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Thrombolytic therapy in acute myocardial infarction in Pakistan.

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Thrombolytic Therapy in Acute Myocardial Infarction in Pakistan

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Abstract

To characterize features of acute myocardial infarction (AM!) in a Pakistani population, and assess the role of thrombolysis in our country, we studied 194 consecutive admitted patients with enzyme positive AM!. Males were affected three times more frequently; women, although affected less, had a higher incidence of complications than men. Premature coronary artery disease (CAD) was present in 5O% patients presenting with AM!. An unusually high incidence of anterior wall myocardial infarction (39%) was seen. Complications were frequent with a predominance of LV failure symptoms. Cardiogenic shock was associated with a very high mortality, in excess of 93%. Streptokinase (SK) was administered in 60% patients with suspected transmural AM!. A statistically significant reduction in mortality was seen in the group that received SK (15.2%) compared to those who did not receive SK (24.7%), (p= <0.05) (JPMA 45: 54, 1995).

Introduction

Atherosclerotic CAD is one of the leading causes of death throughout the world[1]. AMI and its antecedent complications, is an epidemic in most industrialized countries; it now threatens to accelerate in a developing country like Pakistan[2-5]. Since the early 60's, improvements in the management of AMI have ranged from the introduction of Coronary Care Units focusing largely on preventing arrhythmic deaths, to the era in the 70\'s when the predominant focus was reduction of myocardial oxygen demand with beta blocker therapy. Since the mid 80's the cornerstone of AMI management, for reduction of morbidity and mortality, has been that of thrombolysis[6]. While a number of studies in the recent past have shown a declining mortality from CAD in the West[7-9], no study in this country has so far studied the impact of AMI on morbidity and mortality. The introduction of thrombolytic therapy for tmnsmuml AMI has proven beyond doubt the utility of these agents to preserve LV function[10], lyse thrombi in the infarct related artery[11], decrease the incidence of complications and foremost reduce mortality. Thus the overall aim of this study was, first of all, analyze different characteristics of AMI in a Pakistani population and assess differences with previously described studies and secondly to closely ascertain the role of thrombolysis as it pertains to mortality in Pakistan. In this report we present data to indicate that SK has a beneficial effect on mortality in Pakistani subjects.

Patients and Methods

A retrospective medical record analysis of all patients admitted with AM! from January 1, 1992 to July 31, 1993 to the AKUH, Karachi was done. A diagnosis of AMI was based on the World Health Organization (WHO) criteria of acute clinical symptoms, electrocardiographic (ECG) changes and elevation of cardiac enzymes. Accordingly, 194 consecutive patients who met all the above criteria were included in this study. Patients with only borderline enzyme increase were excluded from the study. All relevant patient information and exact location of the AMI was recorded by at least two of

the authors. Our criteria for major Q waves was the presence, 48 hours following the AMI, of prominent and large Q waves or QS complexes and insignificant R wave forces in a group of leads representing the left ventricular wall that was infarcted. Similarly, minor Q waves were assessed as the presence of small Q waves with significant R wave forces 48 hours following the AMI. Absence of Qwavesw'as, when following initial ST segment elevation, no discernible Q waves developed at 48 hours. The rate of complication was deduced by pooling all recorded complications in every patient. Thus, one patient may have had more than one complication. Management of AMI in Pakistan includes the routine use of aspirin, beta blockers and occasionally heparin. Aildescriptive results and data was expressed in percent incidence. A 'p' value of 0.05 or less was considered significant. Fishers Exact test was used to analyze the mortality difference between thrombolytic versus no thrombolytie.

Results

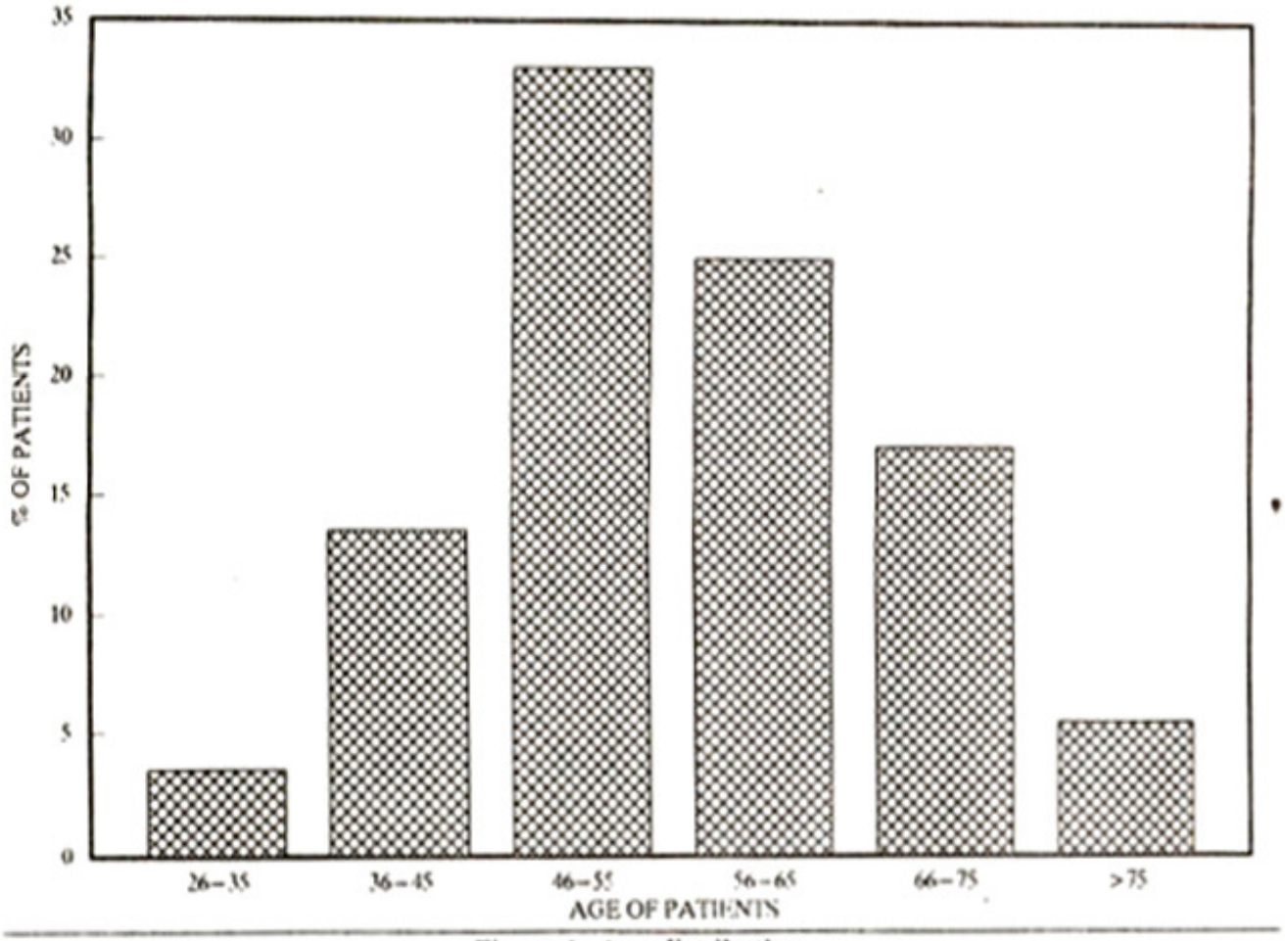

Figure 1. Age distribution.

As evident from Figure 1, 50% patients were less than 55 years of age. The age group 46-55 appeared to be the most vulnerable population, consisting of 33% of all patients. Seventeen percent patients were less than 45 years with the youngest male being 27 years and female 34 years. Very few (<6%) patients were over 70 years probably because the average life expectancy in Pakistan is 60 years for males and 65 years for females. Males (75%) outnumbered females (25%). A subgroup analysis of age and sex groups showed similar pattern of distribution between both sexes. Majority (34%) of the males and

females were in the age group of 46-55 years. Hence, it appears that the protective hormonal effect which delays CAD by 10 years in women may not be a major factor in Pakistan if the appropriate risk factors were present.

The pattern of time distribution of pain or symptom onset varied. Largest number (30%) of patients experienced their first symptom of AM! between 12:00 p.m. and 6:00 p.m. Similarly, patients presenting between 6:00 am, and 12:00 p.m. were of almost similar proportion. This indicates somewhat different circadian or diurnal variation in time of day for onset of AMI in Pakistani patients. Interestingly, a fair proportion of patients also present at other hours of the day (Figure 2).

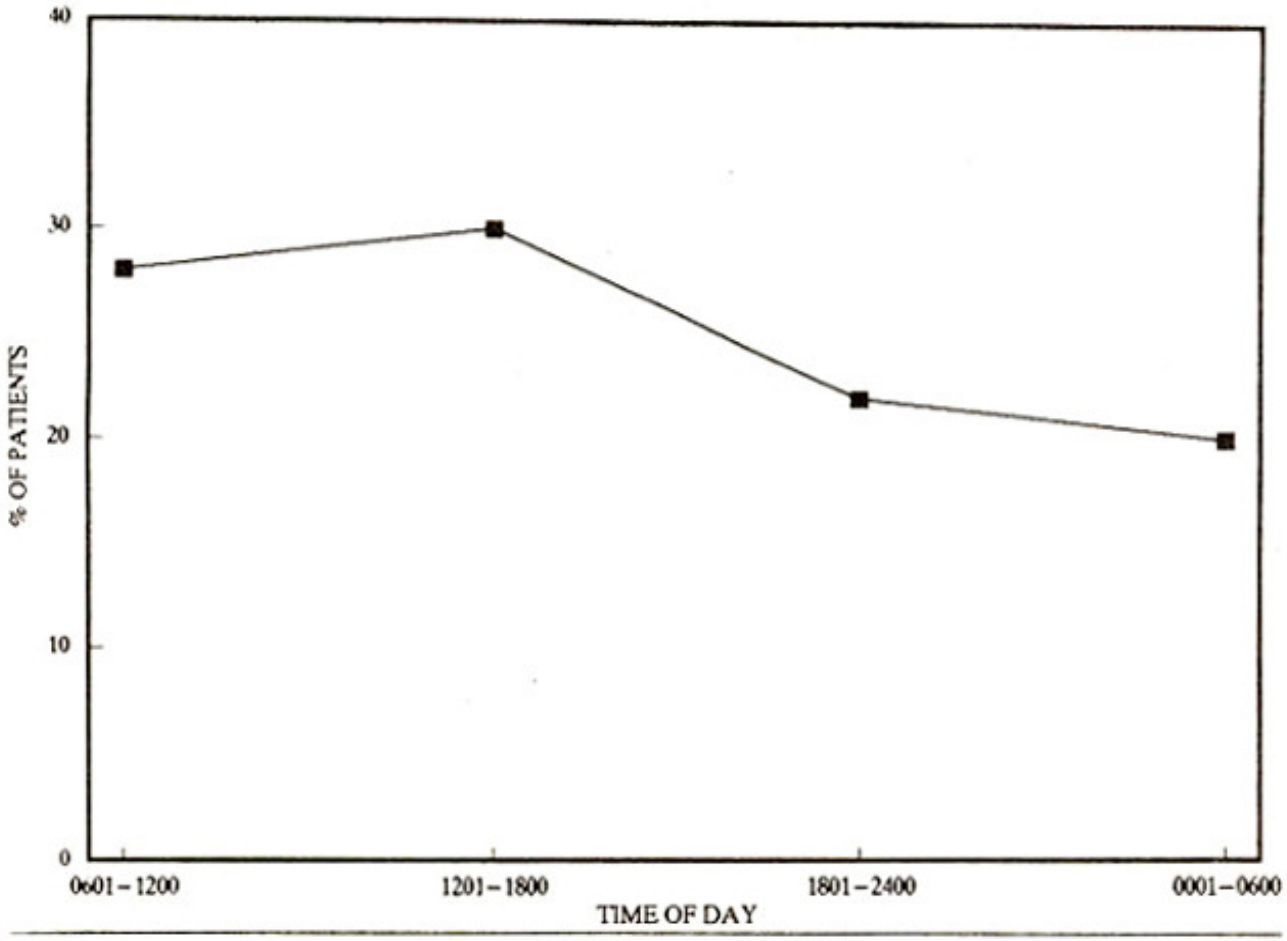

Figure 2. Time of onset of first pain.

Almost 25% patients recorded prodromal symptoms ranging from ito 15 days prior to the actual events. Only 15% were active with their routine chores when the first symptom occurred, the renmining were either at rest or sleeping. Majority of patients presented within reasonable time following symptom onset of AM! (Figure 3)

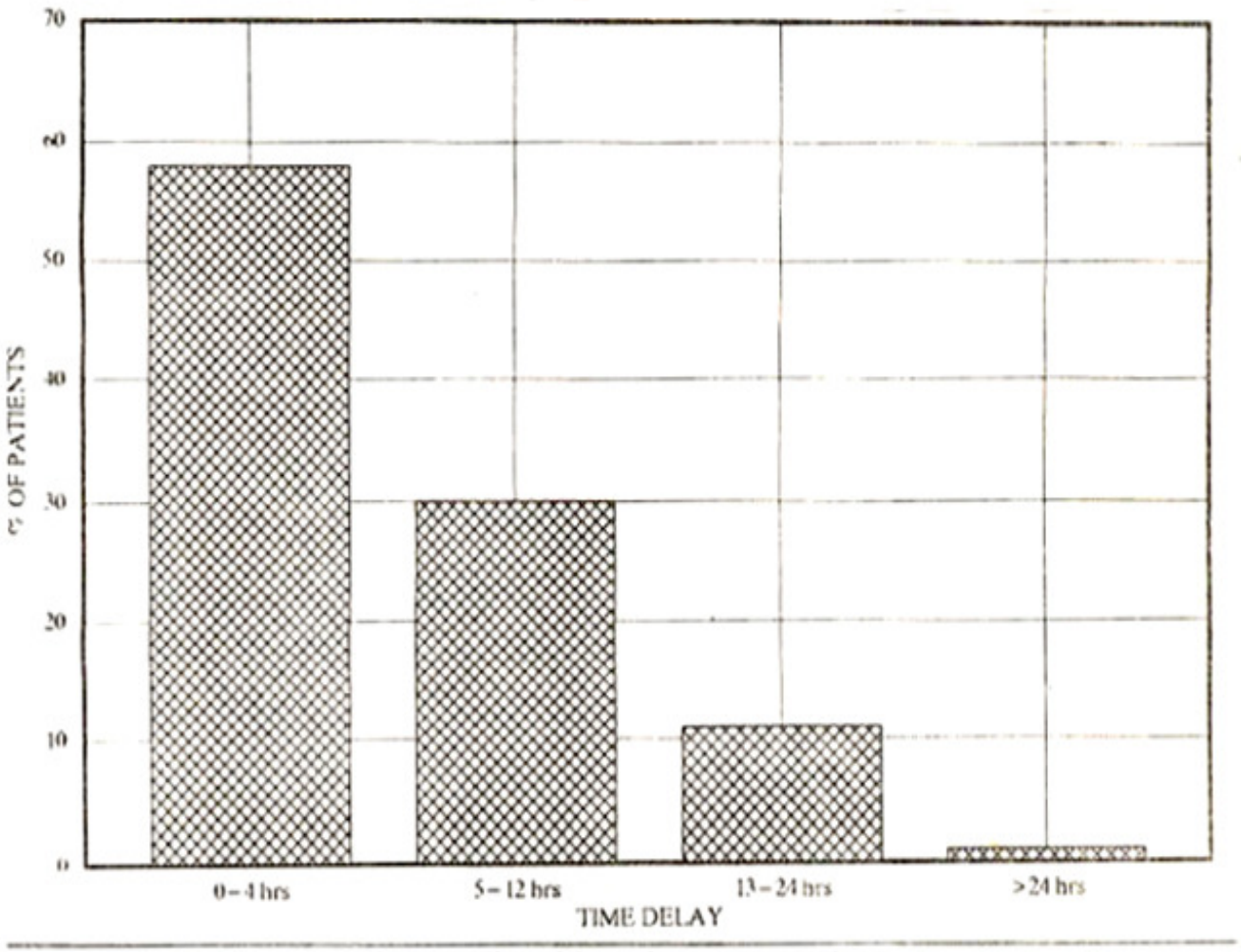

Figure 3. Time delay prior to presentation.

but younger patients presented late to the emergency room. About 58% cases reached emergency room within 4 hours, 30% were seen in 5-12 hours following onset of symptoms. Only two patients had symptoms for more than 24 hours before seeking medical attention. More than 50% presented with symptoms of severe or crushing chest pain with radiation to other areas, accompanied by diaphoresis. Some patients had complaints of anxiety predating 24-48 hours prior to the infarct. Approximately 18% patients presented with more or less localized substernal chest pain; in 14% the predominant symptom was chest heaviness with diaphoresis, 11% complained of no chest discomfort but had other symptoms such as dyspnca, nausea, vomiting, etc. and 5% presented with prominent epigastric pain.An estimated 40% of patients with inferior wall AMI complained of nausea and vomiting. One patient presented with diarrhea as the chief complaint, another patient presented with both AMI related chest pain as well as right lower quadrant pain secondaiy to acute appendicitis. Three patients, all above 75 years of age, presented predominantly with congestive heart failure symptoms. A total of 154 (79%) patients suffered tmiismuml AMI, while the rernainingwere subendocardial non-Q wave infarcts (these also included old LBBB with elevated enzymes). A subgroup analysis of patients in the transmural Q wave group revealed a very high incidence of anterior and anterolateral wail AMI; they comprised 50% of this group and 39% amongst all corners. Inferior wall AMI was also common. The incidence of non-Q wave AMI was 21% (Table I).

Table I. Location of acute myocardial infarction.	
Anterior/Anterolateral	39%
Interior	28%
Lateral	5%
Inferoposterior	2%
Inferolateral	5%
Subendocardial	21%

A total of 154 patients presented initially with suspected transmural AM! (ST segment elevation or new LBBB). Of these, 92 patients received thrombolytic therapy with SK. The predominant reason for not receiving SK was delay in presentation from symptom onset. A number of patients presented to rite emergency room with hypotension, cardiogenie shock or hemodynamically unstable arrhythmias and cardiac arrest which precluded SKadministration. None of the patients who received SK bad ever received this drug before, hence the question of re-dosing with SK did not arise (tPA remains unavailable in Pakistan for such cases). Sixty-five percent patients who received SK presented within four hours or less of symptom onset (Figure 4).

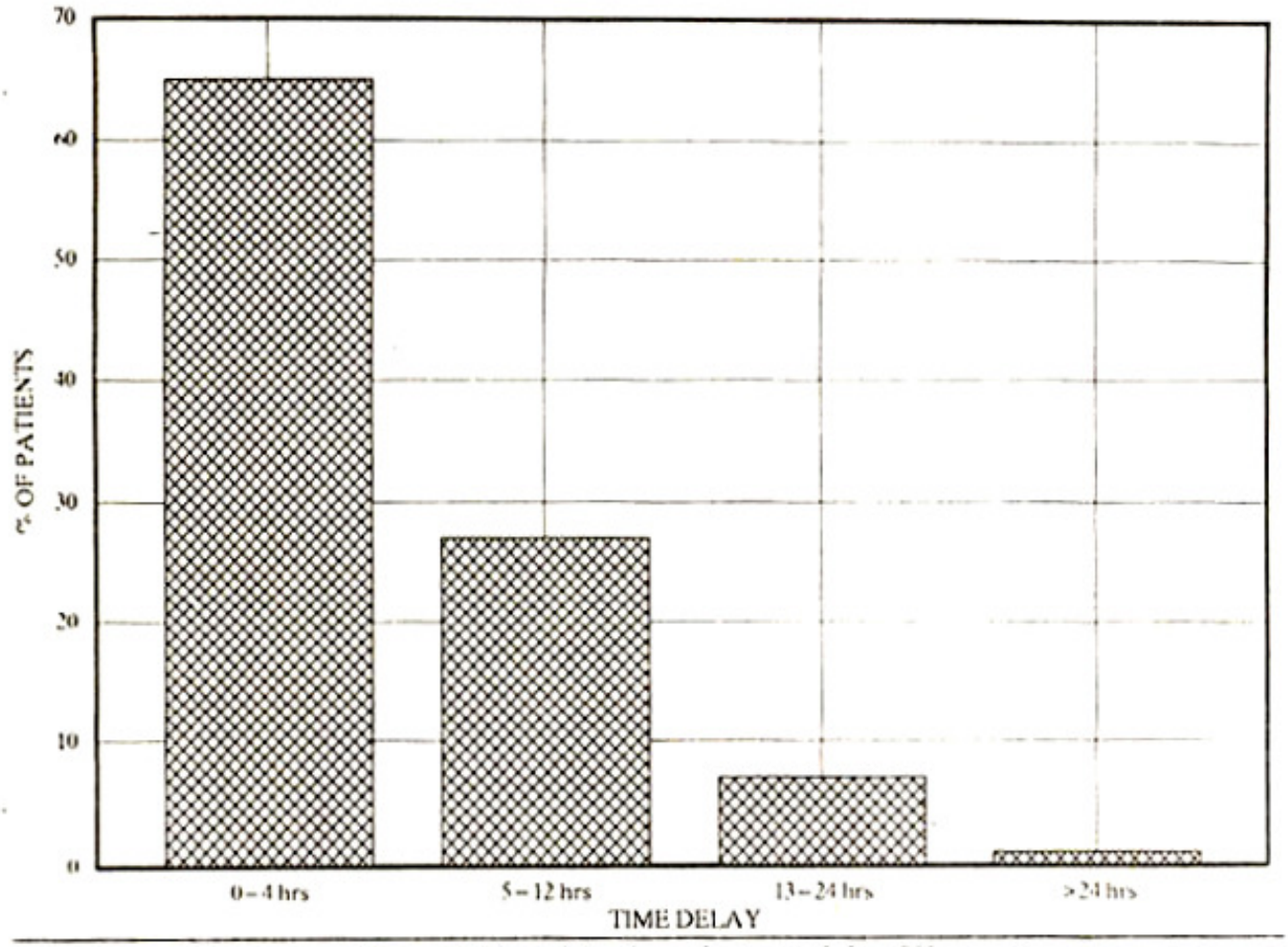

Figure 4. Time delay in patients receiving SK.

A number of patients received SK beyond the four hour window as well. Unfortunately, the time delay inpresentation here only reflects the delay incurred by the patient in arriving to the emergency room. This delay does not factor in the average delay it took to deliver the lytic agent to the patient (the so called “door to needle time”). An analysis of the last 38 patients admitted to the Coronary Care Unit revealed this delay to be approximately 120 minutes. Hence, despite early presentation of patients, greater benefit may have been compromised by the late delivery of the drug in hospital. Presence of major Q waves was seen in 78% of patients who received SK. Although not necessarily true, this may be an indication that despite receiving SK, a large number of patients went on to complete a full thickness transmural myocardial infarction. Only 19% patients had minor Q waves and 3% did not develop any subsequentQwaves following SK administration. In the patients who had small Q waves and the ones that did not develop it, the average time delay in presentation was 3 and 1.5 hours respectively. No mortality was recorded in these two groups. There were 14 deaths during the hospitalization period in patients who received SK, an immediate mortality of 15.2%. In the group that did not receive SK, the immediate mortality was 24.2% ($p=<0.05$). Thus administration of SK led to a 37.1% decline in the immediate mortality (Figure 5).

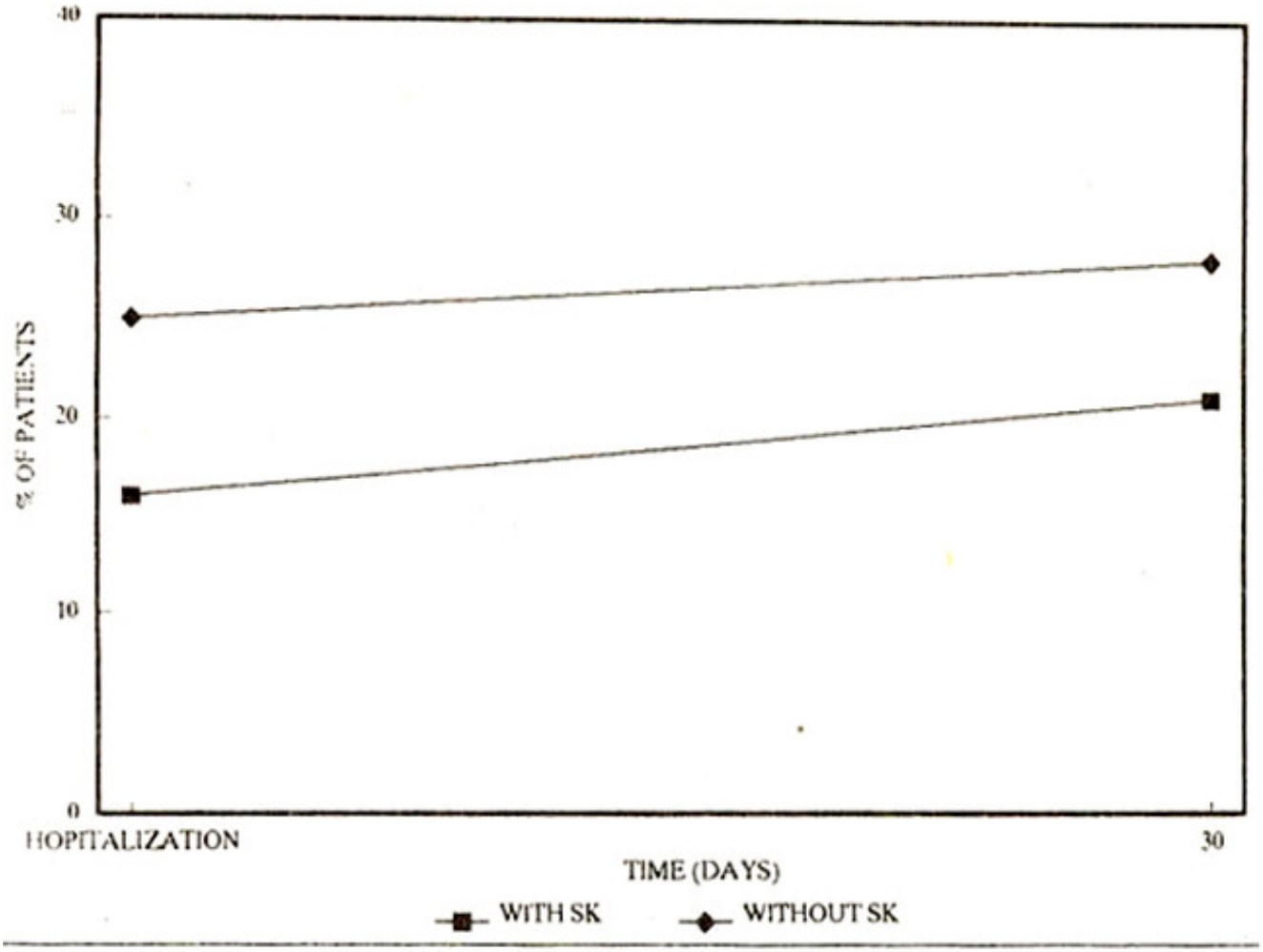

Figure 5. Mortality curves with and without SK.

At 30 days, 19 out of 92 patients in the SK group had died giving a mortality of 19.5%. Similarly. 18 out of 62 patients in the group that did not receive SK had died, giving a mortality of 30.6% again showing a decline in mortality of 36.2% (p=<0.05%). This data convincingly proves that administration of SK led to a statistically significant decline in both early and late mortality from AMI. Table II represents complications experienced by patients in both the transmural and subendocardial infarct groups. Some of the common complications included the development of either mild or prominent LV failure symptoms; this was seen in approximately 25% patients. Post-infarct angina and advanced high grade AV block was experienced by 12% patients. Supraventricular arrhythmias was uncommon. Cardiogenic shock was present in 8% patients with AM!, and all but one patient died, a mortality of 93.3%. The incidence of bleeding with SK was 5%, inclusive of hematemesis, hemoptysis, intra-abdominal and gum bleeding. The incidence of stroke or intracranial bleed was 2%, with the mortality from it being 50%. In 46% of patients no complications were recorded. These patients were apparently discharged in good clinical condition. The practice of risk stratification post AMI with either an exercise stress test (EST) or ambulatory holter monitoring priorto hospital discharge as well as inthe late 6-8 week follow up period was uncommon. While none of the patients were risk stratified prior to hospital discharge, only 5% had an EST in the late follow-up period. Lack of routine risk stratification practice may perhaps have a significant impact on future mortality in these patients.Results

As evident from Figure 1, 50% patients were less than 55 years of age. The age group 46-55 appeared to be the most vulnerable population, consisting of 33% of all patients. Seventeen percent patients were less than 45 years with the youngest male being 27 years and female 34 years. Very few (<6%) patients

were over 70 years probably because the average life expectancy in Pakistan is 60 years for males and 65 years for females. Males (75%) outnumbered females (25%). A subgroup analysis of age and sex groups showed similar pattern of distribution between both sexes. Majority (34%) of the males and females were in the age group of 46-55 years. Hence, it appears that the protective hormonal effect which delays CAD by 10 years in women may not be a major factor in Pakistan if the appropriate risk factors were present.

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respectively. No mortality was recorded in these two groups. There were 14 deaths during the hospitalization period in patients who received SK, an immediate mortality of 15.2%. In the group that did not receive SK, the immediate mortality was 24.2% (p=<0.05). Thus administration of SK led to a 37.1% decline in the immediate mortality (Figure 5). At 30 days, 19 out of 92 patients in the SK group had died giving a mortality of 19.5%. Similarly. 18 out of 62 patients in the group that did not receive SK had died, giving a mortality of 30.6% again showing a decline in mortality of 36.2% (p=<0.05%). This data convincingly proves that administration of SK led to a statistically significant decline in both early and late mortality from AMI.

Table II. Complications.

Congestive heart failure	25%
Post-Infarct angina	12%
High degree AV block	12%
Ventricular fibrillation/V. Tachycardia	8%
Cardiogenic shock	8%
Atrial fibrillation/Flutter	2%
SK-related bleeding	5%
SK-related stroke	2%

*46% of all patients did not suffer any complications.

Table II represents complications experienced by patients in both the transmural and subendocardial infarct groups. Some of the common complications included the development of either mild or prominent LV failure symptoms; this was seen in approximately 25% patients. Post-infarct angina and advanced high grade AV block was experienced by 12% patients. Supraventricular arrhythmias was uncommon. Cardiogenic shock was present in 8% patients with AM!, and all but one patient died, a mortality of 93.3%. The incidence of bleeding with SK was 5%, inclusive of hematemesis, hemoptysis, intra-abdominal and gum bleeding. The incidence of stroke or intracranial bleed was 2%, with the mortality from it being 50%. In 46% of patients no complications were recorded. These patients were apparently discharged in good clinical condition. The practice of risk stratification post AMI with either an exercise stress test (EST) or ambulatory holter monitoring priorto hospital discharge as well as inthe late 6-8 week follow up period was uncommon. While none of the patients were risk stratified prior to hospital discharge, only 5% had an EST in the late follow-up period. Lack of routine risk stratification practice may perhaps have a significant impact on future mortality in these patients.

Discussion

The incidence of CAD has increased in Pakistan[2-5,12,13]. In our current study we have tried to characterize factors relating to an AMI in an urban Pakistani population. Besides the in-depth identification of these factors,we have also for the first time in this country, looked into the role of

thrombolysis and mortality data were computed in this respect. Two notes of caution here; one that this was a retrospective study, hence complete reliability was placed on the recorded medical history and progress notes. Second, the population under study may not be the most representative Pakistanis, since this was a middle to upper class strata. And again, they may be the most vulnerable Pakistanis to atherosclerosis and CAD. When analyzing the age distribution of patients with AMI, it was not surprising that these patients were young and affected by premature CAD. A study published by Ahmed et al[4] and then a report published by the Government of Pakistan in 1983 were both suggestive that a substantial number of Pakistanis suffer their first MI between the relative young ages of 40 and 45 years. Recently, Akhter[3] and colleagues also studied this young population (patients suffering MI's before age 40 years) and found a very high incidence of risk factors for ischemic heart disease in them. The incidence ofcomplications were high, with over 60% patients affected by some form of post-infarct complication within the first el at A study published by Mahju[13] also found the highest incidence of AMI in patients in the age group of 40 and 50 years. The usual diurnal or circadian variation studied in most Western population appears to peak from 6:00 a.m. to 1:00 p.m. in patients suffering an AMI[14-16]. It is believed that both the catecholamine and cortisol surge is at its peak during these hours. In this study, however, we noticed an almost equal incidence in the onset of AMI between the time intervals of 6:00a.m. and 12:00p.m. and from 12:00p.m. to 6:00 p.m. This is indicative of a somewhat different circadian pattern in the onset of AMI symptoms in Pakistani subjects. We believe this to be due to a different cultural set up, where late sleeping and waking are common. The transient risk factors responsible for this circadian variation may perhaps be expressing differently here, including those of plasma catecholamine and cortisol levels, increased platelet aggregability, increase in systolic blood pressure, heart rate, blood viscosity and increased coronary arterial tone. Despite all the diagnostic advances in detecting AMI, clinical history remains very useful. Almost 25% of patients described some form of prodromal symptoms prior to experiencing MI. These figures are consistent with a report published by Alonzo et al[17], where prodromal symptoms were present in 20-60% patients prior to an AMI. The early prodrome in Pakistanis, as previously seen in Alonzo's study was not severe enough to seek medical attention. This being a retrospective study the precipitating events and factors immediately preceding the AM! could not be verified[18]. We were, though, able to record the activity immediately priorto symptom onset. From this it was apparent that only 15% of the patients were active, performing regular day to day work. Again, this was quite surprising in view of the fact that a large number of patients actually presented in the afternoon and evening hours of the day. Tofler et al[19] noted the following patient activities at the onset of AMI: heavy physical exertion 13%, regular daily activities 18%, surgical procedures 6% and 59% were either asleep or at rest. In our analysis, no patient reported heavy physical exertion, 2% of patients suffered pen-operative AMI, while the remainder were at rest or asleep (besides the 15% described earlier). Streptokinase was administered to a wide array of patients ranging in ages from 26 to 80 years and at time periods up to 24 hours post onset of symptoms. Almost 60% patients with clinical symptoms and ST segment elevation or new LBBB on ECG were given SK. These figures are very impressive, in the light of the fact that most published studies have reported that among patients presenting to the emergency room with AMI, only 15-37% were candidates for thrombolysis[20]. Also noteworthy was the fact that patients were not excluded on the basis of age or location of the AMI. Data from this study also confirms the fact that morbidity and mortality benefit is the maximum when thrombolysis is initiated within four hours of symptoms onset, as previously seen in some of the large prospective mega trials like GISSI and ISIS2[21,22]. A statistically significant reduction in mortality was confirmed on both the early hospitalization period and late 30 days following SK administration. The benefit of thrombolysis may perhaps be both a "time dependent" and "time independent" phenomenon as pointed by Tiefenbmnn[23]. The concept of an"open artery is a better artery" may be the key influence in deriving a late beneficial effect on mortality with

SK administration in this study; this is despite the fact that a number of patients presented late, were given SK with a delay of at least 120 minutes and almost 78% went on to develop major Q waves. There are now circumstantial evidence to suggest that even if the infarct- related artery opens too late to salvage myocardium, some benefit may still occur, for example, in facilitating infarct healing, limitation of infarct expansion and a reduced propensity to heart failure and life threatening ventricular arrhythmias. The overall mortality data from this study is high. In the ISIS 2 trial, patients who received placebo had a mortality of 13.2%, while those who received both SK and aspirin had a mortality of only 8.0%. These numbers when compared with figures from this study (albeit this being a very small study) are considerably different. Mortality rates without SK in this study was 24.2% while within the group that received both SK and aspirin was 15.2%. We have tried to analyze reasons behind such a high rate of morbidity and mortality. First, a large number of patients were relatively young who may have ignored or denied the early abnormal symptoms of a MI; and secondly, these patients tend to have multiple risk factors. Other factors include the unusual delay in preparing the SK in fusate, poor facilities in the pen- infarct period for insertion of temporary pacemakers, no access to the cardiac catheterization laboratory for angioplasty or emergent coronary bypass surgery. Post AMI complications like heart failure or angina were all dealt with medical treatment, rather than followed more optimally by definition of the coronary anatomy. Also high mortality may be due to the fact that risk stratification was not performed even in the high risk individuals. Lastly. mortality when correlated with the location of the AMI, it was apparent that a high percentage of Pakistani patients presented with an anterior or anterolateral wall AMI (50% of all Q wave infarcts). This figure is consistent with previously published report by Mahju where anterior infarcts were also more common[13]. Mortality in this subset alone was 31%. It is unclear to us as to why this population was at a high risk for disease predominantly in the left anterior coronary artery (LAD) distribution. Wiseman et al[24] have looked into the influence of various apolipoprotein on the anatomical distribution of systemic arterial disease. In their study they were able to show that in patients with carotid artery disease, cholesterol levels apolipoprotein B and CIII levels were the highest; while in patients with peripheral artery disease, hypertriglyceridemia was common and in patients with coronary artery disease levels of apolipoprotein A was the lowest. Hence these physicians have raised a very interesting issue and pointed out the fact that different interactions of environmental, biochemical and genetic risk factors promote atherosclerosis at particular sites. From our current data it is also evident that the unusually high incidence of coronary artery disease and unstable atherosclerotic plaques in the LAD territory may perhaps also be secondary to multiple risk factors like genetic predisposition and lipid and apolipopro-tei abnormalities. Larger prospective, randomized studies are required in Pakistan to identify these abnormal pathologic influences. In conclusion, acute coronary syndrome is common in the young and middle aged population of Pakistan. Thrombolysis improves morbidity and mortality. Complications from AMI are frequent; overall mortality, despite the advent of thrombolytic in Pakistan, remains high.

Acknowledgements

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