THROMBOLYSIS WITH INTRAVENOUS STREPTOKINASE DOSE NOT ALTER 72-HOURS MORTALITY IN ACUTE MYOCARDIAL INFARCTION

MUHAMMAD RASHID Ch.*, A.K. BUTT**

SUMMARY

Objective: a) To find out mortality in Acute Myocardial Infarction within 72-hours treatment in coronary care unit b) To compare mortality in Acute Myocardial Infarction treated with intravenous Heparin to that of intravenous streptokinase. Design: Observational, retrospective study. Setting: Coronary care unit of Shaikh Zayed Postgraduate Medical Institute Lahore. Subject: Patient above >12 years of age, presenting with acute myocardial infarction to Coronary Care Unit from 1.9.1989 to 31.8.1990 were included and their mortality was compared with subsequent five years up to 31.8.1995. Intervention: Comparison of intravenous Heparin 5000 units stat and 1000 units hourly infusion with 1,500,000 units of streptokinase intravenous in 90 minutes in patients of Acute Myocardial Infarction along with other treatment given in both groups. Main Outcome Measures: Death as a result of Acute Myocardial Infarction during 72-hours stay at Coronary Care Unit. RESULTS: Baseline characteristics of two treatment groups were similar. Mortality rate with IV Heparin alone in 1989-90 were 2.3% (95% CI, 0.07-4.57). With intravenous streptokinase in 1990-91 4.0% (CI 1.28-6.7, P>0.05) in 1991-92 2.8% (CI 0.59-5.01, P>0.05) in 1992-93 2.7% (CI 0.09-5.42, P>0.05) 1993-94 2.8% (CI 0.59-8.54, P>0.05) in 1994-95 4.9% (CI 1.37-8.54, P>0.05). The mortality was slightly increased during 1991-92 but change was not significant P>0.05. There was fall in mortality from 1993-95 again statistically insignificant P>0.05. CONCLUSION: Mortality rates in Acute Myocardial Infarction remained same from 1989-90 to 1994-95. Thrombolysis with 1,500,000 units of streptokinase in acute myocardial infarction did not make any difference in mortality as compared to intravenous Heparin 5000 units stat and 1000 units/hourly within 72-hours of treatment at Coronary Care Unit.

INTRODUCTION

Acute myocardial infarction and unstable angina are the leading causes of death in all racial and ethnic groups. In Pakistan 47% of all cardiac deaths are due to coronary heart disease (1) with high prevalence of hypercholesterolemia, hypertension and smoking in a study of four cities (2). In USA, there were 4,87,000 coronary deaths in 1994 (3). In Wales 30% of all deaths in males and 22% of all deaths in females are due to coronary artery disease (4). Despite extensive research into the etiology; pathophysiology and treatment of coronary artery disease, it remains a serious threat to human life. Early reperfusion of the infarct-related artery using thrombolytic therapy or PTCA is the major determinant of survival:(5-7). While there is a strong agreement that early reperfusion must be accomplished to preserve the ischemic myocardium, the ideal method to achieve this goal is still debatable. Randomized clinical trials using various thrombolytic agents have demonstrated a significant reduction in mortality inpatients with acute myocardial infarction or unstable angina (8-10). As a result the use of these agents has increased rapidly in the past few years and withholding thrombolytic therapy in these patients is now considered, unethical. The benefit of thrombolytic therapy is not seen in the early (up till 2 days) period where an excess of mortality has been demonstrated. However, this early hazard is outweighed by the survival advantage observe in the, subsequent 2-35 days (11). Before 1990, management of patients with acute myocardial infarction and unstable angina was directed towards managing arrhythmias and limiting infarct size using intravenous heparin, nitrates, aspirin and beta-blockers. The high mortality (30%) in the pre-coronary care unit era was reduced to around 15% with improved hemodynamic monitoring, defibrillators and beta-blockers in...
coronary care units. With the advent of thrombolytic therapy, the mortality has now been reduced to 5% or less (11). We started using streptokinase in patients with acute myocardial infarction in coronary care unit of this hospital in 1990 (12). This study reports our experience with intravenous streptokinase over a six-year period.

AIMS AND OBJECTIVES

The specific aim of the study was to evaluate the changes in mortality in the first three days in-patients given intravenous streptokinase and compare it with the mortality in the pre-thrombolytic era.

MATERIAL AND METHODS

We retrospectively analyzed the case records of 172 patients admitted to the coronary care unit of our hospital during 1989 (prethrombolytic) and compared their modality with patients admitted, during the subsequent five years up to 1995. This later group comprising 913 patients received intravenous streptokinase therapy.

Myocardial infarction was diagnosed by (1) suggestive history of chest pain or palpitation (2) ECG, ST-segment elevation of 1 mm in limb leads and 2 mm in chest leads, recent Q-wave or BBB. (ill) Typical pattern of change in cardiac enzymes. Presence of any two of these three criteria was required make a diagnosis of myocardial infarction. Patients, admitted with a provisional diagnosis of myocardial infarction were labeled to have unstable angina if they neither develop ECG changes nor had elevation of cardiac enzyme on serial evaluation.

Treatment Protocol-I (T1)

1. Tab. Aspirin 300 mg oral stat then half per day
2. Tab. Glycerine trinitrate 0.25 mg S/L x 2 tab
3. Inj. Isosorbide dinitrate infusion 1-4 mg/hour
4. Tab. Isosorbide dinitrate 10 mg TDS
5. Inj. Heparin 5000 units stat 1000 unit/hour infusion, titrated with the help of activated partial thromboplastin time and kept 1 1/2 to 2 times the control value.
6. Tab. Propranolol, Diltiazem, Captopril for hypertension angina as required.

Treatment Protocol-II (T2)

Inj. Streptokinase 50,000 units in 90 min. infused within 12 hour of chest pain in addition to the drugs in treatment regimen described above. Heparin 1,000 units/hour intravenous infusion was started post thrombolysis one APTT was less than 80 sec.

Contraindications for Streptokinase

a. Hemorrhagic stroke within one year
b. Bleeding diathesis
c. Active Peptic ulcer
d. Severe uncontrolled hypertension (BP>180/110 mm Hg)
e. Recent trauma or surgery within four weeks
f. Streptokinase infusion within 2-years

Once patients was shifted out of Coronary Care Unit Heparin was discontinued in inferior myocardial. In anterior infarction if there was no Left Ventricular Thrombus on Echocardiography, heparin was discontinued. In patients with left ventricular thrombus Warfarin was started before stopping heparin.

Statistical Analysis

Mortality was reported as percentage and 95% confidence intervals calculated. Chi square test was used to compare mortality of 1989 with the subsequent 5 years. All analyses were considered significant at p 0.05.

RESULTS

A total of 1085 patients were retrospectively analyzed in this study. There was no statistically significant difference in the age distribution during the study period. Male to Female ratio was 1.33:1. Table 1 presents details of age and sex distribution of patients during the study period.

Table 2 presents the mortality figures, for each year from 1989 till 1995 (1st September to 31st August). Total number of deaths, percentages and the 95% confidence interval for each year are presented. Mortality figures increased slightly in 1990-91 (4%) and again in 1994-95 (4.9%) but this increase was not statistically significant ($x^2$ 2.534 p=0.771)
Anticoagulants, antiplatelets and thrombolytics are known to reduce mortality in acute myocardial infarction. Smith et al. reported a reduction of 25% in deaths, 34% in the infarction, 55% in strokes in a study in the prethrombolytic era comparing warfarin with placebo (13). The Antiplatelet Trialists Collaborative Study overview revealed a 13% improvement in vascular deaths, 31% in re-infarction, and 42% in strokes with aspirin (14). Many trials over the last decade have proven the reduction in mortality with intravenous thrombolyis (15-17). The American College of Cardiology/American Heart Association task force on practice guideline of management of acute myocardial infarction makes class-I recommendation for early (<12 hour) thrombolytic therapy in patients (<75 years) of evolving myocardial infarction with ST-segment elevation and bundle branch block. Class-II and Class-IIb recommendations are for patients older than 75 years and for 12-24 hours duration from the start of symptoms respectively (18). This report declares benefits of thrombolysis irrespective of age, gender and co-morbid conditions such as diabetes mellitus, hypertension <180/100 mm Hg. Thrombolysis with intravenous streptokinase was started in September 1990 in this unit. Our results show an increase in mortality from 1990-91 and again in 1994-95. These changes were not statistically significant (P>0.05). During first three years we gave thrombolysis up to 24 hours from the start of chest pain. It was changed to 12 hours in later years. In exceptional cases of stuttering infarction it is used beyond 12 hours. The increase in mortality could have resulted due to late thrombolysis, as reported by the Fibrinolytic Therapy Trialists collaborative group that lysis beyond 12 hours could cause adverse effects (11,19,20). The bulk of myocardium necroses within 6 hours (70% transmural necrosis) of vascular occlusion, with a small amount of additional necrosis between 6-24 hours (21). Reestablishment of coronary flow within 2-hours resulted in maximum myocardial salvage and functional recovery of ischemic myocardium whereas reperfusion as late as 6-hours resulted in limited subepicardial salvage (22-25).

Since the high cost of thrombolysis (approximately US$ 100) is borne by the patients, fewer patients afforded it initially. Slight reduction in mortality in years 1991-92 till 1993-94 could be due to, awareness of benefits of early treatment and that now patients seek immediate attention. As the beneficial effects has become known widely now it is availed by an increasing number of patients. In an earlier study (26) we had published side effects of streptokinase, in this unit, which are similar to those reported elsewhere (hypotension 11%, arrhythmias 8%, bleeding 2%, allergic reaction 2%, nausea 2%). Thrombolysis does initiate a chain of counter acting mechanisms that lead to increased thrombogenesis. This increased thrombogenicity along with un-addressed prothrombotic factors i.e. narrowed vessels, roughened lumen, irritating plaque material, inflammation and infection could off-set the benefit of thrombus dissolution. Whether lysis of the occluding can improve survival while other abnormalities in vascular rheology remained unchanged is questionable. There are reports of inflammation causing plaque instability (27-31). High levels of C-reactive proteins following

### Table-1
**BASELINE CHARACTERISTICS OF STUDY POPULATION**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Patients</th>
<th>Average Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989-90</td>
<td>172</td>
<td>49.00</td>
<td>13.8</td>
<td>62(36.50%)</td>
</tr>
<tr>
<td>1990-91</td>
<td>200</td>
<td>54.00</td>
<td>14.3</td>
<td>100(50.07%)</td>
</tr>
<tr>
<td>1991-92</td>
<td>214</td>
<td>53.50</td>
<td>17.3</td>
<td>125(58.46%)</td>
</tr>
<tr>
<td>1992-93</td>
<td>145</td>
<td>55.00</td>
<td>12.4</td>
<td>65(45.16%)</td>
</tr>
<tr>
<td>1993-94</td>
<td>231</td>
<td>55.00</td>
<td>13.8</td>
<td>134(63.19%)</td>
</tr>
<tr>
<td>1994-95</td>
<td>141</td>
<td>53.50</td>
<td>14.2</td>
<td>74(52.62%)</td>
</tr>
</tbody>
</table>

*Cl = Confidence Interval

### Table-2
**YEARLY MORTALITY OF ACUTE MYOCARDIAL INFARCTION IN CCU**

<table>
<thead>
<tr>
<th>YEARS</th>
<th>TOTAL PATIENTS</th>
<th>DEATHS</th>
<th>95% CONFIDENCE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989/90</td>
<td>172</td>
<td>4 (2.3)</td>
<td>0.07-4.57</td>
</tr>
<tr>
<td>1990/91</td>
<td>200</td>
<td>8 (4)</td>
<td>1.28-6.71</td>
</tr>
<tr>
<td>1991/92</td>
<td>214</td>
<td>6(2.8)</td>
<td>0.59-5.01</td>
</tr>
<tr>
<td>1992/93</td>
<td>145</td>
<td>4(2.7)</td>
<td>0.09-5.42</td>
</tr>
<tr>
<td>1993/94</td>
<td>213</td>
<td>6(2.8)</td>
<td>0.59-8.54</td>
</tr>
<tr>
<td>1994/95</td>
<td>141</td>
<td>7(4.9)</td>
<td>1.37-8.54</td>
</tr>
</tbody>
</table>

### DISCUSSION

Anticoagulants, antiplatelets and thrombolytics are known to reduce mortality in acute myocardial infarction. Smith et al. reported a reduction of 25% in deaths, 34% in the infarction, 55% in strokes in study in the prethrombolytic era comparing warfarin with placebo (13). The Antiplatelet Trialists Collaborative Study overview revealed a 13% improvement in vascular deaths, 31% in re-infarction, and 42% in strokes with aspirin (14). Many trials over the last decade have proven the reduction in mortality with intravenous thrombolyis (15-17). American College of Cardiology/American Heart Association task force on practice guideline of management of acute myocardial infarction makes class-I recommendation for early (<12 hour) thrombolytic therapy in patients (<75 years) of evolving myocardial infarction with ST-segment elevation and bundle branch block. Class-II and Class-IIb recommendations are for patients older than 75 years and for 12-24 hours duration from the start of symptoms respectively (18). This report declares benefits of thrombolysis irrespective of age, gender and co-morbid conditions such as diabetes mellitus, hypertension <180/100 mm Hg. Thrombolysis with intravenous streptokinase was started in September 1990 in this unit. Our results show an increase in mortality from 1990-91 and again in 1994-95. These changes were not statistically significant (P>0.05). During first three years we gave thrombolysis up to 24 hours from the start of chest pain. It was changed to 12 hours in later years. In exceptional cases of stuttering infarction it is used beyond 12 hours. The increase in mortality could have resulted due to late thrombolysis, as reported by the Fibrinolytic Therapy Trialists collaborative group that lysis beyond 12 hours could cause adverse effects (11,19,20). The bulk of myocardium necroses within 6 hours (70% transmural necrosis) of vascular occlusion, with a small amount of additional necrosis between 6-24 hours (21). Reestablishment of coronary flow within 2-hours resulted in maximum myocardial salvage and functional recovery of ischemic myocardium whereas reperfusion as late as 6-hours resulted in limited subepicardial salvage (22-25).
myocardial infarction have, been reported in Physician's Health Study (31). Elevated levels of C-reactive proteins are found to be associated with high mortality in acute coronary syndrome in TIMI-II A sub study (32). High levels of antibodies titre to chlamydia pneumonia have been reported in acute myocardial infarction as well (33,34). It is debatable If anti-inflammatory drugs and antibiotics can reduce mortality. Paradoxical increase in mortality has been seen up to 24 hours after thrombolysis of coronary arteries as reported by Fibrinolytic Therapy Trialists (M) Collaborative Group (10) and GUSTO (35). Earlier studies have shown an excess of deaths in the first 48 hours in patients receiving thrombolytic therapy. GISSI-1 and ISIS-2 suggested an excess of early deaths due to cardiac rupture and electromechanical disassociation (36,37). The exact cause of this early excess, mortality is still disputed but could possibly be related to side effects of thrombolytic agents and various forms of reperfusion injury after successful thrombolysis. Anaphylaxis, reperfusion arrhythmias, stunning of myocardium, microvascular damage, necrosis, myocardial hemorrhage, hemorrhage inside the plaque, thrombosis rebound leading to reocclusion could ail. contribute to this early hazard (38,39). An increase in reocclusion after thrombolysis with Tissue Plasminogen Activator (TPA) leading to adverse prognosis occurred in smokers, hyperlipidemics and hypertensive patients in, a. study of recurrent ischemia after thrombolysis by. Ellis et al. (40). The same, study showed increased reoclussion in patients who had open collateral circulation around the infarct-related artery on angiography. Our mortality due to acute myocardial infarction has been less than 5%, which is same as. reported elsewhere. Intravenous thrombolysis has not made any improvement in the mortality of acute myocardial infarction within three days of treatment in this unit.

CONCLUSION

Mortality rates Acute Myocardial Infarction remained same from 1989-90 to 1994-95. Thrombolysis with 150,000 units of streptokinase in acute myocardial infarction did not make any difference in mortality as compared to intravenous Heparin 5000 units stat and 1000 units/hourly within 72 hours of treatment at Coronary Care Unlit.

LIMITATIONS OF THE STUDY

1. The main limitation of this study is that it is a based on retrospective analysis of data.
2. We did not compare T1 and T2 simultaneously as With holding streptokinase would have been unethical.
3. We analyzed acute myocardial infarction as. a whole and did not evaluate mortality in subgroups based on the, site of myocardial infarction
4. Our patients were not evaluated with coronary angiography to determine the extent and severity of disease
5. We did not evaluate the effect of risk factors for coronary artery disease on mortality in our series.

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