COMPLICATIONS OF STREPTOKINASE IN PATIENTS WITH ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION: NO REASON TO WITHHOLD THIS EFFECTIVE THERAPY

Shah Sawar[1], Bahauddin Khan[2], Amir Taj Khan[3], Naila Noor[4], Fouzia Rahman[5], Nadia Rehman[6]

[1-2] Department of Cardiology, Hayatabad Medical Complex, Peshawar - Pakistan.
[3] Department of Medicine, Hayatabad Medical Complex, Peshawar - Pakistan.
[4] Department of Gynaecology, Hayatabad Medical Complex, Peshawar - Pakistan.
[5] Department of Radiology, Khyber Teaching Hospital, Peshawar - Pakistan.
[6] Sarhad University, Peshawar - Pakistan.

Address for Correspondence:
Dr. Bahauddin Khan
Resident Cardiologist, Department of Cardiology, Hayatabad Medical Complex, Peshawar - Pakistan.
Email: bahauddin.khan@yahoo.com

Date Received: February 06, 2019
Date Revised: September 03, 2019
Date Accepted: September 10, 2019

ABSTRACT

Objective: To determine the complications of Streptokinase in patients with acute ST segment elevation myocardial infarction (STEMI).

Methodology: This descriptive cross sectional study was conducted on 297 patients with acute STEMI enrolled with non-probability consecutive sampling. Patients were diagnosed with Third Universal Definition of Myocardial Infarction. Injection Streptokinase was administered as infusion according to the standard protocol after excluding contraindications. Every patient was continuously monitored for hemodynamic, allergic, electrical and fibrinolytic complications during infusion. Statistical Package for Social Sciences version 20 was used for data analysis. Logistic regression was used to test if low systolic blood pressure and heart rate at presentation are predictors of hypotension. Significance value was set at $p < 0.05$.

Results: Mean age of the patients was 56.26 ±12.38 years. Male were 65.7%. Patients with history of hypertension, diabetes mellitus, past history of acute coronary syndrome, smoking and past history of streptokinase were 51.9%, 33.7%, 23.2%, 14.1% and 8.4%, respectively. Complications observed during Streptokinase infusion were; hypotension 6.7%, nausea and vomiting 6.4%; gums bleeding 3%, allergic reactions 3%, ventricular tachycardia 2.7%, ventricular fibrillation 2%, atrial fibrillation 2.4%, fever 2.4%, bradycardia 2%, hemoptysis 0.7% and intracranial hemorrhage 0.3%. Only one patient expired due to complications.

Conclusion: Significant hemodynamic and electrical complications during Streptokinase infusion in patients with ST segment elevation myocardial infarction were rare.

Key Words: Streptokinase, ST segment elevation myocardial infarction, Complications

This article may be cited as: **Sawar S, Khan B, Khan AT, Noor N, Rahman F, Rehman N. Complications of streptokinase in patients with acute ST segment elevation myocardial infarction: No reason to withhold this effective therapy. J Postgrad Med Inst 2019; 33(4): 293-8.**

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide[1]. Acute presentation of CVD is termed as acute coronary syndrome (ACS). This syndrome is categorized into ST elevation myocardial infarction (STEMI), non ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) based on cardiac biomarkers and electrocardiogram (ECG). The South Asian countries carry the highest burden of CVD[2]. CVD is the most common non-communicable disease in Pakistani population[3]. The burden of STEMI patients has increased in tertiary care hospitals of Peshawar, Pakistan since 1995[4,5]. Although primary percutaneous coronary intervention (PPCI) is the intervention of choice in patients with STEMI, fibrinolysis with Streptokinase remains the most common mode of reperfusion in our region and other developing countries[5,6]. The benefit of Streptokinase is time dependent[7]. In developed countries, where the anticipated time for PPCI is more than 120 minutes, fibrinolysis is recommended en route to the PCI facilitated centers[8]. In our region, 80% patients receive Streptokinase while 20% patients with STEMI become ineligible for thrombolytic therapy because of late presentation[5]. Another researcher found out that 40% patients were ineligible for fibrinolysis due

to late presentation[9]. Many patients with STEMI are referred to tertiary hospitals for fibrinolysis. This referral causes unwanted delay in the reperfusion process. Late presentation by patients, transportation delay, misdiagnosis of STEMI, non-availability of cardiac care facilities and lack of trained medical and paramedical staff are the major causes of this delay[9]. Fear of complications of streptokinase administration is another reason that deprives patients with STEMI from life saving therapy[10].

The administration of streptokinase can be without undue complications[11], but many of the serious complications due to streptokinase are rare or uncommon and the benefit of therapy outweighs the risk of complications[7,12]. Therefore it is important to evaluate the complications of streptokinase in patients with STEMI in our population. It will help the primary care physicians, particularly in rural areas, who are reluctant to give streptokinase to STEMI patients due to its possible complications.

METHODOLOGY

We conducted this study in Coronary Care Unit of Hayatabad Medical Complex, Peshawar, Pakistan from June 01, 2018 to November 30, 2018. It was a descriptive cross sectional study with non-probability consecutive sampling. Two hundred and ninety seven patients with age of ≥18 years diagnosed with acute ST segment elevation myocardial infarction (STEMI) were included in the study. STEMI was diagnosed through Third Universal Definition of Myocardial Infarction[13]. Targeted history was taken including patient eligibility for injection Streptokinase. Clinical examination was done and informed consent was taken from every patient. This study was approved by hospital ethical review committee. Each patient received non-coated chewable Aspirin 300mg, dose-adjusted Clopidogrel and injection Enoxaparin on admission. Adequate sedation and analgesia was given as required.

Injection streptokinase was administered intravenously (IV) as infusion at dose of 1.5 million units in 100 ml normal saline through infusion pump over 30-60 minutes. Patients with onset of symptoms for more than 12 hours and any contraindication were excluded from the study. During infusion of streptokinase, every patient was continuously monitored for hemodynamic, allergic, electrical and fibrinolytic complications. Hemodynamic complications included hypotension. Hives, hot flushes, facial erythema, dyspnea were reported as allergic complications. Any arrhythmia leading to hemodynamic instability and/or symptoms was noted. Fibrinolytic complications included bleeding from any site. Venous puncture sites bleeding were not reported as almost every patient developed this complication which is hemodynamically not significant. All patients with hypotension, vomiting, allergic reaction, fever were managed conservatively through IV normal saline, IV dimenhydrinate, IV anti-histamine, oral anti-pyretic and/or re-assurance. Chest x-ray for patients with hemoptysis was done and treated conservatively.

Streptokinase was temporarily withheld in patients who developed bradycardia during infusion. Heart rate less than 60 beats per minute at presentation and heart rate more than 60 beats per minute at presentation were classified into bradycardia and no bradycardia at presentation, respectively. Similarly, patients with systolic blood pressure less than 90 mmHg at presentation and more than 90 mmHg at presentation were divided into low blood pressure at presentation and normal blood pressure at presentation, respectively. Patients with ventricular tachycardia and ventricular fibrillation were treated according to Advanced Cardiac Life Support protocols. Patients with hemodynamically stable atrial fibrillation were given expectant management first for spontaneous reversion to sinus rhythm or cardioverted to sinus rhythm pharmacologically or through direct current, as appropriate. Post Streptokinase ECG was done at 90 minutes from start of the infusion. Patients were kept admitted in hospital for 48-72 hours or longer depending upon the stability of patients and residual ischemia.

Statistical Package for Social Sciences version 20 was used for analysis. Quantitative variables were expressed using mean ± standard deviation (SD) and categorical variables were expressed with frequency and percentages. Chi square test was used to compare categorical variables, e.g., relationship between streptokinase complications and other categorical variables. Logistic regression was used to test if low systolic blood pressure and heart rate at presentation were predictors of hypotension during streptokinase infusion. Statistical significance was set at $p < 0.05$.

RESULTS

Mean age of the patients was 56.26 ±12.38 years. Males were 65.7% and females were 34.3%. Patients with history of hypertension were 51.9%, diabetes mellitus 33.7%, past history of acute coronary syndrome 23.2%, smoking 14.1% and past history of streptokinase were 8.4%.

The percentage of different ST segment elevation myocardial infarction (STEMI) based on location is shown in Table 1. Patients with Killip class 1 were 78.8%, while Killip class 2, 3, and 4 were 15.2%, 3.7% and 2.4%, respectively.

The frequency of different complications during and after Streptokinase infusion is shown in Table 2. Hypotension was seen in 20 (6.7%) patients as the most common complication. There was no significant relationship between complications of streptokinase and gender (p

Table 1: Percentage of STEMI according to location based on ECG criteria*

Location	Frequency	Percentage
Anterior STEMI	179	60.3
Inferior STEMI	120	40.4
Posterior STEMI	34	11.4
Lateral STEMI	18	6.1

* Isolated locations are shown for each type despite involvement of more than one location. For example: Posterior STEMI was present in 32 cases along with inferior STEMI while in 2 patients it was diagnosed as isolated STEMI.

STEMI = ST segment Elevation Myocardial Infarction; ECG = Electrocardiogram

Table 2: Frequency of complications of streptokinase according to gender

Complications	n = 297 (%)	Male=195 (%)	Female =102 (%)	P Value*
Hypotension	20 (6.7)	11 (5.6)	9 (8.8)	0.30
Nausea & Vomiting	19 (6.4)	15 (7.7)	4 (3.9)	0.21
Gums Bleeding	9 (3)	5 (2.6)	4 (3.9)	0.45
Allergic Reaction	9 (3)	7 (3.6)	2 (2)	0.72
Ventricular Tachycardia	8 (2.7)	5 (2.6)	3 (2.9)	0.56
Ventricular Fibrillation	6 (2)	3 (1.5)	3 (2.9)	0.34
Atrial Fibrillation	7 (2.4)	5 (2.6)	2 (2)	0.55
Fever	7 (2.4)	6 (3.1)	1 (1)	0.43
Bradycardia	6 (2)	4 (2.1)	2 (2)	0.66
Hemoptysis	2 (0.7)	1 (0.5)	1 (1)	1
Intracranial Hemorrhage	1 (0.3)	0 (0)	1 (1)	0.34

* P value is based on gender differences using Chi Square or Fisher's Exact Test

Table 3: Relationship of bradycardia at presentation with streptokinase induced hypotension

Variable	Streptokinase Induced Hypotension		P Value
Bradycardia at Presentation	Yes	No	
Yes	4 (14.3%)	24 (85.7%)	0.09
No	16 (5.9%)	253 (94.1%)	

Table 4: Relationship of low systolic blood pressure at presentation with streptokinase induced hypotension

Variable	Streptokinase Induced Hypotension		P Value
Low Systolic Blood Pressure (SBP) at Presentation, n (%)	Yes	No	
Yes	4 (18.2%)	18 (81.8%)	0.05
No	16 (5.8%)	259 (94.2%)	

>0.05). One patient developed intracranial bleed that expired before intervention could be done.

The relationship of bradycardia at presentation with Streptokinase induced hypotension was not significant, p =0.09. Hypotension during Streptokinase infusion was seen in 14.3% of those patients who had bradycardia at presentation (Table 3).

Similarly, the relationship between low systolic blood pressure at presentation and Streptokinase induced hypotension was also not significant (p =0.05). Twenty two patients presented with low systolic blood pressure out of which 4 (18.2%) patients developed hypotension during Streptokinase infusion (Table 4). Thirty percent hypotension during Streptokinase infusion was seen in patients with anterior myocardial infarction while 70% hypotension was seen in patients with inferior myocardial infarction, (p<0.05).

DISCUSSION

The most common complication in our study was hypotension (6.7%). This is also reported in another study in elderly population as the most common complication[10]. The frequency of hypotension with Streptokinase was higher in other studies[10,14,15]. However, In Gruppo Italiano (GISSI) trial[7], 3% patients developed hypotension; while in second international study of Infarct Survival (ISIS-2) trial[12], 10% patients developed significant hypotension.

We compared association of hypotension during Streptokinase infusion with systolic blood pressure <90 mmHg at presentation and the results revealed a p value of 0.05. Logistic regression (ENTER method) was used and overall the fit of the model was 93.3%; however, the results of regression indicated that the two predictors and their interaction failed to predict hypotension during streptokinase infusion, (p=0.454). This indicates that hypotension during Streptokinase infusion is independent of blood pressure value and bradycardia at presentation. This finding is also supported by ISIS-2 trial[12]. In a study conducted by Bilal et al[15], there was no difference in hypotension between Streptokinase and control group (Streptokinase 24% versus control 24%).

In our study, patients with inferior myocardial infarction (MI) has significant relationship with hypotension during streptokinase infusion as compared to patient with anterior MI. This was also reported by other study[16]. The decrease in systolic blood pressure in patients with inferior MI can also be attributed to concomitant occurrence of right ventricular infarction[17]. In contrast, Lew et al[18], showed that there is no relationship between hypotension during Streptokinase infusion and location of MI. However, patients with inferior MI had lower and greater fall in systolic blood pressure during streptokinase infusion. Lew et al[18] also noticed that the greatest fall in systolic blood pressure after infusion of Streptokinase occurred within first 20 minutes. They reported that the fall in blood pressure was significantly associated with magnitude and increased rate of infusion of injection streptokinase. The fall in blood pressure is generally transient and recovery to baseline occurs within 9 minutes. In those patients in whom the fall in blood pressure persisted, they had severe left ventricular dysfunction. In our study, sinus bradycardia during Streptokinase infusion was seen in 6 (2%) patients. Arrhythmia and bradycardia were reported as 6% by both Qureshi et al[10] and Bilal et al[15]. Bradycardia and hypotension is more common in patients with inferior MI as compared to anterior MI[16].

Ventricular arrhythmia is the most dangerous arrhythmia that demands immediate treatment with DC cardioversion. Ventricular arrhythmia occurred in 4.7% and atrial fibrillation occurred in 2.4% of patients in our study. These results are almost similar to the result of other studies[10,14,15,19]. The development of cerebrovascular accidents are rare with streptokinase. Only one (0.3%) patient developed intracranial hemorrhage in our study. This finding is also consistent with other studies[7,10,15]. Our findings of allergic reaction (3%) is similar to ISIS-2 (4%) and GISSI (2.3%) trials[7,12]. Similar findings are also reported by other studies[10,15]. Fever occurred in 2.4% of our patients. GISSI reported fever in 1.1%, Bilal et al[15] reported in 5% and Qureshi et al[10] reported in 3% of patients. None of the patient developed anaphylactic

reaction from Streptokinase in our study which is consistent with other studies[10,12,15].

We reported only bleeding from gums (as minor bleeding) from Streptokinase which occurred in 3% of patients. In other studies, like ISIS-2 and GISSI trials, minor bleeding occurred in 2.3% and 3.7% of patients, respectively[7,12]. Similarly, nausea and vomiting have been reported by ISIS-2 as allergic reaction and occurred in 6.4% of patients in our study. In one study, it is reported in 10.2% of patients[14].

The greatest advantage of Streptokinase in STEMI is within initial few hours. After this time period, the major advantage of Streptokinase is lost. In GISSI trial, benefit of Streptokinase was greatest within 1-3 hours of onset of symptoms. After 3 hours, mortality benefit suddenly drops although it remains significant. After 6 hours of pain onset, there is no benefit of Streptokinase and placebo[7]. These findings are supported by ISIS-2 trial[12]. Hemodynamically significant complications of Streptokinase are very uncommon as noted in this study as well as reported in literature[7,12,20]. Cerebrovascular accidents are rare with streptokinase. Therefore, there is no reason to withhold streptokinase because of fear of complications.

CONCLUSION

Significant hemodynamic and electrical complications due to streptokinase were uncommon. The risk of complications of streptokinase do not outweigh the benefit; therefore, streptokinase should be given to every eligible patient of STEMI without hesitation.

RECOMMENDATIONS

Government need to establish and maintain well equipped cardiac care facilities in remote areas with well-trained medical, paramedical and nursing staff. Cardiac care ambulance service should be established to minimize transportation delay.

REFERENCES

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 2017; 70:1-25.
2. Reddy KS. Cardiovascular disease in Non-Western Countries. N Engl J Med 2004; 350:2438-40.
3. Naseem S, Khattak UK, Ghazanfar H, Irfan A. Prevalence of non-communicable diseases and their risk factors at a semi-urban community, Pakistan. Pan Afr Med J 2016; 23:151.
4. Noor L, Adnan Y, Khan SB, ur Rehman H, Ahmad F, Hafizullah M. Changing trend of presentation of acute coronary syndrome in Peshawar over the last sixteen years. J Ayub Med Coll Abbottabad 2011; 23:136-9.
5. Zeb S, Hafizullah M, Jan H, Adil M, Zeb R. ST elevation myocardial infarction: An experience at Lady Reading Hospital, Peshawar, Pakistan. Khyber Med Univ J 2017; 9:60-2.
6. Sikri N, Bardia A. A history of streptokinase use in acute myocardial infarction. Tex Heart Inst J 2007; 34:318-27.
7. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet 1986; 1:397-402.
8. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2017; 39:119-77.
9. Beig JR, Tramboo NA, Kumar K, Yaqoob I, Hafeez I, Rather FA et al. Components and determinants of therapeutic delay in patients with acute ST-elevation myocardial infarction: A tertiary care hospital-based study. J Saudi Heart Assoc 2017; 29:7-14.
10. Qureshi AE, Jafri NA, Noeman A, Yasmin S, Khalil H. Streptokinase for acute myocardial infarction in the elderly. J Ayub Med Coll Abbottabad 2014; 26:535-8.
11. Califf RM, Fortin DF, Tenaglia AN, Sane DC. Clinical risks of thrombolytic therapy. Am J Cardiol 1992; 69:12A-20A.
12. Second International Study of Infarct Survival Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349-60.
13. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Circulation 2012; 126:2020-35.
14. Aslanabadi N, Safaie N, Talebi F, Dousti S, Entezari-Maleki T. The streptokinase therapy complications and its associated risk factors in patients with acute ST elevation myocardial infarction. Iran J Pharm Res 2018; 17:53-63.
15. Bilal H, Niaz Z, Shah ZH, Razzaq A, Ahsen W, Saleem A, et al. Complications of streptokinase during infusion in acute myocardial infarction. Ann King

Edward Med Uni 2006; 12:220-2.

16. Koren G, Weiss AT, Ben-David Y, Hasin Y, Luria MH, Gotsman MS. Bradycardia and hypotension following reperfusion with streptokinase (Bezold-Jarisch reflex): a sign of coronary thrombolysis and myocardial salvage. Am Heart J 1986; 112:468-71.
17. Lateef F, Anantharaman V. Hypotension in acute myocardial infarction patients given streptokinase. Singapore Med J 2000; 41:172-6.
18. Lew AS, Laramee P, Cercek B, Shah PK, Ganz W. The hypotensive effect of intravenous streptokinase in patients with acute myocardial infarction. Circulation 1985; 72:1321-6.
19. Taheri L, Boroujeni AZ, Kargar Jahromi M, Charkhandaz M, Hojat M. Effect of streptokinase on reperfusion after acute myocardial infarction and its complications: An ex-post facto study. Glob J Health Sci 2015; 7:184-9.
20. Grijseels EWM, Bouten MJM, Lenderink T, Deckers JW, Hoes AW, Hartman JAM et al. Pre-hospital thrombolytic therapy with either alteplase or streptokinase. Practical applications, complications and long-term results in 529 patients. Eur Heart J 1995;16:1833-8.

CONTRIBUTORS

SS conceived the idea, designed the study and drafted the initial manuscript. BK, ATK and NN helped collection of data, compiled results and carried out bibliography. FR and NR critically appraised the draft and did corrections after reviewers' suggestions. All authors contributed significantly to the submitted manuscript.