*Original Article*

# Accelerated Streptokinase versus Standard Dose Streptokinase in ST-Elevation Myocardial Infarction in Nakornping Hospital

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***Background***: ST-segment elevation myocardial infarction (STEMI) patients who do not have primary percutaneous coronary intervention (PPCI) as an immediate option, should have fibrinolysis initiated expeditiously. A standard dose of streptokinase (SK) is 1.5 MU infusion at 30 to 60 minutes, as recommend by ESC and ACCF/AHA. An accelerated dose of SK is 0.75 MU over 10 minutes with a repeated dose at 50 minutes if there is an absence of electrocardiography reperfusion, It has been demonstrated that an accelerated dose of SK was associated with higher rates of coronary reperfusion than the standard dose of SK in patients with acute STEMI.

***Objective***: The present study sought to compare the efficacy and safety between the standard dose SK and the accelerated SK regimens.

***Materials and Methods***: The present research was a retrospective cohort study. The authors reviewed the medical record of patients admitted to the cardiac care unit in Nakornping Hospital due to acute STEMI between January 2017 and December 2018. The efficacy calculation was the coronary perfusion rate at 90 minutes after starting SK infusion. The safety calculation was the incidence of thrombolysis in myocardial infarction (TIMI) major bleeding and the in-hospital mortality.

***Results***: There were 423 STEMI patients in CCU of Nakornping Hospital, 211 patients were treated with SK infusion, but 87 patients from the 211 patients were excluded due to missing data. Therefore, 124 patients were included in the present study. Baseline characteristics were comparable between the two groups. The rate of coronary reperfusion was numerically higher in the accelerated SK dose (60.2%) than in the standard dose (57.1%), but this difference did not reach statistical significance (p=0.81). No TIMI major bleeding occurred in both groups. There was no statistically significant difference in the hospital mortality rates (accelerated SK dose 3.9% versus standard dose 9.5%, p=0.27).

***Conclusion***: The efficacy and safety of the accelerated SK dose was comparable with the standard dose SK in STEMI patients in Nakornping Hospital.

***Keywords***: Acute myocardial infarction, Accelerated streptokinase

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Acute coronary syndrome (ACS) is one of the leading causes of death in Thailand. From the European Society of Cardiology (ESC)[1], the American College of Cardiology Foundation (ACCF), and the American Heart Association (AHA)[2], the guideline for the management of ST-elevation myocardial infarction (STEMI) recommend the primary percutaneous coronary intervention (PPCI), which is the preferred reperfusion strategy in patients with STEMI within 12 hours of symptom onset, provided it could be performed expeditiously (120

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minutes from STEMI diagnosis) by an experienced team. However, in some circumstance, PPCI is not an immediate option and fibrinolysis could be initiated expeditiously. Pre-hospital management of STEMI patients is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make PPCI available to as many patients as possible.

Cardiac networks to manage STEMI patients in Chiang Mai were set by geographic area. Nakornping Hospital and Maharaj Nakorn Chiang Mai Hospital were the only two PCI center hospitals. The other 23 government hospitals were non-PCI hospital. The hospitals that were in the northern region and some area of central region of Chiang Mai were the responsibility of Nakornping Hospital, and the others were the responsibility of Maharaj Nakorn Chiang Mai Hospital. About 50% of the non-PCI center could refer to PCI hospital within 120 minutes.

From the Thai Registry of ACS study[3], 55% had STEMI, thrombolysis was given to 42.6%, and PPCI was performed in 24.7%. Consequently, fibrinolysis is still a main reperfusion strategy for STEMI patients in Thailand. Thus, the efficacy and safety of streptokinase (SK), which is the main fibrinolysis used in Thailand, play a major role on the morbidity and mortality in STEMI patients.

A Romanian (ASK-ROMANIA) study[4] compared the efficacy and safety of four SK regimens in STEMI patients. The regimens were 1.5 million units (MU) over 60 minutes, 1.5 MU over 30 minutes, 1.5 MU over 20 minutes, and 0.75 MU over 10 minutes. They were repeated after 50 minutes if no electrocardiographic (ECG) criteria of reperfusion was met. It was found that the coronary reperfusion rates according to the non-invasive criteria (clinically, electrocardiographically, and physiologically) were higher in the 0.75 MU group than the standard dose of 1.5 MU over 60 minutes (72.85% versus 64.03%, p=0.006). Notably, 83.03% in the 0.7 MU group received only one dose of SK.

The present study was a retrospective cohort study to compare the efficacy and safety of accelerated SK dose compared with the standard dose of SK in STEMI patients in Nakornping Hospital.

## Materials and Methods

### *Patient population*

The present study included acute STEMI patients admitted to the cardiac care unit at Nakornping Hospital between January 2017 and December 2018. All patients were 18 or older. Patients who had contraindication to SK according to the ESC guideline, and missing ECG data were excluded.

### *Streptokinase regimen*

Accelerated SK dose regimen defined as 0.75 MU over 10 minutes and followed after 50 minutes by second infusion of 0.75 MU over 10 minutes if there were no ECG signs of coronary reperfusion. The standard dose regimen was defined as 1.5 MU over 60 minutes infused intravenously.

### *Assessment of coronary reperfusion*

Coronary reperfusion was defined by clinical chest pain and ECG criteria. The clinical chest pain was evaluated at before and at 90 minutes from the time starting SK infusion (time 0), intensity of chest pain using a subjective scale ranging from 0 (no pain) to 10 (unbearable pain) and coronary reperfusion was defined as improvement or sudden improvement of the pain. Based on the previous study[5], the reduction in ST segment of more than 25% within three hours from the time starting SK infusion indicate either a patent infarct artery or preserved the left ventricular function. A standard 12-lead ECG (with or without V3R, V4R, V7-9) before and at 90 minutes from the time starting SK infusion (time 0) were analyzed. The percentage of ST segment resolution defined as the percentage changes of the sum deviation (sum of ST segment elevation and depression) pre- and post-SK infusion 90 minutes. Thereafter, the status of ST segment resolution was categorized in three groups, complete (more than 70%), partial (30% to 70%), and no resolution (less than 30%).

### *Clinical endpoint and definition*

The efficacy was the coronary perfusion rate at 90 minutes from starting SK infusion (time 0). The safety was the incidence of thrombolytic in myocardial infarction (TIMI)[6] major bleeding, and in-hospital mortality. Bleeding was defined by TIMI bleeding criteria. Major bleeding was defined as any intracerebral hemorrhage (ICH) or bleeding that directly resulted in death within seven days or clinically overt signs of hemorrhage associated with drop in hemoglobin 5 g per dL or more occurring during admission. Minor bleeding was defined as clinically overt (including imaging), resulting in hemoglobin drop of 3 to less than 5 g per dL occurring during admission. Minimal bleeding was defined as any overt bleeding event that did not meet the criteria of major or minor bleeding. Mortality rates were assessed before discharge. Against advice

**Table 1.** Demographic characteristics and clinical status of patients

| | Accelerated half dose 0.75 MU/10 minutes (n=103) n (%) | Standard dose 1.5 MU/60 minutes (n=21) n (%) | p-value |
|---|---|---|---|
| Age (year); mean±SD | 61.89±11.05 | 60.24±9.78 | 0.84 |
| Less than or equal 30 | 1 (0.80) | 0 (0.0) | |
| 31 to 59 | 42 (33.90) | 9 (7.30) | |
| More than or equal 60 | 60 (48.40) | 12 (9.70) | |
| Sex | | | 0.45 |
| Male | 69 (55.65) | 12 (9.68) | |
| Female | 34 (27.42) | 9 (7.25) | |
| Body weight (kg); mean±SD | 60.30±13.34 | 62.53±13.80 | 0.52 |
| Underlying disease | | | |
| DM | 40 (32.25) | 6 (4.83) | 0.46 |
| HT | 58 (46.77) | 11 (8.87) | 0.81 |
| DLP | 95 (76.61) | 18 (14.52) | 0.47 |
| Smoking | 51 (41.13) | 11 (8.87) | 0.51 |
| CKD | 22 (17.74) | 4 (3.23) | 0.53 |
| EF; mean±SD | 53.92±12.40 | 52.51±14.57 | 0.69 |
| Area of infarction | | | |
| LAD | 30 (24.19) | 6 (4.84) | |
| RCA | 71 (57.26) | 15 (12.09) | |
| LCX | 2 (1.61) | 0 (0.0) | |
| Killip class I | 80 (81.5) | 17 (80.9) | 0.19 |
| Onset to SK (minute); median (IQR 1st, 3rd) | 170 (27, 579) | 135 (55, 644) | 0.76 |

DM=diabetes mellitus; HT=hypertension; DLP=dyslipidemia; CKD=chronic kidney disease; EF=ejection fraction; LAD=left anterior descending artery; RCA=right coronary artery; LCX=left circumflex artery; SK=streptokinase; SD=standard deviation; IQR=interquartile range

discharge status was presumed dead. The authors also explored the complication related to the SK regimens. Hypotension from SK infusion in the present study was defined as a decrease in systolic blood pressure (SBP) less than 90 mmHg after SK infusion, or decreased of SBP 20 mmHg or more if SBP prior to SK infusion was less than 90 mmHg.

### *Statistical analysis*

Categorical variables were reported as number (%). All continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range first to third) as appropriated. Group comparisons were analyzed using Student's t-test or Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. Results were considered to be statistically significant if the p-value was less than 0.05. All analyses were conducted using the SPSS statistics, version 16.0 (SPSS Inc., Chicago, Ill, USA).

## Results

### *Baseline characteristics*

Between January 2017 and December 2018, there were 423 patients with acute STEMI admitted to cardiac care unit at Nakornping Hospital. Of the 423 patients, 211 patients (49.9%) were treated with SK infusion; however, 87 of 211 patients (41.2%) were excluded from the current study due to missing ECG data. Finally, 124 patients were included in the analyses. Demographic characteristics and clinical status of patients in the present study are detailed in Table 1. There were no significant differences in patient's demographic data, onset to treatment interval, area of myocardial infarction, ejection fraction, and Killip classification. No patient in accelerated SK group received a second 0.75 MU.

### *Rate of coronary reperfusion*

The coronary perfusion rates were comparable between the two groups. The proportion of reperfusion

**Table 2.** Efficacy, safety, and adverse events between standard dose and accelerated half dose regimens

| | Accelerated SK dose 0.75 MU/10 minutes (n=103) n (%) | Standard dose 1.5 MU/60 minutes (n=21) n (%) | p-value |
|---|---|---|---|
| Successful reperfusion | | | 0.81 |
| Complete reperfusion | 44 (42.72) | 10 (47.62) | |
| Partial reperfusion | 18 (17.48) | 2 (9.52) | |
| In-hospital mortality | 4 (3.90) | 2 (9.50) | 0.27 |
| Bleeding rates | | | |
| TIMI major | 0 (0.0) | 0 (0.0) | |
| ICH | 0 (0.0) | 0 (0.0) | |
| TIMI minor | 3 (2.90) | 1 (4.80) | 0.53 |
| Minimal bleeding | 21 (16.93) | 4 (19.04) | 0.58 |
| SK induce hypotension | 34 (33.0) | 8 (38.1) | 0.81 |

SK=streptokinase; TIMI=thrombolysis in myocardial infarction; ICH=intracerebral hemorrhage

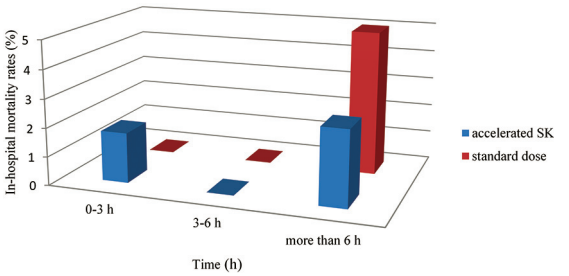


**Figure 1.** In-hospital mortality rates and time interval to reperfusion.

status is showed in Table 2. Coronary perfusion rates in the accelerated SK group (60.2%) were higher than in the standard dose group (57.1%), but this difference did not reach statistical significance, p=0.81. Upon comparison of the proportion of complete resolution (ST segment resolution of more than 70%), there were no significant differences between an accelerated half-dose and a standard dose (42.7% versus 47.6%, p=0.489). The median time interval from onset of symptom to SK infusion in the present study was 170 minutes and 135 minutes in accelerated SK dose and standard dose, respectively. The shortest time interval to SK infusion was 27 minutes and longest time was 644 minutes.

### *In-hospital mortality*

Mortality rate was lower in accelerated SK dose than in standard dose, but it did not reach a statistically significant difference (3.9% versus 9.5%, p=0.27). Mortality rate in both groups regimen were high in patients presenting more than six hours after onset of chest pain, but this was not statistically significant different (2.63% for accelerate SK dose and 5.0% for standard dose, p=0.13) (Figure 1). The causes of dead included three cardiogenic shock, two ventricular arrhythmia, and one unclear etiology (against advice).

### *Bleeding complication*

No clinical of TIMI major bleeding and ICH in both groups of SK. TIMI minor and minimal bleeding occurred less frequently in accelerated SK dose than in standard dose (2.9% versus 4.8%, p=0.53 and 16.9% versus 19.0%, p=0.58), but this was not statistically significant different. Puncture site hematoma and gastrointestinal tract hemorrhage were the most common bleeding site complication in the present study. Nausea symptom occurred in only one patient (0.97%) in the accelerated SK dose and did not occurred in the standard dose.

### *Complication related to streptokinase regimen*

SK induced hypotension occurred less frequently in patients receiving the accelerated SK dose regimen than in the standard dose regimen (33% versus 38%, p=0.81), but it was not statistically significant different. In most case, hypotension was benign and usually improved within 10 to 20 minutes without specific treatment.

## Discussion

The present study assessed the efficacy and safety of an accelerated SK dose compared to a standard dose of SK in patients presenting with acute STEMI in Nakornping Hospital, Thailand. The major findings of the current study are 1) coronary perfusion rates

were comparable between the two groups, 2) no TIMI major and ICH were occurred in both groups and the incidence of bleeding complication either TIMI minor or minor bleeding were slightly less than in the accelerated SK dose, 3) in-hospital mortality rate was slightly less in the accelerated SK dose, 4) SK-induced hypotension occurred more frequently in the standard dose than accelerated SK dose, 5) all patients in the accelerated SK dose received half dose of SK (0.75 MU).

### *Efficacy and safety of accelerated SK dose and standard dose regimen*

Compared to ASK-ROMANIA multicenter registry, the accelerated SK dose regimen in the present study had lower rates of coronary reperfusion (60.2% versus 72.8% in ASK-ROMANIA). The plausible causes of these findings are 1) ASK-ROMANIA study had excluded patients treated later than six hour but in the present study they were not excluded, 2) 17% of the accelerated dose SK regimen group in ASK-ROMANIA received the additional dose of 0.75 MU of SK but in the present study none of the patients received the additional dose of 0.75 MU of SK, and 3) the criteria of successful ECG coronary reperfusion in ASK-ROMANIA trial was defined as a reduction of sum of ST segment elevation greater than 50% in the first 180 minutes whereas the present study used the sum of ST segment deviation at 90 minutes greater than 30%. Many studies have developed an evaluation of the extent of ST segment elevation resolution after thrombolysis to predict coronary reperfusion. Bar FW et al stated that the amount of jeopardized myocardium and subsequent prognosis can be reflected by either ST segment elevation or depression from ECG[7]. Hlatky MA et al stated that the presence of precordial ST segment depression in patient with acute inferior wall myocardial infarction increased risk of hospital mortality and the long term prognosis of patient with precordial ST depression is worse than that of patients without this finding[8]. Saran RK et al mentioned that the reduction of ST segment of less than 25% in greatest ST segment elevation lead within three hours of thrombolysis have both persistent coronary occlusion (specificity 97%) and a lower ejection fraction[5]. Finally, Schröder et al reported a sum of ST segment resolution of less than 30% was highly specific for lack of coronary reperfusion and associated with the development of large infarcts and high short- and long-term mortality rates, the most powerful predictor of 21-day mortality was a reduction of 30% or less in summation of ST segment resolution and mortality rates in the partial ST segment resolution group (30% to 70%) was close to the complete ST segment resolution group[9]. According to previous research, the authors decided to use the extent of resolution of ST segment deviation (sum of ST segment elevation and depression) to assess the successful of SK despite the conventional ST segment elevation resolution as appeared in the current guideline.

The explanation for the accelerated SK dose regimen that have the coronary reperfusion rates higher than the standard dose was from the study of Lew et al[10]. They found that in STEMI patients who received high-dose intravenous SK, the time interval to reperfusion could be minimized by increasing the infusion rate up to at least 500 U per kg per minute and by shortening the delay from onset of symptoms to treatment and faster infusion rates that were more likely to cause significant hypotension. At low serum concentrations, SK induces relatively weak exogenous thrombolysis after initial formation of SK plasminogen complexes. At high concentrations, a larger number of SK-plasminogen or plasmin complexes are formed. SK complexes with plasminogen or plasmin and free SK may activate plasminogen in clots, inducing intense local thrombolysis[11]. Theoretically, an average 70 kg adult patient will require a minimum dose of 35,000 U per minute for reperfusion whereas the conventional regimen of 1.5 MU over 60 minutes will provide suboptimal dose of SK 25,000 U per minute compared to 75,000 U per minute in the accelerated half-dose regimen.

Compared with the 2013 ACCF/AHA guidelines for the management STEMI[2], patency rate (90 minutes TIMI 2 or 3 flow) of standard dose SK was 60% to 68% and comparable with the accelerated SK dose regimen in the present study (60.2% versus 60% to 68%) but more than standard dose in the present study (57.1% versus 60% to 68%).

With regards to the safety, in the present study, no clinical of TIMI major bleeding and ICH in both groups of SK regimens. Comparing with the ASK-ROMANIA study, TIMI major bleeding and ICH was lower in the accelerated SK dose than in the standard dose (0.40% versus 0.77% and 0.19% versus 0.38%, p=NS, respectively). SK induced hypotension in accelerated SK dose in the present study (33%) was comparable to other reports (35.5% in ASK-ROMANIA study and 34.9% in Tatu-Chitoiu et al report)[12]. However, it was higher in the standard dose in the present study than in ASK-ROMANIA 38%

versus 23.2%. The plausible causes that explain this are that the present study was a retrospective study and the sample size was too small in the standard dose regimen. SK induced hypotension is usually improved by intravenous saline infusion without others treatment.

In-hospital mortality in the present study was lower in both groups than in ASK-ROMANIA (3.9% versus 7.38% in the accelerated SK dose and 9.1% versus 11.6% in the standard dose). As for the mortality rate in patients who had late treatment, more than six hours after the event, we had similar result as in ASK-ROMANIA.

### *Limitation*

Several limitations in this study should be acknowledged. First, the current study was a retrospective study, thus, crucial data such as onset of symptoms, time to SK infusion, and ECG timing after SK infusion might not be completely captured. Second, the consideration to give SK regimen was based on consultant cardiologist discretion, which might lead to a selection bias according to patient characteristics.

## Conclusion

The efficacy and safety of the accelerated SK dose and the standard dose SK regimen was comparable in acute STEMI patients in Nakornping Hospital. In patients presenting more than six hours after onset of chest pain may be benefit in mortality rate by using the accelerate SK dose.

## What is already known in this topic?

Fibrinolytic could be initiated expeditiously with standard dose SK infusion 30 to 60 minutes in patients when the PPCI was not available or not an immediate option. It has been demonstrated that accelerated dose of SK was associated with higher coronary perfusion rate than standard dose of SK.

## What this study adds?

From this study, coronary perfusion rate in accelerated SK dose (no additional dose of 0.75 MU of SK) was higher than standard SK dose, but did not reach statistical significance. It also had a lower in hospital mortality, again, with no statistical significance.


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## Conflicts of interest

The authors declare no conflict of interest.

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