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Pre- and In-Hospital Delay in Treatment and in-Hospital Mortality after Acute Myocardial Infarction

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Purpose. 1) To identify the time taken from symptom onset to the arrival at the hospital (pre-hospital delay time) and time taken from the arrival at the hospital to the initiation of the major treatment (in-hospital delay time) 2) to examine whether rapid treatment results in lower mortality. 3) to examine whether the pre- and in-hospital delay time can independently predict in-hospital mortality.

Methods. A retrospective study with 586 consecutive AMI patients was conducted.

Results. Pre-hospital delay time was 5.25 (SD=10.36), and in-hospital delay time was 1.10 (SD=1.00) hours for the thrombolytic therapy and 50.24 (SD=121.18) hours for the percutaneous transluminal coronary angioplasty (PTCA). In-hospital mortality was the highest when the patients were treated between 4 to 48 hours after symptom onset using PTCA (p=.02), and when treated between 30 minutes and one hour after hospital arrival using thrombolytics (p=.01). Using a hierarchical logistic regression model, the pre- and in-hospital delay times did not predict the in-hospital mortality.

Conclusion. Pre- and in-hospital delay times need to be decreased to meet the desirable therapeutic time window. Thrombolytics should be given within 30 minutes after arrival at the hospital, and PTCA should be initiated within 4 hours after symptom onset to minimize in-hospital mortality of AMI patients.

Key Words: Acute myocardial infarction, Delay in treatment, Mortality

INTRODUCTION

Significance

Acute myocardial infarction (AMI) is a major cause of death in Korea and worldwide. (American Heart Association, AHA, 2003; Korea National Statistics Office, KNSO, 2003). Approximate 10,000 people die from the ischemic heart disease each year in Korea (KNSO, 2003).

Owing to the development of emergency medicine and the critical care technology, survivals from this disease are increasing. Mortality from the heart disease has been decreased by 14.9 per 100,000 during the last decade between year 1991 and 2001 (KNSO, 2003). However, because of the rapid process of this disease, early mortality rate of AMI is high. Although there are some discrepancies among statistical resources, approximately 50% of death occurs before the patients' arrival at the hospital; and the mortality rate for the first one-hour and 24 hours reach 68% and 85% respectively (KNSO, 1999, retrieved in 2003).

Early reperfusion therapy using thrombolytic agents or the percutaneous transluminal coronary angioplasty (PTCA) contributed to decreasing the early mortality of AMI patients over the last few decades in the US

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(Blohm, Hartford, Karlsson & Herlitz, 1998; Mitic, & Perkins, 1984). Timely reperfusion therapy consistently improved hemodynamic conditions, decreased infarct size and improved survival in previous studies (Berger, Holmes, Califf, & Criger, 1997; Berger, Radford, & Krumholz, 2000; Cannon & Goldhaber, 1995; Hwang, 1995; Leizorovicz, Boissel & Robert, 1992).

The extent of protection from mortality, however, appears to be directly related to the rapidity of reperfusion after the onset of symptoms of an AMI. Although the intravenous thrombolysis is a feasible and the most recommended therapy, the benefits of this treatment decreased because of the delay between the onset of the symptoms and the treatment (Yoo et al., 1995). If the thrombolytic therapy can be initiated within one hour after symptom onset, it reduces the mortality of the AMI by 45.8%. The mortality rate can be reduced only 15% when the thrombolytics begun between two and six hours (Gruppo Italiano per studio della streptochinasinell Infarcto miacardico, GISSI, 1986).

Although the major portion of the total delay time consisted of the pre-hospital delay time, the in-hospital delay time is still important for following reasons: the in-hospital delay can be reduced by efforts of health care providers (Gonzalez, Jones, Ornato, Bleecker & Strauss, 1992). Therefore, understanding both pre- and in-hospital delay time is important to reduce the total delay time and increase the survivals from the AMI.

Along with the health care providers' recognition of the importance of early diagnosis and treatment, delay time to the treatment tend to be decreased in the US and European countries (Boersma, Mass, Deckers & Simons, 1996; Goldberg et al., 1992; GISSI, 1986). Particularly in-hospital delay time has been remarkably decreased during the past seven years in the series of nationwide trials in the US and European countries (Chareonthaitawee, 1997; Gilber et al., 2002; GISSI, 1986; Goldberg et al., 1992).

However, there are lack of data regarding the time delay between the symptom onset and the treatment among Koreans. Although several studies have been conducted regarding the delay time between the symptom onset and treatment after AMI among Korean, data from those studies are not sufficient to be conclusive and far more studies are needed (An, 2001; Kim & Kim, 1999; Park, Kim, Lee & Lee, 2000, Song, 1997; Yoo et al., 1995).

The first limitation of the previous studies regarding associations between delay times and mortality was the small number of cases in Korea. In addition, previous studies mostly focused on the pre-hospital delay time, and the in-hospital delay times haven't been sufficiently investigated (Kim & Kim, 1999; Park et al., 2000; Yoo et al., 1995; Jung et al., 1997; Hwang, 1995). Some studies even exclusively obtained cases only from the AMI patients who were presented at the hospital within the therapeutic time window, and reported the delay time that may not represent average delay time of the AMI patients in Korea (Hwang, 1995). Therefore, this study aimed to describe the actual pre- and in-hospital delay time and to examine whether the longer delay time was associated with the higher mortality after AMI.

Purpose of the study

The purposes of the study were 1) to describe the time taken from symptom onset to the arrival at the hospital (pre-hospital delay time) and time taken from the arrival at the hospital to the major treatments (in-hospital delay time), 2) to examine whether more rapid time to treatment results in lower mortality, 3) to examine whether the pre- and in-hospital delay in treatment, after controlling the effects of other risk factors on mortality, can independently predict the in-hospital mortality.

Definition of Terms

Pre-hospital delay time has been defined as the time taken from symptom onset to the arrival at the hospital.

In-hospital delay time has been defined as the time taken from the arrival at the hospital to the initiation of the major treatment (either PTCA or thrombolytics).

Overall delay time has been defined as the time taken from symptom onset to the initiation of the major treatment.

Hypotheses

Hypothesis 1. In-hospital mortality will be lower in the patients who arrive at the hospital earlier than the patients who arrive at the hospital later after the symptom of AMI.

Hypothesis 2. In hospital mortality will be lower in patients who were treated earlier than who were treated later using thrombolytics.

Hypothesis 3. In hospital mortality will be lower in patients who were treated earlier than who were treated later using PTCA.

Hypothesis 4. Pre-hospital delay time will indepen-

dently predict the in-hospital mortality after controlling other traditional risk factors.

Hypothesis 5. In-hospital delay time will independently predict the in-hospital mortality after controlling other traditional risk factors.

METHOD

A retrospective observation study of the data recruited from five university hospitals and one large tertiary hospital located in Seoul and Pusan.

Subjects

Medical records of 852 AMI patients who were admitted to one of the research sites were reviewed for the purpose of this study. After applying the inclusion and exclusion criteria, 586 cases were analyzed for this study. Among these 138 patients were directly interviewed and others were retrieved from medical record review. Inclusion criteria were who met two of followings: 1) typical chest pain lasting longer than 20 minutes; 2) ST segment elevation or signs of AV block on EKG; 3) elevation of CK, CKMB or troponin. Additionally AMI patients who were diagnosed by the echo cardiogram or cardiac angiogram were also included. Exclusion criteria were patients who didn't meet the inclusion criteria described above, who had no confirmative data for the diagnosis, who had primary treatment visiting the target hospital, and patients who couldn't be followed up for mortality.

Instrument

A structured chart abstract form was used for collecting data. This form was developed by the researcher and tested for the content validity by the panel of experts consisting of four faculties in cardiovascular nursing, one cardiologist, and one psychologist.

Data were either obtained by interview after the informed consents were granted for data collection or extracted anonymously from the medical record review. The chart abstract form included following information: 1) socio-demographic variables such as age, sex; 2) major health history including history for previous heart disease; 3) time for the symptom onset, arrival at the hospital, the time of initiation of diagnostic tests, and the time of initiation of treatment; 4) clinical information for the adjustment of severity of the disease using APACHE III such as the first vital sign, the worst vital sign during the first 24hours after arrival at the hospital, level of consciousness, Killip classification, co-morbidity of diabetes and hypertension, episode of ventricular tachycardia, episode of ventricular fibrillation, and other complications in early stage of the disease 5) basic data for the confirmative diagnosis of an AMI 6) survival or death.

Data analysis

Data were analyzed using descriptive statistics to describe the time taken from the time of symptom onset to arrival at the hospital, time taken from symptom onset to the treatment, time taken from the arrival at the hospital to the diagnosis and treatment. Extreme cases were excluded for data analysis. To describe the in-hospital delay times were obtained by reviewing available medical records, and the time taken from the arrival at the hospital to the major treatment were calculated for each group of subjects who had either thrombolytic therapy or the PTCA. The overall delay time was calculated by summating pre- and in-hospital delay times.

Chi-square and ANOVA were conducted to examine whether there are significant differences in the mortality by the pre- or in-hospital delay times. Separate Chi-square and ANOVA were conducted to identify factors associated with the mortality. A hierarchical logistic regression was conducted to examine whether the delay times can be independently predicted the in-hospital mortality after controlling other physiologic predictors. All statistical analysis was conducted using SPSSWIN 10.0.

RESULTS

General and Clinical Characteristics of the Subjects

Total 586 AMI cases were analyzed including 426 men (72.7%) and 160 women (27.3%) for the purposes of this study. The age of subjects ranged from 21 to 96 years with the mean of 60.21 (±13.27) years. Women were older than men (69.37±10.84 vs. 56.78±12.49 years). The in-hospital mortality of the AMI patients in this study was 9.7% (57 out of 586 patients). Women show higher in-hospital mortality than men (10.8 vs. 8.6%)(χ^2=6.975, *df*=1, *p*=.008). Clinical characteristics of the subject are summarized in Table 1.

The pre-hospital delay time and the in-hospital delay time are summarized in Table 2.

The mean of the pre-hospital delay was about 5.25 hours. The in-hospital delay time was 1.10hours for the

patients treated by thrombolytic therapy, and 50.24 for the patients treated by PTCA. The overall delay time was 5.02 hours for the patients who were treated by thrombolytics and 55.91 for the patients treated by PTCA. Additionally, the mean of the time taken from the arrival at the emergency room to the diagnosis an AMI was 14.51 minutes.

Table 1. Clinical Characteristics of the Subjects (N=586)

	N	Minimum	Maximum	Mean	Std. Deviation
APACHE III[1]	448	4.00	157.00	35.64	28.22
Total number of risk	448	0	7.00	2.56	1.24
KILLIP Class[2]	573	1.00	4.00	1.56	0.98
LVEF(%)[3]	522	15	90	49.07	12.34
CKMB	573	0	8700.00	341.42	745.30
Troponin	477	0	5680.00	34.23	266.24

[1]a modification method for the severity of the disease using first vital sign, the worst vital sign during the first 24 hours after arrival at the hospital, level of consciousness.
[2]classification method for pulmonary complications: class I to IV.
[3]Left ventricular ejection fraction.

Hypothesis testing

Chi-square tests were conducted to examine the differences in the mortality between/among groups of pre-, in-hospital, and the overall delay times (Table 3). There was no significant difference in the mortality between the group who arrived at the hospital within the first two hours and who arrived at the hospital after two hours. Therefore the first hypothesis, 'in-hospital mortality will be lower in the patients who arrive at the hospital earlier than the patients who arrive at the hospital later after the symptom of AMI' has been rejected.

Among the patients who had thrombolytic therapy, pa-

Table 3. In-hospital Mortality by the Pre- and in-hospital Delay Times

	χ^2	*df*	*p*
Symptom to Arrival at ER	1.03	1	0.31
Symptom to Thrombolytics	0.52	3	0.92
Symptom to PTCA	9.63	3	0.02
ER to diagnosis	2.23	2	0.33
ER to Thrombolytics	11.79	3	0.01
ER to PTCA	5.66	3	0.13

Table 2. Pre- and in-hospital Delay Times

	Hours/minutes	N(%)	M(SD)
Symptom to Arrival at ER (Hrs)	less than 2	256 (44.6)	1.23 (0.56)
	and longer	318 (55.4)	8.49 (13.04)
	Total	574(100.0)	5.25 (10.36)
Symptom to Thrombolytics (Hrs)	less than 2	61 (21.0)	1.59 (0.41)
	2 and longer less than 4	109 (37.6)	2.95 (0.54)
	4 and longer less than 6	65 (22.4)	4.87 (0.57)
	6 and longer	55 (19.0)	13.13 (13.85)
	Total	290 (100.0)	5.02 (7.26)
Symptom to PTCA (Hrs)	less than 4	38(22.5)	2.98 (0.86)
	4 and longer less than 8	47 (27.8)	5.86 (1.15)
	8 and longer less than 48	39 (23.1)	17.74 (8.20)
	48 and longer	45 (26.6)	185.96 (184.92)
	Total	169 (100.0)	55.91 (123.18)
ER to diagnosis (min)	0	175 (58.3)	0 (0)
	less than 5	114 (38.0)	11.91 (12.50)
	5 and longer	11 (3.7)	272.27 (239.86)
	Total	300	14.51 (67.48)
ER to Thrombolytics (Hrs)	less than 0.5	69 (23.3)	0.24 (0.20)
	0.5 and longer, less than 1	102 (34.5)	0.79 (0.14)
	1 and longer, less than 1.5	73 (24.7)	1.27 (0.14)
	Longer than 1.5	52 (17.6)	2.61 (1.47)
	Total	296 (100.0)	1.10 (1.00)
ER to PTCA (Hrs)	less than 1.5	45 (25.9)	0.90 (0.28)
	Longer than 1.5, less than 4	45 (25.9)	2.51 (0.76)
	Longer than 4, less than 48	40 (23.0)	13.80 (9.98)
	Longer than 48	44 (25.3)	182.65 (186.77)
	Total	174 (100.0)	50.24 (121.18)

tients who were treated between 30 minutes and one hour since the arrival at the hospital showed higher mortality compared to the group who were treated either earlier than 30 minutes or later than one hour since the patients' arrival at the hospital (χ^2=11.065, *df*=3, *p*=.011). Therefore the second hypothesis, 'in hospital mortality will be lower in patients who were treated earlier than who were treated later using thrombolytics' was rejected.

Among who were treated by PTCA, there was a significant difference in mortality among groups of the time taken from the symptom onset to the PTCA (χ^2=8.7, *df*=3, *p*=.033). However, patients who had PTCA between 4 to 48 hours had higher mortality compared to those who had PTCA either earlier than 4 hours or later than 48 hours since their symptom onset, and the third hypothesis 'in hospital mortality will be lower in patients who were treated earlier than who treated later using PTCA' was rejected.

A hierarchical logistic regression was conducted to examine whether, after controlling the effects of physiological predictors, delay times can independently predict the mortality. From chi-square tests for the categorical variables and ANOVA tests for the continuous variables, factors significantly associated with the mortality were identified (Table 4 and 5).

For the logistic hierarchical regression, sex, number of risk factors, Killip-classification, age, APACHE III, and LVEF, were entered into the model, followed by the pre- and in-hospital delay times (Table 6 & 7)(see also Table 4 and 5 for the significance of factors included in the model). At the first step of the hierarchical model, APACHE III and the EF appeared as significant predictors of the in-hospital mortality as shown in Table 6. At the second step, entering two new variables did not improve the predictability of mortality in the model as shown in Table 7 (ΔR^2=.003, ($X_{diff,2}^2$=1.142, *p*=.565). Therefore, the forth and fifth and sixth hypotheses were rejected.

Table 4. Factors Associated with Mortality I

		χ^2	*df*	*p*
Sex	(n=448)	6.77	1	.007
Risk Factor	(n=448)	31.57	7	.000
Killip Class	(n=437)	67.69	3	.000

Table 5. Factors Associated with Mortality II

		M(SD)	*t*	*p*
Age	Survival (n=469)	58.48 (13.00)	- 6.330	.000
	Death (n=57)	69.85 (10.99)		
APACHE III	Survival (n=391)	28.39 (16.61)	- 19.23	.000
	Death (n=57)	85.33 (39.42)		
LVEF (%)	Survival (n=354)	50.25 (11.44)	5.61	.000
	Death (n=41)	39.46 (13.47)		
CKMB	Survival (n=385)	405.88 (885.79)	.60	.551
	Death (n=53)	332.33 (358.73)		
Troponin	Survival (n=304)	14.45 (25.93)	.70	.483
	Death (n=41)	11.51 (18.58)		

DISCUSSION

This study aimed to describe the pre- and in-hospital delay times in treatment and to examine whether more rapid treatment reduces the mortality and increases survivals after acute myocardial infarction. This is the first

Table 6. Predicting the In-hospital Mortality Including Risk Factors (Reduced Model)

	B	Ward F	*p*	Odd ratio	95%Confidence interval	
					Lower	Upper
Age	0.04	1.93	0.16	1.04	0.98	1.11
Sex	- 0.21	0.07	0.80	0.81	0.17	3.90
APACHE III	0.06	18.22	0.00	1.06	1.03	1.09
Risk Factor	- 0.40	1.17	0.28	0.67	0.33	1.38
Killip Class		1.04	0.79			
Killip (1)	- 0.69	0.64	0.42	0.50	0.09	2.70
Killip (2)	- 0.31	0.09	0.77	0.73	0.09	6.00
Killip (3)	- 0.92	0.61	0.44	0.40	0.04	4.01
EF	- 0.05	4.12	0.04	0.95	0.91	0.10
(Constant)	- 3.54	1.72	0.19	0.03		

Negelkerk R^2 = .542

Table 7. Predicting In-hospital Mortality Including Risk Factors and Pre-hospital and In-hospital Delay Time (Full Model)

	B	Ward F	*p*	Odd ratio	95%Confidence interval	
					Lower	Upper
Age	0.04	1.59	0.21	1.04	0.98	1.10
Sex	-0.07	0.01	0.93	0.93	0.19	4.71
APACHE III	0.06	18.42	0.00	1.06	1.03	1.09
Risk Factor	-0.38	1.09	0.30	0.68	0.33	1.40
Killip Class		1.32	0.72			
Killip (1)	-0.85	0.94	0.33	0.43	0.08	2.40
Killip (2)	-0.31	0.09	0.77	0.73	0.09	5.97
Killip (3)	-0.93	0.64	0.43	0.40	0.04	3.85
EF	-0.05	3.63	0.06	0.95	0.91	1.00
Pre-hospital delay time	0.10	0.75	0.39	1.11	0.88	1.40
In-hospital delay time	0.00	0.67	0.41	1.00	0.10	1.01
(Constant)	-3.91	2.03	0.15	0.02		

Negelkerk R^2 = .542

domestic study that includes more than five hundreds patients recruited from five university hospitals and one tertiary hospital in Seoul and Pusan. With the large number of cases, findings from this study may provide better understanding of the pre- and in-hospital delay times in AMI patients and their outcomes in terms of the in-hospital mortality.

Both the pre- and in-hospital delay times appeared remarkably shorter in this study compared to the previous studies conducted among Koreans (An, 2001; Jung, 1997; Kim & Kim, 1999; Song, 1997; Yoo et al., 1995). Moreover, exclusion of the last quartile for the overall delay time, the mean of the delay time will be a lot shorter and close to the mean of the delay time reported in the US and European countries (Berger et al., 1997; Berger et al., 1999; Berger et al., 2000; Canon et al., 1999, Canon et al., 2000; Herlitz, Hartfort, & Blohm, 1989; Herlitz et al., 1992; Kelion, Banning, Shahi & Bell, 1998; Kereiakes, Gibler, Martin, Pieper & Anderson, 1992).

There were significant discrepancies in the mean of the pre-hospital delay times between the group who presented at the hospital within the first two hours and the group who presented at the hospital after the first two hours (1.23 vs. 8.49 hours). Similarly, most of delay times were skewed except the time taken from the arrival at the emergency room to the initiation of the thrombolytic therapy. The last 19%, and 26% of patients contributed to raising the mean delay time in thrombolytic group and PTCA group, respectively (Table 2).

It is also of interest that for the patients who were treated by PTCA, the mortality was affected by the overall delay time, where as the mortality was affected by the in-hospital delay time among patients who were treated by thrombolytics (Table 3).

Older age, female, higher score of the adjusted severity of the disease (APACHE III), and total number of risk factors, poorer pulmonary condition represented as the higher Killip class, and lower ejection fraction appeared as significant predictor of mortality from AMI in this sample (Table 4 and 5). This finding is mostly consistent with previous studies conducted in the US or European countries (Anderson, Karagounis, & Muhlestein, 1996; Becker et al., 1998; Berger et al., 1999; Castella, Gilabert, Torner & Torres, 1991; Berger et al., 1997; Cannon et al., 2000; Schwarz, Schoberberger, Rieder & Kunze, 1994). Moreover, the logistic regression model confirmed the APACHE III and LVEF as the most consistent and stable predictor of the mortality (Table 6 and 7).

Not finding significant linear relationship between the delay times and mortality is of interest. Among those who had PTCA, mortality was higher when they treated between 4 to 48 hours compared to those who had either earlier than 4 hours or later than 48 hours. Among those who had thrombolytic therapy, the mortality was higher in the group of patients who were treated between 30 minutes and one hours since arrived at the emergency room compared to those who were treated either earlier than 30 minutes or later than one hour. This finding provide an important clinical implication: for the best chance of survival of the patients, thrombolytics should be given within 30 minutes and PTCA should be initiated within 4 hours after the symptom onset. Higher mortality of the same group compared to late comers may be due to the larger effects of the physiologic condition that over to the effects of time variable. The poorer physiologic markers, such as older age, higher Killip class, severer condition in terms of the APACHE III, lower EF among the patients who died compared to the patients who survivals support this assumption.

The time variables did not independently predict the mortality in this study. This finding shows that the time variable alone may not make a good predictor for the mortality. Rather it should be counted as a covariates in the predict model.

CONCLUSION

For the best chance of survival of the patients, thrombolytics should be given within 30 minutes , and PTCA should be initiated within 4 hours after symptom started. Descriptive statistics of the pre- and in-hospital delay time in this study suggested that both pre- and in-hospital delay times are diminishing than the delay times reported in previous studies. The time taken from the symptom onset to the PTCA and the time taken from the arrival at the hospital to the thrombolytic therapy were significantly associated with the in-mortality whereas other delay times were not significantly associated with the in-hospital mortality. Neither pre- nor in-hospital delay times did not predict the in-hospital mortality.

Further studies are needed to reduce both pre- and in-

hospital delay time and subsequent mortality among AMI patients.

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