Original Article

Efficacy of Two Streptokinase Formulations in Acute Myocardial Infarction: A Double-Blind Randomized Clinical Trial

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Abstract

Background: *We sought to evaluate the efficacy and safety of the different trade forms of streptokinase available in our country, namely Heberkinasa (Heberbiotec, Havana, Cuba) and Streptase (Aventis Behring GmbH, Marburg, Germany).*

Methods: *We conducted a double-blind randomized clinical trial to compare the two streptokinase formulations, i.e. Heberkinasa (HBK) or Streptase (STP), in patients with acute myocardial infarction who needed thrombolysis. Thrombolysis success was evaluated angiographically and/or clinically. Clinical follow-up was done 30 days after thrombolysis.*

Results: *We randomly allocated 221 patients with a mean age of 56.9±10.8 years (males: 88.2%) to HBK (n=119) and STP (n=102) groups. Baseline clinical and demographic characteristics were similar between the two groups, and the two groups were not significantly different in terms of door-to-needle and pain-to-needle intervals. The rate of complications was not significantly different between the groups (44.1% [HBK] vs. 42% [STP]). Angiography was done for 158 (71.5 %) patients in the first 24 hours (9%) and in the first 72 hours (38.8%) after thrombolysis. Lesion morphology and lesion/patient ratio were not significantly different between the two groups (1.87[HBK] vs. 1.67[STP]). The two groups were similar with respect to angiographic patency rate (67.5% [HBK] vs. 67.6% [STP]). The study groups were also similar as regards clinical outcome and complications of both streptokinase formulations.*

Conclusion: *The present study demonstrated that Heberkinasa is as effective and as safe as a standard streptokinase, namely Streptase, in a clinical setting.*

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Introduction

Increasing affluence in the developing countries has ushered in soaring rates of coronary heart disease and death from acute myocardial infarction necessitating increases in treatment, mainly with thrombolysis and primary percutaneous coronary intervention. In fact, tackling coronary artery disease has become a strategic priority for the World Health Organization.[1] Currently, thrombolytics such as streptokinase are the leading agents for the treatment of acute myocardial infarction. Streptokinase is now produced in many countries worldwide. Furthermore, approximately

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400,000-500,000 patients receive this thrombolytic therapy per year the world over.[2] There are various streptokinase preparations in different countries.

Streptokinase is a 47-kDa protein that interacts with the protein plasminogen to form a streptokinase-plasminogen complex capable of converting other plasminogen molecules to plasmin, the well-known proteolytic enzyme, culminating in significant reduction of thrombosis formation and further clotting, because plasmin cannot only degrade fibrin but also fibrinogen. Therefore, this streptokinase-plasminogen complex with its potentials produces a systemic lytic state.[2]

In our country, Iran, different streptokinase products, including Heberkinasa and Streptase, are available. The former, manufactured by a company in Cuba, is a recombinant streptokinase which is obtained by the isolation and cloning of a streptokinase gene of a strain of Streptococcus equisimilis group C. It contains five mutated amino acids in relation to streptokinase of S. equisimilis of group C. However, these amino acid changes in the molecule do not affect the safety, purity, and potency of this product. Moreover, no difference has thus far been observed regarding tissue distribution and clearance mechanism when comparing Heberkinasa with the natural production in pharmacokinetic studies.[3]

The latter, Streptase, is a highly purified streptokinase derived from the culture filtrate of beta-hemolytic streptococci of Lancefield group C. Being produced by Aventis Behring GmbH, a marketing authorization holder in Germany, it has been frequently used as the reference formulation for measuring the potency of a number of streptokinase preparations due to its strongest fibrinolytic activity.

Interestingly, there has been a debate among our cardiologists over some significant differences between these two formulations of streptokinase in terms of potency, efficacy, and complications. In other words, Heberkinasa, streptokinase produced in Cuba, was used cautiously and under suspicion of not being as effective and as safe as a reference streptokinase such as Streptase, although there were no supporting and documented data for this claim.

Not only have previous studies been successful in confirming that Heberkinasa meets the standard criteria for being an effective anti-thrombolytic agent such as using clot lysis assay described in the British Pharmacopoeia of 1998 for the determination of potency of streptokinase in quality control laboratories,[3] but also clinical implications have frequently confirmed this claim through different investigations.

More importantly, there are several means by which the efficacy and success rate of a thrombolytic agent in bringing back the patency of vessels can be evaluated. As an example, angiography done within 90 minutes post-myocardial infarction is a very efficient way in assessing the efficacy of thrombolysis. As it is a time-consuming and money-demanding procedure that sometimes can be threatening to the patient's unstable hemodynamic status, it would not be feasible for all patients. Nevertheless, there are some other invaluable criteria such as noticeable ST resolution in leads which have ST-segment elevation, or abrupt cessation or moderate significant diminish in the chest pain, and the different pattern of enzyme rise that are specific for myocardial infarction and myocardial tissue reperfusion like creatine kinase MB (CKMB), which can be addressed as a sign of improvement in the tissue reperfusion and success of thrombolysis.[4-9]

In this randomized double-blind clinical trial, we evaluated the efficacy and safety of these two formulations.

Methods

This survey is an ongoing randomized double-blind clinical trial that commenced collecting participants in 2004 in Tehran Heart Center. The data in this article, however, have a limited time interval, namely between December 2004 and January 2006. The project was confirmed by the Ethics Committee of Tehran Heart Center Research Bureau, according to the Declaration of Helsinki. All the streptokinases were safe to use. In this study, we did not require informed consent of the patients inasmuch as we sought to decrease the probable potential stress and the acuity of the clinical situation.

The study group was comprised of patients who were between 18 and 75 years of age and met the characteristics of acute myocardial infarction for which thrombolysis was indicated. These characteristics were: chest discomfort within the last 12 hours in addition to one of the following: ST segment elevation more than 2 mm in two or more contiguous precordial leads, ST segment elevation more than 1 mm in two or more contiguous limb leads, posterior infarction (dominant R waves and ST depression in V1-V3), and finally new onset left bundle branch block.

Patients in whom thrombolysis was contraindicated were excluded from our study. These contraindications were active bleeding and a history of stroke, which was defined with creatinine blood level more than 2 mg/d, systolic blood pressure more than 200 mmHg, diastolic blood pressure more than 110 mmHg, being on warfarin, and pregnancy.

After the inclusion of patients, a study coordinator used a computer-driven random number algorithm to assign each patient to receive either Heberkinasa (n=119) or Streptase (n=102). All streptokinases were delivered to the observer in syringes coded by a randomizer. The staff of the emergency department was unaware of coding. The sample size was estimated to be 102 patients in group 1 (Streptase) and 119 patients in group 2 (Heberkinasa).

The observer took the patients' data using a special questionnaire. Demographic, clinical, procedure conduct, hemodynamic, and angiographic data as well as clinical

adverse events or side effects were all recorded by the observer and angiographers and were refined by the study coordinator using a standard data collection form. The patients were infused with streptokinase in accordance with a well-defined protocol ordered by a cardiologist.

According to our protocol, our ideal plan was to perform angiography within 72 hours for all the patients, and the patency rate according to thrombolysis in myocardial infarction (TIMI) was computed. TIMI 3 flow was regarded as patent arteries.

Systemic blood pressure was monitored, and any change in hemodynamic stability was recorded during streptokinase infusion.

Electrocardiogram (ECG) at baseline and three hours after starting thrombolysis was obtained. In ECG, the significant ST resolution that could be addressed as a sign of successful treatment was defined as at least a 50% decrease in the sum of ST segment elevation on concordant leads and was assessed in both groups. Blood samples were collected at baseline, 12, and 24 hours within starting infusion to monitor the serum levels of the CKMB isoenzyme level, total CK, and troponin.

The patients were followed closely for adverse events during and 24 hours after the thrombolysis. The side effects were categorized according to their severity and were defined as follows:

1) Severe side effects: life-threatening conditions, including intracranial hemorrhages, anaphylaxis, or compromised hemodynamic. In this case, streptokinase was discontinued and could not been reordered. 2) Moderate side effects: streptokinase was discontinued, but it could be restarted on the physician's order. 3) Mild side effects: minor complaints. The medication was continued with no intervention or only treated conservatively. Within 48 hours, coronary angiography was performed with standard technique and the TIMI flow was documented. The patency rate according to TIMI was computed. TIMI 3 flow was regarded as patent arteries. The catheterization laboratory staff was blinded to the categorization of the patients.

All the patients were followed for 30 days by revisiting or calling to assess 30 days' mortality or reinfarction. The normally distributed continuous data were presented as mean±SD and analyzed using the Student's t-test, and the paired t-test was applied to compare before and after intervention levels of the favorable parameters in each group. The non-parametric data (analyzed by Kolmogorov-Smirnov and Shapiro-Wilk tests) were reported as the median (25%, 75%) for the quantitative variables and were analyzed using the Mann-Whitney U-test and Wilcoxon signed ranks tests as appropriate. For the categorical data, the chi-square test was utilized if applicable. All the statistical analyses were performed using Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA). Probability values of $P< 0.05$ were considered statistically significant.

Results

The mean age of the patients was 56.93±10 years, and men accounted for 88.2% of the study population. The average of body mass index was 26.61±3.65. The patients' characteristics are summarized in Table 1. The mean pain-to-needle time and door-to-needle time was 262.7±220 minutes (ranged from 0 to 1500 min) and 102.3±62.2 minutes (ranged from 0 to 370 min), respectively.

Chest pain did not subside in 48 (21.7%) patients, while in 6 patients streptokinase infusion was discontinued due to life-threatening side effects. From 139 patients whose pain was subsided, 66 (72 %) patients had ST segment resolution. The clinical success rate and frequency of ST resolution were not significantly different between the two groups. Approximately, half of the streptokinase-treated patients either with Streptase or Heberkinasa were reported having ST segment resolution (Table 2).

Angiography was done for 158 (71.5%) patients: within the first 24 hours for 20 (9%) patients and within 72 hours for 88 (39.8%) patients. The rest of them had angiography after 72 hours. The angiographic patency rate was 69.3% for Heberkinasa and 74.2% for Striptease (P=0.448). The success rate of streptokinase treatment was also similar between the groups (67.7% for Streptase and 67.5% for Heberkinasa; P=0.23). The clinical success rate, which was defined as improvement in the clinical presentation of myocardial infarction in the patients, was 64.5% for Heberkinasa and 68% for Streptase (P=0.583).

Overall, 95 (43%) patients developed complications within the first 24 hours, which were hemorrhage in 4 (1.8%), allergic reactions in 34 (15.4%), hyperthermia in 4 (1.8%), hypotension in 46 (20.8%), and arrhythmia in 27 (12.2%). Some uncommon complications only with Streptase were found, namely hypertension in 3 patients and respiratory distress and cerebrovascular accident, both occurring only once. During hospitalization, 12 (5.4%) patients died; only one patient died due to streptokinase side effects and 11 patients died from other cardiac causes. During follow-up, we documented 4 cases of reinfarction (2 cases in each group) and 3 cases of cardiac death (2 cases in the Streptase group and one in the Heberkinasa group) among the study population up. In-hospital and short clinical outcomes were not significantly different between the two streptokinase-formulation groups (Table 2).

Discussion

Mortality reduction in acute myocardial infarction is dependent upon the efficacy of thrombolytic regimens in terms of re-establishing a normal infarct-related artery flow. Successful reperfusion of initially occluded infarct-related coronary arteries is the result of complex interplay

among clinical, hemodynamic, mechanical, and biochemical factors. Clinical variables that determine the efficacy of thrombolytic therapy, however, have been poorly described. The Global Utilization of Streptokinase and t-PA for occludedcoronary arteries (GUSTO-I) angiography study of fered the unique opportunity to determine the clinical determinants of infarct-related artery patency.

Table 1. Patients' characteristics*

	Streptase (n=102)	Heberkinasa (n=119)	P value
Age (y)	56.9±11.1	57±10.6	0.944
Male	92 (90.2)	103 (86.6)	0.402
Positive family history	15 (16.9)	15 (13.2)	0.462
Hypertension	38 (40)	33 (28.2)	0.070
Systolic blood pressure (mmHg)	142.2±17.1	126.5±20.6	0.007
Diastolic blood pressure (mmHg)	91.5±16.3	78.4±23.2	0.034
Diabetes mellitus	28 (30.1)	27 (23.3)	0.265
Cigarette Smoking	51 (55.4)	50 (42.4)	0.060
Dyslipidemia	43 (44.8)	54 (47)	0.753
MI location			
Posterior	0	2 (1.8)	
Inferior	45 (47.4)	51 (45.5)	
Anterior	28 (29.5)	28 (25)	
Anteroseptal	15 (15.8)	23 (20.5)	
Lateral	2 (2.1)	5 (4.5)	
RV	5 (5.3)	3 (2.7)	0.483
Unknown	7 (6.9)	7 (5.9)	
LVEF (%)	46.5±12	46.4±12.4	0.958
CKMB (IU/l)			
Baseline	30 (22, 50)	33 (24.7, 67.5)	0.370
At 12h	117 (57.5, 186.5)	101.5 (52.7, 171.6)	0.489
At 24h	74 (46, 137.3)	74 (37.5, 102.6)	0.303
Pain-to-needle time (min)	252.2±201.4	270.9±235.8	0.592
Door-to-needle time (min)	105.7±68.9	99.5±56.3	0.475
Coronary angiography not performed	33 (32.3)	30 (25.2)	0.243
Stenosis >50%			
LAD			
Proximal	54 (78.3)	67 (75.3)	0.661
Middle	46 (66.7)	51 (57.3)	0.231
Distal	22 (31.9)	19 (21.3)	0.134
LCx			
Proximal	34 (49.3)	34 (38.2)	0.257
Middle	0	3 (3.4)	0.163
Distal	31 (44.9)	25 (28.1)	0.028
RCA			
Proximal	41 (59.4)	53 (59.6)	0.987
Middle	30 (43.5)	44 (49.4)	0.457
Distal	18 (26.1)	25 (28.1)	0.779

*Data are presented as the number of patients (related percentage in parenthesis) or mean±SD

MI, Myocardial infarction; RV, Right ventricle; LVEF, Left ventricular ejection fraction; CKMB, Creatine kinase MB; LAD, Left anterior descending; LCx, Left circumflex; RCA, Right coronary artery

Table 2. In-hospital and short-term clinical outcomes and complication of the patients with acute MI

	Streptase	Heberkinasa	P value
Systolic blood pressure (mmHg)	86.1±14.8	81.4±18.9	0.370
Diastolic blood pressure (mmHg)	59.7±13	54.1±15.1	0.194
Clinical response (n=193)			
Sustained pain	28 (32.2)	20 (18.9)	
Pain improvement	56 (64.4)	83 (78.3)	
Incomplete Thrombolysis therapy	3 (3.4)	3 (2.8)	0.093
ST resolution	48 (54.5)	53 (49.5)	0.486
Patency rate of Thrombolysis (n=158)			
TIMI 3 flow	48 (69.3)	66 (74.2)	0.448
Clinical	(67.7)	(67.5)	0.230
	66 (64.5)	81 (68)	0.583
Complications	45 (44.1)	50 (42)	0.753
Hypotension	20 (19.6)	26 (21.8)	0.687
Allergic reactions	14 (13.7)	20 (16.8)	0.524
Arrhythmia	13 (12.7)	14 (11.8)	0.838
Bleeding	3 (2.9)	1 (0.8)	0.238
Fever and chill	1 (1)	3 (2.5)	0.404
Re-infarction	2 (2.9)	2 (2.5)	0.854
In-hospital mortality	6 (6)	6 (5)	0.744
Total mortality	7 (6.9)	8 (6.7)	0.953

MI, myocardial infarction; RV, right ventricle; LVEF, left ventricular ejection fraction; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery

Streptokinase has been produced extensively by several medication-producing companies, and several research projects have been conducted to evaluate the efficacy of these streptokinases in order to standardize them as safe and effective thrombolytics. In a double-blind multi-centric and parallel study done in India, researchers compared the efficacy and safety of indigenous recombinant streptokinase (Shankinase, r-SK) and natural streptokinase in 150 patients. They reported that in establishing reperfusion, which was assessed by non-invasive parameters such as myocardial creatinine kinase and ST-segment resolution, recombinant streptokinase was as efficacious as natural streptokinase.[10] Furthermore, in a clinical trial in China, scientists found out that the China-made recombinant streptokinase was a safe and effective thrombolytic agent.[11] In another multi-center, randomized, comparative study of recombinant vs. natural streptokinase in acute myocardial infarction carried out in Cuba in 1999, the researchers randomized 224 patients and investigated fibrinogen levels, Fibrine degradation products (FDP), and thrombin time in all the patients. Coronary angiography was also performed after 5-10 days in patients who had given consent, and the rate of side effects was evaluated in both groups of patients. They found out the recombinant streptokinase behaved similarly to natural streptokinase in terms of coronary patency assessed by angiography and the changes induced on fibrinogen, FDP, and thrombin time. They concluded that recombinant streptokinase met the criteria of being a potent and effective

thrombolytics.[12]

In May 2005, the researchers reported that there was enough clinical experience throughout Cuba to support Heberkinasa as a safe streptokinase. First, coronary patency (TIMI 3) was achieved in 14/20 (70%) acute myocardial infarction patients after intracoronary administration of this product. Then clinical studies were performed in acute myocardial infarction patients treated with intravenous $1.5x10^6$ IU of recombinant streptokinase. A randomized trial in 224 patients compared it to the same reference product used by Hermentin et al. (natural streptokinase: Streptase).[12] Similar results were obtained with respect to coronary patency, changes in hemostasis, and safety profile. Additionally, anti-streptokinase antibody titres and their anti-streptokinase neutralizing activities in serum were not only comparable between both groups, but also cross-reacting, which shows that the small differences in structure do not seem to have clinical or immunological repercussions. A recent study with this recombinant streptokinase in an albumin-free formulation suggested that its intravenous administration was a safe and appropriate therapy to obtain early (90 min) coronary patency in patients with acute myocardial infarction.[13] Moreover, this product had already been successfully used in other applications of thrombolysis such as heart valve prosthesis thrombosis.[14] Therefore, they concluded that Heberkinase was clinically useful and safe.[15]

Furthermore, a national extension study in 2923 acute myocardial infarction patients from 52 hospitals throughout Cuba evaluated Heberkinasa in clinical practice. A 28.3% relative and 4% absolute mortality reduction was found when compared with a survey made before recombinant streptokinase treatment was introduced. Intracranial hemorrhage was only reported in 9 (0.3%) patients.[16]

More importantly, it is worth mentioning here a study conducted to compare the in vitro characteristics of 16 different streptokinase preparations (among which 3 were recombinant).The amino acid sequences of these three recombinant products tested (recombinant streptokinase from China, Heberkinasa, and STPase) were deviated from the published S. pyogenes streptokinase sequence. Furthermore, the behavior of the recombinant streptokinase proteins in polyacrylamide gel electrophoresis (PAGE) differed considerably from that of the purified native protein. Two of the recombinant products [i.e. Heberkinasa and STPase (two batches)] exhibited very low biological activity [37.2% (Heberkinasa) respectively 20.8% and 23.3% (STPase, two batches) the label claim], and the activity of the third recombinant product (recombinant streptokinase from China) resisted determination. Therefore, the observed differences in recombinant protein sequence and behavior in PAGE were correlated with alterations in the activity of the drug.[17]

In the present study, the rising ambiguity about the potency of a type of streptokinase preparation namely Heberkinasa prompted us to compare this formulation with a reference streptokinase such as Streptase in several ways. We mainly focused our analysis of their discrepancy on the results of angiographic findings performed most frequently within 72 hours. However, we did not overlook other criteria, albeit less strong, of successful thrombolysis such as ST-segment elevation, the degree of resolution, and subsiding of chest pain. Our data were consistent with those in previous articles in terms of the efficacy and rate of complications of meeting the criteria of a potent streptokinase. With regard to the angiographic patency rate of TIMI 3 flow, Heberkinasa was obviously as efficient as Streptase. In addition, the frequency of the resolution of elevated ST-segment in the patients who had received Heberkinasa was very close to this number in the patients who had been given Streptase. In fact, several studies have demonstrated the standard efficacy of recombinant streptokinase using laboratory assays such as euglobulin lysis test, plasminogen activation assay, and clot lysis assay plus clinical assessment by means of angiography and ST-segment resolution. Not only were our clinical findings successful in confirming these surveys, but also we showed that the rate of complications of this formulation does not exceed its European counterpart.

Conclusion

Streptokinase is the most widely used thrombolytic agent in Iran, and different trademark formulations of this product that may vary in terms of cost-effectiveness and rate of side effects are available on the market. We evaluated a frequently used streptokinase in our hospitals throughout Iran, namely Heberkinasa, to confirm its effectiveness as a standard thrombolytic formulation. The results of this study were consistent with those of other research programs in demonstrating the standard efficacy of this formulation.

Acknowledgments

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