A COMPARATIVE STUDY OF EFFICACY OF 7.5 LAKH UNITS VERSUS 1.5 MILLION UNITS OF STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION IN ELDERLY PATIENTS

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ABSTRACT

BACKGROUND

In developing countries like India, as the life expectancy has increased, more and more elderly patients having ischemic heart disease are being diagnosed and treated. We wanted to evaluate as to whether thrombolysis with a lower dose of 7.5 lakh units of streptokinase was as efficacious as with streptokinase in conventional doses of 1.5 million units in achieving reperfusion of the infarct related coronary artery.

METHODS

The present study was conducted in elderly patients aged more than 65 years over a period of one year from Nov. 2016 to Oct. 2017 at GMC, Jammu which is a tertiary care centre. Sixty elderly patients with acute myocardial infarction were enrolled in the study, presenting within 12 hours of onset of symptoms and having no contra-indication to thrombolytic therapy.

RESULTS

A total of 60 cases included in our study. The mean age of the patients in the study group (cases) was 69.33 ± 5.78 years, while that of control group was 69.00 ± 4.83 years. Majority of the patients (19) were observed to be in the age group of 70-75 years in the study as well as control group. In the study group (cases), 9 (30%) were females and 21 (70%) were males, while in the control group 5 (16.7%) were females and 25 (83.3%) were males.

CONCLUSIONS

Low dose (7.5 lakh units) of streptokinase was as effective as the standard dose (1.5 million units) of streptokinase in achieving reperfusion of the infarct related coronary artery, in the elderly patients of acute myocardial infarction.

KEY WORDS

Acute Myocardial Infarction, Coronary Artery, Streptokinase, Thrombolysis

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BACKGROUND

Myocardial infarction is a frequent catastrophic cardiovascular event encountered in the setting of our hospital emergency rooms and coronary care units. Despite impressive studies in diagnosis and management over the last three decades, acute myocardial infarction (AMI), continues to be a major public health hazard in the industrialized world. Each year approximately 900,000 persons in the United States experience AMI and about 225,000 of them die. At least one-half of these patients die within 1 hour of onset of symptoms and before reaching the hospital emergency department[1]. A steady decline in mortality rate from AMI has been observed across several population groups since 1969.[2]

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In mid 1960 the concept of coronary care unit [CCU] was introduced. Subsequently, introduction of the pulmonary artery balloon flotation catheter set the stage for bedside hemodynamic monitoring and more precise management of heart failure and cardiogenic shock associated with AMI. The modern reperfusion era of coronary care was ushered in by intra-coronary and then intravenous thrombolysis, increased use of aspirin and development of percutaneous transluminal coronary angioplasty [PTCA] for AMI.[3] AMI has been found to be the leading cause of death in elderly over the age of 65 years. It accounts for 80% of deaths in the elderly, with 6.8% of the population of India over 60 years. The mortality in elderly is two-times more after AMI as compared to the younger counterparts.[4] Though the traditional dose of streptokinase fixed at 1.5 million units,[5] has been widely accepted, some recent clinical trials have provided non-invasive evidence of reperfusion with half dose streptokinase with comparable results.[6,7]

METHODS

The present work is a is a randomized control trail study for a period of one year from nov. 2016 to oct. 2017 that included 60 patients of acute myocardial infarction in elderly that presented within 12 hours of onset of symptoms and had no contraindication to administration of streptokinase for thrombolysis. Sample size was taken based on the convenience of the study. The patients were divided into two

groups: the study group to whom 7.5 lakh units of streptokinase was administered intravenously over 30 minutes, while the control group received the standard dose of 1.5 million units of streptokinase intravenously over one hour. Detailed history was taken, and thorough clinical and biochemical profile was done. AMI was diagnosed by criteria defined by World Health Organization (WHO). Got approval from IEC and consent was taken from all patients.

Statistical Analysis

The data was collected and analysed using standard statistical chi – square test, $P < 0.05$ statistically significant. Data was entered in Microsoft excel and analysis was done using SPSS version 22.

RESULTS

All the patients included in the study had presented within 12 hours of onset of symptoms and had no contraindication to administration of streptokinase for thrombolysis. The observations made were considered as follows:

In the study group, 21 (70.0%) were males and 9 (30.0%) were females, while as in control group 25 (83.3%) were males and 5 (16.7%) were females. Overall, 46 (76.7%) males and 14 (23.3%) females were included in the study. Majority of the patients were in Killip Class I and II at presentation in study as well as control group. None of the patients were having cardiogenic shock at the time of administration of streptokinase. Severity of cardiac dysfunction was similar in both the study and control groups. More than one risk factor was found in cases of both study and control groups. The major risk factor in both study group (60.00%) and control group (66.67%) was smoking, followed by hypertension (53.33% and 46.67 respectively).Both groups were comparable with respect to the distribution of coronary risk factors. Mean therapeutic window in the study group was 6.32 ± 2.23 hours, while in control group was 4.90 ± 1.96 hours. No statistically significant difference was found in the therapeutic windows of both the groups. Mean time to pain relief in the study group was 5.90 ± 4.76 hours and in the control group was 5.61 ± 3.36 hours. In the subset of patients having pain relief within 6 hours of completion of streptokinase infusion, the mean time in the study group was 4.14 hours and in control group was 3.22 hours. Applying 't'-test, p-value = 0.22 is statistically non-significant, thus showing no difference in time to pain relief at different doses of streptokinase. Reperfusion occurs if Fc ≥ 0.5 and Fc<0.5 signifies no reperfusion. No statistically significant difference was observed in the reperfusion rates assessed by Fc criterion in the two groups.

The mean CPK-MB base level in study group was 69.83 ± 54.76 hours, while the mean CPK-MB peak level was 225.77 ± 77 hours. The mean CPK-MB base level in control group was 69.77 ± 45.26 hours, while the mean CPK-MB peak level was 257.73 ± 88.11 hours. Applying, chi-square test, no significant difference was observed in the reperfusion rates by the above criterion in the two groups. Mean time to peak CPK-MB in study group was 9.47 ± 2.25 hours, while in control group was 9.47 ± 2.58 hours.

Subjects	Gender		Total
	Male No. (%)	Female No. (%)	
Study group	21 (70.0)	9 (30.0)	**30 (100.0)**
Control group	25 (83.3)	5 (16.7)	**30 (100.0)**
Total	**46 (76.7)**	**14 (23.3)**	**60 (100.0)**

Table 1. Gender Wise Distribution of Cases

Subjects	Killip Class			Total
	Class I	Class II	Class III	
Study group	23 (76.7)	7(23.3)	-	30 (100.0)
Control group	10(33.3)	18 (60.0)	2 (6.7)	30 (100.0)
Total	33 (55.0)	25 (41.7)	2 (3.3)	60(100.0)

Table 2. Distribution of Killip Class at Presentation in Study Group Versus Control Group

Risk Factors	Study Group (n = 30) No. (%)	Control Group (n = 30) No. (%)	'p'-Value (z-Test)
Smoking	18 (60.0)	20 (66.67)	0.352 NS
Hypertension	16 (53.33)	14 (46.67)	0.358 NS
Diabetes	8 (26.67)	4 (13.33)	0.180 NS
Family H/o CAD	6 (20.0)	8 (26.67)	0.333 NS
Hyperlipidaemia	4 (13.33)	12 (40.0)	0.493 NS

Table 3. Distribution of Coronary Risk Factors in Study Group Versus Control Group

NS Non-significant

Subjects	Mean ± Standard Deviation	
	Therapeutic Window (Hours)	Time to Pain Relief after STK (Hours)
Study group	6.32 ± 2.23	5.90 ±4.76
Control group	4.90 ± 1.96	5.61 ± 3.36

Table 4. Comparative Evaluation of Therapeutic Window to Thrombolysis and Time to Pain Relief in Study Group and Control Group

Fractional Change (Fc)	Study Group (n=30) No. (%)	Control Group (n=30) No. (%)	'p'-Value (χ^2-test)
≥ 0.5	26 (86.7)	24 (60.0)	0.2 NS
< 0.5	4 (13.3)	6 (20.0)	

Table 5. Comparative Evaluation of Reperfusion Using Single Non-Invasive Criterion- Fractional Change on ECG in Study Group Versus Control Group

NS=Non-significant

Time to Peak CPK-MB (Hours)	Study Group (n = 30) No. (%)	Control Group (n = 30) No. (%)	'p'-value (X^2-test)
0 to 12	22 (73.3)	18 (60.0)	0.06 **NS**
≥ 12	8 (26.67)	12 (40.0)	

Table 6. Comparative Evaluation of Reperfusion by Single Non-Invasive Criterion- Time from Completion of STK Infusion to Peak CPK-MB in Study Group Versus Control Group

Non-significant

Time from STK to Peak CPK-MB (Hours)	Study Group (n = 30)		Control Group (n = 30)		'p'-value (χ^2 – Test)
	Fc≥ 0.5 No. (%)	Fc < 0.05 No. (%)	Fc≥ 0.5 No. (%)	Fc < 0.05 No. (%)	
0 to < 12	22 (73.3)	-	16 (53.3)	2 (6.7)	0.13 **NS**
12 to 24	4 (3.3)	4 (13.3)	8 (26.7)	4 (13.3)	

Table 7. Comparison Between Reperfusion by Combined Criteria- Fractional Change and Time from STK to Peak CPK-MB in Study Group Versus Control Group

NS = Non-significant

No statistically significant difference was observed between both the groups when reperfusion was evaluated by combination of criteria.

Complications	Study Group (n = 30) No. (%)	Control Group (n = 30) No. (%)	p-Value (Z-test)
Minor bleed	-	2 (6.6)	0.016
Major bleed	-	-	-
Anaphylaxis	-	-	-
Hypotension	-	-	-

Table 8. Comparison Between Complications Following Streptokinase Infusion in Study and Control Groups

Mean time to peak CPK-MB in those re-perfused by this criterion in both the groups was 9.04 hours.

There was a greater incidence of minor bleed in the control group (1.5 million units) which was statistically significant. However, no major complication (Major bleed, anaphylaxis etc.) were noted in our study in both study and control group.

DISCUSSION

The present study titled "Comparative efficacy of 7.5 lakhs units vs 1.5 million units of streptokinase in acute myocardial infarction in elderly patients was conducted in a prospective manner in Postgraduate Department of Medicine, Government Medical College Hospital, Jammu over a period of one year. Sixty elderly patients with acute myocardial infarction were enrolled in the study, presenting within 12 hours of onset of symptoms and having no contra-indication to thrombolytic therapy. The patients included in the study were randomized into two groups - 30 patients in the study (Cases) group were thrombolysed with 7.5 lakh units of streptokinase (Half dose) over thirty minutes while the rest 30 patients in the control group were administered 1.5 million units of streptokinase (Conventional full dose) over one hour.

The mean time to pain relief from streptokinase infusion in the study group (Cases) was 5.90 ± 4.75 hours compared to 5.61 ± 3.22 hours in the entire control group. 73.33% (22) of patients had complete pain relief within 6 hours of completion of streptokinase infusion in the study group (cases), 60% (18) of the patients had complete pain relief within 6 hours of completion of streptokinase therapy in the control group. There was no statistically significant difference between the two groups by Z-test (p = 0.219). In the subset of patients having pain relief within 6 hours of completion of streptokinase infusion, the mean time in the study group (Cases) was 4.136 hours compared with 3.22 hours in the control group, the difference of which was not significant. This was comparable with the studies of Sivan et al.[8] and Ahmed et al.[6] Reperfusion is characterized by a rapid progressive decrease in pain intensity within 30 minutes of onset of its abatement (Shah et al.,).[9] However, this is a subjective phenomenon and no definite time period has been documented to signify reperfusion.

Reperfusion using the criterion of fractional change (Fc) on ECG was achieved in 86.67% (26) and 80% (24) of the patients in the study and the control group, respectively. The difference between the two groups by chi-square test was p = 0.2, which is not statistically significant. According to fractional change, the patients were said to be re-perfused if Fc ≥ 0.5 and not re-perfused if Fc < 0.5. A fractional change value of Fc ≥ 0.5 had been found to 67%) specific and 93% sensitive for predicting a patent artery (Hogg et al).[10]

The mean time to peak CPK-MB was observed to be 9.47 ± 2.25 hours in the entire study group (cases) and 9.47 ± 2.58 hours in the entire control group. When reperfusion was assessed by early peaking of CPK-MB within 12 hours, 73.33%) (22) and 60%) (18) of the patients were re-perfused in the study and control groups, respectively. No statistically significant difference was found in the two groups by chi-square test (p = 0.057). The mean time to peak CPK-MB in those re-perfused by this criterion in both the groups in combination was 9.04 hours compared with 11.6 hours in those not re-perfused. This observation and result of our study was comparable to that of Gottlich et al.[11] There was a significant difference between the two groups with p-value of 0.031. This indicated that serum CPK-MB

Levels peak earlier in the re-perfused than the non-re-perfused group. Isoforms of creatine kinase (CPK-MB) are a reliable plasma marker of myocardial necrosis. It has been observed that CPK-MB levels peak earlier when there is reperfusion of the occluded coronary artery. The time from streptokinase infusion to peak CPK-MB of less than 12 hours has been said to signify reperfusion, while peaking at 18 or 24 hours represents that no reperfusion has taken place, as proved angiographically. This demarcation segregated patients with and without reperfusion and yielded a sensitivity of 95% and specificity of 88% (Alderman et al,)[12] In a study taking time from streptokinase infusion to peak CPK as a criterion for reperfusion, it was found that peaking of CPK occurred at 9.7 ± 6.3 and 12.3 ± 4.8 hours in those receiving 7.5 lakh units and 1.5 million units of streptokinase, respectively (difference not statistically significant) (Gottlich et al,)[11] In this study, in the group receiving, 7,50,000 IU of streptokinase, 89%) patients showed peaking of CPK-MB within 12 hours, while 67% of patients did so in the group given 1.500,000 IU. This compares well with the data of the present study.

The study has shown that in a dose-related comparison of thrombolytic therapy, there was no significant difference in the number of patients re-perfused by non-invasive criteria, singly and in combination between the group receiving 7.5 lakh units of streptokinase (Study group) and 1.5 million units of streptokinase (Control group). Dose ranging studies of thrombolysis and streptokinase have yielded similar comparable results using variable criteria for assessing reperfusion (Gottlich et al,[11] Six et al,[13] Ahmed et al,[6] Bose et al.[7])

Ahmed et al.[6] in their study used both CPK-MB and rapid resolution of ST-segment elevations as evidences of reperfusion while comparing half-dose streptokinase (7,50,000 units) regimen with the conventional full dose (15 lakh units) regime. The results of their study were in concordance with our study, wherein they concluded that a dose of 750,000 units of streptokinase was clinically satisfactory in coronary reperfusion and produced results similar to those reported previously with 1.5 million units of streptokinase.

The results of our study also corroborate with those of Sivan et al[8] who analysed the efficacy and safety of streptokinase in full conventional dose (15 lakh), half dose (7.5 lakh) and no thrombolysis in the elderly population (> 75 years). Successful thrombolysis in their study was defined as ST-segment resolution of 50% or more. They concluded that half dose (7.5 lakh units) streptokinase has equal efficacy, better clinical outcome, and reduced rate of complications compared to full dose (15 lakh) streptokinase. Of all the 60 patients, 34 (56.6%) patients re-perfused by Fc criterion had therapeutic window less than 6 hours as compared with 16 (26.67%>) patients having therapeutic window of 6-12 hours. Significant statistical difference was observed in the two subsets (p = 0.026). Similarly, 28 (46.6%>) and 12 (20%) patients re-perfused using the criteria of early CPK-MB peaking within 12 hours had therapeutic window less than 6

and 6-12 hours, respectively, p-value for difference between the two groups was 0.007, which was statistically significant. Patients who are given thrombolytics earlier following onset of symptoms obtain reperfusion in a greater proportion of patients. This is also validated and supported by studies that have shown that older thrombi are more resistant to lysis (Karsch et al).[14] According to AHA/ACC guidelines for management of acute myocardial infarction, therapeutic window should be less than 12 hours (Ryan et al),[15] though the rates of reperfusion was 60-70% in studies that delayed treatment for more than 6 hours after onset of chest pain (Anderson et al 1984.

CONCLUSIONS

Low dose (7.5 lakh units) of streptokinase was as effective as the standard dose (1.5 million units) of streptokinase in achieving reperfusion of the infarct related coronary artery in elderly patients of acute myocardial infarction. Also, low dose streptokinase (7.5 lakh units) infusion was found to be associated with a lower incidence of haemorrhagic complications as compared to 1.5 million units of streptokinase infusion.

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