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Hypotension in Acute Myocardial Infarction Patients Given Streptokinase

F Lateef, V Anantharaman

ABSTRACT

Objective: This is a prospective cohort study done over a period of one year to look at hypotension that developed in the local Acute Myocardial Infarction (AMI) patients given Streptokinase (SK).

Method: Suitable patients with AMI (those with ischaemic chest pain most severe within the last 8 hours, ST-segment elevation and no contraindications) were selected for thrombolysis with SK given as the standard dose of 1.5 mega-units diluted in 100 mls of normal saline and infused over 60 minutes. (Group A). The AMI patients who did not receive SK (Group B), were analysed separately and acted as "controls", as it was not possible to withold thrombolytic therapy in a group of patients in a completely randomised fashion.

The pulse, non-invasive blood pressure and electrocardiogram were monitored and recorded.

Results: Of 120 patients analysed, 70 received SK (Group A) and 50 (Group B) did not due to a variety of reasons. There was no statistically significant difference in the sex, age and body weight distribution as well as the initial mean arterial blood pressure (MAP) in the two groups. The MAP showed a statistically significant decrease at 15 minutes (105.6 to 81.4 mmHg, 95%CI: 13.965, 28.178) and 30 minutes (105.6 to 89.6 mmHg, 95%CI: 10.929, 19.814) after the commencement of SK in Group A patients. When analysed separately, the decrease in MAP was also statistically significant at 15 minutes (95%CI: 4.263, 22.014) for those with anterior AMI and both at 15 (95%CI: 19.112, 41.299) and 30 minutes (95%CI: 1.191, 28.716) for those with inferior AMI. There was no statistically significant decrease noted in Group B patients and the door-to-needle time for Group A patients was 37.2 ± 6.0 minutes. The SK infusion time for Group A patients who developed hypotension was prolonged to 95.3 ± 14.1 minutes.

Conclusion: Hypotension was more commonly noted in the AMI patients given SK. The MAP tend to decrease in the first 30 minutes after commencing the SK infusion. It is thus possible to conclude that the hypotension was at least partly due to SK and is probably a rate-related phenomenon.

Keywords: hypotension, Streptokinase, door-to-needle time

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Department of Emergency Medicine
Singapore General Hospital
Outram Road
Singapore 169608

F Lateef, MBBS, FRCS (A&E, Edin)
Senior Registrar

V Anantharaman, MBBS, FRCP (Edin), FAMS
Senior Consultant and Head

Correspondence to:
Dr F Lateef
Email:
f_lateef@hotmail.com

INTRODUCTION

The treatment of acute myocardial infarction (AMI) has evolved dramatically over the past 20 years. From observation, bed rest and management of complications whilst the infarct completed its course, to aggressive treatment during and after the acute event in the coronary care unit and now to the current paradigm of limiting the extent of myocardial damage by early reperfusion of the jeopardized myocardium and measures to reduce myocardial damage[1].

With the advent of thrombolytic therapy for AMI, mortality has been reduced[2,3,4,5]. The administration of thrombolytic therapy has now in more and more centres, shifted from coronary care units to Emergency Departments (ED)[1,5,6].

The American Heart Association (AHA) has recommended that patients eligible to receive thrombolytic therapy should do so within 30 to 60 minutes of arrival at the Emergency Department (ED)[1,4]. The working group from the National Institutes of Health (National Heart, Lung and Blood Institute) further advocates that EDs strive for the minimum AHA goal of treatment within 30 minutes of ED arrival[1]. Locally, streptokinase (SK) is the thrombolytic agent commonly utilised. Important considerations before thrombolysis include patients' characteristics, area at risk, time to treatment, presence of contraindications as well as the risks involved[5]. One of the problems seen with administration of SK in the AMI patient is that of hypotension[6,7,8]. Currently, there are limited numbers of studies addressing this issue in detail. Moreover, hypotension may be an inherent phenomenon in the pathophysiology of AMI or it may result as a complication of the SK infusion[7,8,9]. Therefore, we set

forth to look at hypotension in AMI patients given SK to help shed light on this issue.

OBJECTIVE

The aim of this study was to look at hypotension in AMI patients given SK ie. the degree of hypotension, when it developed and any complications[10] as a consequence of the hypotension.

METHODOLOGY

This was a prospective cohort study whereby suitable patients with AMI (those with ischaemic chest pain most severe within the last 8 hours, ST-segment elevation and no contraindications to thrombolysis) were selected for thrombolysis with SK (Group A), which was given as 1.5 mega-units diluted in l00mls of Normal Saline and infused over 60 minutes[8.10.11]. The patients were monitored continuously for heart rate, blood pressure, electrocardiogram and pulse oximetry in the resuscitation room and recordings were taken every 5 minutes. 200mg of intravenous hydrocortisone was given before the SK infusion was commenced.

All the patients were given 300mg of Aspirin[4] (allergies and contraindications excluded) and a sublingual Nitroglycerine tablet[4]. The patients who did not receive thrombolytic therapy with SK (Group B) were analysed separately and patients, who at presentation had systolic blood pressure persistently less than 90mmHg, were in pulmonary oedema or cardiogenic shock, were excluded from the analysis. The Group B patients acted as "controls" as it was not possible to establish a perfect control group in a completely randomised fashion as it would have been unethical to withold thrombolytic therapy from eligible patients, SK having now been proven beneficial in appropriately selected patients[12-16].

Following the initiation of streptokinase infusion, the blood pressure was monitored closely All patients were observed for development of malignant arrhythmias, hypotension as well as other complications. The decrease in the mean arterial blood pressure at 15, 30 and 60 minutes was then compared by statistical testing. For patients who developed hypotension (defined as systolic blood pressure of <90 mmHg), the streptokinase infusion was temporarily stopped, patients placed in the head-down position and intravenous normal saline infused until the systolic blood pressure returned to at least 90 mmHg when monitored at 5-minute intervals. The streptokinase infusion was then recommenced.

RESULTS

For the period 1 August 97 to 1 August 98, 70 patients with AMI were given SK (Group A) and another 50 AMI patients who came within 8 hours of the onset of chest pain, were not. (Group B) (Table I). Of the 70 patients in Group A, 37 (52.9%) had anterior AMI and 33 patients (47.1%) had inferior AMI. Of those not given SK, (Group B), 34 (68.0%) underwent acute or primary percutaneous transluminal coronary angioplasty (PTCA), 5 patients (10.0%) had haemorrhagic cerebrovascular event (CVA) within the last 6 weeks and 3 (6.0%) had recent major surgery. There were two patients, (4.0%) with active peptic ulcer disease and recurrent episodes of malaena, 1 (2.0%) with proliferative diabetic retinopathy and another 1 (2.0%) with a new-onset pan-systolic murmur. 4 patients (8.0%) refused consent for thrombolysis (Table II). There was no statistically significant difference in terms of

Table I. Breakdown of Patients in Groups A and B

	Group A (SK)	Group B (No SK)
Total Number of Patients	70	50
Anterior AMI	37	32
• Anterior	23	18
• Antero-lateral	8	10
• Antero-septal	6	4
Inferior AMI	33	18
• Inferior	12	8
• Inferior + RV	10	5
• Inferior + Posterior	4	2
• Inferior + RV + Posterior	7	3

Table II. Group B (No SK): Reasons for not receiving SK

Reasons	Number of Patients
Acute PTCA	34
Stroke (last 6 weeks)	5
Recent surgery (last 2 weeks)	3 2 - cholecystectomy 1 - Hepatectomy
Peptic ulcer disease with reccurent episodes of malaena	2
Proliferative Diabetic Retinopathy	1
New-onset Pan-Systolic Murmur	I
Refusal of consent	4

Table III: Comparison of Parameters in Groups A and B

	Group A SK (70)	Group B No SK (50)
% Male	77.1(54)	76.0 (38)
Mean Age (years)	60.5 $\pm$ 5.8	61.8 $\pm$ 7.2
Mean MAP at presentation (mmHg)	105.6 $\pm$ 12.3	104.8 $\pm$ 10.2
Mean Time of Presentation after onset of chest pain (mins)	119.2 $\pm$ 28.3	128.1 $\pm$ 12.6
Mean Weight (kg)	60.8 $\pm$ 7.1	62.2 $\pm$ 5.7

Table IV-A. Mean arterial pressure and 95%CI for Groups A and B

	Group A	Group B
Mean MAP before SK (mmHg)	105.6	104.8
Mean MAP at 15 mins (mmHg)	81.4	102.1
Change in MAP (mmHg)	24.2	2.7
95%CI	(13.965, 28.128)*	(-1.236, 13.216)
Mean MAP before SK (mmHg)	105.6	104.8
Mean MAP at 30 mins (mmHg)	89.6	100.2
Change in MAP (mmHg)	16.0	4.6
95%CI	(10.929, 19.814)*	(-1.764, 7.408)
Mean MAP before SK (mmHg)	105.6	104.8
Mean MAP at 60 mins (mmHg)	100.2	102.9
Change in MAP (mmHg)	5.4	1.9
95%CI	(-3.995, 8.651)	(-4.276, 11.657)

** Statistically significant*

Table IV-B. Mean arterial pressures and 95%CI for Anterior AMI in Groups A and B

	Anterior AMI (A) (With SK)	Anterior AMI (B) (No SK)
Mean MAP before SK (mmHg)	102.5	105.8
Mean MAP at 15 mins (mmHg)	83.2	100.3
Change in MAP (mmHg)	19.3	5.5
95%CI	(4.263, 22.014)*	(-13.113, 7.913)
Mean MAP before SK (mmHg)	102.5	105.8
Mean MAP at 30 mins (mmHg)	96.9	101.4
Change in MAP (mmHg)	5.6	4.4
95%CI	(-5.977, 18.838)	(-9.288, 24.841)
Mean MAP before SK (mmHg)	102.5	105.8
Mean MAP at 60 mins (mmHg)	109.3	112.9
Change in MAP (mmHg)	-6.8	-7.1
95%CI	(-12.143, 7.466)	(-6.045, 12.315)

** Statistically significant*

Table IV-C. Mean arterial pressure and 95%CI for Inferior AMI in Groups A and B

	Inferior AMI (A) (With SK)	Inferior AMI (B) (No SK)
Mean MAP before SK (mmHg)	104.9	101.9
Mean MAP at 15 mins (mmHg)	73.7	96.8
Change in MAP (mmHg)	31.2	5.1
95%CI	(19.112, 41.299)*	(-7.163, 20.174)
Mean MAP before SK (mmHg)	104.9	101.9
Mean MAP at 30 mins (mmHg)	81.6	95.3
Change in MAP (mmHg)	23.3	6.6
95%CI	(1.191, 28.716)*	(-6.918, 1.951)
Mean MAP before SK (mmHg)	104.9	101.9
Mean MAP at 60 mins (mmHg)	93.8	108.0
Change in MAP (mmHg)	11.1	-6.1
95%CI	(-2.557, 12.787)	(-4.266, 21.211)

** Statistically significant*

sex and age and body weight distribution as well as the initial MAP amongst patients in both Groups A and B (Table III).

Patient Data and Parameters

There were 54 male patients (77.1%) in Group A and 38 (76.0%) in Group B. The mean age was 60.5 $\pm$ 5.8 years and 61.8 $\pm$ 7.2 years respectively. The mean MAP (mean arterial blood pressure) at presentation were 105.6 $\pm$ 12.3 mmHg and 104.8 $\pm$ 10.2 mmHg for the two groups. The mean time of presentation after the onset of chest pain was 119.2 $\pm$ 28.3 and 128.1 $\pm$ 12.6 minutes respectively for the 2 groups (Table III). For the patients given SK (Group A), the door-to-needle time (DTN) was 37.2 $\pm$ 6.0 minutes.

Mean Arterial Pressure

When looking at the MAP, the decrease was statistically significant in Group A patients at 15 minutes (105.6 —> 81.4 mmHg, 95%CI:13.965, 28.178) and 30 minutes (105.6 —> 89.6mmHg, 95%CI:10.929, 19.814) from the commencement of the SK infusion (Table IV-A).

When the MAP was analyzed separately for the anterior and inferior AM patients given SK (Group A), the decrease was statistically significant at 15 minutes for the former (Table IV-B) and both at 15 and 30 minutes for the latter (Table IV-C). There was no statistically significant decrease in the MAP amongst the Group B patients (Table IV-A, B, C).

Streptokinase Infusion / Hypotension

Owing to the development of hypotension, the SK infusion time was prolonged in some of the patients. The mean infusion time was 95.3 $\pm$ 14.1 minutes for those who developed hypotension (defined as systolic blood pressure less than 90 mmHg). This was about 35 minutes longer than the usual recommendation of 60 minutes[6,8]. 28 of the 37 patients with anterior AM (75.7%) given SK had documentation of hypotension during the infusion of SK. This was noted in 16 of the 33 patients (48.5%) with inferior AMI. For Group B, 2 of 32 (6.0%) anterior AMI and 4 of 18 (22%) inferior AMI patients had documented hypotension (Table V).

Of the 16 inferior AMI patients in Group A who developed hypotension, 7 had inferior, right ventricular and posterior AMI, 4 had inferior and right ventricular AMI, 4 had only inferior AM and 1 had inferior and posterior AMI. As for the 4 Group B patients with inferior AMI who developed hypotension, 3 had inferior, right ventricular and posterior AMI and 1 had inferior and right ventricular AMI. For the Groups A and B patients who experienced hypotension, there was no

statistically significant difference in terms of body weight and initial MAP but the mean time of onset of hypotension was 12.1 ± 7.3 and 29.7 ± 8.5 minutes respectively (Table VI).

Table V. Hypotension in Group A and B Patients

Group A (70)		Group B (50)	
Hypotension	No Hypotension	Hypotension	No Hypotension
Anterior AMI			
28/37 (75.7%)	9/37 (24.3%)	2/32 (6.3%)	30/32 (93.7%)
Inferior			
16/33 (48.5%)	17/33 (51.5%)	4/18 (22.2%)	14/18 (77.8%)
Total			
44/70 (62.9%)	26/70 (37.1%)	6/50 (12.0%)	44/50 (88.0%)
SK Infusion Time			
95.3 ± 14.1 mins	60.4 ± 3.8 mins		

Table VI. Group A and B Patients who experienced Hypotension

	Group A (SK)	Group B (No SK)	Statistical Significance
Number with hypotension observed	44 out of 70	6 out of 50	–
Mean initial MAP (mmHg)	99.3 ± 3.7	96.7 ± 4.9	NS
Mean time for SBP <90 mmHg (minutes)	12.1 ± 7.3	29.7 ± 8.5	P = 0.04
Mean Body Weight (kg)	58.7 ± 5.6	60.1 ± 4.3	NS

Adverse Effects

For all the 70 patients given SK, there were no reports of any serious bleeding[9,10] malignant arrhythmia or allergic reaction[9]. Neither was there any cerebrovascular events as a result of the hypotension in this group of patients.

CONCLUSION

Hypotension was more commonly noted in the AMI patients given SK. The MAP tend to decrease in the first 30 minutes after commencement of the infusion of SK and as a consequence of the hypotension, the mean SK infusion time was prolonged to 95 minutes. Thus, it is possible to conclude that hypotension was at least partly due to SK and it is most likely a rate-related phenomenon.

DISCUSSION

The last two decades have witnessed dramatic changes in the management of AMI. From the conservative approach and few therapeutic interventions, there has evolved a multifaceted strategy comprising pharmacological agents, emergency cardiac catheterization and early cardiac rehabilitation. Thrombolytic therapy has now become at least the minimum standard of care for the suitable AMI patient[1,4].

Many major thrombolytic agents have been subjected to large randomised clinical trials[12-16] since 1958, when Fletcher and Sherry et al[17] first reported on the use of intravenous SK in the AMI patient. The dose of SK has always been set at 1.5 mega-units as an infusion over 60 minutes. The reason as to how and why this standard dosage came about remains unclear[4,6,8]. There were no documented evidence-based studies pertaining to this. Hypotension was reported ranging from 1.6%[13] to about 10%[14].

From this study it was noted that a fair proportion of the local patients experienced hypotension during the infusion of SK. Therefore, the question arises as to whether there is a need to decrease the dose of SK or perhaps, to give the current dose over a longer infusion time. Should the SK dose be based on body weight, like many other pharmacological agents that are prescribed? In this analysis, weight did not prove to be a major factor as there was no statistically significant difference noted between the two groups. Whatever dose or infusion time is decided upon, it has to be sufficient to overcome the antistreptolysin antibody which is found in many patients and cause minimal or only minor side-effects[3,5,9,10].

Lev and Laramee[18] commented that "rapid intravenous administration of SK tend to produce transient but potentially severe hypotension, presumably related to the release of kinins and vasodilation, which can be prevented or minimized by an infusion rate of less than 500 units/kg/min, maintenance of a Trendelenburg posture and occasionally, transient vasopressor support". For the present dose of 1.5 mega-un its, the average local patient of 60 kg gets about 417 units/kg/min. Hypotension is still being observed at this dosage. Since the mean infusion time for those who developed hypotension during SK infusion was 95 minutes, this would amount to a mean infusion rate of 263 units/kg/min. We would venture to suggest that the optimal dose of SK required to minimise SK-mediated hypotension be 250 units/kg/min. The impact of such a dose on the coronary artery reperfusion rates, blood pressure and bleeding complications will need to be studied further. The impact of a relatively low-cost fibrinolytic (SK costs about 10% of the equivalent dose of recombinant-tissue plasminogen activator, r-tpa), a slower minute-by-minute dose and its potential for lesser adverse effects as well as the potential benefits of a longer infusion time and therefore, longer lasting effect all merit a carefully randomised controlled study first comparing this lower regimen with the standard

SK regimen, and if found to be superior, a second study comparing it to the other thrombolytic agents such as r-tpa.

Kawai and Nakamura[19] suggested that in the Asian patient of smaller built, 750 000 units may be used instead. To date, there has been no significantly large scale studies or evidence to support this.

At the Department of Emergency Medicine, Singapore General Hospital, the current dose will continue to be used for the patients selected to receive SK until further evidence become available to do otherwise. They will receive it in the Resuscitation Room and be monitored closely and continuously for any complications. Those developing hypotension during SK infusion will be managed appropriately based on decisions made for each individual patient, by either stopping the infusion transiently, decreasing the infusion rate or any other actions deemed relevant.

REFERENCES

1. Emergency Department Rapid Identification and Treatment of Patients with Acute Myocardial Infarction. National Institutes of Health, National Heart, Lung and Blood Institutes. US Department of Health and Human Services. Sept 1993.
2. Julian DG (Chairman). Acute Myocardial Infarction. Pre-hospital and In-hospital Management Guidelines. The Task Force on the Management of AM of the European Society of Cardiology. Europ Ht Jour,1996; 17:43-63.
3. Connes CL, DeMaria AN. Optimal Utilisation of Thrombolytic Therapy for Acute Myocardial Infarction. Concepts and Controversies. Jour of Am Coll of Cardiol,1990; 16(1):223-31.
4. Guidelines for the management of patients with Acute Myocardial Infarction. American College of Cardiologyl American Heart Association Task Force on Practice Guidelines, 1996.
5. Lee TH, Weisberg MC. Candidates for thrombolysis among Emergency Room patients with acute chest pain. Ann Int Med,1989; 110(12):957-62.
6. Kruse KR, Califf RM. Thrombolytic Therapy: A Critical review of Clinical Trials,1995; 434-70.
7. Henning R, Grenvile A. Critical Care Cardiology. Ref: The hypotensive eftect of IV Streptokinase in patients with AMI. Circul,1985; 22:1321-29.
8. Verstraele M, Tygat G. Thrombolysis with SK using a standard dose. Throm, Diath and Haemor, 1996; 16 Suppl 21:454.
9. Anderson J, Willerson JT Thrombolysis in AMI. New Eng Jour of Med,1993; 329(10):703-9.
10. Sane DC, Califf RM. Bleeding during Thrombolytic Therapy for AMI:Mechanism and Management. Ann of Int Med, 1989; 11(12):1010-22.
11. Cairns J, et al. Special Report. Canadian Consensus Conference on Coronary Thrombolysis. Update 1994. Can Jour of Cardiol, June 1994; 10:5-10.
12. Calift RM, et al. One year results from the Global Utilisation of SK and TPA for Occluded Arteries (GUSTO-1) Trial. Circulation, 1996; 94:1233-38.
13. Rovelli F (Chairman, Steering Committee). Effectiveness of IV Thrombolytic Treatment in AMI (GISSI). Lancet,1986;1:397-402.
14. Second International Study of Infarct Survival (ISIS-2). Collaborative Group. Randomised trial of IV SK, oral Aspirin, both or neither among 17 187 cases of suspected AMI. Lancet, 1988; 11:349-60.
15. ISIS-3. A randomised comparison of SK versus TPA versus Anistreplase and Aspirin plus Heparin versus Aspirin alone among 41 299 cases of suspected AMI. Lancet, 1992; 339:753-70.
16. Wilcox RG, et al. Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Lancet,1990; 335:1175-78.
17 Fletcher AP, Sherry S, et al. Treatment of patients suffering from AMI with SK therapy. Trans Assoc Am Phys, 1958; 71:287-96.
18. Lev AS, Laramee P, et al. The Hypotensive effect of IV SK in patients with AMI. Circul,1985; 72:1321-26.
19. Kawai C, Nakamura C. Cardiovascular Medicine. Natural History. 1994:566.