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Factors associated with delay to reperfusion therapy in patients with ST-Segment Elevation Myocardial Infarction in a hospital in the southeast of Mexico

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Abstract

Introduction and subject: *The aim of the study was to determine the factors involved in the delayed medical care of patients with ST-Segment Elevation Myocardial Infarction.* **Methods:** *A prospective observational study was conducted in patients admitted to the coronary care unit at Dr. Juan Graham Casasús hospital with a diagnosis of ST-Segment Elevation Acute Myocardial Infarction. In all patients, clinical data, type and time of reperfusion treatment, and factors associated with delay were identified.* **Results:** *Between November 2012 and January 2015 we included 213 patients with ST-Segment Elevation Myocardial Infarction. Age, diabetes, atypical chest angina and patient arrival period (night or weekend), were more frequent in patients presenting after 12 hours of onset of symptoms of myocardial infarction. Of these, hospital admission at night or weekend was the only independent predictor for delay to the emergency room.* **Conclusions:** *This study shows that in a referral hospital in southeast of Mexico, the delay attributable to the patient was the most common factor associated with care in patients with ST-Segment Elevation Myocardial Infarction. Patient arrival period was associated with delay to medical care.* (Gac Med Mex. 2016;152:446-52)

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Introduction

Cardiovascular disease remains the main cause of death in the world, and myocardial infarction represents the main contributor to this mortality. Prompt initiation of reperfusion therapy in patients with ST-segment elevation myocardial infarction (STEMI) either with fibrinolytic therapy or with primary percutaneous coronary intervention (PCI) limits infarct size, preserves ventricular function and improves survival[1,2].

From the patient's perspective, the delay between the onset of symptoms and reperfusion treatment administration is possibly the most important factor and it reflects total myocardial suffering time[3]. The delay on medical care of patients with STEMI has been associated with

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higher short and long-term mortality[4]. Previous studies have investigated factors associated with delayed search for medical care and suggest that demographic variety and clinical characteristics intervene on this delay[5]. In Mexico, there are important regional differences in myocardial infarction-care opportunities. The purpose of the present study was to determine factors associated with the time delay for reperfusion therapy in patients with STEMI in a hospital of southeastern Mexico.

Material and methods

A prospective, observational study was carried out in STEMI-diagnosed patients admitted to the coronary unit of the Regional High Specialty Hospital "Dr. Juan Graham Casasús" in Villahermosa, Tabasco, Mexico. All patients had clinical and anthropometric data recorded. Documented risk factors were the following: Type 2 diabetes mellitus was considered in previously-diagnosed cases or cases on hypoglycemic treatment and/or with insulin. High blood pressure was considered in previously diagnosed cases or cases on antihypertensive treatment. Hypercholesterolemia and/or hypertriglyceridemia were established when there was a previous history thereof or in cases taking statins and/or fibrates. Patients were considered as being smokers if they smoked 5 cigarettes or more per day for a period longer that one year. Typical chest pain was regarded as precordial oppression or on thorax anterior face at rest or with exercise with radiation to anterior face of neck and/or left arm > 1 minute with or without adrenergic manifestations; atypical chest pain was regarded as pain that doesn't meet the criteria for ischemic-profile pain, but is suggestive of myocardial ischemia, with oppression at inferior maxillary, anterior face of neck, epigastrium, etc. A patient was considered as having STEMI when there was presence of chest pain or discomfort with characteristic ischemic profile or not, longer than 20 minutes and associated with a new elevation of the J point in at least 2 contiguous leads ≥ 2 mm in men or 1.5 mm in women in leads V2-V3, and ≥ 1 mm in any other lead, or newly appearing left branch complete block[6]. Body mass index was calculated using the formula (weight [kg]/height [m]^2). Killip & Kimball classification, I: no signs of ventricular dysfunction; III: third left ventricular noise and/or basal rales or crackles; III: acute pulmonary edema, and IV: cardiogenic shock. The protocol was approved by the committee of ethics on research and in all patients was the informed consent obtained.

In all patients, time of delay was established since the onset of symptoms associated with myocardial infarction and the arrival to the emergency department. Whether they received medical care somewhere else prior to hospital arrival was identified (first medical contact [FMC]). The patient population was divided into 2 groups: those attending within the first 12 hours of evolution, and those attending with more than 12 hours. The cause for delay was identified in the latter: 1) Patient-attributable delay, which refers to the delay occurring between the onset of symptoms and FMC, which might be due to lack of economic resources for transportation, lack of transportation, lack of knowledge about the symptoms or not giving importance to the symptoms, and 2) FMC-attributable delay: in this section, patients attending any medical service who were assessed by a physician prior to arriving to our hospital were considered.

Finally, in patients who attended within the first 12 hours but did not receive reperfusion treatment, the delay was considered to be hospital-related. Patients with any contraindication for thrombolysis administration or angioplasty were excluded in this group. In all patients, clinical evolution follow-up was made until discharge.

Statistical analysis

Descriptive statistics with means and standard deviations or median with minimum and maximum values was used for quantitative variables according to their distribution, and absolute values and percentages were used for qualitative variables. Continuous variables between groups were compared with Student's t-test or Mann-Whitney U-test, according to their distribution. Differences between categorical variables were assessed using the chi-square test. Multiple regression analysis was made including those variables previously showing a p-value < 0.1 in the univariate analysis. Odds ratio with 95% confidence interval was calculated for the variables included in the model. Statistical significance was established at $p < 0.05$. The statistical package SPSS, version 18, was used (Chicago, IL, USA).

Results

Clinical and biochemical characteristics

From November 1, 2012 through January 30, 2015, 213 patients were consecutively included. In table 1, patient socio-demographic and clinical data are shown as related to time of delay. Age was higher in those patients with more than 12-hour delay ($p = 0.01$). Patients admitted at the night shift or on weekend attended with longer time of delay ($p = 0.02$). Longer delay in hospital arrival was observed in diabetic patients (p

Table 1. Socio-demographic and clinical data in patients with ST-segment elevation myocardial infarction

Variable	< 12-hour delay (n = 109)	≥ 12-hour delay (n = 104)	Total (n = 213)	p-value
Age, mean ± SD	58.8 ± 12.1	62.8 ± 11.4	60.8 ± 11.9	0.01
Male sex, n (%)	90 (82.6%)	87 (83.7%)	177 (83.1%)	0.83
Primary education or illiterate, n (%)	64 (62.1%)	71 (74.0%)	134 (67.8%)	0.07
Sub-region, n (%)				0.06
– Chontalpa	38 (36.9%)	27 (28.4%)	65 (32.8%)	
– Center	40 (38.8%)	32 (33.7%)	72 (36.4%)	
– Mountain	9 (8.7%)	8 (8.4%)	17 (8.6%)	
– Swamplands	6 (5.8%)	11 (11.6%)	17 (8.6%)	
– Rivers	5 (4.9%)	2 (2.1%)	7 (3.5%)	
– Others	5 (4.9%)	15 (15.8%)	20 (10.1%)	
Place of origin:				0.269
– Spontaneous	31 (28.4%)	18 (17.3%)	49 (23.0%)	
– Transferred from another hospital	61 (56.0%)	65 (62.5%)	126 (59.2%)	
– Referred by private doctor	15 (13.8%)	18 (17.3%)	33 (15.5%)	
– Same hospital	2 (1.8%)	3 (2.9%)	5 (2.3%)	
Night shift or weekend admission	31 (28.4%)	45 (43.3%)	76 (35.7%)	0.02
Smoking	41 (37.6%)	40 (38.5%)	81 (38%)	0.89
Diabetes mellitus	44 (40.4%)	58 (55.8%)	102 (47.9%)	0.02
High blood pressure	48 (44%)	57 (54.8%)	105 (49.3%)	0.11
Dyslipidemia	36 (33%)	47 (45.2%)	83 (39%)	0.69
Previous myocardial infarction	9 (8.3%)	13 (12.5%)	22 (10.3%)	0.30
Atypical-type precordial pain	10 (9.2%)	23 (22.1%)	33 (15.5%)	0.009
Body mass index	28.4 ± 4.2	27.7 ± 3.8	28.1 ± 4.0	0.19
Overweight or obesity	89 (82.4%)	74 (71.8%)	163 (77.3%)	0.067

Numerical data are expressed in means. Qualitative data are shown in absolute values and percentages.
SD: standard deviation.

= 0.02), and patients with typical angina pectoris attended earlier in comparison with patients referring atypical pain (0 = 0.009). No significant differences were observed in the remaining clinical data.

Biochemical parameters of patients with myocardial infarction are shown in table 2. No significant differences were observed in the levels of glucose, azoates and cardiac enzymes with regard to the time to arrival to the emergency department.

Median time of delay from infarction symptoms onset to FMC was 4 hours; for the early care group, the observed mean was 3 hours, and for the late care group it was 11 hours (Table 3). Median time of delay for arrival to the emergency department of our institution was 12 hours. Patients with a delay longer than 12 hours had more signs and symptoms of pulmonary congestion and heart failure at their arrival (Table 4). Antiplatelet regimen was mainly based on clopidogrel in addition to aspirin, whereas 9.1% of patients arriving within the first 12 hours of infarction evolution received prasugrel or ticagrelor. The most widely used reperfusion therapy in our center was thrombolysis in 63.3% of patients, with streptokinase being the most common lytic in 67% of cases. Primary angioplasty was performed only in 6.3% of patients. There were statistically significant differences in the days of hospital stay, with hospitalization being longer in the group with delayed arrival to the emergency department (5.0 ± 2.4 vs. 6.1 ± 2.8; p = 0.004). Total hospital mortality of 16% was observed in patients with myocardial infarction, with no statistical difference with regard to the time to arrive to the emergency department. However, when the first 6 hours is used as a cutoff point for infarction early care, hospital mortality of 12.3% is observed for patients attending within the first

Table 2. Biochemical data in patients with ST-segment elevation myocardial infarction (n = 213)

Variable	< 12-hour delay (n = 109)	≥ 12-hour delay (n = 104)	Total (n = 213)	p-value
Glucose	167 (84-860)	158 (42-641)	165 (42-860)	0.83
Creatinine	1.1 (0.3-4.2)	1.2 (0.67-6.2)	1.2 (0.3-6.2)	0.11
Urea	35 (11-251)	42 (13-209)	37 (11-251)	0.24
CPK	558 (48-8203)	736 (81-3637)	636 (48-8203)	0.16
CPK MB fraction	67 (7.6-503)	69 (10-435)	69 (7.6-503)	0.94

Data shown in medians and minimum and maximum values, since they have a non-parametric distribution.
CPK: creatine phosphokinase.

Table 3. Times of delay, medical management and hospital mortality in patients with ST-segment elevation myocardial infarction (n = 213)

Variable	< 12-hour delay (n = 109)	≥ 12-hour delay (n = 104)	Total (n = 213)	p-value
Time of delay from symptoms onset to FMC (h)	3 (0.2-12)	11 (0.5-289)	4 (0.2-289)	N/A
Time of delay from symptoms onset to hospital admission (h)	4.9 (0.3-12)	35 (13-289)	12 (0.3-289)	N/A
Killip & Kimball ≥ II	19 (18.2%)	43 (41.9%)	62 (29.7%)	0.0001
Infarction location on anterior face	43 (46.2%)	50 (48.5%)	93 (43.9%)	0.40
Antiplatelet agent				0.02
– Clopidogrel	99 (90.8%)	103 (99%)	202 (94.9%)	
– Prasugrel	2 (1.85)	1 (1.0%)	3 (1.4%)	
– Ticagrelor	8 (7.3%)	0	8 (3.7%)	
Reperfusion therapy, n (%)	69 (63.3%)	N/A	69 (32.4%)	N/A
– Thrombolysis	65 (59.6%)		65 (30.5%)	
– Primary PTCA	4 (3.6%)		4 (1.8%)	
Thrombolytic treatment				
– Streptokinase	44 (40.4%)	N/A	44 (20.6%)	N/A
– Alteplase	10 (9.1%)		10 (4.7%)	
– Tenecteplase	11 (10.1%)		11 (5.2%)	
Hospitalization days	5.0 ± 2.4	6.1 ± 2.8	5.6 ± 2.7	0.004
In-hospital decease, n (%)	17 (15.6%)	17 (14.3%)	34 (16.0%)	0.881

Quantitative variables are presented in medians with minimum and maximum value.
FMC: first medical contact; h: hours; N/A: not applicable; PTCA: percutaneous transluminal coronary angioplasty.

6 hours and mortality of 18.4% (more than 6 percentage points) for patients attending after 6 hours of evolution.

Figure 1 shows times of delay by categories according to elapsed hours. Observe how more than 30% of patients attend with more than 24 hours' delay.

Causes of delayed arrival to the emergency department

Of a total of 210 patients, 33.3% attended with no delay, i.e., within the first 12 hours of infarction evolution and benefited by any of both reperfusion therapies; 30.4% had some patient-attributable delay, in 20.5% FMC-attributable delay was observed, and 15.8% had delayed treatment at the hospital itself (Table 4).

Independent predictors of delayed arrival to emergency department

In the multiple regression model, variables with significant differences between groups ($p < 0.01$) were included in the univariate analysis, with night shift or

Table 4. Causes of medical care delay in patients with ST-segment elevation myocardial infarction with regard to gender*

Causes of delay	Females (n = 36)	Males (n = 177)	Total (n = 210)
No delay	11 (30.6%)	59 (33.3%)	70 (32.9%)
Delay attributed to the patient	12 (33.3%)	52 (29.9%)	64 (30.4%)
Lack of money	1 (2.8%)	3 (1.8%)	4 (1.9%)
Ignorance about symptoms	4 (11.1%)	23 (13.2%)	27 (12.7%)
Symptoms regarded as unimportant	4 (11.1%)	22 (12.6%)	26 (12.4%)
Other	3 (8.3%)	4 (2.3%)	7 (4.2%)
Delay attributed to FMC	7 (19.4%)	36 (20.7%)	43 (20.5%)
Treatment delay at the hospital	6 (16.7%)	27 (15.5%)	33 (15.8%)

*p-value = 0.79 (no statistically significant difference). Three patients with contraindications for thrombolysis were excluded from the treatment-delay group.
FMC: first medical contact.

weekend admission being identified as the only independent predictor to attend late the emergency department. The other variables included in the model failed to reach statistically significant difference (Table 5).

Discussion

This work shows that the presence of advanced age, diabetes mellitus, atypical precordial pain and arrival to the emergency department on the night shift or on weekend are variables associated to longer than 12-hour delay in patients with STEMI. Admission on shifts other than usual was an independent predictor for delayed arrival of patients with STEMI, which is directly related to the possibility of receiving reperfusion therapy. It has been demonstrated that up to 2 thirds of patients with STEMI attend at nocturnal shifts or on weekends, which has been associated with longer time to receive reperfusion therapy and higher mortality in patients undergoing mechanical reperfusion therapy[5]

Worldwide data indicate that the percentage of patients attending early during the evolution of a myocardial infarction is low. Some of these studies report that patients with STEMI do not seek help for approximately 1.5 to 2 hours after the onset of symptoms[7,8]. It has been documented that only about 15% of patients attend within the first hour from symptom onset and up to 40% of patients have a delay longer than 6 hours[9]. This delay is largely influenced by the decision of seeking medical attention[10]. Previously reported factors influencing on time of delay have to do with socio-demographic aspects (economic aspects or remoteness of the place), cognitive status of the patient and factors associated with underlying conditions. Other reported factors are older age, female gender, living alone, lack of symptom recognition, disproportion between expected symptoms and actual symptoms, self-medication, stress and altered emotional states[11,12]. Other reasons for delay in seeking treatment include inappropriate reasoning that symptoms are self-limiting or not serious, attribution of symptoms to other preexisting conditions, fear of embarassment if symptoms turn out to be a "false alarm", lack of knowledge on the importance of rapid action and on the availability of reperfusion therapies[13]. Other important cause of delay in medical care is ischemic pain atypical characteristics. Culic et al.[14] identified diabetes mellitus, female gender and older age as independent predictors of

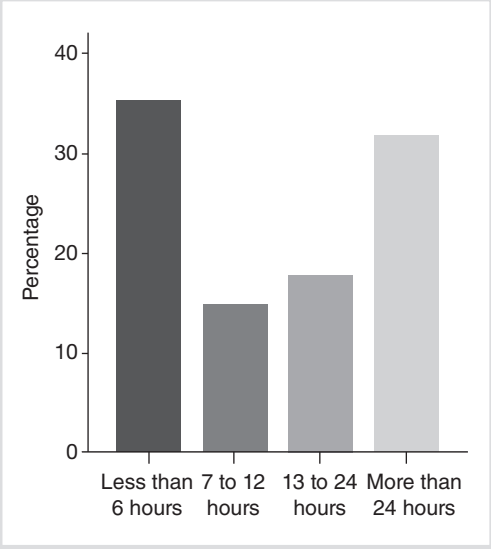

Figure 1. *Times of delay in patients with ST-segment elevation MI.*

Table 5. Multiple logistic regression analysis to determine independent predictors of delayed medical attention in patients with myocardial infarction

Variable	OR (95% CI)	p-value
Age	1.0 (0.98-1.04)	0.23
Diabetes mellitus	1.5 (0.83-2.82)	0.16
Atypical precordial pain	1.5 (0.62-3.70)	0.35
Low level of education	1.5 (0.72-3.15)	0.26
Arrival at night shift or on weekend	2.3 (1.23-4.53)	0.009

myocardial infarction atypical clinical presentation. Similar to our study, they identified older age, diabetes mellitus and atypical pain as the main factors associated with delayed infarction care. In addition, a low level of education has been associated with delay in time of arrival to the hospital after the onset of infarction symptoms. Primary-school or lower level was present in 74% of patients in comparison with 62% in those attending early. A recent study identified that a high level of education is correlated with the shortest times of delay at hospital arrival[15].

The presented data analyze times of delay in a reference hospital in southeastern Mexico. A highly valuable characteristic of this study is that causes of delay were identified from each patient's point of view. The main cause of patient-attributable delay in the present study was lack of knowledge about myocardial infarction-related symptoms, which is susceptible to modification with health education, since it has to do with information availability to open population.

A considerable number of patients attending with delay (around 60%) were admitted via ambulance transportation. Being a reference hospital, patients are received from general hospitals of different municipalities of the state, in addition to other states' near cities. The present study shows that 20.5% of patients arrive late to receive therapy due to FMC-attributed delay. Median time to attend FMC was 4 hours; however, the group of patients attending the hospital late shows a median time to arrive to FMC of 11 hours, with a minimum of 30 minutes and in some cases more than 1 week. Patients attending at thrombolysis time-window may have their treatment delayed owing to diagnostic failure, impossibility to perform an electrocardiogram or lack of a reperfusion method in the medical unit. The main diagnostic mistakes in patients with atypical infarction symptoms are attributed to musculoskeletal and gastrointestinal pathologies. One factor that delays myocardial infarction primary care is attending a doctor's office rather than an emergency department, since many times the place has no electrocardiographic equipment available or the resources to administer thrombolysis. Hitchcock et al. identified that attending a primary care physician instead of resorting to an ambulance service was associated with thrombolysis administration delay.

Treatment delay at the hospital accounted for one fourth part of all causes of delay, which enables inferring that even if the patient promptly attends an emergency department, it may not be enough to receive the recommended reperfusion therapy.

It is important establishing that the factors associated with a decrease in delays for treatment are the perception of higher risk, fear of death, symptoms' severity and easy access to emergency services[17].

In the present study, a reperfusion percentage of 33.5% was observed in patients with STEMI, which is very similar to data published in the RENASICA II trial[18] (37%) in 2005. The two reperfusion methods recommended for treatment within the first 12 hours of infarction evolution, primary angioplasty and thrombolysis, were possible only in one third part of patients. The most effective and safe, angioplasty, was only performed in 3.6% of eligible patients. In spite of new and better thrombolytic agents, the percentage of patients who receive them remains low (only 30% of all patients). Delayed arrival to emergency departments was associated with more hospitalization days in the present study.

The identification of factors associated with delay should impact on the search for and implementation of specific measures of strategies to reduce times to treatment in patients with myocardial infarction, since this might reduce the risk of permanent myocardial damage and death.

Myocardial infarction represents a pathological state that puts life at high risk. It has been suggested that up to half the patients with myocardial infarction can die before arriving to an emergency department[19]. Myocardial damage extension is directly related to the time ischemia lasts, and it can be: minimal or absent if it is resolved within the first

30 minutes, or extensive and irreversible if more than 12 hours are elapsed since the onset of symptoms. In short, the longer the time, the larger the myocardial damage is. A large number of studies have demonstrated that delay in medical attention is associated with higher risk for lethal arrhythmias, heart failure and death. Similarly, numerous studies have shown that early care is associated with decreased reinfarction and mortality in these patients[20]. The REACT study investigators assessed a strategy to decrease time delays for hospital arrival. At baseline assessment, median time between the onset of symptoms and arrival to the emergency department was 2.3 hours and only 25% had delays longer than 5.2 hours. After massive information in the media, a reduction was achieved in times of delay[21].

We consider that new and better population-directed public education campaigns should be established, as well as programs to reduce treatment delay to the minimum in patients with myocardial infarction. These programs should have a follow-up in order to improve quality of care. Both massive diffusion in the media and better access to healthcare systems can impact on infarction primary care. To avoid these delays, health promotion should help patients as much as possible in the development of foresight plans for recognition and opportune response to an acute event. In other countries, relatives and close friends have been recruited to reinforce rapid action when patients experience symptoms of possible STEMI[22].

Infarction medical attention state systems that include ambulance transportation services and electrocardiogram taking by trained personnel have shown good results[23]. These well established systems are the preamble for the establishment of pre-hospital thrombolysis, which is the ideal reperfusion method for places most distant from reference hospitals.

Increased life expectancy of the population and higher incidence of chronic conditions such as diabetes mellitus represent a major challenge for health services in the Mexican population with regard to infarction early care and appropriate management.

The present study has the limitation that it was carried out in a single reference center with a limited number of patients. Large studies are required that allow for a situational diagnosis to be made for each Mexican population.

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