Original Article

Fibrinolytic Therapy With Streptokinase vs Tenecteplase for Patients With ST-Elevation MI Not Amenable to Primary PCI

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ABSTRACT

Background: Although primary percutaneous intervention (PCI) is the preferred reperfusion strategy in patients with STEMI, not all patients are good candidates for PCI—mainly because of a delay in requesting medical care and longer 1st medical contact to balloon time. The objective of this study was to compare the efficacy and side effects of 2 known fibrinolytic therapies, streptokinase (SK) and tenecteplase (TNK).

Methods: This descriptive, analytic cross-sectional study recruited patients not amenable to primary PCI. From a total of 142 patients recruited, 88 patients received SK and the other 54 patients received TNK. Thereafter, the efficacy of the agents, their side effects, territory of the culprit vessel, minor and major bleeding, relation to diabetes mellitus, and mortality in the index hospitalization were compared.

Results: Patients who were administered SK showed a 2.09-mm ST elevation after the drug administration as opposed to 1.95 mm in the TNK group (P=0.340). Minor bleeding was reported in 22.7% of the SK group and 24.1% in the TNK group. Major bleeding in the SK and TNK groups was 11.1% and 5.7%, respectively, with no significant difference. In the patients' index admission, death due to STEMI occurred in 10 (11.4%) patients in the SK group and 8 (14%) patients in the TNK group; the difference did not constitute statistical significance.

Conclusions: The results of our study showed that SK and TNK were similar in terms of major complications, mortality rates, and efficacy. Thus, if TNK is not available, SK would be a reasonable choice. ***(Iranian Heart Journal 2017; 18(2):43-49)***

Keywords: ST elevation MI, Primary PCI, Fibrinolytic therapy, Streptokinase, Tenecteplase

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There is no debate about primary percutaneous coronary intervention (PCI) as the preferred reperfusion strategy in patients with ST-elevation myocardial infarction (STEMI). Nonetheless, in some situations, primary PCI cannot be performed early enough and there is, as such, an urgent need for fibrinolytic therapy as an alternative to prevent myocardial damage. [1, 2] Even in developed countries, not all referral STEMI centers are capable of primary PCI 24/7, and this capability varies by region prominently. In the United States, it has been reported that 50% of patients with STEMI initially present to centers that are not primary PCI-capable. Therefore, thinking about fibrinolytic therapy as our last resort is a reasonable decision in many centers. [3, 4, 5] As the door-to-balloon time lengthens, the superiority of primary PCI over fibrinolytic therapy lessens and its mortality benefit diminishes. [6, 7] Fibrinolytic agents were introduced by their leading agent streptokinase (SK) in about one hundred years ago, and newer agents have been developed to decrease the side effects and improve the benefits of this fibrinolytic agent ever since. Nowadays, 4 known agents are available across the globe and they are compared in terms of fibrin specificity, efficacy, side effects, route of administration, and complications. [8, 9, 10]

The present study was conducted to compare 2 available fibrinolytic agents in our health system, SK and tenecteplase (TNK), in terms of efficacy, complications, and mortality rates in Iranian patients with STEMI.

METHODS

This descriptive, analytic cross-sectional study was conducted in Ekbatan Hospital, Hamedan, Iran, in 2013. All STEMI patients who were not a good candidate for primary PCI were included. The patients received SK or TNK according to both the availability of the drugs and cost issues based on the patients' preferences. The study population was meticulously assessed in accordance with the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) on the reperfusion therapy of patients presenting with STEMI. The subjects of the 2 groups were matched based on their door-to-needle time, age, sex, and type of MI. Patients with a history of MI, PCI, coronary artery bypass graft surgery, left ventricular dysfunction, or significant valvular heart disease were excluded from the study. Before the administration of the fibrinolytic therapy, all relative and absolute contradictions were also assessed and patients with any of these contradictions were excluded from the study (Table 1). [1] Totally, 142 patients were enrolled in our study. Eighty-eight patients were administered SK and 54 patients received TNK. The patients were assessed in terms of their demographic features, major bleeding (intracerebral hemorrhage and gastrointestinal bleeding), minor bleeding (epistaxis, hematuria, and ecchymosis), left ventricular ejection fraction after fibrinolytic therapy, myocardial territory involved according to ECG, diabetes mellitus as a major factor of the efficacy of the drug, ST resolution after therapy, and mortality at the patients' index admission. Diabetes mellitus was defined as the patients' past history of fasting blood sugar more than 126 mg/dL or HgA1c more than 6.5 in their lab data obtained during their hospital course. All the patients also were treated with ASA and clopidogrel based on the guidelines of the ACC/AHA. A priori 2-tailed level of significance was set at 0.05.

Table 1. Absolute and relative contraindications of systemic fibrinolytic therapy

Absolute contraindications
Any previous intracranial hemorrhage
Known structural cerebrovascular lesion
Known malignant intracranial neoplasm
Ischemic stroke within the past 3 months (except for acute stroke within 3 hours)
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 months
Relative contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (systolic pressure >180 mm Hg or diastolic pressure >110 mm Hg)
History of prior ischemic stroke >3 months previously, dementia, or known intracranial pathology not covered in absolute contraindications
Traumatic or prolonged CPR (>10 min) or major surgery (within past 3 wk)
Recent internal bleeding (within past 2 to 4 wk)
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Current use of anticoagulants agents: the higher the International normalized Ratio, the higher the risk for bleeding
Previous exposure (>5 days previously) or previous allergic reaction to streptokinase or anistreplase

RESULTS

From all the 142 patients enrolled in the study, 88 (62%) were treated with SK and 54 (38%) with TNK. The mean age of the patients in the study was 52.33 (SD=7.25): 52.07 (SD=7.99) in the SK group and 52.75 (SD=7.26) in the TNK group; the difference between the 2 groups was not statistically significant (*P*=0.593). The door-to-needle time was 42 minutes in the SK group and 45 minutes in the TNK group. Eighty (56%) patients were men and 62 (43.7%) patients were women. There were 50 (56.8%) men in the SK group and 55.6% of the TNK group patients were also men (*P*=0.883). ST resolution in the 2 groups after fibrinolytic therapy was 0.81 mm in the SK group and 1.02 mm in the TNK group (*P*=0.340), which showed no significant difference between the 2 study groups. Based on the patients' past medical history and their laboratory data obtained at their hospitalization, 37 (42%) patients in the SK group and 18 (33%) patients in the TNK group had diabetes mellitus (*P*=0.301).

Major bleeding (intracerebral hemorrhage and gastrointestinal bleeding) was reported in 5 (5.7%) patients in the SK group and in 6 (11.1%) patients in the TNK group (*P*=0.392); the difference failed to constitute statistical significance. Minor bleeding was detected in 20 (22.7%) patients of the SK group and in 13 (24.1%) patients of the TNK group (*P*=0.332); the difference between the 2 groups was not statistically significant. Myocardial territories involved in the 2 groups were also compared. The most prevalent territory was inferior STEMI (Table 2). The patients were followed up through their hospital course and 10 (11.4%) patients in the SK group and 8 (14.8%) patients in the TNK group died of STEMI and its complications (*P*=0.854), with no significant difference between the 2 groups.

Table 2. Patients' myocardial injury based on ECG changes

Myocardial Injury	SK	TNK	Total	*P*
Anterior	16 (18.2%)	7 (13%)	23 (16.2%)	0.288
Inferior	26 (29.5%)	18 (33.3%)	44 (31%)	
Lateral	18 (20.5%)	10 (18.5%)	28 (19.7%)	
Extensive	14 (15.9%)	15 (27.8%)	29 (20.4%)	
RV MI	14 (15.9%)	4 (7.4%)	18 (12.7%)	

SK, Streptokinase; TNK, Tenecteplase; RV, Right ventricle; MI, Myocardial infarction

DISCUSSION

The major pathology of the occlusion of the coronary artery is plaque rupture, defined initially by Carl Weigert and William Osler. [12] Up to the mid-20th century, STEMI management was totally medical and no invasive method existed to reperfuse the culprit vessel. Fibrinolytic activity with SK was introduced by Tillett in 1933. [13] It took 30 years for physicians to fully appreciate its application in cardiology. [14] Since then, a large number of trials have demonstrated its usage in the reperfusion era and the medical community now believes in its applicability and efficacy in decreasing myocardial injury in patients with STEMI. [14, 15] As SK had some untoward side effects such as allergic reaction and shivering at the time of its administration, hypotension, and rarely anaphylactic reactions, the next generation of fibrinolytic therapy was developed with fewer side effects and easier routes of administration. [16-20] Many large trials such as the GISSI-1 trial and the ISIS-2 trial have shown the efficacy of SK, which may explain the widespread use of SK around the world. [21, 22] TNK, which is genetically engineered and developed by multiple point mutations of the recombinant tissue plasminogen activator, [23] has a longer half-life and is administered as a single weight-based intravenous bolus. Indeed, TNK is as useful as other fibrinolytic agents based on the results of the TIMI 10A trial, ASSENT 1 trial, and ASSENT 2 trial. [24-26]

Given the dearth of data in the existing literature on the comparison between SK and TNK, we sought to conduct the present study to address this issue. What should also be borne in mind is that in many parts of the world SK is the most available agent and TNK is the preferred agent with higher costs and less availability. [27] In our study, both of the SK and TNK groups were matched in terms of mean age, sex, door-to-needle time, ST elevation before fibrinolytic therapy (2.95 mm in the SK group and 2.97 mm in the TNK [*P*=0.322]), and type of STEMI according to ECG changes. Vikas et al [29] concluded in their study that other than the agent selected for fibrinolytic therapy, other factor such as door-to-needle time, myocardial territory involved, and presence of microvascular dysfunction might contribute to the final outcome. Taha et al [30] added other reasons for fibrinolytic failure such as misdiagnosis of STEMI, late presentation of patients, female gender, and inferior STEMI. Accordingly, in the present study, we tried to level these confounding factors in the 2 groups. Although the best door-to-needle time in the GRACE and NCDR registries were less than what we achieved in our study, this lag might have been due to the delay in the diagnosis of the patients and the preparation of the thrombolytic therapy. [31-34] Up to now, only the GUSTO trial has demonstrated the mortality benefit of newer agents in comparison to SK and many other trials have reported the same mortality benefit, exactly concordant with our findings. [35-39]

In our study, major bleeding was similar between the 2 groups. Many other studies have considered age a major determining feature in the assessment of bleeding. Other comparisons of SK with newer agents have shown less non-cerebral bleeding in the newer

agents. The mean age of our patients was 57 years old and there was no difference between the 2 groups in this regard. [28, 36, 37] Other considerable factors for bleeding are history of bleeding, bleeding tendency, history of treatment with anticoagulants, and past history of vascular abnormality. [40, 41]

What we should consider in the reperfusion era is that not all patients presenting to the emergency department fulfill the primary PCI category. Undoubtedly, we still need fibrinolytic therapy as our 2nd method of choice for STEMI patients. Finally, every cardiologist should be cognizant of the side effects of fibrinolytic therapy at the time of administration. [1, 28]

In conclusion, we can regard both SK and TNK as effective fibrinolytic agents. In patients with a risk factor for bleeding and provided that the cost is not too serious a consideration, TNK is the preferred agent; otherwise, in other conditions, SK is a reasonable choice.

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