Streptokinase Versus Alteplase: Comparison of Echocardiographic Parameters and Post-coronarography Treatment - our Experience

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1. INTRODUCTION

Fibrinolysis presents the dissolution of thrombus achieved by intravenous infusion of plasminogen activator who activates the fibrinolysis system. Plasminogen, who comes firstly in an inactive form, becomes activated by plasminogen activator into a plasmin who dissolves fibrin to soluble fibrin degradation products. If this happens in coronary arteries it stops the development of myocardial necrosis, rescues viable myocardium, preserve left ventricular function (1, 2) what is the most important predictor of successful recovery of patient (3, 4, 5). It also reduces the number of major adverse cardiac events (MACE) (2, 5, 6, 7).

Wide clinical use of fibrinolytic therapy in AMI began after the publication of the GISSI study results. The next major studies who monitored and compared the effects of fibrinolyses were GISSI 2, ISIS 3 and GUSTO study (2, 7, 8, 9).

In our clinical practice only 2 fibrinolytics are available to us: a) streptokinase, fibrin nonselective because the process of fibrinolysis occurs in the whole blood stream and not just in clot (so called “systemic lytic state); b) Alteplase, fibrinolytic of second generation, fibrin-specific and identical to human tissue plasminogen activator. Alteplase dissolves blood clots without systemic activation of plasminogen (7). It shows bigger activity of plasminogen linked to fibrin rather than the one that is free in plasma - it is selective for clot and does not lead to „a systemic lytic state”. This is one of the advantages over streptokinase, second one is slightly faster recanalization of coronary arteries compared to streptokinase (40% vs. 79% in the first 90 minutes) (6).

Although the benefits of primary PCI over fibrinolytic therapy are undoubtedly proven, in our conditions primary PCI is only occasionally available. Furthermore only a small number of patients may be subjected to this intervention and for most patients fibrinolytic therapy remains therapy of choice.
2. GOAL
The primary aim of this study was to compare the effect of streptokinase and alteplase in AMI by analyzing echocardiographic and coronarographic signs of the achieved myocardial reperfusion and to investigate physician’s preferences in choice of fibrinolytic therapy.

3. PATIENTS AND METHODS
This was retrospective-prospective study conducted at the Clinic for heart disease and rheumatism and Center for the Heart, Clinical Center University of Sarajevo in a period January - July 2012.

Patients
It was included 53 patients hospitalized in AMI who came within 6 hrs. from origin of chest pain. AMI diagnosis was based upon symptoms (chest pain or dyspnea) and ECG changes. From the study were excluded patients who came at the clinic later than 6 hours after the beginning of chest pain as well as patients with contraindications for fibrinolytic therapy.

Patients were divided into two groups: alteplase group (n=22) and streptokinase group (31). Furthermore, all patients were divided into three subgroups depending on the time from the appearance of chest pain to the admission at the Clinic: a) first subgroup– patients admitted at the clinic within 1,5 hour from beginning of subjective symptoms b) Second subgroup– patients admitted within 1, 5- 3 hrs. c) Third subgroup– patients admitted in a period of 3-6 hrs. from pain occurrence.

Methods
Streptokinase (STREPTASE) is ordered in infusion: 1,500.000 IU in 150 ml of 0,9% NaCl over 60 minutes. Alteplase (ACTYLISE) was given firstly as a bolus dose of 15 mg i.v., then 50 mg in 50 ml of 0,9% NaCl by perfusion over 30 min and at the end 35 mg in 50 ml of 0,9% NaCl over 60 min. All patients were given 300 mg of acetylsalicylic acid, 300 mg of clopidogrel perorally and low molecular weight heparin.

All patients underwent a two-dimensional Doppler echocardiographic examination on Philips I30e ultrasound device and it were estimated dimensions of atriums and ventricles, left ventricle ejection fraction (LVEF), diastolic function, existence and degree of mitral regurgitation and signs of left ventricular remodeling with the development of ischemic cardiomyopathy.

All patients subsequently underwent invasive diagnostic imaging (coronarography) performed on the Siemens Axion Artis device. Observed coronarographic indicators were: number, localization and degree of affected coronary vessels. We also collected data about further patient treatment: medicamentous therapy, invasive –PCI (percutaneous coronary intervention) with stenting or surgical revascularization.

Statistical analysis
If normally distributed continuous variables are presented as mean +/-SD, or if non-normally distributed as median- interquartile range. Normally distributed continuous variables were compared with Student’s t-test, non-normally distributed were compared with Mann-Whitney U test.

Categorical variables are presented as percentages and compared using the chi-squared test. A p value <0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 10.0 for Windows.

4. RESULTS
There was no significant difference in age (58.12(37.0-79.0) vs. 50.318 (36.0- 64.0 yrs., p NS) and gender (p=0.3) between groups, although in the alteplase group were more men and patients were slightly younger. Mean time from occurrence of pain to the admission at the clinic was not statistically different in streptokinase vs. alteplase group (2.8 ± 1.7 vs. 2.2 ± 2, 2 hrs, p=0.28). Although no significant, shorter time in alteplase group proves that we preferred alteplase in patients who came earlier.
We found no statistically significant difference in incidence and severity of mitral regurgitation (p = 0.233) and the existence of ischemic cardiomyopathy (p = 0.082) between streptokinase and alteplase group. The patients from the alteplase group had significantly higher percentage of preserved diastolic function (p=0.037) (Figure 1).

Comparing recommended treatment after coronaryography (medication, PCI with stent or surgery), not taking into consideration time from pain occurrence to admission, we did not get statistically significant difference between the streptokinase and alteplase group (x² = 1.678, p = 0.432), although there were more alteplase than streptokinase (36.4% vs. 22.6 %) patients who were treated only with medications (no need for revascularization). Also more patients after streptokinase was treated invasively (PCI with stenting) compared to alteplase (58.1% vs. 40.9%).

When we compare treatment after coronaryography between subgroups we came to different results. In alteplase first subgroup (< 1.5 hour) significantly more patients was treated by medications (without need for revascularization) compared to streptokinase first group (62.5 %vs. 28.6%, p=0.047). In second alteplase subgroup (1.5-3 hrs.) less patients needed a CABG (coronary artery bypass graft) compared to streptokinase (60% vs. 83.3% of patients) (Figure 2).

The significant statistical differences were noted in the incidence and degree of MR: in the first subgroup of the alteplase group 30.8% patients were without MR vs. 11% in streptokinase group (p=0.045). In second and third subgroup of alteplase there were no moderate or severe MR, while in 3rd subgroup of the streptokinase 10% of patients had MR 2-3+ (Figure 3).

There was significantly more occurrence of ischemic cardiomyopathy in all three streptokinase subgroups. In first subgroup streptokinase vs. alteplase (<1.5 h) there was 3 vs. 0 patients with cardiomyopathy, in second group (1,5-3 hrs.) there was 5 vs. 1 patients and in third subgroup (3-6 hrs.) there was 6 vs. 0 patients (p=0.009).

There were significant difference in occurrence of normal diastolic function in alteplase first subgroup vs streptokinase first subgroup (100% vs. 40%, p=0.008). In the streptokinase third group (>3 hrs.) all patients had diastolic dysfunction of the restrictive type.

5. DISCUSSION

There were 3 large studies with more than 100.000 participants who compared fibrinolytic effects and benefits of streptokinase and alteplase. GUSTO 1 (The Global Utilization of streptokinase and t-PA for Occluded Arteries) trial (4, 9) showed that 30 day mortality was 7.3% in the group with streptokinase, and 6.3% in the group with alteplase (2, 3, 7, 10). However in the same study, the risk of big hemorrhagic incidents (CVI) increased from 0.2% to 0.3% in patients treated with alteplase in comparison with streptokinase (3, 4, 9, 11, 12).

Contrary, in the GISSI 2 (Gruppo Italiano per lo Studio Della Sopravivenza Nell infarto Miocardico) and ISIS 3 (International Study of Infarct Survival) (3) there was no significant difference in survival of patients treated with these two fibrinolytics. We note that in GUSTO 1 was used a rapid 90 minute alteplase protocol plus intravenous heparin, which was not the case with GISSI 2 and ISIS 3 (8, 10, 12, 13).

In the GUSTO 1 study it was found that complete reperfusion of the infarct artery after 90 minutes was achieved in 54% of patients who received alteplase vs 30% of patients who received streptokinase (2, 8, 10, 12, 13).

Conclusion of these studies were that this two fibrinolysis generally have small absolute difference (1, 3) but alteplase may be better in patients who are younger, who were hospitalized in a shorter period from the occurrence of subjective problems, who had anterior AMI and who was treated with streptokinase in previous AMI (2, 6, 9, 12, 15).

Our results are similar: although there were no significant differences in age, gender and time from occurrence of pain in streptokinase vs. alteplase, more male and younger patients were in alteplase first subgroup. That means that doctors in our Coronary care unit preferred alteplase in younger patients and patients who came in shorter period from pain beginning.

All three studies have also indicated that the choice of fibrinolytic agent is less important for the survival of the patient, i.e. the of primary importance has the time from initial symptoms to treatment (1, 5, 8, 9, 10, 11, 14). The reduction of mortality with fibrinolytic therapy if is used within 1 hour from the beginning of symptoms is 50%, in the first two hours after chest pain 45% and after two hours mortality reduction is 20% (1, 2, 4, 6, 8).

Our results are similar: we didn't prove significant difference when we analyze only type of fibrinolytic drug, but when we took into consideration time then benefits of alteplase became more convincing.

It is important to notice that searching in literature we didn't not find studies of streptokinase and alteplase comparison by analyzing echocardiographic indices. We found statistically significant difference in diastolic dysfunction, but there were no difference in incidence of cardiomyopathy and MR.

However, when the groups were compared in relation to the time from the beginning of pain to admission at the clinic difference between groups became significant. A statistically significant difference was noticed in post-coronarography treatment: in alteplase first subgroup the most common outcome was medicamentous without need for revascularization 62.5 % vs. 28.6% in streptokinase group. In the second alteplase subgroup (1.5-3 hrs) 60% of patients needed bypass vs. 83.3% of patients in streptokinase.

Kostic et al. (2) observed 127 patients in AMI and found no significant difference in the presence of the residual stenosis in culprit lesion, occurrence of reperfusion arrhythmias and MACE. Significantly more patients in alteplase group achieved TIMI-3 flow in previously blocked coronary artery (2, 6).

Our results are similar with ones of Kostic et al (2). We found that more patients with the streptokinase were referred to surgical revascularization compared to alteplase (23% vs 7%).

A statistically significant difference in the development of cardiomyopathy was observed in relation to the time of occurrence and applied fibrinolytics. The highest percentage of patients
without cardiomyopathy was noted in patients with alteplase in the first subgroup, while the majority of patients with developed cardiomyopathy are noted in streptokinase third subgroup. Likewise, in the observation of diastolic function we found a statistical significant difference according to the time and medication: all patients in the first alteplase subgroup had normal diastolic function while in the third streptokinase subgroup all patients had restrictive type of diastolic dysfunction.

However, myocardial function remains poor in 30% of patients with re-established reperfusion and re-opened coronary arteries. This points that futures strategies are needed for the further optimization of fibrinolytic therapy until the time when all patients with AMI would be hospitalized in optimal time interval and subjected to PCI.

6. CONCLUSION

There was a statistically significant difference in favor of alteplase in echocardiographic and coronaryography reports only when patients are divided into alteplase and streptokinase subgroups according to time from beginning of subjective symptoms. No matter how you treat the time is more important. We decided more often to give alteplase in male patients, younger age patients and patients who were admitted to the clinic in a shorter period of time from the appearance of chest pain.

REFERENCES