THROMBOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION: THE BAHRAIN EXPERIENCE 1988-1995

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Objective and Settings: To study the outcome after thrombolytic therapy for acute myocardial infarction (AMI) at Salmaniya Medical Centre (SMC), which is the premier referral centre in Bahrain. Five year average pre-thrombolytic era mortality after AMI at SMC provided a base-line (10.9 %).

Design: Review of medical records of all 686 patients who received thrombolytic therapy for AMI from April 1988 to March 1995 either with 100 mg tissue plasminogen activator (t-PA) or 1.5 million units streptokinase (SK).

Results: Bahrainis constituted 44.9 % of the patients, rest being expatriates. Mean age was 50.2 (SD 11.2) years; 48.9 (SD 11) years among males and 59.9 (SD 7.7) years among females (M:F = 7:1).

Base-line risk factors were: smoking 60.5 %, hypertriglyceridemia 40.2 %, hypercholesterolemia 32.2 %, diabetes mellitus 31.7 %, systemic hypertension 20.1 %, previous angina 13.9 % and family history of ischaemic heart disease 10.9 %.

Non-cerebral bleeds occurred in 5.8 % (8.9 % with t-PA, 3.7 % with SK, $p = 0.004$). With t-PA the incidence of total strokes and haemorrhagic strokes were 1.8 % and 1.4 % with t-PA and with SK 1.5 % and 1.2 % with SK (p = NS). Bahraini females had a higher incidence of post-thrombolytic strokes (7.1 %) than Bahraini males (0.4 %, $p = 0.01 < p < 0.001$).

The total in-hospital mortality and 24 hour mortality were 4.4 % and 2.8 % respectively, with no statistically significant difference between t-PA and SK. Females had a higher total in-hospital mortality (11.9 %) than males (3.4 %, $p = 0.0004$).

Conclusion: Thrombolytic therapy utilisation has more than halved (59.6 % reduction) the in-hospital mortality for AMI at SMC, with acceptable safety profile, except for the higher risk of post-thrombolytic strokes in Bahraini females.

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Bahrain is an island nation with a population of half a million[1]. Rapid transition in the socio-economic status, increasing incidence of obesity and sedentary life style have contributed to an increase in th total deaths due to cardiovascular diseases in Bahrain[2,3].

The advent of thrombolytic therapy has heralded a universal reduction in the mortality and morbidity associated with acute myocardial infarction (AMI). While coronary care (CCU) and haemodynamic monitoring could reduce the overall mortality after AMI from around 30 % to 10-15 %, the use of clot-selective fibrinolytic agents such as tissue plasminogen activator (t-PA) in CCU patients 75 years of age or less has further halved this figure[4,5]. Several largescale trials have established the relative safety of different thrombolytic agents, as also the benefit of adjunctive treatments.

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Salmaniya Medical Centre (SMC), a 775 bedded multispeciality hospital, is the premier referral centre of the country and the majority of patients with AMI are treated here. The average CCU mortality for AMI in the pre-thrombolytic era here (calculated for a 5 year period from 1983-1987) was 10.9 %. Thrombolytic therapy for AMI was first used at SMC on 14/4/1988, with increasing utilisation in the subsequent years. We studied the impact of thrombolytic therapy on the outcome after AMI in our institution.

METHODS

A retrospective analysis of case data of all patients admitted to the Cardiology Department of SMC with a diagnosis of AMI who received thrombolytic therapy from the day it was first introduced in April 1988 till the end of March 1995 was carried out. During this study period, a total of 2133 AMI cases were seen out of which 671 patients received thrombolytic therapy on one or more occasions, totaling 686 administrations.

The selection of patients for thrombolytic therapy was based on standard criteria as shown below:

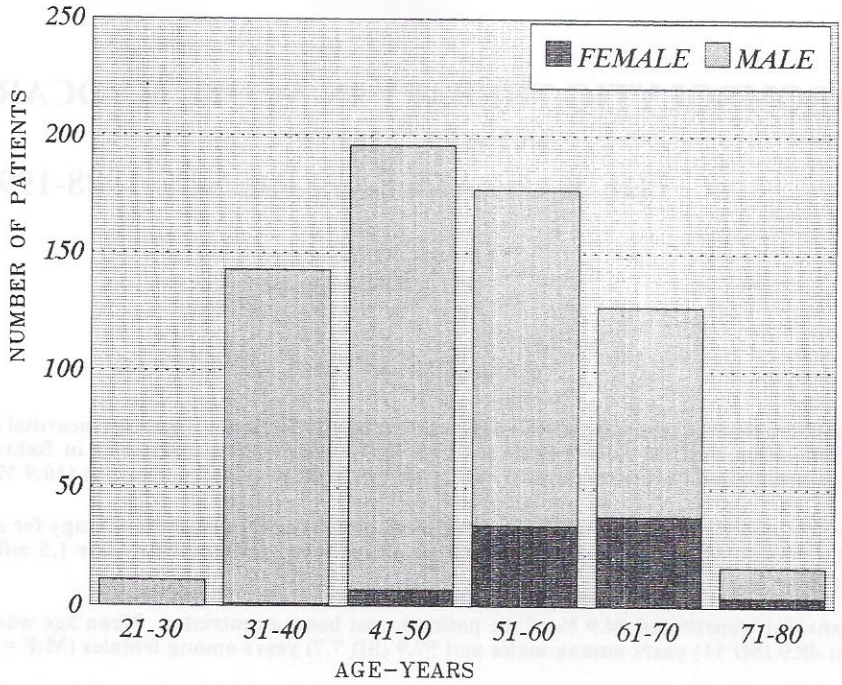

Figure 1. Age and sex distribution among 671 patients receiving thrombolysis for acute myocardial infarction

(1). Patients with documented AMI showing ≥ 1 mm ST segment elevation in at least 2 limb leads or ≥ 2 mm in at least 2 contiguous precordial leads in the electrocardiogram (ECG). (2). Duration of pain less than 6 hours. (3). Duration of pain between 6-24 hours (or rarely more), if there was evidence of ongoing myocardial ischaemia in the form of persistent chest pain or fresh ECG changes.

Patients with bleeding diseases, history of stroke or major surgery in the past 6 months, uncontrolled severe systemic hypertension and proliferative diabetic retinopathy were excluded from thrombolytic treatment. Apart from these exclusion criteria, availability of thrombolytic agents was also a decisive factor in the initial years. The time gap between the onset of chest pain and the institution of thrombolytic therapy was noted in all cases.

heparin intravenous (iv) / subcutaneous (sc) according to the activated partial thromboplastin time. All patients were followed-up with serial ECG, cardiac enzyme and coagulation profiles. CT scan of brain was done whenever neurological events were suspected.

The 'z' test, Chi-square test and Chi-square test with Yate's continuity correction were used for statistical analysis.

RESULTS

We had used t-PA on 281 occasions and streptokinase (SK) on 405 occasions in the total group of 671 patients (14 had re-thrombolysis - 13 twice and 1 thrice) - thus totaling 686 administations (Table 1).

Table 1. **Thrombolytic agent use at SMC 1988-1995**

Agent	1988	1989	1990	1991	1992	1993	1994	1995 till 3/95	Total
t-PA*	2	34	44	49	24	64	54	10	281
SK**	0	0	13	59	115	91	101	26	405
Total	2	34	57	108	139	155	155	36	686

**t-PA : tissue plasminogen activator ** SK: streptokinase*

Tissue plasminogen activator was administered in a dosage of 100 mg over 90 minutes (15 mg as test dose; 0.75 mg/kg over 30 minutes, not to exceed 50 mg; and then 0.50 mg/kg, not to exceed 35 mg, over 60 minutes). Before the Gusto results were available < the total dose was given over 3 hours[6]. Streptokinase (SK) was given in a dose of 1.5 million units (10500 units as test dose, rest over 1 hour). All patients received aspirin 150 mg and

Nationality

The patient population was a mixture of multi-ethnic groups representing the heterogeneity of Bahrains' population. Out of the total population 301 patients (44.9 %) were Bahrainis, 309 (46.1 %9) were Indian subcontinent subjects (ISS) (from India, Pakistan, Bangladesh, Sri Lanka, Nepal) and the rest 9 %

belonged to 17 different nationalities.

Age and Sex Distribution

The age group ranged from 21-80 years with a mean age of 50.2 ± 11.2 years; 48.9 ± 11.0 years among the males and 59.9 ± 7.7 years among the females. The male / female ratio was 7:1 in the total group (587 males, 84 females). The age distribution for either sexes and the total group is given in Figure 1. Whereas 154 (22.9 %) of the total group were 40 years or younger, only 17 (2.5 %) were above 70 years. While 180/154 (70.1 %) of this young group were from the Indian subcontinent, 37/154 (24 %) were Bahrainis. (35 % of the ISS and 11.2 % of Bahrainis were 40 years or younger).

Presentation

Six hundred and forty (93.3 %) patients presented with typical ischemic chest pain.

Time of treatment

Out of the 686 thrombolysis, 452 (66 %) received thrombolysis within 6 hours of symptom onset. In 117 (17.1 %), this period was 6 to 12 hours, in 50 (7.3 %) it was 12 to 24 hours, in 57 (8.3 %) it was more than 24 hours and in 19 (1.3 %) cases the period was not specified.

Baseline risk variables

Smoking - prevalent in 406 (60.5 %) patients - was the commonest risk factor related to ischemic heart disease (IHD). Prevalence of other risk factors were as follows: systemic hypertension (HTN) - 135 (20.1 %), diabetes mellitus (DM) -213 (31.7 %), hypercholesterolemia (serum total cholestrol > 240 mg %) - 32.2 % (155/481), hypertriglyceridemia (serum triglyceride > 165 mg %) - 40.2% (192/478), previous myocardial infarction - 4.6 % (31), previous history of angina - 13.9 % (93) and family history of IHD - 10.9 % (73) (Fig. 2).

History of coronary revascularisation procedures (coronary bypass graft surgery / percutaneous transluminal coronary angioplasty) in the past was present in 12 (1.8 %) patients.

Type of MI and Thrombolysis

While 50.7 % (348) of the thrombolysis were for anterior wall myocardial infarction (AWMI), 41% (281) had inferior wall myocardial infarction (IWMI), and 6.1% (42) had AWMI + IWMI. In 2.2 % (15) of the total who received thrombolysis, there was no subsequent corroborative evidence to prove the occurrence of an AMI. Among the 348 patients with AWMI, 194 (55.7 %) received t-PA and 154 (44.3 %) received SK. Among the 281 patients with IWMI, 59 (21 %) received t-PA and 222 (79 %) received SK.

Thrombolytic therapy had to be discontinued in 4.1 % (28) cases. Bleeding complications (various sites) were responsible for the stoppage of thrombolysis in 53.6 % (15) of these incomplete cases, whereas allergic reactions to SK / sudden hypotension were responsible for 39.3 % (11) cases. One patient died before the completion of thrombolysis and in another case the thrombolysis was stopped midway, as the basal prothrombin time was reported as prolonged.

Medications

Thrombolysis was followed by heparin iv/sc on 94.5 % of the time, with a total average heparin days of 5.5 (SD:2.2). Most (95 % -652) of the patients received aspirin.

Betablockers and ACE inhibitors were administered to 348 (51 %) and 168 (25 %) patients respectively, whereas 156 (23 %) received calcium channel blockers (48 % of these were hypertensives). Whereas 665 (97 %) of patients received nitrates, 152 (22 %) of them had initial nitroglycerin infusion. In

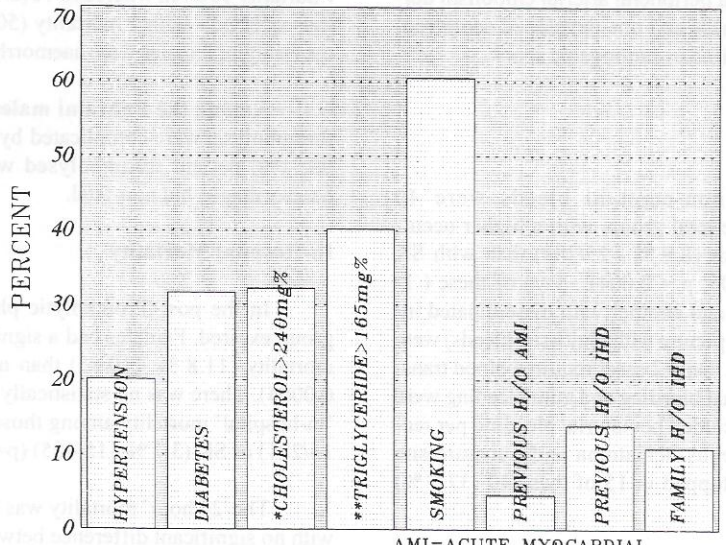

Figure 2. Risk factors among 671 patients receiving thrombolysis for acute myocardial infarction

Table 2. **Incidence of post-thrombolytic strokes and their outcome**

Thrombo-lytic *agent*	No. of thrombo-*lysis*	Total strokes	HGE#	Non HGE	Fatality for *strokes*	Non fatal disabling *strokes*
SK	405	6(1.5%)	5(1.2%)	1(0.2%)	2(33.3%)	1(16.7%)
t-PA	281	*5(1.8%)	*4(1.4%)	1(0.4%)	*4(80.0%)	—
Total	**686**	**11(1.6%)**	**9(1.3%)**	**2(0.3%)**	**6(54.5%)**	**1(9.1%)**

#*HGE: Haemorrhagic (* One Saudi Arabian male patient developed generalised seizure post-t-PA; became comatose and died within 13 hours of admission. CT scan of brain could not be performed)*

278 (41 %) cases some anti-arrhythmic agents (38 % - xylocaine, 4 % - aminodarone) were administered. Thirty (4.4%) patients received DC shock - 29 for ventricular fibrillation (VF) and 1 for ventricular tachycardia (VT).

In-Hospital Events

Cardiac Arrhythmias

The incidence of various significant cardiac arrhythmias during the 686 thrombolyses were as follows: VF - 9 (1.3%) on presentation and 20 (2.9 %) post-thrombolysis; VT - 121 (17.6 %); Atrial fibrillation - 13 (1.9 %); Fascicular blocks - 156 (8.2 %), II/III Atrioventricular block - 39 (5.7 %). In 4 patients (0.6 %) temporary pacemaker insertion was performed.

Other In-Hospital Cardiovascular Events

Clinical evidence of left ventricular dysfunction (Killip class II/III) was observed during the hospital stay in 212 (30.9 %) of patients, whereas cardiogenic shock - necessitating inotropic support - was noted in 65 (9.5 %). The incidence of early post-myocardial angina during the index hospitalisation was 39 (5.7 %). Two (0.3 %) patients had peripheral arterial embolism during the post-thrombolytic phase and one developed acute ventricular septal defect and expired in cardiogenic shock.

Bleeding Complications

The incidence of non-cerebral bleeds were 40 thrombolysis (5.8 %) in the total group, with a higher occurrence with t-PA thrombolysis (8.9 % - 25/281) than with SK thrombolysis (3.7 % - 15/405; p = 0.004). Two of these (1- upper gastrointestinal bleed and another with disseminated intravascular coagulation - like picture with multi-site bleeds) were fatal (both SK thrombolysis). Only 2 cases required blood transfusions. Upper gastrointestinal bleeding and gum bleeding were the most common; others included hematuria, bleeding per rectum, hemoptysis, subcutaneous hematoma and puncture-site oozes. Thrombolysis was stopped in 15 of these 40 (37.5 %) cases.

Strokes

The incidence of various categories of stroke in the post-thrombolytic phase is given in table 2. The incidence of total strokes and haemorrhagic strokes were higher in those who received t-PA thrombolysis (1.8 % - 5/281 and 1.4 % - 4/281 respectively) than in those who received SK thrombolysis (1.5 % - 6/405 and 1.2 % - 5/405 respectively), though these differences were not statistically significant. The mortality rate for strokes were also higher in the t-PA group (4 deaths / 5 strokes, 80 % v/s 2 deaths / 6 strokes, 33.3 % in the SK group). While the haemorrhagic strokes had a mortality rate of 55.6 % (5 deaths / 9 strokes), one of the 2 non-haemorrhagic strokes ended fatally. Considering both varieties of strokes, the cumulative mortality for strokes among Bahrainis was 66.7 % (4/6) and among the non-Bahrainis - 40 % (2/5).

Among Bahrainis, 5 out of the 70 (7.1 %) thrombolysis in females were complicated by a stroke (aged 42, 55, 56, 61, 62 years), whereas only 1 out of 242 (0.4 %) thrombolysis in males were thus afflicted (age 40 years) ('p' - for the difference in incidence: between 0.01 and 0.001). All the 5 non-Bahrainis (5/374 - 1.3 %) who suffered strokes were males.

Among the Bahraini females, 10 % (3/30) of the t-PA administrations were complicated by strokes - all ending fatally (mortality 100 %), whereas 5 % (2/40) of SK thrombolysis were thus affected - with 1 mortality (50 %). All the fatal strokes in the Bahraini females were haemorrhagic.

Among the Bahraini males, none among the 143 t-PA thrombolysis were complicated by stroke, whereas one (out of 99; 1%) patient thrombolysed with SK suffered a stroke - haemorrhagic, but non-fatal.

In-Hospital Mortality

In the post-thrombolytic phase 30 (4.4 %) of the total group expired. Females had a significantly higher 'in-hospital' mortality (11.8 % - 10/85) than males (3.3 % - 20/601) (p = 0.0004). There was no statistically significant difference in the 'in-hospital' mortality among those who received t-PA (5.3% - 15/281) or SK (3.7 % - 15/405) (p=0.30) (Table 3).

The '24 hour' mortality was 2.8 % (19) in the total group, with no significant difference between t-PA (2.8 % - 8) and SK (2.7 % - 11) (p = 0.92). Again, females had a significantly higher '24 hour' mortality (5.9 % - 5/85) than males (2.3 % - 14/601) (p = between 0.05 and 0.025).

Table 3. **Total 'In-hospital' and '24 hour' mortality among patients receiving t-PA & SK**

Mortality	Total thrombolysis (n=686)		t-PA thrombolysis (n=281)		SK thrombolysis (n=405)		p value
	Deaths	*%*	*Deaths*	*%*	*Deaths*	*%*	*t-PA/SK*
Total 'In hospital'	30	4.4	15	5.3	15	3.7	0.30
24-hour	19	2.8	8	2.8	11	2.7	0.92

t-PA - tissue plasminogen activator SK - streptokinase

In the subgroup of 348 patients who were thrombolysed for AWMI, the 'in-hospital' mortality was 17/348 (4.9 %); in those AWMI thrombolysed with t-PA - 11/194 (5.7 %) and with SK - 6/154 (3.9 %) (p = 0.44). The '24 hour' mortality in the AWMI subgroup was 2.3 % (8/348); in AWMI who had t-PA- 2.6 % (5/194) and who had SK - 3/154 (1.9 %) (p = NS).

Majority of patients who expired had cardiogenic shock as a bad prognostic factor (present in 66.7 % - 20/30) and died within 24 hours of hospital admission (63.3 % of total deaths - 19/30).

DISCUSSION

Thrombolytic therapy has revolutionised the management of AMI in the last decade. With increasing availability and growing experience, thrombolysis utilisation has steadily improved to the present level of 57.9 % at SMC[7]. Though two-thirds (66 %) of our eligible patients could be thrombolysed within 6 hours of symptom-onset, further efforts to cut down the 'door to needle' time is being envisaged.

While Bahraini and ISS formed the bulk of our patient population, as much as 22.9 % of the total group were younger than 40 years in contrast to the observed < 5 % prevalence of AMI in this age group in Western literature[8]. The bulk (70.1 %) of this young AMI sufferers were from the Indian subcontinent. It is now well recognised that coronary atherosclerosis among Asian Indian migrants occurs very early, with a high prevalence of diffuse, triple vessel disease and follows a malignant course[8,9]. The percentage of females in our group (12.5 %) is considerably less than the reported 27 % in the ISIS-3 and 25 % in the Gusto trials[10,11].

We have observed a very high incidence of base-line risk factors in this study. In ISIS-3[10] and Gusto[11] trials the incidence of smoking was 41.3 % and 43 % and the incidence of DM was 11.3 % and 15 % respectively, whereas our group had a prevalence of smoking - 60.5 % and DM - 31.7 %. This high prevalence of smoking in our AMI patients contrasts with the community prevalence of smoking in Bahrin of 15.4 % kin the above 12 years age group (22.1 % among males, 5.2 % among females)[2]. The prevalence of DM among Bahraini population in general is not clearly known. A community based survey had estimated the prevalence of DM among Bahraini mothers aged 18-48 years to be 8.5 % and in the elderly > 65 years of age as 13.4 %[12]. But, a recent random survey of 573 Bahraini subjects aged 20 years and above, attending health centres for any problem, revealed prevalence of DM at 25.5 % with a further 14.7 % having impaired glucose tolerance[13]. The prevalence of hypertriglyceridaemia and hypercholesterolaemia is also quite significant in our patient group (40.2 % and 32.2 % respectively). Whether triglyceride levels have additional predictive power beyond that of HDL-cholesterol is unresolved[14]. Hughes et al proposed that increased triglyceride and free fatty acids may predispose to greater ischaemic damage in jeopardised myocardium[9].

The relative safety of thrombolytic therapy in AMI is now well documented. While the non-cerebral bleeds were more with t-PA (8.9 %) than with SK (3.7 %, p=0.004) in our group the Gusto study however had showed higher incidence of these bleeds with SK regimes (0.4 % life threatening, 5.1% moderate, 5.4% moderate to worse bleeds with t-PA v/s 0.3 % life-threatening, 5.6 % moderate, 5.8 % moderate to worse bleeds with the SK and s/c heparin regimen)[6].

In the pre-thrombolytic era, incidence of stroke after AMI was about 2.5%[15]. Incidence of cerebral bleeds after SK is reported to be around 0.1 % - 0.5% and ischemic strokes during SK treatment of AMI around 0.8% - 1.5%, the risk of intracranial bleeding being greater with advancing age and hypertension[16]. The TAPS study reported an incidence of 0.9% of cerebral bleeds each with the front-loaded t-PA and anisoylated plasminogen streptokinase activator complex (APSAC) regimens[17]. In the ISIS-3, the incidence of cerebral bleeds were: SK -0.3%, APSAC - 0.5%, Duteplase - 0.6%, and the incidence of disabling or fatal strokes was higher after t-PA than SK (1.39% v/s 1.04%, 4/1000)[10]. In the Gusto study also, the overall incidence of strokes was higher in the t-PA group (1.55%) compared to the 2 SK regimens (SK with iv heparin: 1.40%, with sc heparin: 1.22%)[6]. The rate of haemorrhagic strokes was also higher - 0.72% in the t-PA group v/s 0.54% in the SK + iv heparin and 0.49% in the SK + sc heparin group[6].

In our experience also, the overall incidence of strokes and haemorrhagic strokes were higher with t-PA (1.8%, 1.4% respectively) than with SK (1.5 %, 1.2% respectively), though these differences were not statistically significant. The Bahraini females had a very high (10%) incidence of fatal, haemorrhagic post-thrombolytic strokes after t-PA thrombolysis. Women have been documented to suffer a higher incidence of strokes and bleeding complications after t-PA than with SK and female sex is an indenpendent risk factor for haemorrhagic strokes for unknown reasons[18,19]. The risk of haemorrhagic strokes with t-PA is also documented to be higher in either sexes in lighter subjects (men <80 kg, women <70 kg)[19].

The pre-thrombolytic era mortality for AMI of 10.9% has come down to the present 4.4% in our institution with thrombolytic therapy utilisation (59.6% reduction). Pooled data from the International t-PA/SK trial[20], GISSI-2[21], ISIS-3[10] and other smaller trials had indicated identical short-term mortality after SK and t-PA[10]. But, in the Gusto trial - where only patients

presenting within 6 hours were included - accelerated t-PA regimen with iv heparin was superior to SK in reducing early mortality (24 hour mortality : 2.3 % in accelerated t-PA group v/s 2.8% and 2.9% in the SK with sc heparin and iv heparin respectively; 30 day mortality: 6.3% v/s 7.2% and 7.4% in the same groups) and achieving a net clinical benefit, as defined by survival without a disabling stroke[6]. The lack of apparent thrombolytic agent dependent difference in mortality in the earlier studies is now explained on the basis of omission of iv heparin - without which the outcome is likely to be adversely affected - especially with clot-selective fibrinolytic agents than non-selective agents, a relatively late onset of treatment and inclusion of elderly patient groups in these studies[22]. Though survival benefit after thrombolytic therapy is greatest if treated earlier after symptom onset[22], meta-analysis of several trials have also suggested a net benefit of later thrombolytic therapy[15]. All the placebo-controlled trials of iv thrombolytic therapy have shown that survival benefit, observed during the hospital phase, is maintained for at least one year[23].

Till September 1990, only t-PA was available in our institution, and with increasing use of SK after its availability, we found no statistically significant difference in the in-hospital mortality rates between these 2 regimens - either in the total group or in the subgroup of patients with AWMI. The fact that the 'accelerated t-PA' protocol - which has been proved to have the best survival benefit - was adopted only after the Gusto results in late 1993, and SK was more often used in patients with IWMI may partly explain this lack of t-PA associated benefit observed here. The higher early mortality among women after AMI is consistent with observations in other larger studies and is explained mainly by the older age and more unfavourable risk characteristics of women[18].

CONCLUSION

Thrombolytic therapy utilisation has helped to reduce the in-hospital mortality for AMI by more than half at SMC, Bahrain. A strikingly high incidence of DM, hyperlipidemia and smoking among the subjects with AMI underlies the need for strategies for proper control of risk factors and health education to control the rising cardiovascular morbidity and mortality in Bahrain. The incidence of undesirable side-effects of thrombolytic therapy in our group compares favourably with that reported in World literature. The high incidence of fatal post-thrombolytic strokes after t-PA among Bahraini females calls for exercising caution in using this agent in them.

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