value < 0.001) but also to have a history of hypertension (p value < 0.001), diabetes mellitus (p value = 0.093), hypercholesterolemia (p value = 0.003), and renal failure (p value < 0.001) (Table1).

Logistic regression was performed to identify which socio-demographic, clinical, or lifestyle characteristics of the patients contributed significantly to the prediction of late (> 2 hours) versus early (≤ 2 hours) treatment. The results of this analysis showed that the patients with a history of diabetes mellitus (OR: 1.90, 95% CI: 1.26-2.87), hypertension (OR: 1.55, 95% CI: 1.08-2.23), and prior CHD (OR: 1.47, 95% CI: 1.17-1.84) were significantly more likely to receive treatment late (p value < 0.001) (Table 2).

The overall median (25^{th} and 75^{th} percentiles) time between the onset of symptoms and treatment was 158 (30 and 420) minutes. Moreover, 46 (9%) patients sought medical care at least 6 hours after the onset of symptoms, while only 97 (19%) patients presented at the hospital within two hours from the onset of symptoms. The mean time from the onset of symptoms to calling EMS was 61 ± 19 minutes. The mean time from the onset of symptoms of acute MI to admission to

Table 1. Baseline characteristics of patients treated with thrombolytic agents with the extent of treatment delay (n=513)*

	≤ 2-hour delay (n=82)	> 2-hour delay (n=431)	P value
Men	63 (77)	366 (85)	0.033
Age(y)	61.17±11.07	65.17±11.07	<0.001
Diabetes Mellitus	21 (25)	134 (31)	0.093
Hypertension	31 (38)	237 (55)	<0.001
Hypercholesterolemia	39 (47)	211 (49)	0.003
Renal Failure	3 (4)	26 (6)	<0.001
Prior CHD	34 (42)	203 (47)	0.745
Current Smoking	27 (33)	198 (46)	<0.001
Prior Medication			
ACE Inhibitor	6.56 (8)	60.34 (14)	0.021
Beta Blocker	4.92 (6)	38.79 (9)	0.065
Diuretic	4.10 (5)	51.72 (12)	0.034
Calcium Antagonist	5.74 (7)	56.03 (13)	<0.001
Statin	9.84 (12)	64.64 (15)	0.013

*Data are presented as mean±SD or n(%)
CHD, Coronary heart disease

hospital was 146 ± 20 minutes. The mean transportation time from the patient place to the hospital was 34 ± 12 minutes, and the interval between symptom onset and initiation of thrombolytic therapy was162 ± 42 minutes.

After controlling the confounding factors, we found no significant difference in time of symptom to ambulance arrival and ambulance arrival to treatment with respect to age (p value = 0.23), sex (p value = 0.061), history of hypertension (p value = 0.063), diabetes mellitus (p value = 0.071), hypercholesterolemia (p value = 0.059), renal failure (p value = 0.079), prior CHD (p value = 0.053), and current smoking (p value = 0.064) (Table 3).

Table 2. Factors significantly associated with treatment delay of more than 2 hours

Characteristics	Adjusted OR (95% CI)
Diabetes Mellitus	1.90 (1.26-2.87)
Hypertension	1.55 (1.08-2.23)
Prior CHD	1.47 (1.17-1.84)

CHD, Coronary heart disease

Discussion

The result from this study showed that thrombolytic therapy delay contains two different components: pre-hospital and intra-hospital delay. Pre-hospital delay includes the two major components of decision and transportation periods, and decision time represents the interval between the onset of symptoms until the patient notices the gravity of the problem and seeks medical attention. Decision delay was more pronounced than were the other elements of the patients' treatment (transfer and intra-hospital delays).

As treatment efficacy is reduced by the passage of time, we conducted this study to investigate reasons for thrombolytic therapy delay in Tehran. Recognition of factors contributing to thrombolytic therapy delay could enlighten our vision to change our country-based guidelines of chest pain management. By recognition of treatment delay factors, healthcare policy makers can perform interventions in different levels of treatment delay and finally reduce the enormous mortality and morbidity burden caused by STEMI.

The mean age of the patients in this study was similar to that in the Behjati et al. study (61.20 ± 12.38).[17] Our result indicates that 83% of the entire pre-hospital delay was related to the time from symptom onset to the first medical contact and only 19% of the subjects made a call for help within two hours of the onset of coronary symptoms; and in 9%, the delay was greater than six hours, which is compatible with other studies.[18] Symptoms were not recognized as coronary in origin in most cases. In all the cases where delay was more than one hour, the main reason for the delay was thinking that symptoms would go away or that they were not serious. Disinclination to call the EMS reflected the belief that the symptoms were not grave enough to warrant an ambulance.

Our results also show that the older patients are more likely to receive treatment late, which is consistent with prior studies of in-hospital fibrinolysis.[19] This could be due to the frail general health condition of the elderly at large and the fact that most of the time they suffer from different kinds of pains, most of them impermanent. Consequently, old patients are more prone to assume that the symptoms are temporary and will sooner or later go away.

The female patients in our study had called for help earlier than the male patients, which is not consistent with prior studies. Previous research showed that female patients with STEMI were more likely to present to hospital by ambulance but conversely had delayed time from symptom onset to in-hospital fibrinolysis.[18] This could be a reflection of different cultural views over health and life, between Iranian men and women. Iranian women constitute the bulk of the audience of most radio and television health programs, and they are in general more concerned about their health. On the other hand, the delay between admission to hospital and initiation of fibrinolysis in the women in the present study could be in consequence of lower rates of STEMI in women and high prevalence of psychosomatic syndrome among them.

Our study demonstrates that transportation time in Tehran is about 34 minutes, which is not longer than that reported

Table 3. Mean time of components of treatment delay in patients with STEMI*

	Symptom onset to ambulance call/min	Symptom onset to hospital admission/min	Symptom onset to treatment/min
Sex			
Male	70.1±20.4	148.6±21.4	169.3±49.8
Female	65.4±19.5	143.1±19.8	159.6±39.6
Diabetes mellitus	89.3±25.1	169.9±25.7	188.4±47.5
Hypertension	83.6±23.3	165.4±24.3	184.5±46.6
Hypercholesterolemia	85.5±23.2	169.4±23.2	189.1±47.7
Renal failure	79.8±22.2	162.7±23.3	181.4±45.5
Prior CHD	75.7±21.4	159.3±22.6	178.3±46.7
Current smoking	71.4±19.2	152.4±19.7	173.3±44.9

*Data are presented as mean±SD
STEMI, ST elevation myocardial infarction; CHD, Coronary heart disease

in other countries.[20] Needless to say, the existence of high urban traffic in large cities such as Tehran may contribute to delayed treatment.

Although it would be ideal that the time between patient arrival and thrombolytic infusion was no more than 30 minutes (door-to-needle time), in our study, the median door-to-needle time was 44 minutes, which is compatible with a prior study.[20] One of the probable delay factors is the time required to transfer patients to the coronary care unit (CCU), where the thrombolytic is administered. There is reduction in the thrombolytic therapy administration time when it is administered in the emergency department. A previous study showed a reduction of 58 minutes when these procedures started in the emergency department rather than exclusively in the CCU.[21] By contrast, another study[22] found an increase from 3.4% to 12% in the death rate when the therapy was administered in the emergency department. Another factor reported as a reducing factor in door-to-needle time is night shift care. This factor can be considered a time reducer, considering that during the night shift there is a reduction in the number of patients, thus care is provided faster.

In conclusion, major efforts are needed to understand and modify behavior of patients with chest pain to further reduce delays in treatment. It is important to inform the general population and especially high-risk persons about manifestations of myocardial ischemia and a need to prompt hospital referral by means of ambulance in case of STEMI symptoms. While chest pain is the most important symptom of heart attack, results from the National Registry of Myocardial Infarction, USA suggested that 33% of the patients admitted to the hospital with MI did not have chest pain on admission to the hospital. Less knowledge of common symptoms is also important for prompt health seeking. In the REACT study, 67% of the participants identified arm pain or numbness, 51% identified shortness of breath, and 10% classified jaw, neck, or back pain as heart attack symptoms. There may be an urgent need for the public to recognize multiple symptoms of heart attack. Strategies to reduce patient delay times must focus on educating the public on the recognition and diversity of coronary symptoms and the benefits of prompt presentation to the hospital by the emergency ambulance service. Health care professionals should review and consult with patients and their families the need to seek urgent medical attention for a pattern of symptoms, including chest discomfort, extreme fatigue, and dyspnea, especially if accompanied by diaphoresis, lightheadedness, palpitations, or a sense of impending doom.[23, 24]

A meta-analysis of studies comparing pre-hospital and in-hospital thrombolysis has shown a relative reduction in short-term mortality of about 7%with pre-hospital thrombolysis.[25] Pre-hospital fibrinolysis also has been associated with much shorter ischemic times and a 30% mortality reduction compared with in-hospitalfibrinolysis.[26] Public campaigners and medical care providers have a substantial role in this regard. Precise data registration and monitoring of the duration of pre-hospital delays are crucial for planning strategies and protocols to abolish referral delays of patients with acute MI and establish early reperfusion, which can subsequently decrease mortality.[27] In the meantime, efforts should be made to lift the early management of patients with STEMI from the emergency department to the ambulance because this saves at least 30 to 60 minutes in time to proper treatment. An organized network of assessment, treatment, and transfer should be established and adapted to the local situation to manage STEMI patients optimally, with continuous monitoring of the clinical results achieved. Similarly, building the necessary systems of care to coordinate EMS and hospitals so that catheterization laboratories can be activated before the patient arrives at the hospital may require capital equipment, training of emergency medical personnel, and collaboration across service providers not under the control of the hospital. An organized network of assessment, treatment, and transfer should be established and adapted to the local situation to manage STEMI patients optimally, with continuous monitoring of the clinical results achieved.

It is fundamental for the health care delivery team to make an effort to develop health care protocols so as to improve the quality of emergency services. This would help to provide quicker service to patients with heart disease, which would significantly reduce the time spent between the onset of the event and myocardial reperfusion. From the moment a patient with chest pain arrives at the hospital, there is a race against time. Chest pain guidelines recommend that every patient with suspected acute coronary syndrome (ACS) in the emergency room get an ECG immediately, in the first 5 to 10 minutes after reaching the hospital. One of the reasons for door-to-ECG delay is that the examination is performed only upon medical order, after assessment. Since the nursing team is responsible for the first part of the assessment, it is important for one specific nurse to screen the cases and determine emergency care procedures through initial assessment and requesting an ECG. This would provide agility, quickness, and effectiveness in the care process. Thrombolytic therapy must be initiated in emergency departments, and it should be instituted by the first physician capable of making the diagnosis and of determining the patient's eligibility for this treatment. The use of thrombolytic therapy can be increased by raising public awareness of acute MI symptoms, not least amongst those at higher risk, i.e. the elderly, smokers, diabetics, and hypertensives, as well as by providing necessary equipment and transportation facilities for the timely transfer of patients to emergency departments with adequately trained medical staff. The issue of documenting organizational practices is complex; however, our approach was designed to reflect the combined views of key staff involved with treating patients

with STEMI.

The findings of this study are meant to stimulate discussion about the main factors associated with treatment delay in patients with STEMI in Tehran. The present study, however, has some limitations, first and foremost amongst which is that because its sample was limited to adults from three major hospitals of Tehran, the results may not be generalizable to broad populations of Iran. It is worthy of note, however, that in order to decrease the effect of this selection bias, we selected the hospitals in different socio-economic classes of Tehran. Another weakness in the current study is that although the data were produced using a rigorous methodology, they came from cross-sectional, self-report assessments and did not include history of chronic medical problems of the patients and medication use for heart disease: this may reflect certain biases. Much work also remains to be done to evaluate the opportunities and pitfalls of electronic communication between patients and health professionals and to integrate these tools into clinical practice if they prove to be effective, without disadvantaging those who have different preferences or those who benefit from more traditional modes of communication.

Conclusion

We observed that the total time between the onset of symptoms in the patients with STEMI and the initiation of thrombolytic therapy was longer than treatment golden time. Shifting the place of diagnosis and treatment from the emergency department of hospitals to where the patient is located can reduce this gap time.

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