The Efficacy Of Thrombolytic Treatment On Patients Who Are Above 75 Years Of Age

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Citation

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Abstract

Background: For acute myocardial infarction (AMI) patients above the age of 75, the efficacy of thrombolytic treatment could not be demonstrated clearly. Recently, depending on the data obtained from observational studies, it has been advocated that thrombolytic treatment might not be showing any effect or even be harmful to these patients. The aim of this study is to investigate the efficacy of thrombolytic treatment on patients above the age of 75.

Methods: 67 consecutive patients above 75 years of age (34 males, 33 females, average age 79±4 years), who were hospitalized within the first 12 hours of the chest pain in the coronary intensive care with the diagnosis of AMI with ST elevation and who did not have any contraindication for receiving thrombolytic therapy were recruited in this study. These patients were then randomized into thrombolytic treatment (streptokinase, n=34) and conservative treatment (n=33) groups.

Results: First 30 day mortality rate of the patients was 23.8%. In the conservative treatment group, the 30 day mortality rate was 24.2%, and in the thrombolytic therapy group it was 23.5% (p=0.7). In the thrombolytic group, there were two incidents of intracranial bleeding (5.8%), 1 major bleeding (2.9%) and 2 minor bleedings (5.8%) during the hospitalization period. In the conservative treatment group, there was only 1 minor (3%) bleeding episode.

Conclusions: In our study, the mortality rates for the groups receiving thrombolytic treatment and not receiving this treatment were similar. This finding supports the idea that thrombolytic treatment was not beneficial.

INTRODUCTION

Thrombolytic treatment is one of the most important developments in the field of acute myocardial infarction (AMI) treatment. The efficacy of thrombolytic treatment in reducing mortality in patients below the age of 75 has been demonstrated by large scale randomized trials without giving place to any substantial doubt.[1,2,3,4] In western societies, 30% of all AMI patients are above the age of 75 and the efficacy of thrombolytic therapy could not be clearly demonstrated for this age group. Subgroup analysis of randomized studies and meta-analyses talk about a benefit of thrombolytic treatment that does not reach the limit of statistical significance.[5,6] In the guidelines published for the treatment of acute coronary syndromes, for ST elevated AMI patients admitting to the hospital within the first 12 hours of the chest pain, thrombolytic treatment is a Class 1 indication for patients below the age of 75, while being a Class 2a indication for those above the age of 75.[7] In the observational studies published within the last tow years, thrombolytic treatment has been regarded as not being beneficial even as being harmful, thus aggravating the discussion as to what the ideal reperfusion treatment should be for these patients.[8,9,10]

In this randomized prospective study, we aimed at investigating the efficacy and the safety of thrombolytic treatment in ST elevated AMI patients who were above the age of 75 having emergency admissions while not having any contraindications for treatment with thrombolytic treatment. As elderly patients have lower risks of stroke,[11] we have chosen streptokinase which is the most commonly used thrombolytic agent in our department for thrombolytic treatment.

METHODS

Consecutive AMI patients above the age of 75 who were hospitalized in our department were included in this study.

67 patients were randomized into thrombolytic and conservative treatment arms. Inclusion criteria were; chest pain of more than 30 minutes duration correlating with AMI, at least 1 or more mm (0.1mV) of ST elevation on two or more adjacent leads on ECG and having been admitted to the hospital within the first 12 hours after the initiation of the chest pain. Patients having any relative or absolute contraindications for being treated with thrombolytic agents were not included in the study. Such contraindications were: previous history of stroke, known intracranial diseases, recent history of surgery or trauma, treatment resistant hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure > 120 mmHg), active bleeding and lengthened cardiopulmonary resuscitation. The demographic features (age and sex), histories of hypertension, diabetes and smoking, the time of hospital admission (how many hours after the initiation of symptoms) and the Killip class[12] at the time of hospitalization in the coronary intensive care unit were all recorded. Informed consent for the investigational protocol was obtained from all patients, and protocol was approved by the Investigational Review Board of the Ankara Numune Education and Research Hospital.

The patients who were randomized into the thrombolytic therapy group received 1.500.000 units of streptokinase with an infusion to be completed within one hour. All patients were made to chew 300 mg aspirin and received the same dose in the consecutive days. If there were no contraindications, they received low molecular weight heparin during their stay in the hospital. Regardless of the group they were randomized into, all the patients received beta blockers and angiotensin converting enzyme (ACE) inhibitors unless they had specific contraindications. The choice of beta blockers and ACE inhibitors and their relevant doses were left to the discretion of the physician in charge of the patient.

Total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol levels were measured and recorded for all the patients. CK-MB levels were measured every 6 hours on the day of admission, every 8 hours on the following day and once a day on the consecutive days. The highest CK-MB measurement was recorded as the peak value. The complications that have occurred during the hospital stay (heart failure, atrio-ventricular (AV) block, ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation (AF), acute mitral insufficiency, and ventricular septal defect), major and minor hemorrhages, cerebrovascular incidents and duration of hospital stay were all recorded. On the day of discharge, all the patients underwent transthoracic echocardiography and left ventricle ejection fractions were measured by employing Modified Simpson's method. Primary end point of the study was the 30 day mortality rate.

The data were expressed as mean ± standard deviation. The differences between basal variables were evaluated with Student t-test for continuous variables and chi-square test for categorical variables. P value of <0.05 was accepted as being statistically significant.

RESULTS

67 patients were recruited in this study. 34 of these were randomized into trombolytic therapy and 33 to conservative treatment arms. The general characteristics of trombolytic therapy and conservative treatment arms are compared on Table I.

Figure 1

Table 1: Baseline characteristics and risk factors in the thrombolytic and conservative treatment groups

	Thrombolytic group (n=34)	Conservative group (n=33)	P value
Age, years (median)	78 ± 3	80 ± 5	0,03
Male/Female	18/16	16/17	>0,05
HT (%)	15 (%44,1)	10 (%30,3)	>0,05
DM (%)	4 (%11,8)	10 (%30,3)	0,06
Smoking (%)	10 (%29,4)	8 (%24,2)	>0,05
Time from onset of pain (hour)	5,8 ± 2,6	6,6 ± 2	>0,05
Duration of hospitalization (day)	6,2 ± 1,7	6 ± 2,6	>0,05
Peak CK-MB (u/L)	281,8 ± 167,6	198,8 ± 127,6	>0,05
Total cholesterol (mg/dl)	177 ± 45,9	190,1 ± 41,3	>0,05
Triglyceride (mg/dl)	120,2 ± 36,5	119,2 ± 52,5	>0,05
HDL-cholesterol (mg/dl)	41,5 ± 9,1	46,7 ± 13,3	>0,05
LDL-cholesterol (mg/dl)	112 ± 41,7	119,6 ± 36,2	>0,05
Anterior MI (%)	19 (%55,9)	20 (%60,6)	>0,05
LV EF (%)	44 ± 11,6	43,3 ± 13,1	>0,05

HT: hypertension, DM: diabetes mellitus, MI: myocardial infarction, LV EF: left ventricular ejection fraction

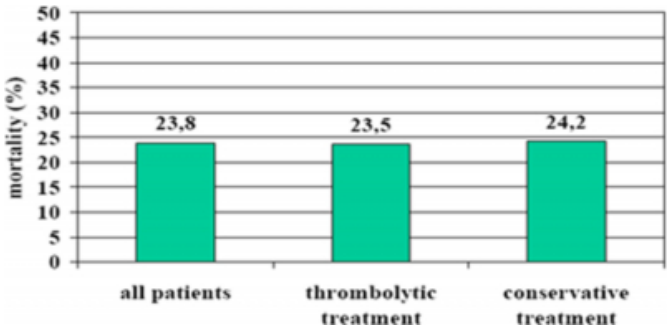
As can be followed from the table, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol values, peak CK-MB measurements, left ventricular ejection fractions, the infarct localizations (the ratio of anterior myocardial infarctions), the time that has elapsed until the admission to the hospital, the length of hospital stay, the rates of

hypertension and smoking did not differ between the groups (p>0.05). As the number of patients in our study was limited, the patients randomized into the trombolytic therapy arm had an average age of 2 years below than that of the conservative treatment group (mean age for trombolytic therapy group 78±3 years, mean age for conservative treatment group 80±5 years). The groups did not differ as the rates of utilizing beta blockers, ACE-inhibitors, digoxin and aspirin upon discharge from the hospital.

30-day mortality was calculated as 23.8% for all patients. The mortality for thrombolytic treatment group was 23.5% and this was 24.2% for the conservative treatment group. The difference between the mortality rates of the two groups was not statistically significant (p=0.7) (Figure I).

Figure 2

Figure 1: 30 day mortality rates for the treatment groups



The distribution of the AMI complications developing during the hospital stay is demonstrated on Table II.

Figure 3

Table 2: Acute myocardial infarction complications developing during the hospital stay in the thrombolytic treatment and conservative treatment groups.

	Thrombolytic group (n=34)	Conservative group (n=33)	P value
Heart failure (%)	8 (%23,5)	9 (%27,2)	>0,05
AV complete block	3 (%8,8)	3 (%9,1)	>0,05
VSD	0 (%0)	1 (%3)	>0,05
VT-VF	1 (%2,9)	1 (%3)	>0,05
AF	4 (%11,8)	10 (%30,3)	0,06
ICH	2 (%5,8)	0 (%0)	>0,05
Major bleeding	1 (%2,9)	0 (%0)	>0,05

AV: Atrioventricular, VSD: ventricular septal defect, VT: ventricular tachycardia, VF: ventricular fibrillation, AF: atrial fibrillation, ICH: intracranial hemorrhage

The rate of developing heart failure was 23.5% in the conservative treatment group, and 27.2% in the treatment group, the difference between the groups was not statistically significant (p>0.05). A total of 6 patients (9%) developed AV complete block. 3 of these were in the conservative treatment group and the remaining three in the thrombolytic treatment group. All the patients were suffering from inferior myocardial infarction and all returned to sinus rhythm within a week. As a mechanical complication, only one patient (1.5%) developed ventricular septal defect. This patient was not receiving thrombolytic treatment and did not accept any intervention, the patient died within the end of second week. Only two patients (3%) developed VT-VF during the hospital stay. One of these patients was in the conservative treatment group and the other in the thrombolytic treatment group and both died during their hospital stay. There was a tendency to have more number of AF in the conservative treatment group, however the difference between the groups did not reach the level of statistical significance (30.3% and 11.8%, p=0.06 respectively). The mortality rate of the patients developing and not developing AF were not different.

During the hospital stay, two minor (5.8%) bleedings and one major (2.9%) bleeding (gastrointestinal bleeding necessitating blood transfusion). Two patients developed intracranial hemorrhages (5.8%). Both of these had the bleeding within the first 24 hours of thrombolytic treatment and the patients died within 12 hours following the development of complications. In the conservative treatment group only one patient (3%) had minor bleeding.

DISCUSSION

The most striking point in our study was the high AMI mortality rate for patients above the age of 75 (when compared to the AMI mortality without making any age group distinction) (30 day mortality 23.8%). Despite the fact that this patient group constitutes nearly one third of all AMI patients in Western societies, they have not been included in thrombolytic trials or they have always been underrepresented.[13] In a meta-analysis conducted by fibrinolytic treatment study group including all the randomized trombolytic trials of more than 1000 participant, patients who were 75 or older constituted less than 10% of all the patients.[6] In this meta-analysis, 35 days mortality of patients having receiving thrombolytic treatment was 24.3%, for patients not receiving thrombolytic treatment this was 25.3%. The difference between these two groups was not statistically significant. 95% confidence interval for trombolytic treatment changed between -16 to +36. Despite the fact that there was a decrease in mortality that was not of statistical significance, the possible hazardous potential of thrombolytic treatment could not be denied. In a recently

published trial published by Minai et al,[14] the results of the group who have undergone primary angioplasty and the group who was treated conservatively without even not having received any thrombolytic treatment. In-hospital mortality was reported as 20% for conservative treatment group and 16% for primary angioplasty group (p>0.05). In a randomized prospective trial comparing angioplasty and thrombolytic treatment one-month mortality rate was reported as 22% .[15] The researchers in this study planned to randomize 266 patients, however after randomizing 87 patients, the mortality rate in the thrombolytic therapy group was higher than that of the primary angioplasty group which resulted in premature cessation of the randomization (respective mortality rates for the groups were 22% and 7%, p=0.03).

In our study, 30 day mortality rate was 23.5% in the thrombolytic treatment group and 24.2% in the conservative treatment group (p=0.7). The absolute decrease of 0.7% and relative decrease of 3% in the mortality was not statistically significant. In the literature, there is no specific study comparing thrombolytic therapy with conservative approach on patients who are 75 or above. In the meta-analysis of FTT, in this subgroup of patients who had a share of less than 10%, there was an absolute decrease of 1% and relative decrease of 4% in mortality which was not statistically significant.[6] In conclusion, the high mortality rates in our study were in accordance with the high mortality rates observed in the literature.

The first observational study that started the discussion about the value of thrombolytic therapy in this group of patients was carried out by Ayanian et al.[16] In this study the data of 7864 AMI patients who were above the age of 65, who had indications of trombolytic therapy as identified by the guidelines based on the clinical and ECG findings and who did not have any contraindications for this treatment were retrospectively analyzed. In patients who were between the ages of 65 to 75 trombolytic therapy were shown to have significant benefits in accordance with the findings of randomized trials. For the patients between the ages of 76 to 86, thrombolytic treatment was shown to be hazardous (30 day mortality rate was 15.4% for the group not receiving trombolytic treatment and 18% for the trombolytic therapy). In this study group no patient subgroup was identified to have any specific benefits from the trombolytic therapy. The authors brought forward the comment that “in clinical practice thrombolytic therapy was not beneficial for patients above the age of 75 and could even be harmful and that perfusion studies directed at elderly patients should urgently be performed”. Following this study, it was stated that studies comparing thrombolytic therapy and placebo or primary have analyzed 5-year medical records of 37 hospitals in Minnesota region and have identified 719 AMI patients above the age of 75 who abided by the criteria for receiving trombolytic therapy. Only 63% of these patients had received trombolytic agents. Their results pointed out to the fact that use of thrombolytic agents resulted in a decrease in mortality for patients below the age of 80 whereas there was an increase in mortality for patients who were 80 or above. angioplasty had to be performed on patients who were 75 and older and that an appropriate reperfusion strategy had to be identified for these patients.[6] Berger et al have screened the data from 37.973 patients above the age of 75 who had admitted within the first 12 hours of chest pain and were diagnosed as AMI with ST elevation.[8] In this group of patients 14.341 (37.8%) had received trombolytic therapy, while 1.599 (4.2%) had undergone primary angioplasty. Researchers have realized that 30 day mortality rates for patients receiving thrombolytic therapy and for those not receiving any type of treatment for reperfusion were not different, whereas primary angioplasty was shown to reduce mortality rates. Soumerai et al[9] have analyzed 5-year medical records of 37 hospitals in Minnesota region and have identified 719 AMI patients above the age of 75 who abided by the criteria for receiving trombolytic therapy. Only 63% of these patients had received trombolytic agents. Their results pointed out to the fact that use of thrombolytic agents resulted in a decrease in mortality for patients below the age of 80 whereas there was an increase in mortality for patients who were 80 or above.

There are number of opinions that are brought forward for explaining why thrombolytic therapy was not beneficial or even harmful for very elderly patients. First of all, these patients have higher risks of hemorrhagic stroke and major hemorrhages when compared to younger patients.[17] In the study by Thiemann et al,[10] for the patients who were above the age of 75 and were receiving thrombolytic agents, the risk of developing stroke during the time of hospital stay was reported as 2.7%, whereas Soumerai et al [9] reported this rate as 2.4%. This rate was considerably high in our study (5.8%). In other words, 2 out of 9 deaths that were observed in the thrombolytic therapy group were related to intracranial hemorrhages that have taken place within the first 24 hours after the initiation of streptokinase treatment. In patients receiving thrombolytic therapy, death due to mechanical ruptures increased together with the increase in age. In an

autopsy study performed on 84 patients who were above the age of 70 and who had died during their hospital stay, the rate of identifying mechanical ruptures was 86% [18]. However, this rate was only 19% for patients below the age of 60. One of the possible explanations for the failure of thrombolytic therapy in these patients is that they might be arriving at the hospital at a later stage. In our patients, the time that has elapsed between the initiation of the symptoms and the arrival in the hospital was barely more than 6 hours on average.

The most important limitation of our study is having a small study population. Therefore we could not avoid having certain differences as to demographical and clinical features of our patients. The average age of the conservative treatment group was 2 years older when compared to the thrombolytic therapy group. Furthermore, despite not reaching the levels of statistical significance, the number of diabetic patients was higher in the conservative treatment arm. Despite all these existing disadvantages for the conservative treatment, there was no significant mortality benefit in the thrombolytic therapy arm making its efficacy more questionable.

In conclusion, in this prospective randomized study, thrombolytic therapy did not reveal any significant benefit for patients above the age of 75. This result supports the opinion that thrombolytic therapy is inefficient for very elderly patients. We certainly require larger scale randomized trials to identify the value of thrombolytic therapy and to delineate the best reperfusion option in these patients. Until that time, the decision to administer thrombolytic therapy to patients above the age of 75 should be based on meticulous questioning of their absolute and relative contraindications and calculation of individual risk to benefit ratio for each and every patient.

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