Research Article

Effectiveness and comparison of reteplase versus streptokinase thrombolytic agents in the patients of acute myocardial infarction

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Received: July 07, 2016; **Accepted:** October 06, 2016

ABSTRACT

Background: Streptokinase and reteplase are commonly used for thrombolytic therapy in the patients with acute myocardial infarction (AMI). A comparative study was designed to evaluate the effectiveness of both thrombolytic agents. **Objective:** The objective of this study was to compare the effectiveness, reperfusion rates, mortality, and safety profile of two thrombolytics (reteplase and streptokinase) in the patients of AMI. **Materials and Methods:** The effectiveness of both thrombolytics (reteplase and streptokinase) was compared on AMI patients during hospital stay, at 1-month and 1-year follow-up. The difference of both groups was assessed by Chi-square and Student's *t*-test wherever required. **Results:** A total of 414 patients of AMI were included in the study. No significant difference was apparent between the effectiveness of both thrombolytics agents at 1-month follow-up of AMI patients. Patients thrombolysed with reteplase showed a significantly low mortality ($\chi^2 = 3.96$, d.f. = 1, $P = 0.0466$) at 1-year post-AMI follow-up. The mean age of patients of reteplase group was 56.7 ± 4.95 years and for patients of streptokinase was 53.2 ± 9.19 years ($P < 0.001$). The mean age of occurrence of AMI in female was 61.0 ± 8.04 years and in male was 52.9 ± 8.39 years ($P < 0.001$). **Conclusion:** Both thrombolytic agents have similar effectiveness in the treatment of AMI at 1-month post-AMI follow-up. At 1-year follow-up, the study demonstrated the superiority of reteplase over streptokinase. As a conclusion, there is a statistically significant difference in hospital stay of AMI patients thrombolysed with reteplase as compared to streptokinase.

KEY WORDS: Reteplase; Streptokinase; Thrombolytic Therapy; Acute Myocardial Infarction.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the main leading causes of mortality and morbidity worldwide, caused by the complete occlusion of a coronary artery with thrombus.[1] Intervention with thrombolytic agents in AMI is an effective means of limiting myocardial damage.[2] Several thrombolytic agents currently being used differ with respect to fibrin affinity, fibrin specificity, method of administration (bolus vs. infusion), allergic reactions, and multiple other parameters. Streptokinase and reteplase are established therapies for the patients of AMI. Reteplase is a fibrin-specific new thrombolytic agent that can be given as a double bolus in the treatment of AMI.[3] The objectives of the present study were to evaluate the effectiveness, reperfusion rates, mortality, and safety profile of both reteplase and streptokinase thrombolytic agents in the patients of AMI receiving thrombolytic therapy.

Access this article online	
Website: http://www.ijmsph.com	Quick Response code
DOI: 10.5455/ijmsph.2017.0740906102016	

MATERIALS AND METHODS

The present comparative parallel study between streptokinase and reteplase was carried out in the district of Hapur and Bulandshahr from 2013 to 2015. Patients with characteristic chest pain (ischemic origin) occurring not more than 8 h were considered for inclusion if there was ST-segment elevation >0.1 mV in 2 limb leads or 0.2 mV in 2 chest leads, chest

pain for ≥30 min. The diagnosis was confirmed by serial documentation of 12-lead electrocardiogram and by serial cardiac enzymes (creatine kinase-MB and troponin I) level determination. Exclusion criteria included patients with severe renal and hepatic failure, pregnant women; patients had a contraindication to thrombolytic therapy including recent head/facial trauma and or ischemic stroke within last 3 months, intracranial tumor, and prior intracranial hemorrhage, suspected aortic dissection, active internal bleeding, or bleeding diathesis, and severe uncontrolled hypertension. 414 eligible patients of AMI were included in the study for the thrombolytic therapy. Of 414 eligible patients of AMI, 345 were thrombolysed with streptokinase and 69 with reteplase. All patients referred to the intensive care unit for the treatment of AMI.

All patients concurrently received a loading dose of 325 mg aspirin, 300 mg of clopidogrel, and systemic heparin 60 mg/kg bolus (maximum 4000 units), followed by continues infusion of 12 units/kg/min (maximum 1000 units/h) to prolong the activated partial thromboplastin time to 50-70 s. Patients were randomized for thrombolytic therapy with streptokinase (Behring; 1.5 million U intravenous [IV] within 1 h) or reteplase (MIRel, Reliance Life Sciences Pvt. Ltd.). Among patients of AMI who presented to the hospital within 8 h of symptoms onset, 83.3% were thrombolysed with streptokinase and 16.7% with reteplase. Reteplase was administered with the usual adult dose of AMI as 10 units IV bolus over 2 min as soon as possible after the onset of AMI symptoms, followed by a second 10 unit IV bolus 30 min later over 2 min. If the serious bleeding or anaphylaxis occurred, the second dose was withheld. All patients receiving thrombolytic therapy with streptokinase or reteplase were monitored for an adverse reaction. Clinical data of the patients were done through completing a questionnaire by reviewing the patient's medical files and documentation as well as interviewing with the patients. The questionnaire includes the demographic information, past medical history, drug history, familial, habitual and social history, laboratory, and echocardiographic information.

The difference in both groups was assessed by Chi-square and paired *t*-test wherever required. Data are presented as a mean ± standard deviation. We regarded $P < 0.05$ as statistically significant.

RESULTS

A total of 414 patients of AMI were included in the study. The most number of patients were male (369, 89.1%) while 45 (10.9%) patients were female (Table 1 and Figure 1). Of total patients, 345 (83.3%) were thrombolysed by streptokinase, and 69 (16.7%) by reteplase (Table 1 and Figure 2). Of the 345 patients thrombolysed with streptokinase, 308 (89.3%) were male and 37 (10.7%) were female. The total patients thrombolysed with reteplase, 61 (88.4%) were male and 8 (11.6%) were female.

Table 1: Number and percentage of AMI patients received thrombolytic therapy

Thrombolytic agents used	*n* (%)	Male (%)	Female (%)
Streptokinase	345 (83.3)	308 (89.3)	37 (10.7)
Reteplase	69 (16.7)	61 (88.4)	8 (11.6)
Total	414	369 (89.1)	45 (10.9)

AMI: Acute myocardial infarction

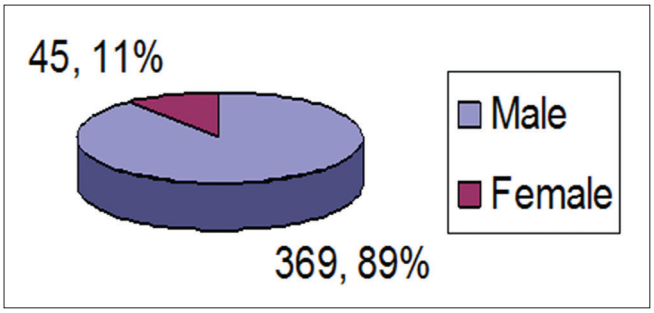

Figure 1: Comparison of number and percentage of male and female acute myocardial infarction patients included in the study

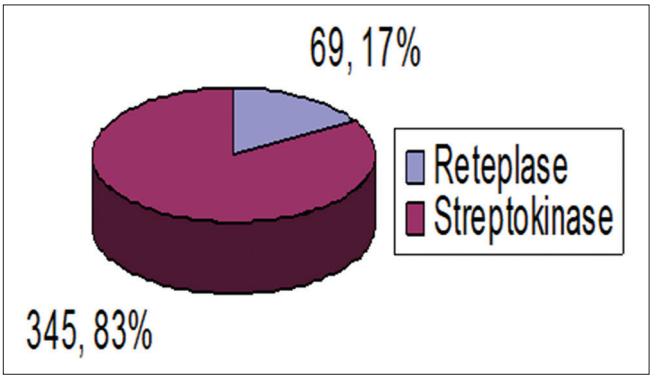

Figure 2: Comparison of number and percentage of acute myocardial infarction patients received thrombolytic therapy

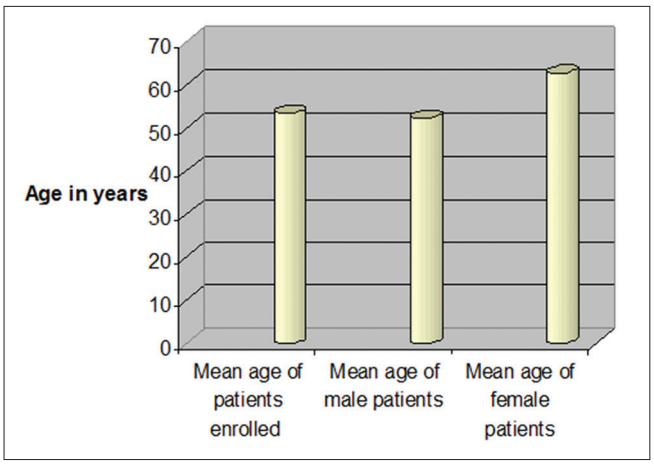

Figure 3: Mean age of acute myocardial infarction male and female patients

The mean age of total patients included in the study was 53.8 ± 8.73 years. The mean age of female and male patients was 61.0 ± 8.04 and 52.9 ± 8.39 years, respectively (Figure 3). The mean age of male and female patients treated with streptokinase was 52.3 ± 8.93 and 60.2 ± 8.50 years, respectively. While the mean age of male and female patients treated by reteplase was 56.6 ± 3.98 and 65.0 ± 3.59 years, respectively. Of 414 AMI patients included in the study, streptokinase-treated male patients were 74.4%, and female patients were 8.9%, while male and female patients treated with reteplase were 14.7% and 1.9%, respectively.

Table 2 shows the effectiveness of thrombolytic agent in each group during hospital stay, at 1-month and 1-year post-AMI follow-up. Mortality rate during hospital stay and at 1 month after thrombolytic therapy does not differ in both groups. The mortality rate in the group treated with reteplase had 4.5% and group treated with streptokinase had 5.2% during hospital stay. These groups had mortality 3.5% and 13.9% in reteplase and streptokinase thrombolysed groups, respectively, at 1-month follow-up. Likewise, no significant difference was apparent between the both groups up to the 1-month duration. However, mortality rate at 1-year follow-up indicates significant difference ($\chi^2 = 3.96$, d.f. = 1, $P = 0.0466$) in both groups.

The mean age of patients of reteplase group was 56.7 ± 4.95 years and for patients of streptokinase group was 53.2 ± 9.19 years (Table 3). Table 4 shows the mean age of occurrence of AMI in male and female patients. The mean age was 61.0 ± 8.04 years and 52.9 ± 8.39 years in female and male patients, respectively ($P < 0.001$). Table 5 shows the average hospital stay of both groups. Reteplase group had a mean hospital stay of 5.23 ± 0.89 days, and streptokinase group has 5.67 ± 1.15 days ($P < 0.0007$).

DISCUSSION

The present study evaluated the comparative effectiveness of reteplase and streptokinase. On univariate analysis, rate of mortality by reteplase, after thrombolytic therapy, during hospital stay, and at 1-month follow-up was lower as compared to streptokinase; however, this difference was not statistically significant. Similar to these two large studies of comparing the efficacy of thrombolytics in patients of AMI, reported that there were no significant differences in 30-35 days mortality with three thrombolytic agents,

Table 2: In hospital, 1-month and 1-year mortality of ST-segment elevation myocardial infarction patients receiving thrombolytic therapy

Mortality during hospital stay	*n*	Improved	Mortality (%)	OR (95% CI)
Streptokinase[C]	345	327	18 (5.2)	1
Reteplase	69	66	3 (4.5)	0.701 (CI 0.20-2.42)
Mortality at 1-month follow-up				
Streptokinase[C]	303	261	42 (13.9)	1
Reteplase	58	56	2 (3.5)	0.24 (CI 0.06-1.04)
Mortality at 1-year follow-up*				
Streptokinase[C]	251	212	39 (15.5)	1
Reteplase	51	49	2 (3.9)	0.28 (CI 0.08-0.93)

[C]Reference category, *χ^2=3.96, d.f.=1, P=0.0466. CI: Confidence interval, OR: Odds ratio

Table 3: Mean age of the AMI patients thrombolysed either streptokinase or reteplase

Characteristic	Age in years of total patients enrolled mean ±SD	Age in years of patients thrombolysed with streptokinase mean±SD	Age in years of patients thrombolysed with reteplase mean±SD	*P* value
Mean age of total patients in years	53.8±8.73	53.2±9.19	56.7±4.95	P<0.001

AMI: Acute myocardial infarction, SD: Standard deviation

Table 4: Mean age of male and female AMI patients received thrombolytic therapy

Characteristic	Age in years of total patients enrolled mean±SD	Age in years of male patients enrolled mean±SD	Age in years of female patients enrolled mean ±SD	*P* value
Total patients of AMI enrolled	53.8±8.73	52.9±8.39	61.0±8.04	P<0.001

AMI: Acute myocardial infarction, SD: Standard deviation

Table 5: Mean hospital stay of the AMI patients thrombolysed either streptokinase or reteplase

Characteristic	Total mean±SD	Patients treated with streptokinase mean±SD	Patients treated with reteplase mean±SD	*P* value
Mean hospital stay of the AMI patients in days	5.59±1.12	5.67±1.15	5.23±0.89	*P*=0.0007

AMI: Acute myocardial infarction, SD: Standard deviation

i.e. streptokinase, reteplase, and tenecteplase.[4-6] In a study comparing the efficacy of thrombolytics in AMI patients, revealed the significantly lower mortality in the patients thrombolysed by reteplase as comparing to streptokinase at 1-year post-AMI follow-up.[7] Above finding is consistent with the present study, in which a significantly lower mortality rate ($\chi^2 = 3.96$, d.f. = 1, $P = 0.0466$) was observed in the patients of reteplase as compared to streptokinase at 1-year post-AMI follow-up. A simple double-bolus regimen of reteplase administration may permit earlier initiation of thrombolysis with fewer dosing errors than continuous infusion regimens and thus afford a reduction in the morbidity and mortality risks in patients with AMI.[8] However, these findings should be interpreted with a caution due to limited use of reteplase as compared to streptokinase in present study based on the higher cost. Contrary to above, several studies[6,9] reported no significant difference in the mortality rate between reteplase and streptokinase thrombolytic treatments, so the significance of this difference is yet to be determined.

Rama et al. evaluated treatments with reteplase and streptokinase, comparing the both therapies during hospital stay. It was estimated that reteplase is better tolerated than streptokinase in older patients, mean age 64.29 ± 10.03 versus 56.03 ± 8.71 years ($P = 0.001$) and hospitalization stay 13.04 days versus 17.97 days ($P = 0.01$).[3] The present study also showed that older patients of AMI thrombolysed with reteplase were attributed to better tolerate than streptokinase. The mean age of reteplase thrombolysed group was 56.7 ± 4.95 years and streptokinase-treated group was 53.2 ± 9.19 years ($P < 0.001$). The mean hospital stay of AMI patients thrombolysed with reteplase and streptokinase was 5.23 ± 0.89 and 5.67 ± 1.15 days, respectively ($P < 0.0007$). The present study observed that the mean age of occurrence of AMI in male patients is significantly low as compared to female patients ($P < 001$). The present study suggests that male persons are more vulnerable to face AMI as compared to female persons.

Data from the available literature suggest that reteplase is fast-acting and effective thrombolytic treatment for patients of AMI. Reteplase given as a double bolus of 10 + 10 MU achieves more rapid, complete, and sustained thrombolysis of the infarct-related artery than the standard dose of streptokinase, without an apparent increased risk of complications. This was associated with improved global and regional left ventricular function at hospital discharge.[10,11] In the present study, mortality benefit seen from reteplase suggests that there should be a change in the pattern of use of thrombolytic agents in India. The use of streptokinase needs to be discouraged.

CONCLUSION

In the present study, AMI patients were thrombolysed by either streptokinase or reteplase. As a conclusion, there is a statistically significant difference in hospital stay of AMI patients thrombolysed with reteplase as compared to streptokinase. The use of reteplase thrombolytic agents in high-risk patients was appropriate. Reteplase was associated with significantly lower mortality at 1-year follow-up compared to streptokinase. Mortality benefit seen from reteplase suggests that it is an effective drug in the treatments of AMI patients.

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How to cite this article: Goel SK, Goel I, Agarwal S. Effectiveness and comparison of reteplase versus streptokinase thrombolytic agents in the patients of acute myocardial infarction. Int J Med Sci Public Health 2017;6(3):568-572.

Source of Support: Nil, **Conflict of Interest:** None declared.