Efficacy of Rapid Infusion of Streptokinase in Patients with Acute Myocardial Infarction

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Abstract

The early use of thrombolytic agents is now the most important treatment in acute myocardial infarction (AMI). The earlier reperfusion should result in a higher survival rate. To determine whether the faster infusion of streptokinase (SK) will produce earlier reperfusion. 40 patients were enrolled to the trial. Half of them received 1.5 mu. of SK in one hour while the others received 1.5 mu. in half an hour. The rapid infusion group tended to have earlier reperfusion but there was no statistically significant difference in the reperfusion time. Hypotension was observed in both groups but more in the conventional group and responded to intravenous fluid replacement. Bleeding complication was low in both groups. Four patients died, one from re-occlusion and developed severe bradycardia, the remainder had cardiogenic shock which did not respond to treatment. It can be concluded that SK infusion in half an hour is safe but the beneficial effect remains to be seen in a large scale study.

Key word : Acute Myocardial Infarction, Streptokinase, Efficacy of Rapid Infusion

Thrombolytic agents are now the most important treatment in acute myocardial infarction (AMI)[1-8]. The more rapid restoration of blood flow through the infarct-related artery may better preserve myocardial tissue and improve survival. In a recent report, GUSTO investigators group showed that accelerated infusion of tissue plasminogen activator (tPA) within one and a half hours instead of 3 hours can improve left ventricle function and reduce the mortality rate[9,10]. In this study, we sought to determine that the rapid infusion of streptokinase (SK) within 30 minutes instead of 60 minutes will result in higher rate of reperfusion. The adverse reactions and early mortality rate were also determined.

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MATERIAL AND METHOD
Patients population

Patients with chest pain lasting at least 20 minutes within 6 hours from onset of symptom and ST segment elevation of 1 mm. or more for at least 2 consecutive leads of standard EKG, admitted to the coronary care unit of Chulalongkorn University Hospital since November 1992, were enrolled in the study. The exclusion criteria were, age under 15 or over 75, previous stroke within 6 months, active bleeding, recent trauma or major surgery within 2 weeks, severe uncontrolled hypertension (systolic BP > 180 and/or diastolic BP > 110 mmHg), aortic dissection, pericarditis, cardiogenic shock, severe electrolyte and acid-base imbalance, prolonged cardiopulmonary resuscitation and previous treatment with SK.

SK administration

The patients were randomized into 2 groups, rapid infusion group (SK30 - SK 1.5 mu. infused within 30 minutes) and conventional group (SK60 - SK 1.5 mu. infused within 60 minutes). Standard treatment for AMI were maintained as required.

Measurement of reperfusion

1. Duration of disappearance of chest pain after SK infusion was recorded.
2. Significant reduction of ST segment more than 25 per cent of baseline was used by monitoring the highest lead of ST segment elevation every 5 -15 minutes[11,12] for 4 hours.
3. Early peak of CKMB isoenzyme[13,14].

Statistical analysis

Unpaired student T test and chi-square test were used. P value < 0.05 was considered statistically significant.

RESULTS

Forty patients were randomized into 2 groups, SK30 and SK60. Mean age, sex, coronary risk factors such as diabetes, hypertension, smoking, dyslipidemia were similar in both groups. Location and clinical presentation of AMI also showed no statistically significant difference. Initial mean arterial blood pressure was 89 ± 13 and 87 ± 18 mmHg. Left ventricular ejection fraction was 0.45 ± 0.12 and 0.49 ± 0.10. Duration before thrombolytic infusion was 5.01 ± 2.2 and 5.10 ± 1.3 hours

Table 1. Base-line characteristics of the patients.

	Duration of infusion	
	SK 30 (%)	SK 60 (%)
Total of cases	20	20
Age (yr)	54.1 ± 9.0	58.2 ± 8.6
Sex M : F	19:1	15 : 5
Diabetes	7 (35)	6 (30)
Hypertension	3 (15)	8 (40)
Smoking	13(65)	12 (60)
Dyslipidemia	3 (15)	10 (50)
Previous Hx of IHD	3(15)	4 (20)
Duration before SK (h)	5.01 ± 2.2	5.10 ± 1.3
Needle time (min)	169 ± 96	173 ± 110
Location of MI		
: Anterior	9 (45)	8 (40)
: Inferior	11 (55)	12 (60)
Initial mean BP (mmHg)	89 ± 13	87 ± 18
Killip classification		
: Class I	16 (80)	14 (70)
: Class II	2 (10)	3 (15)
: Class III	0	1 (5)
: Class IV	2 (10)	2 (10)
Ejection fraction	0.45 ± 0.12	0.49 ± 0.10

Note : P value > 0.05

Table 2. Blood pressure after SK infusion.

	SK 30			SK 60		
	Pre SK	Post SK	P value	Pre SK	Post SK	P value
Systolic BP	119	110	NS	117	96	0.025
Diastolic BP	75	66	NS	71	59	NS
Mean BP	89	81	NS	87	72	0.037

Table 3. Result of treatment.

	Duration of infusion		P value
	SK 30	SK 60	
Total of cases	20	20	NS
Duration of pain free (min)	76 ± 55	65 ± 33	NS
Reperfusion time (min)	92 ± 48	119 ± 70	NS
Peak CKMB (h)	15 ± 2.9	15 ± 4.0	NS
No. of patients with hypotension	5 (25)	10 (50)	NS
Successful reperfusion	16 (80)	15 (75)	NS
Re-occlusion	2 (10)	1 (5)	NS
Major bleeding	0	0	NS
Death	2 (10)	2 (10)	NS

and door to needle time was similar in both groups. Overall baseline characteristics are shown in Table 1.

After treatment with SK, average systolic, diastolic and mean arterial pressure in SK30 were not significantly changed but systolic and mean arterial pressure in SK60 were significantly low (Table 2). Five patients (25%) in SK30 and 10 patients (50%) had significant hypotension. Most of them responded to intravenous fluid therapy. Duration of pain relief was 76 ± 55 and 65 ± 33 minutes. ST segment reduction time (reperfusion time) was 92 ± 48 and 119 ± 70 minutes, in which there was no significant difference in both groups. Mean peak CKMB was also similar. Sixteen patients (80%) in SK30 and 15 patients (75%) in SK60 were successfully reperfused. Two and 1 were re-occluded in SK30 and SK60 respectively. No major bleeding complication was detected. Four patients died, 2 in the SK30 and the others in SK60. Three cases presented with extensive anterior wall MI and progressed to cardiogenic shock requiring intra-aortic balloon pump after SK treatment. One patient had coronary angiography and emergency coronary artery bypass graft, he died from intra-abdominal sepsis secondary to antibiotic associated colitis. The fourth case had re-occlusion after successful reperfusion and progressed to severe bradycardia and hypotension which did not respond to treatment. Overall results are shown in Table 3.

DISCUSSION

Thrombolytic agents are most important to restore reperfusion in patients with occluded coronary artery. Although some authors believe that primary coronary angioplasty gives higher reperfusion and improves the survival rate especially in the case of extensive anterior wall MI and cardiogenic shock [15,16], but the procedure requires a 24-hour availability of catheterization laboratory and an experienced team. The rationale that earlier and rapid reperfusion improved mortality rate in GUSTO was the basis of our study. In this study, there was no statistical significance of the reperfusion rate in both groups (80% in SK30 and 75% in SK60) which is consistent with previous studies [17-21]. The reperfusion time (the time interval from onset of SK infusion to the time of reperfusion) in SK 30 is less than in SK60 (92 minutes and 119 minutes respectively) (P>0.05). Allan SL [22] showed that the reperfusion time was inversely related to the rate of SK infusion but the effect of infusion rate appeared

to plateau at a rate of greater than 500 u/Kg/minute which is equal to infusion of SK 1.5 mu. in 50 kg-patient over 60 minutes. The reperfusion time was 34 minutes in rapid and intermediate infusion, 54 minutes in slow infusion. The reperfusion time in this study is higher than Allan's study may be due to the longer door to needle time of thrombolytic treatment. The incidence of hypotension was 25 per cent in SK30 and 50 per cent in SK60 and higher than

that of the large previous studies[1,23]. Neither allergic reaction nor major bleeding complication were observed. The limitation of this study is the small number of cases. So it does not have enough power to detect the small beneficial differences between the two groups. However, it can be concluded that it is safe to give SK infusion in half an hour instead of one hour but the beneficial effect remains to be seen in a large scale trial.

REFERENCES

1. ISIS II (Second International Study of Infarct Survival) collaborative group : Randomised trial of intravenous streptokinase, oral aspirin or neither among 17,187 cases of suspected acute myocardial infarction : ISIS II. Lancet 1988;2:349-60

2. ISIS III (Third International Study of Infarct Survival) collaborative group : A randomised comparision of streptokinase VS tissue plasminogen activator VS anistreplase and of aspirin plus heparin VS aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992; 339:753-70.

3. GISSI (Gruppo Italiano perlo Studio della Streptochinasi nell Infarto miocardico). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397-402.

4. GISSI II : A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Lancet 1990;336:65-71.

5. ISAM Study Group : A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM). Mortality, morbidity and infarct size at 21 days. N Engl J Med 1986;314:1465-71.

6. ASSET Study Group. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Lancet 1988;2:525-30.

7. AIMS Trial Study Group. Long-term effect of intravenous anistreplase in acute myocardial infarction : final report of the AIMS study. Lancet 1990; 335:427-31.

8. Fibrinolytic Therapy Trialists' collaborative group. Indications for fibrinolytic therapy in suspected acute myocardial infarction : collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311-22.

9. The GUSTO Investigators. An international randomisd trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.

10. The GUSTO Angiographic Investigation. The effect of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function. N Engl J Med 1993;329:1615-22.

11. Califf RM, O Neil WW, Stack RS, et al. Failure of simple clinical measurement to predict perfusion status after intravenous thrombolysis. Ann Intern Med 1988;108:658-62.

12. Francesco M, Aldo PM, Maria GF, et al. for the GISSI-2 Investigators. A simple electrocardiographic predictor of the outcome of patients with acute myocardial infarction treated with a thrombolytic agent : GISSI-2 derived analysis. J Am Coll Cardiol 1994;24:600-7.

13. Lee TH, Goldman L. Serum enzyme assays in the diagnosis of acute myocardial infarction. Ann Intern Med 1986;105:221-33.

14. Ong L, Reiser P, Coromilas J, et al. Left ventricular function and rapid release of creatinine kinase MB in acute myocardial infarction : Evidence for spontaneous reperfusion. N Engl J Med 1983; 309:1-6.

15. Grines CL, Browbe KF, Marco J, et al. Primary Angioplasty in Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.

16. Zjistra F, Jan de Boer M, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.

17. Verstraete M, Arnold AE, Brower RW, et al. Acute coronary thrombolysis with recombinant human tissue-type plasminogen activator : initial patency and influence of maintained infusion on re-occlusion rate. Am J Cardiol 1987;60:231-7.

18. Six AJ, Louwerenburg HW, Braams R, et al. A double-blind randomised multicenter dose-rang-

ing trial cf intravenous streptokinase in acute myocardial infarction. Am J Cardiol 1990;65: 119-23.

19. Spann JF, Sherry S, Carabello BA, et al. Coronary thrombolysis by intravenous streptokinase in acute myocardial infarction : acute and follow-up studies. Am J Cardiol 1984;53:655-61.

20. Brochier ML, Quiller L, Kulbertus H, et al. Intravenous anisoylated plasminogen streptokinase activator complex versus intravenous streptokinase in evolving myocardial infarction. Preliminary data from a randomised multicenter study. Drug 1987;33:140-5.

21. Monnier F, Sigwart U, Vincent A, et al. Anisoy-lated plasminogen streptokinase activator complex versus streptokinase in acute myocardial infarction. Preliminary results of randomised study. Drug 1987;33(Suppl 3):175-8.

22. Allan SL, Pierre L, Bojan C, et al. The effects of the rate of intravenous infusion of streptokinase and durationb of symptoms on the time interval to reperfusion in patients with acute myocardial infarction. Circulation 1985;72:1053-8.

23. The Internation Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. Lancet 1990;2:71-5.

การใช้ยาสเตร็พโตไคเนส ในผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันโดยวิธีการให้ทางเส้นเลือดดำหยดอย่างรวดเร็ว

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ปัจจุบันการให้ยาละลายลิ่มเลือดอย่างรวดเร็วเป็นสิ่งที่สำคัญที่สุดในการรักษาผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลัน ยิ่งทำให้มีการเปิดเส้นเลือดที่อุดตันได้เร็วเท่าไรก็จะทำให้ผู้ป่วยมีอัตรารอดชีวิตสูงขึ้นเท่านั้น เพื่อจะดูผลการรักษาโดยการใช้ยาสเตร็พโตไคเนสหยดทางหลอดเลือดดำอย่างรวดเร็วจะสามารถทำให้มีการเปิดของเส้นเลือดที่อุดตันได้เร็วขึ้นหรือไม่ โดยทำการศึกษาผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นกล้ามเนื้อหัวใจตายเฉียบพลันจำนวน 40 ราย โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มที่ให้การรักษาด้วยยาสเตร็พโตไคเนส 1.5 mu. หยดทางหลอดเลือดดำภายในเวลา 30 นาที เปรียบเทียบกับกลุ่มที่ 2 ซึ่งได้รับการรักษาแบบดั้งเดิมซึ่งใช้ยาสเตร็พโตไคเนส 1.5 mu. หยดทางหลอดเลือดดำภายใน 60 นาที พบว่า กลุ่มที่ได้รับยาสเตร็พโตไคเนสหยดภายใน 30 นาที มีแนวโน้มว่าจะใช้เวลาในการเปิดเส้นเลือดที่อุดตันได้เร็วกว่ากลุ่มที่ให้ยาแบบดั้งเดิม แต่ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ ภาวะความดันโลหิตต่ำพบบ่อยกว่าในกลุ่มที่ให้ยาแบบหยดภายใน 60 นาที ซึ่งตอบสนองดีต่อการให้น้ำเกลือหยดทางหลอดเลือดดำ ภาวะแทรกซ้อนจากการที่มีเลือดออกในที่ต่าง ๆ พบน้อย ผู้ป่วยเสียชีวิต 4 ราย หนึ่งรายเกิดมีลิ่มเลือดอุดตันซ้ำใหม่และเกิดภาวะหัวใจเต้นช้ามาก อีก 3 รายมีภาวะช็อคจากการทำงานของหัวใจล้มเหลวและไม่ตอบสนองต่อการรักษา จากการศึกษานี้สามารถสรุปได้ว่า การให้ยาสเตร็พโตไคเนสหยดทางหลอดเลือดดำภายใน 30 นาทีสามารถใช้ได้อย่างปลอดภัยแต่ประโยชน์ที่ชัดเจนนั้นคงต้องรอการศึกษาที่มีจำนวน ผู้ป่วยมากกว่านี้

คำสำคัญ : กล้ามเนื้อหัวใจตายเฉียบพลัน, สเตร็พโตไคเนส

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