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Original Article

Intracranial hemorrhage in normotensive and hypertensive patients receiving streptokinase after decreasing elevated blood pressure

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ABSTRACT

Background: Many patients with suspected acute myocardial infarction (AMI) and eligible for thrombolytic therapy may not be treated because of association between hemorrhagic complications especially intracranial hemorrhage (ICH), and severe hypertension (HTN) at presentation. Unfortunately, this leads to under use or delay in thrombolytic therapy. We assessed effect of decreasing elevated blood pressure before thrombolytic therapy in order to reduce the incidence of ICH without increasing mortality rate.

Methods: This observational and analytical cohort study enrolled 293 patients (215males and 78 female) with ST-segment elevation (AMI) that were hospitalized in emergency department of Noor hospital, Isfahan, Iran. Severe hypertension (blood pressure ≥180/110mmHg) was diagnosed in 132 patients. All of them received 1.5 million units streptokinase within one hour intravenously. In the hypertensive group, elevated blood pressure was lowered to less than180/110mmhg before thrombolysis and they were observed to detect development of symptomatic ICH and they underwent Brain CT scan, if required.

Results: The incidence of total stroke, ICH and death were 1.4%, 0.7% and 4.8%, respectively. The incidence of death and ICH in patients with severe hypertension was less than control group (P value=0.13 and 0.59, respectively)

Conclusion: Although we did not find any increase in ICH incidence in severe hypertensive patients treated be streptokinase due to AMI, but we recommend a multi-centric study with more cases and varied thrombolytic protocols.

Key words: Acute myocardial infarction, Intracranial hemorrhage, Thrombolytic therapy

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Thrombolytic therapy reduces mortality rate in patients with ST-segment elevation, acute myocardial infarction (AMI) or bundle-branch block from 20% to 6.5%-7% [1-4]. It is the most widely used form of reperfusion therapy for AMI [5,6], but some its benefits are opposed by the hazards of hemorrhagic stroke [7-14].

History of hypertension (HTN) is a risk factor for 30 days mortality after AMI. Patients with AMI and history of severe HTN or elevated blood pressure on admission have had a higher risk of intracranial hemorrhage (ICH) [14-18] and therefore, were excluded from such therapy.

On the other hand, the possibility of performance of emergency percutaneous intervention (PCI) is not available in most emergency units and patients with a previous history of hypertension represent a higher risk group and have a worse clinical, outcome including higher cardiac death and hemorrhagic stroke rates.

In the previous studies, the rate of ICH related to thrombolytic therapy is about 0.5% [19-24]. Most information about ICH risk of thrombolytic therapy in AMI drive from the experience of patients participating in clinical trials, in which stringent enrollment criteria

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are applied before thrombolytic therapy is administered. Patients at risk for ICH generally excluded from thromboly tictrials. So the frequency and predictors of ICH reported from these studies may not be widely applicable [25, 26].

The incidence of ICH in community-based studies is higher than clinical trials [27]. The risk of ICH associated with t-PA and alteplase, especially in the presence of hypertension is higher than streptokinase [4, 28–30]. Therefore, streptokinase is the choice agent in hypertensive patients with AMI [31].

Unfortunately there is considerable controversy regarding the decision about thrombolytic therapy in hypertensive patients with AMI [32, 33]. In some studies, thrombolytic therapy in severe hypertensive patients with AMI defined as absolute or partial contraindication [4–34]. The ISIS-2 trial among patients with systolic blood pressure greater than 175mmHg, found that the mortality rate was lower in those receiving streptokinase than in control subjects [35]. This controversy often leads to inappropriate decision about thrombolytic therapy and under use of this treatment in such patients.

Our strategy included the treatment of severe hypertensive patients with streptokinase after lowering their blood pressure instead of excluding them, and evaluation of cardiac mortality and ICH rates.

Subjects and Methods

In an observational and analytical cohort study, we evaluated 293 patients with ST-segment elevation (AMI) hospitalized in cardiac emergency ward, Noor hospital, Isfahan, Iran since April 2003 to June 2004. The patients admitted to the hospital within12 hours after onset of symptoms, chest pain lasting ≥20minutes and accompanied by ECG signs of ≥0.1mv of ST-segment elevation in two or more leads were enrolled.

Exclusion criteria included active bleeding, recent trauma or major surgery, history of stroke, pregnancy, hemorrhagic retinopathy and previous treatment with streptokinase. Patients with history of hypertension or elevated blood pressure on arrival were not excluded from the study.

Clinical characteristics included history of ischemic heart disease (IHD), stroke, diabet mellitus (DM), hypertension, hyperlipedemia and smoking. Systolic and diastolic blood pressures were specified according to the first measurement recorded at presentation.

The study sample was stratified into two groups: (1) Severe HTN group; patients with systolic blood pressure ≥180mmHg or diastolic blood pressure ≥110mmHg on arrival. (2) Control group; patients with blood pressure<180/110mmHg on arrival.

All patients received streptokinase (SK) 1.5 million units over a period of one hour within 12 hours after the onset of AMI. Before SK therapy, patients with severe HTN underwent antihypertensive therapy until control of blood pressure to lessthan180/110mmHg.

Antihypertensive agents were nitroglycerin intravenous TNG (IV), TNG (IV) plus Propranolol (PO), TNG (IV) plus Propranolol (PO) plus Captopril (PO), and Nitroprosside sodium if necessary.

An ICH was defined as sudden onset of an acute focal neurological event with confirmation of intra parenchymal ICH, determined by brain CT scan.

The data were statistically analyzed by SPSS software, using Chi square test, ANOVA and Fisher Exact test. P-value less than 0.05 were considered statistically significant.

Results

Total mean age of 293 patients (73.4%men and 26.6%women) was 59.20±12.70 years. The mean age of women (63.58±12.21) was higher than women (57.61±11.64)(P value=0.000).

Demographic characteristics and prevalence of risk factors for IHD are shown in Table1. The prevalence of smoking in men and history of DM, HTN, IHD, and older age in women were significantly higher.

Heart rate, systolic and diastolic blood pressures on arrival are shown in Table2. Systolic blood pressure on arrival in women was significantly higher than men. In control group

(54.9%), blood pressure was lower than 180/110mmHg on arrival. In severe HTN group (45.1%), blood pressure was 180/110 mmHg or more and in 29 patients (29.9%), systolic blood pressure was 200mmhg or more.

Table 3 shows the prevalence of anti hypertensive drugs used for patients with severe HTN before administration of streptokinase. Mean duration time of antihypertensive therapy until control of blood pressure was 40.05±23.13 minutes (ranged from15 to150).

Table 1. The prevalence of basic and demographic characteristics of patients

	Men (215)		Women (78)		Total (293)		P-value Chi-square test
	Count	%	Count	%	Count	%	
Diabetes mellitus	47	21.9	28	35.9	75	25.6	0.015
HTN	81	37.7	61	78.2	142	48.5	< 0.001
Hyperlipidemia	56	26	26	33.3	82	28	0.22
IHD	45	20.9	30	38.5	75	25.6	0.002
Old age(>65 years old)	53	24.7	39	50	92	31.4	< 0.001
Smoking	115	53.5	6	7.7	212	41.3	< 0.001

Table 2. The statistical parameters of heart rate and blood pressure on admission

	Mean	Standard deviation	Median	Min	Max
Heart rate/minute	76.87	16.79	76	20	145
Systolic blood pressure (mmHg)	153.33	34	160	65	240
Diastolic blood pressure (mmHg)	95.07	19.72	100	40	140

Table 3. The prevalence of anti hypertensive drugs used for patients with severe HTN before administration of streptokinase

Drug	Count	%
TNG (IV)	75	57
TNG (IV)+Propranolol(PO)	43	32.6
TNG(IV)+Propranolol(PO)+ Captopril(PO)	12	9
Sodium Nitroproside(IV)	2	1.4
Total	132	100

Forty-five patients (16.4%) developed complications of AMI and thrombilysis. Most common complications were hypotension (4.1%), bradycardia (3.8%), ventricular tachycardia and fibrillation (3.1%), extracranial bleeding at different sites (2.7%), ventricular septal defect (1%) and ischemic stroke (0.7%). Only 2 patients (0.7%) complicated from ICH. The most common source of bleeding was gastrointestinal tract in almost 2% of overall population.

ICH did not observe in any patients with severe HTN and all of them (1.2%) were men (P value=0.53) and from control group (P value=0.59). The mean age of ICH cases was 69±5.66 years in comparison with 59±12.08 years in other patients without significant difference (ANOVA, P value=0.25).

In-hospital mortality duo to AMI was 4.8%, (3.7% in men and 7.7% in women) (P value=0.14). The mean age of expired and survived patients were 70.71±8.42 and 58.62±11.94 years, respectively (P value=0.001). In hospital mortality rate in severe HTN and in control groups were 3% (4patients) and 6.2% (10patients), respectively (P value=0.13).

The incidences of death and ICH in patients with or without cardiac risk factors (DM, IHD,

smoking, HTN, hyperlipidemia) have not statistically significant difference.

Discussion

High-risk patients for ICH are generally excluded from thrombolytic trials, but we decreased elevated blood pressure of patients with AMI before thrombolysis for reducing the incidence of ICH without increasing mortality rates.

The sampling method of this study was similar to community based studies, then its incidence of ICH must be near them, but we observed ICH rate (0.7%) less than similar studies: 0. 95% [27] and 1.43% [36], which selective patients were enrolled with 75 years old and more, consequently higher rate of ICH achieved [36]. Our results can be reflecting greater society because of no selection in the patients.

In our study, ICH rate in older patients and women is higher than others [37, 38], probably due to lower sample size. Some previous studies noted a strong relation between female sex and thrombolytic related ICH, but it dose not persist after controlling of other factors [38 - 40].

The history of HTN increases the incidence of stroke, ICH and death [11 - 18] but in our study, the lack of this association may partly reflects specific characteristics of thrombolytic agent. We used streptokinase "which has lower rate of ICH in hypertensive patients, compared to other agents", instead of Alteplase in many studies [28 - 30]. The incidence of total stroke and ICH would increase, as systolic blood pressure at admission increased, particularly high for systolic blood pressure of about 175mmHg or more [11-18, 41- 44]. In one study, the risk of ICH was doubled if the systolic blood pressure was≥175mmHg at study entry [15]. Our patients with AMI and very elevated blood pressure have not ICH with streptokinase.

We did not find any similar study for comparing the results. Although, this results were not statistically significant, but it should be noted that any of the 132 patients with sever HTN on admission with AMI had not symptoms of ICH after receiving streptokinase. More than that, 29 patients had systolic blood pressure of 200mmHg or more which defined as absolute contraindication of thrombolysis in some studies [34,35]. Several studies showed that immediate beta blocker therapy before thrombolysis associated with significant reduction in the ICH rate [45, 46]. We used beta-blockers that might be similar role in achieved results.

In-hospital mortality rate of patients with AMI underwent thrombolysis were between 5.7%-7% [4 , 35], but it was 4.8% in our study.

In conclusion, ICH is infrequent after thrombolysis in AMI. Administration of streptokinase after lowering elevated blood pressure with antihypertensive agents does not increase the risk of ICH or death. During thrombolysis for AMI, HTN does not increase the risk of ICH, but additional studies should assess the net clinical benefit of thrombolysis after lowering of blood pressure in these patients.

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