Fibrinolysis of ST-elevation myocardial infarction in the emergency department: prognosis of elderly patients treated with streptokinase

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Abstract

The use of fibrinolytic therapy for ST-segment elevation myocardial infarction can lead to fatal complications. Streptokinase, a non-specific fibrinolytic, remains used in developing countries. The safety of this fibrinolytic agent is under study in the elderly population.

Objectives: This study aimed to compare the prognosis of elderly patients (> 75 years old) treated with Streptokinase for ST-segment elevation myocardial infarction versus 75 years old concerning hemorrhagic complications and mortality.

Methods: Prospective study (2009-2018). Inclusion of patients treated with Streptokinase for STEMI. Comparison of two groups: elderly patients and patients less than 75 years old.

Results: Inclusive of 624 patients. Mean age=59±11 years. Sex-ratio=5.

Patients aged over 75 represented 10% of the study sample. The comparative analysis of the elderly group (n=63) and patients less than 75 years (n=561) found that elderly patients were more frequently male Sex-ratio = 1 vs 7, p<0,001) and had more hypertension (59%) vs (25%) (p<0,001). Atypical clinical presentation was more frequent in the elderly group (30% vs 16%). No difference was found in the two groups concerning fibrinolysis success (57% vs 61%), and intracranial hemorrhage (0 vs 2 patients). In-hospital and one-week mortality were higher in the elderly group (4.8% and 8% vs 0.7% and 1.2%, respectively). Mortality predictors among elderly patients were anterior myocardial infarction (OR=6.37, p=0.044, 95%IC 1.19-34) and cardiogenic shock (OR=38, p<0.001, 95%IC 5.02-287.43). Streptokinase is an effective therapeutic alternative for the elderly with ST-segment elevation myocardial infarction. It causes reperfusion in 57% of cases with no significant increase in major hemorrhagic events.

Keywords: Fibrinolysis, STEMI, Elderly, Complications, Outcomes, Emergency

Introduction

Older age is an independent prognostic factor of mortality for patients with ST-segment elevation myocardial infarction (STEMI) (1). Elderly adults (aged >75 years) account for up to 25% of the STEMI community population, with mortality being four times as high as that of their younger counterparts (2,3). Primary percutaneous coronary intervention (PCI) is the treatment of choice for those patients. Fibrinolysis is a valuable alternative when mechanical reperfusion is not timely available. However, the value of these therapies in old patients is not well established because elderly patients have been either excluded or rarely enrolled in reperfusion clinical trials (4).

The main limit to the use of this strategy was the bleeding risk. In the STREAM study (5), fibrinolysis with a full dose of Tenecteplase, a specific fibrinolytic, was associated with an increased risk of intracranial bleeding in aged patients.

The Streptokinase, a non-specific fibrinolytic agent, is still recommended but not well evaluated in real life on the elderly.

This study aimed to compare the prognosis of elderly patients (aged more than 75 years old) treated with Streptokinase for STEMI versus patients aged less than 75 years old concerning hemorrhagic complications and mortality.

Methods

We conducted a prospective observational study over 10 years from January 2009 to December 2018.

Inclusion criteria (all of these criteria): (1)Patients who were admitted to the emergency department for STEMI and treated with Streptokinase as a reperfusion strategy, (2) STEMI was identified by the onset of typical chest pain lasting more than 20 minutes, unrelieved by nitrate, and associated with typical ST-segment elevation on at least two contiguous leads of a standard 12-lead ECG or a new onset of left bundle branch.

Exclusion criteria: Patients with non-persistent ST-segment elevation, and/or a diagnosis other than STEMI after investigations.

Study protocol: Patients included in the study were divided into two groups: (1) Patients > 75 years old: received 250 mg of salicylate intravenously (IV), 75 mg of Clopidogrel orally, and subcutaneous (SC) dose of 0.75mg/kg of enoxaparin; (2) Patients ≤ 75 years old: received 250 mg of salicylate intravenously, 300 mg of Clopidogrel orally and enoxaparin (30mg IV bolus followed 15 minutes later by 1mg/kg SC).

All patients received 1.5 MU of Streptokinase over 60 minutes IV. An ECG was used to assess the success of thrombolysis at 90 minutes. Angiography was performed as soon as possible. Hemodynamic and hemorrhagic complications were assessed during the first 24 hours.

Statistical analysis: Data are expressed as numbers and rates. Descriptive statistics were used to illustrate subjects' demographic characteristics. Comparison of characteristics of the two groups was performed by the χ^2 test or Fischer's exact test as appropriate. Continuous variables were expressed as means ± standard deviation, and the subgroups were compared by Student's t-test. Risk factors were evaluated in univariate analysis for the compared data. A p-value of less than 0.05 was considered statistically significant.

Results

We included 624 patients with a mean age of 59±11 years and a sex ratio of 5. Sixty-three patients were aged more than 75 years old. The comparative study of the two groups is detailed in Tables 1 and 2.

Table 1: Comparative analysis of demographic and cardiovascular risk factors.

	All N=624	>75 years N =63	≤75 years N =561	P
Age mean ±SD (years)	59±11	79±4	56±9	<0.001
Male gender n (%)	518(83)	32(51)	488(87)	<0.001
Current Smoking n (%)	458(74)	24 (38)	434 (77)	<0,001
Hypertension n (%)	180 (29)	37 (59)	143 (25)	<0,001
Diabetes n (%)	173(28)	15 (24)	158 (28)	NS
Known coronary artery disease (%)	45(7)	7 (11)	45 (7)	NS
Ischemic stroke n	4	1	3	NS

Table 2: Comparative study of clinical and biological parameters

	All patients N=624	>75 years N=63	≤ 75 years N=561	P-value
Mean delay chest pain-FMC (min) mean±SD	183±144	251±169	175±139	<0.001
Atypical presentation n (%)	209 (23)	19 (30)	190 (16)	0.006
Heart rate (bpm) mean±SD	79±21	82±24	79±20	NS
Systolic blood pressure (mmHg) mean±SD	139±33	136±40	139±32	NS
SpO2 (%)) mean±SD	96±2	94±6	96±2	NS
Killip ≥2 n (%)	56 (13)	12(19)	42(7.5)	0.002
Creatinine (µmol/l) mean±SD	83±28	101±6	82±20	<0.001
Hemoglobin (g/dl) mean±SD	14.6±1.7	13.7±2	14.7±2	0.002

The mean delay between first medical contact and fibrinolysis was 29±20 minutes in the aged group versus 25±19 min (p=0.12).

The fibrinolysis failure rate was similar in the two groups (57% versus 62%; p=0.32). The angiography was performed at the same delay in the two groups. Table 3 details the comparative analysis of complications in the two groups of patients. Univariate analysis identified two factors linked to mortality in elderly patients: an extended anterior wall and cardiogenic shock (Table 4)

Table 3: Comparative study of complications and mortality in the two groups

	All patients N=624	>75 years N=63	≤75 years N=561	P-value
Hemodynamic complications:				
Cardiac arrest n(%)	39 (9)	8(12)	31(5,6)	0,027
Asystole n (%)	6 (3)	3(5)	3 (0,5)	0,016
Ventricular fibrillation n (%)	33 (6.5)	5(8)	28(5)	NS
Cardiogenic shock n (%)	30 (12)	6(10)	24(4,3)	0,06
Acute heart failure n (%)	80(18)	16(25)	64(11)	0,004
High grade AVB n (%)	31(4)	2 (3,1)	29(5)	NS
Hypotension n (%)	109(18)	13(20)	96(17)	NS
Sinus bradycardia n (%)	78 (14)	10(16)	68(12)	NS
Hemorrhagic complications:				
Cerebral bleeding n	2	0	2	NS
Gingival hemorrhage n (%)	37(2)	4	33(6)	NS
Hematemesis n	11	0	11	NS
Mortality				
First day n	7	3	4	0.004
First week n	12	5	7	<0.001

Table 4: Factors associated with early mortality in elderly patients

	Death N=5	Survivor N=58	P	OR (CI 95%)
Extended anterior wall n (%)	3(60)	9(15)	0,044	6,37 (1,19-34)
Cardiogenic sh1ck n (%)	4(80)	2(3,4)	<0,001	38 (5,02-287,43)

Discussion

The study shows that older adults with STEMI treated with a full dose of Streptokinase fibrinolysis had the same reperfusion success rate as younger patients without increasing bleeding risk. However, the mortality rate remains higher.

This study is a prospective cohort evaluating the management of elderly patients with STEMI in 'real life'. However, it had several limitations: the relatively small sample of elderly group patients and the difficulty in collecting outcomes after the 7th day of management.

In this study, we used a non-specific fibrinolytic agent. The use of fibrinolysis for the treatment of STEMI in the elderly has been controversial. Thiemann et al (6) concluded after an observational study of 7864 patients treated for acute myocardial infarction in the USA that the use of fibrinolytic therapy in patients over 75 may do more harm than good. In the same study, 30-day mortality in patients aged 76-86 was significantly higher in those who received fibrinolytic therapy than in those who did not (18·0% vs 13·6%; p=0·003). These results appear to contradict the Fibrinolytic Therapy Trialists' (FTT) overview of 58,600 patients randomized into thrombolytic trials, which concluded that the 35-day mortality rate in the 5788 patients aged over 75 was lower in those who received thrombolytic therapy than in those who did not (24·3% vs 25·3%). The difference was not significant. However, the absolute mortality reduction in patients over 75 was like that of patients under 55 (7). On the other hand, the benefits of fibrinolysis in STEMI patients over 75 years have been proven in many different studies.

The analysis of 3897 elderly patients from the 'Swedish register of information and knowledge about Swedish heart intensive care admission' found that fibrinolytic therapy was associated with a 13% adjusted relative reduction in the composite of mortality and cerebral bleeding complications after 1 year (95% confidence interval, 0.80-0.94; P =.001) (8).

In our series, the elderly patients' fibrinolysis success rate with Streptokinase was like younger patients (57% versus 61.3%) and higher than most previous published studies. The success rate was 43%, 44% and 53% in Chesebro et al (9), Stack et al (10), and Hogg et al (11) studies, respectively. A recent study found a successful fibrinolysis with Streptokinase in 70% of patients. This finding can be explained using modern adjunctive therapy containing dual antiplatelet therapy and low-weight molecular heparin. The benefits of the dual antiplatelet therapy are explained by the fact that Clopidogrel is a potent antiplatelet agent with a synergistic antithrombotic effect with aspirin because platelet activation can still occur through thromboxane A2-independent pathways despite the inhibition of cyclooxygenase by aspirin, leading to the aggregation of platelets and the formation of thrombin (12).

However, the use of those molecules in the elderly population can have limits because of the higher vulnerability related to distinct pharmacokinetic and pharmacodynamic responses of those patients (13). The adaptation of doses, regarding age, weight, and potential renal impairment, should be considered and can prevent side effects.

The most serious side effects of the use of fibrinolytic agents are bleeding, especially

intracerebral bleeding. This complication increases with age (14). The incidence of this complication remains rare, even in elderly populations, and varies from 0.5% in controlled studies and meta-analysis to 3% in prospective analysis (15,16). That can be explained by the exclusion of the elderly from clinical trials in acute myocardial infarction (17).

The use of specific fibrinolytics such as Tenecteplase can reduce the incidence of bleeding complications. In the ASSENT-2 trial, the incidence of this complication was 1.1% with Tenecteplase versus 3% with Streptokinase (18). However, in a most recent study, the use of plasminogen activators in elderly patients versus Streptokinase was an independent predictive factor of intracranial hemorrhage (19). It is feasible that, because increased fibrin specificity is more effective in producing clot lysis, it also increases the risk of intracranial hemorrhage (18).

In our study, we didn't observe any cerebral bleeding in elderly patients, which can be explained by the small sample size, the strict use of a written protocol, and the extension of the contraindication of fibrinolysis to all patients with a history of stroke, independent of his delay.

The other, more important, complications were hemodynamic and were dominated by acute heart failure. In our study, acute heart failure occurred in 25% of elderly STEMI patients versus 11% of younger ones. In the literature, the incidence of this complication ranges from 18% to 37 % (20).

Cardiogenic shock is the most serious complication because of the high-risk mortality and the decrease in efficacy of fibrinolytic agents. In the SHOCK trial, fibrinolysis success was observed in 15% of patients (21). It's explained by the fact that fibrinolytic agents depend on coronary perfusion pressure to achieve patency (22).

Mortality in STEMI patients increases exponentially with age. In the Gusto I trial, it varies from 3% of patients aged less than 65 years to 30% of patients aged more than 85% (4).

The meta-analyses fibrinolytic therapy trialists found that the mortality increases with age and is independent of the reperfusion strategy. In this study, 24.3% of patients aged more than 75 years treated by fibrinolytic agent died in the first month, versus 25,3% in the control group.

The predictive factors of mortality in our study were an extended anterior wall and cardiogenic shock.

The cardiogenic shock was the first cause of mortality found in the literature. The ventricular rupture is more frequent in aged patients, and it's due to anatomical and physiological modifications of the myocardium by age.

The mortality rate in our population was lower than in the literature; it can be explained by the rigorous application of a written protocol.

Conclusion

Full-dose Streptokinase is an effective therapeutic alternative for the elderly. It causes reperfusion in 57% of cases with no significant increase in major hemorrhagic events.

In contrast, mortality in this population is higher than in patients under 75 years old patients and it's related to the extent of myocardial infarction and the development of cardiogenic shock.

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