Original Article

COMPARISON OF RETEPLASE DOUBLE-BOLUS ADMINISTRATION WITH STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Objective: To evaluate the thrombolytic treatment in acute myocardial infarction (AMI) and to compare the costs and the effectiveness of Reteplase double-bolus vs Streptokinase in our clinic, to compare this data with other studies.

Methods: Two thrombolytic treatments were compared; Reteplase and Streptokinase in AMI by following the patients during hospital stay and at certain periods of time of 6 months, 12 months and 24 months. Differences between the two groups (streptokinase and reteplase) for discrete variables were performed by the Student test for two samples and Hi-square test. Data analysis was performed with SPSS statistical package, version 18

Results: The analysis showed no significant differences between the treatments regarding the effectiveness. After 6 months, 12 months and 24 months observation, the survival rate was 96.4% for reteplase group and 96.9% for streptokinase group. The mean age was 64.29 years for reteplase group and 56.03 years for streptokinase group (p=0.001). Hospitalization in reteplase group was at an average of 13.04days, and in streptokinase group was at an average of 17.79days (p=0.01)

Cost in each respective group was 90184.90 Lek (646€) and 54148.63 Lek (388€). The difference is 36036.27 Lek or 258€ (p=0.001).

Conclusion: Both thrombolytics (reteplase and streptokinase) have similar effectiveness in treatment of Acute Myocardial Infarction. Reteplase is an effective drug in the treatment of clinically Acute Myocardial Infarction, but the cost of reteplase is higher than streptokinase. It is safe, easily applied and it will be a useful addition to the valid list of thrombolytic drugs.

Keywords: Cardiovascular disease, Acute myocardial infarction, Thrombolytics, Tissue plasminogen activator (t-PA), Reteplase, Streptokinase, Cost-effectiveness, Lek= Albanian money.

INTRODUCTION

Acute myocardial infarction remains a leading cause of morbidity and mortality worldwide, caused by the complete occlusion of a coronary artery with thrombus [1]. The thrombus occurs at the site of a plaque which has ruptured, exposing its inner core and thus promoting thrombus formation.

The goals of therapy in acute MI are the expedient restoration of normal coronary blood flow and the maximum salvage of functional myocardium. These goals can be met by a number of medical interventions and adjunctive therapies. The primary obstacles to achieving these goals are the patient's failure to recognize MI symptoms quickly and the delay in seeking medical attention. When patients present themselves at the hospital, there are a variety of interventions to achieve treatment goals [2].

Early treatment aims to reduce the extent of myocardial damage. As the myocardium is damaged by a diminished oxygen supply due to the obstructed coronary artery, infarct size can be reduced in two ways:

- Dissolution of the thrombus to restore coronary blood flow

- Decreasing myocardial oxygen consumption

Thrombolytic therapy has been a major advance in the management of acute myocardial infarction. Thrombolytic therapy works by lysing infarct artery thrombs and achieving reperfusion, thereby reducing infarct size, preserving left ventricular function, and improving survival[3].

These drugs are most effective if administered immediately after infarct has been determined. The advantage of administration is highest within the first sixty minutes after a thrombotic event, but may extend up to six hours after the start of symptoms [4].

These drugs are often administered in combination with anticoagulant drugs such as intravenous heparin or low molecular weight heparin, for synergistic antithrombotic effects and secondary prevention.

Streptokinase and alteplase are established therapies in acute myocardial infarction. Reteplase is a new thrombolytic agent that can be given as a double bolus [5].

The 'first generation' thrombolytics had clinical disadvantages such as low specificity for fibrin, increased risk of allergic reactions (in particular with streptokinase) and short half-life. Newer thrombolytic agents such as reteplase and tenecteplase have been developed with potential advantages that include: prolonged half-life, increased fibrin specificity and increased resistance to inhibition by plasminogen activators. However, these laboratory-measured advantages may not translate into measurable clinical benefits [6].

It was proved that there is no significant difference between reteplase and streptokinase: reteplase reduced absolute 35-day mortality by 0.51% (NS, 95%CI 0.96% to 1.98%). At the lower extreme therefore, this fits within the definition of equivalence and therefore it may be said that reteplase is no worse than streptokinase INJECT study [7].

Although clear differences between thrombolytic agents are evident in the speed with which the agents achieve reperfusion, the similar survival rates in these previous trials suggested that factors other than rapid or sustained coronary reperfusion might be important in reducing mortality [8].

Reteplase produced rapid and effective coronary artery thrombolysis in a number of dose-finding and comparative studies. Double-bolus administration of reteplase 10U+10U produced

significantly higher coronary artery patency rates than accelerated alteplase (100 mg as a 1.5-hour infusion) in patients with AMI in the RAPID-II study [9].

By other studies, it was proved that there were no significant differences between reteplase and streptokinase following up 6-months post AMI treatment [10].

At 1-year follow-up, survival status was ascertained in 97.4% of the 15 059 patients enrolled in the GUSTO-III trial. At 1 year, the mortality rate for the t-PA–assigned group was 11.06%, and for r-PA it was 11.20% (P= 0.77). The absolute mortality difference of 0.14% has 95% CIs of 21.21% to 0.93%. There were no significant differences in outcome by intention-to-treat for the 2 different plasminogen activators in the pre specified groups (age, infarct location, time-to-treatment). The absolute difference in mortality rates between t-PA and r-PA progressively narrowed over the predetermined observation times after random assignment; it was 0.31% at 24 hours, 0.26% at 7 days, 0.23% at 30 days, and 0.14% at 1 year. Of note, mortality rate in the trial between 30 days and 1 year in 13 883 patients was 4.02% and did not differ between the treatment groups [11].

While the morbidity and mortality from acute myocardial infarction is too high, finding out cost-effective treatments is the goal of the clinicians.

The aim of this study is to evaluate thrombolytic cost-effectiveness therapy in acute myocardial infarction in an intensive care hospital in Tirana as a better choice to reduce mortality, calculation of the hospital treatment cost and finally finding out the cost-effective treatment. This cost-effectiveness analyse will be a novel solution for hospital treatments here in Albanian hospitals where cardiology intensive care is offered.

This trial was designed to determine whether the effect of reteplase on survival was at least equivalent to that of a standard streptokinase regimen.

MATERIALS AND METHODS

In our study 120 cases were included with acute myocardial infarction (AMI); 56 cases treated with Reteplase and 64 cases treated with Streptokinase in the period 2010-2013. Data was obtained by clinical records in Intensive Care Clinic of the University Hospital Centre "Mother Teresa". The selection is made randomly in the both treated groups. Observation in time is achieved by contacting the patients on phone and interviewing them. The patients are followed up in hospital stay, 6 months after hospitalization, 12 months and after 24 months after hospitalization.

There was not included the patients with contraindications of thrombolytics. There was collected data about the condition of the patients, the duration of hospitalisation, the therapy for each patient. We evaluate the total cost of medicaments used for each patient. A cost-effectiveness analyse was performed for each group.

Statistical analysis

Continuous data were presented at the average value and standard deviation.

Discrete data were presented in absolute value and as percentages.

Differences between the two groups (streptokinase and reteplase) for continuous quantitative variables were performed by the Student test for two independent samples.

Differences between the two groups (streptokinase and reteplase) for discrete variables were performed by the Student test for two samples and Hi-square test.

Data analysis was performed with SPSS statistical package, version 18.

RESULTS

The study enrolled a total of 120 patients, 18 females (15 %) and 102 males (85) diagnosed with AMI. The results are shown below by tables and figures.
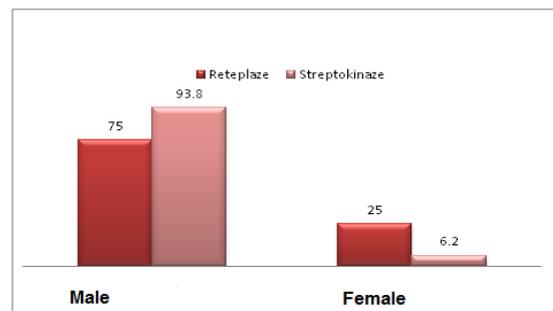

Fig. 1: It shows comparing results by gender in both groups

This fig. shows that acute myocardial infarction affects more men than women. In streptokinase group 93.8% are men and 6.2% of the patients are women; in reteplase group 75% are men and 25% women.

The table (1) indicates that there are not statistically significant differences in death of the patients in both groups. Group treated with Reteplase had one case of death, mortality (3.6%) within 30 days (hospital rehabilitation), the group treated with Streptokinase had one case of death, mortality (3.1%). Our results are equivalent to those at INJECT study [7].

Table (2) shows the effectiveness of each group after 6 months, 12 months, and 24 months post AMI treatment. Survival rate after 6 months, 12 months and 24 months after thrombolytic therapy does not differ in the both groups. In reteplase group no one feel bad, while in streptokinase group 6.4% of patients feel bad; 71.4 % of patients in reteplase group feel good vs. 54.8% in streptokinase group; 25% feel very good in reteplase group vs. 38.6% in streptokinase group. These results show no important differences.

Likewise, no significant difference was apparent between the reteplase and streptokinase groups regard 6-month mortality post AMI.

Table (3) shows a statistically significant differences between the group with streptokinase related reteplase group, mean age 56.03±8.71 in streptokinase group vs. 64.29±10.03 in reteplase group, P=0.001. Reteplase group has an average hospital rehabilitation of 13.4 days, and the streptokinase group 17.97 days with a difference of 4.57 days, (p=0.01). There is a statistically significant difference between the group of streptokinase and Reteplase related to the total cost of treatment (p =0.001), where the total average cost in Reteplase group is 658.5 €/patient and 386.8 €/patient in streptokinase group, with a difference of 271.7€.

**Table 1: It shows the situation at the end of hospital treatment**

		Treatment		Total (N=120)
		Reteplase (N=56)	streptokinase (N=64)	
Condition after treat	dead	1	1	2
		3.6%	3.1%	3.3%
	improved	55	63	118
		96.4%	96.9%	96.7%

Table 2: It shows comparison between thrombolytics during a period of time

|		Treatment		Total
		Reteplase (N=56)	streptokinase (N=64)	
Condition after 6months	dead	1 (3.6)	1 (3.1)	2 (3.3)
	No good	0 (0.0)	2 (6.3)	2 (3.3)
	good	41 (71.4)	37 (53.1)	78 (61.7)
	Very good	14 (25.0)	24 (37.5)	38 (31.7)
Condition after 1 year	dead	1 (3.6)	1 (3.2)	2 (3.3)
	No good	0 (0.0)	2 (6.4)	2 (3.3)
	good	41 (71.4)	37 (54.8)	78 (61.7)
	Very good	14 (25.0)	24 (38.6)	38 (31.7)
Condition after 2 years	dead	1 (3.6)	1 (3.2)	2 (3.3)
	No good	0 (0.0)	2 (6.4)	2 (3.3)
	good	41 (71.4)	37 (54.8)	78 (61.7)
	Very good	14 (25.0)	24 (38.6)	38 (31.7)

Table 3: It shows the comparison between age, total cost of treatment and hospital stay duration

	treatment	Nr of cases	Mean	SD	SE	t	df	Value p
age	Reteplase	56	**64.29**	10.03	1.89	3	58	0.001
	Streptokinase	64	56.03	8.71	1.54			
hospitalization	Reteplase	56	13.04	5.92	1.12	-3	58	0.010
	Streptokinase	64	**17.97**	8.14	1.44			
Total cost	Reteplase	56	**92184.90**	11191.19	2114.94	12	58	<0.001
	Streptokinase	64	54148.63	13693.78	2420.74			
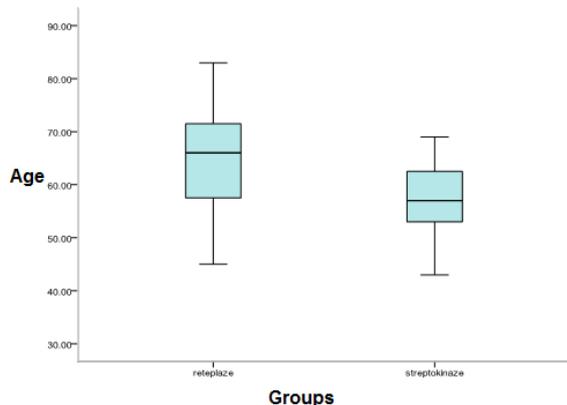
**Fig. 2: It shows the mean age in both groups**

Fig. (2) shows the comparison of age in two groups, where reteplase group has the higher mean age than streptokinase group. Older patients are treated with reteplase.
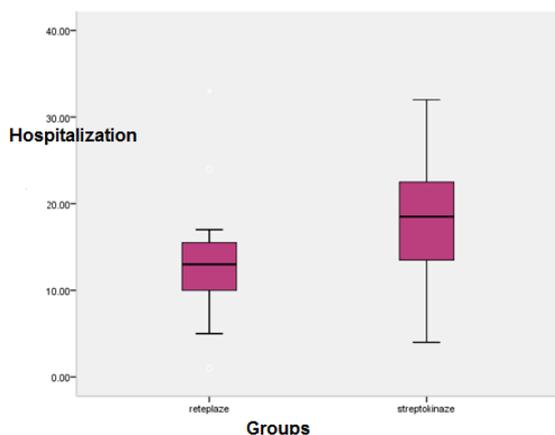
Fig. 3: It shows the hospital rehabilitation stay in both groups

Fig. (3) shows that Streptokinase group has longer hospital stay than reteplase group.

There is a statistically significant difference between the group with Reteplase and streptokinase related hospital rehabilitation 13.04 days vs. 17.79 days (p = 0.01), where the group with Reteplase has an average hospital stay fewer than group with streptokinase
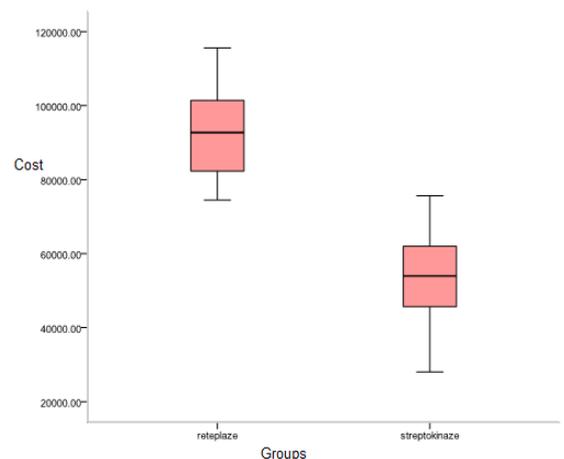
Fig. 4: It shows cost treatment comparison

Fig. (4) presents difference between the group of streptokinase and Reteplase related to the total cost of treatment. Reteplase group has a total treatment cost of 92184.9lek vs. 54148.63 Lek in streptokinase group, or 685.5 € vs. 386.8 € with a difference of 271.7 € (p<0.001), where the average total cost of Reteplase group is higher than that of streptokinase group.

DISSCUSION

Data from the available clinical trials suggest that reteplase is a fast-acting and effective thrombolytic treatment for patients with AMI. r-PA given as a double bolus of 10+10 MU achieves more rapid, complete, and sustained thrombolysis of the infarct-related artery

than standard-dose TPA, without an apparent increased risk of complications. This was associated with improved global and regional left ventricular function at hospital discharge [11, 12].

We evaluated the treatments with reteplase and streptokinase, comparing the both therapies during hospital stay, the survival and the cost treatments. It was estimated that reteplase is better tolerated than SK in older patients mean age 64.29±10.03 vs. 56.03±8.71 (P=0.001) and hospitalization period 13.04days vs. 17.97 days (P=0.01).

In the INJECT–study there were 270 deaths (9.02%) in the reteplase and 285 deaths (9.53%) in the streptokinase group, a non-significant difference (95% CI-1.98% to 0.96%)[6,8]. Among patients who received treatment (98.8%) there were 263 deaths (8.90%) in the reteplase compared with 279 deaths (9.43%) in the streptokinase group (a difference of-0.53%). Because the upper limit of the 90% CI for this difference is 0.71%, this result shows that reteplase is at least as effective as streptokinase [13-16].

In a study comparing directly the thrombolytics it is confirmed that there is no difference between reteplase and streptokinase (absolute difference in mortality of 0.53% vs. ITT analysis of 0.51%) [17].

Regarding the mortality in our study, there were no significant changes in both groups (it was one dead patient (3.6% and 3.1%). Group treated with reteplase has the lead in terms of age, where effective treatment has emerged in greater age (mean age 64.29 versus 56.03) p = 0.001.

The simple double-bolus regimen of reteplase administration may permit earlier initiation of thrombolysis with fewer dosing errors than with continuous infusion regimens and thus afford a reduction in the morbidity and mortality risks in patients with acute myocardial infarction [18].

Reteplase treatment is simple and quick to realize and time recovery is shorter (average hospitalization13.4). Survival time in both groups is relatively flat, which shows almost identical performance between the two treatments.

CONCLUSION

As a conclusion thrombolytic therapies are more successful in Acute Myocardial Infarction treatment. They improve life quality and reduce mortality. Reteplase is at least as effective as streptokinase. So Reteplase(r-Pa) is an effective drug in the treatment of clinically Acute Myocardial Infarction. It is safe, easily applied and will be a useful addition to the valid list of thrombolytic drugs.

The treatment cost of reteplase is higher compared with streptokinase and it should be estimated the cost/life saved as well.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the content of this article

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