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RISK FACTORS ASSOCIATED WITH THE OCCURRENCE OF STREPTOKINASE INDUCED HYPOTENSION AMONG ST ELEVATION MYOCARDIAL PATIENTS (STEMI)

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ABSTRACT

Background: Hypotension is a common adverse drug reaction that occurs during Streptokinase (SK) infusion. Despite this, there is paucity of data available to prevent and manage this reaction.

Objective: We conducted a study to determine the occurrence pattern and predict risk factors associated with this reaction.

Setting: The study was conducted in a tertiary care hospital.

Methods: Data from 183 patients that were given SK for ST Elevations Myocardial Infarctions in 2018 and 2019 were retrieved.

Main outcome measure: Systolic Blood Pressure (SBP) measurements and corresponding durations during the occurrence of this reaction were obtained.

Results: Hypotension was reported as the most common adverse drug reaction that occurred among 22.4% of patients in the study. SK induced hypotension occurred at a median (IQR) of 15(13) minutes after starting SK infusion. Hypotensive episode recovered in a median duration of 15(10) minutes with appropriate interventions. Apart from temporarily withholding SK, most patients (58.5%) required a combination of fluid therapy and vasopressor support to restore SBP. Although duration of SK infusion was prolonged in all patients (20.7 ± 13.5 minutes), interventions instituted were shown to be successful in restoring SBP. Patients with inferior MI were shown to be a significant predictor for the occurrence of SK induced hypotension (OR =2.34; 95% CI = 1.16 – 4.74; p-value = 0.018).

Conclusion: The risk and benefit of administering SK to inferior MI patients must be assessed and effective strategies can be implemented to ensure SK treatment is safe to all STEMI patients.

Keywords: Streptokinase, ST Elevation Myocardial Infarction, Risk factors, Hypotension

Impact of Findings on Practice Statements:

- Facilitate in efforts to prevent this reaction especially among inferior Myocardial Infarction patients to ensure safe administration of Streptokinase.
- Effectiveness of current treatment strategies is proven and thus can continue to be instituted to manage this reaction.
- Data on the occurrence pattern allows in early preparation prophylaxis to ensure drop of blood pressure rapidly recovers to prevent complications.

INTRODUCTION

Ischemic heart disease (IHD) is the primary cause of death globally and accounts to 15.6% death in Malaysia in 2019(1, 2). One of the serious complications of IHD is Acute Coronary Syndrome (ACS). Based on Malaysian National Cardiovascular Disease Database (NCVD) registry 2014- 2015, a total of 46.2% of ACS patients presented with ST Elevation Myocardial Infarction (STEMI) with 10.4% in – hospital mortality rate and 12.3% 30 day mortality rate (3).

Mainstay treatment of patients presenting with STEMI is reperfusion strategy that involves opening the occluded artery by either administering fibrinolytic agent or primary percutaneous coronary intervention (PPCI). In Malaysia, fibrinolytic therapy is the most common mode of reperfusion strategy used for STEMI. This is due to its cost and convenient geographical access which makes it a more viable option compared to PPCI (3). However, safety related to fibrinolytics have been a major concern in the treatment of STEMI.

Streptokinase (SK) is the first fibrinolytic agent discovered for the treatment of ACS (4). It is widely used for the treatment of STEMI in Malaysia. SK is a metabolic product of beta hemolytic streptococci and acts as a non-fibrin selective fibrinolytic that activates fibrinolysis by forming complexes with plasminogen leading to the dissolution of fibrin (clot).

SK have been shown to reduce mortality of STEMI patients based on findings reported in large scale established

studies (6, 7). However, concerns on its use as a safe fibrinolytic agent have emerged due to the prevalence of adverse drug reactions which requires close monitoring and prompt interventions to prevent complications.

Hypotension is a common adverse drug reaction that occurs during SK infusion. Previous studies have reported a prevalence of 34 - 48% among patients given SK for STEMI (7, 8, 9). SK induced hypotension have been defined as a drop in systolic blood pressure(SBP) of less than 90mmHg or drop in diastolic blood pressure(DBP) of less than 60mmHg after the commencement of SK infusion in studies conducted on this reaction((9,10). Infusion rate and comorbidities was shown to be associated with the occurrence of this reaction (9, 11).

Despite the prevalence of this reaction, there is currently limited evidence on appropriate interventions or prevention strategies to manage this reaction. This is due to paucity of data regarding this reaction as most studies conducted were regarding all adverse drug reactions related to SK rather than focused on the occurrence of hypotension alone.

There is a need to further analyze the occurrence of SK induced hypotension reported in previous studies in order to ensure SK treatment does not cause complications that can increase the mortality risk associated with STEMI. Hence, this study aim to understand the occurrence pattern of SK induced hypotension and to identify common treatment strategies as well as predict risk factors associated with the occurrence of this reaction.

AIM OF STUDY

This study aim to analyze the occurrence pattern, identify effective treatment strategies and predict risk factors associated with this reaction.

ETHICAL APPROVAL

The ethical approval for this study was sought from Medical Research & Ethics Committee (MREC) Ministry of Health, Malaysia (NMRR-19-3830-52249)

METHODS AND MATERIALS

Study Design

This was a retrospective cross sectional study involving STEMI patients who were given IV SK for treatment of STEMI in a tertiary care hospital, Kuala Lumpur. Medical records of patients given SK for STEMI in 2018 and 2019 were traced and eligible patients were conveniently sampled in the study. Patients that presented with signs of shock (SBP< 90/60 mmHg) prior to SK administration or had insufficient important data were excluded from the study.

Data Collection

A data collection form was used for the purpose of documenting required information for the study. This form was used to gather patient's demographics such as age, gender, race, nationality, co morbidities and weight. This information was used to describe the study population and assess risk factors of developing SK induced hypotension.

Details on STEMI such as location of myocardial infarction was also documented. Apart from this, information on SK treatment were gathered such as time of initiation and completion of SK infusion as well as medications given prior to SK infusion. Relevant blood pressure measurements during the occurrence of SK induced hypotension which was defined as a drop in SBP to below 90mmHg after the initiation of SK until the completion of SK infusion was recorded.

In addition to this, information on type of interventions done during the event of hypotension related to SK administration and the outcome of the thrombolysis were also gathered in the form.

Statistical Analysis

Statistical analysis were performed using SPSS Version 24. Descriptive statistics were used to describe patient's demographics, clinical characteristics, as well as risk factors of SK induced hypotension. Categorical data such as gender, age, race, weight, nationality and co – morbidities were presented as frequencies and percentages. Continuous data such as blood pressure readings, duration of SK infusion, duration of SK induced hypotension were presented as mean and standard deviation or median and interquartile range depending on normality distribution. Kolmogorov-Smirnov equation was used to test for normality for all continuous variables in this study.

Univariate logistic regression analysis was used to analyse risk factors that are significantly associated with the occurrence of SK induced hypotension. Variables with p value < 0.25 were included in multivariate logistic regression analysis to assess independent predictors for occurrence of SK induced hypotension. Results were presented as odd ratios with a confidence interval of 95%. All statistical tests with p - value of < 0.05 denote statistical significance.

RESULTS

A total of 183 patients were recruited in the study (Table 1). Majority of the patients were male (90.2%) with predominantly Malays (33.3%) followed by Indian (18%) and Chinese (7.7 %). Most patients were less than 65

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years old (78.1%) and had a body weight above 50 kg (97.3%). More than half of the patients (57.4%) had pre-existing comorbidities prior to admission for STEMI. Hypertension was recorded as the highest comorbid condition (45.9%). Inferior MI (62.3%) was the most common location of MI compared with anterior MI that comprised of 37.7%.

All patients were given anticoagulants prior to SK treatment as recommended for the treatment of STEMI with most patients were given S/C Fondaparinux 2.5 mg (93.4%). Nearly all patients (96.7%) received dual antiplatelet with loading doses of Tablet Clopidogrel and Tablet Aspirin. Some patients also received sublingual Glyceryl Trinitrate for quick relieve of chest pain and some IV Morphine for chest pain in titrating doses as recommended together with IV Metoclopramide to prevent emesis.

Most of the patients that received SK for STEMI treatment did not experience any adverse drug reactions (Table 2). However, 29% of patient had documented adverse drug reactions that was associated with the administration of SK. Hypotension was reported as the most common adverse drug reaction(ADR) that occurred among 22.4% of patients in the study. Other ADRs were rashes, minor bleeding and arrhythmia.

Mean SBP of patients included in this study prior to commencement of SK treatment was 132.1 ± 20.8 mmHg. (Table 2). Median (IQR) SBP recorded during the onset of hypotension (defined as SBP < 90 mmHg that occurred after initiation of SK until completion of SK infusion) was 82mmHg (18) with an average drop of mean SBP fall of 49.7 ± 23.5 mmHg. The median (IQR) onset of SK induced hypotension is 15(13) minutes from the commencement of SK infusion. Duration of SK induced hypotension was approximately 15 minutes. Although for most patient the hypotension resolved within 15 minutes with interventions, 6 patients took more than 30 minutes to recover.

Based on univariate analysis (Table 3), patients that develop SK induced hypotension and those that did not develop SK induced hypotension differed significantly with regards to the location of MI (x^2 = 5.73; df = 1;p-value = 0.017). Patients with pre-existing dyslipidemia (p - value = 0.188) was found to have close probability value of less than 0.25 and thus were included into the multivariate analysis.

Multivariate analysis (Table 4) adjusted for location of MI and comorbidity of dyslipidemia revealed that inferior type MI (OR =2.34; 95% CI = 1.16 – 4.74; p-value = 0.018) is a significant predictor of the occurrence of SK induced hypotension. Patients presenting with inferior MI have a two times higher chance of developing SK induced hypotension compared with patients that presented with anterior MI.

Most patients (73.2 %) that developed SK induced hypotension required a combination of fluid (Normal Saline 0.9%) and vasopressor (IV Noradrenaline infusion) to manage the drop in blood pressure (Figure 1). Others patients required either fluid therapy alone (4 patients) or vasopressor alone (7 patients).

The main outcome measured was successful thrombolysis which was observed in all 41 patients that developed SK induced hypotension. Although SK was withheld in all patients when the hypotension occurred, the infusion was resumed once hypotension resolved (SBP ≥ 90mmHg). However, SK infusion was prolonged in all patients that developed SK induced hypotension with an average of 20.75 ± 13.5 minutes longer than the usual 60 minutes SK infusion (Table 2).

DISCUSSION

SK induced hypotension have not been studied extensively although it was a common adverse drug reaction reported to occur. Hence, our study was able to shed some light on the occurrence of this reaction.

Almost all patients in the study were given dual antiplatelet with Aspirin and Clopidogrel as recommended by local as well as international guidelines(14,15) due to their proven benefits in reducing mortality, patency rate of the infarct-related artery, ischemic complications and major vascular complications among STEMI patients(16,17). Some patients were given Ticagrelor instead of Clopidogrel. This was due to reasons such as an allergy history to Clopidogrel and also because the presenting patient was planned for a PPCI prior to deciding for fibrinolytic therapy as Ticagrelor are preferred for PPCI due to their faster onset of action and short acting nature, thus can be used in patients who may need surgery without increasing the risk of bleeding (15). Patients in our study also received anticoagulants due to their benefit in preventing mortality and reinfarction (18, 19).

The most common ADR reported in our study was hypotension that occurred in 22.4% (N= 183) of patients that was given SK. This finding were substantially much lower than reported in a similar study conducted in a secondary care hospital in 2019 in which 48.5 % (N = 65) of patients developed hypotension associated with SK (9). This could be attributed to differences in patient's demographics such as age and comorbidities.

Drop of blood pressure can compromise the hemodynamic stability of patients thus in this study the drop of SBP was also reported that may reflect the severity of this reaction. Mean SBP drop among hypotensive patients in our study were higher than reported in another study which showed a mean SBP drop of 35 ± 19mmHg(11). This could be due to differences in measuring SBP drop as the mentioned study analysed the drop in SBP without any defined

hypotension range unlike our study which defined hypotension as SBP below 90mmHg.

Our study findings have confirmed the findings of other studies that also demonstrated that this reaction occurs within 30 minutes of commencing SK infusion (9, 10, 11). This implies that this reaction appears rather early and thus it is vital to ensure patients are given adequate monitoring during this phase. Patients in our study recovered slightly faster with appropriate interventions compared to another study that reported recovery time of 20 ± 66 minutes(9). This could be attributed to the difference in initiation of the interventions that was given during the onset of the hypotension.

Predicting risk factors associated with SK induced hypotension is one of the objectives of this study in order to prevent this reaction. Based on our findings, only location of MI is a significant predictor in which patients that presented with inferior MI have two times higher chance of developing SK induce hypotension compared to anterior MI patients. To our best knowledge, this is the first study to report on a significant association between location of MI and SK induced hypotension.

Inferior MI have been associated with lower mortality rates and a better prognosis than anterior MI (18, 19). However, up to 60% patients with inferior MI may develop hypotension (22). This could be because 40% of inferior MI patients have concomitant right ventricle infarction which may cause systemic hypotension due to decreased right heart function (23, 24). Based on this, inferior MI patients in our study were more likely to develop SK induced hypotension due to the possibility that the administration of SK may aggravate the development of hypotension among inferior MI patient. Due to these reasons, administration of SK must be given with great caution to inferior MI patients.

SK is administered to all patients over a standard 60 minutes infusion in current practice. SK induced hypotension was thought to be associated with infusion rates that are weight based. However, the findings of our study showed that weight of a patient which was used to determine the infusion rate of SK was not significantly associated with the occurrence of SK induced hypotension. This is in contrast to a study which reported that patients given SK infusion rates < 500 unit/kg/min (11) had less hypotensive episode associated with SK infusion. Another study also mentioned that infusion rate of less than 250 unit/kg/min is probably more appropriate because hypotension was still observed in infusion rate < 500 unit/kg/min (10). Thus, our study showed that the recommended infusion rate of 60 minutes which is not weight based should be used until further studies prove otherwise.

It is interesting to note that contrary to the findings of a similar study that reported pre –existing dyslipidaemia, hypertension and stroke as significant predictors of SK induced hypotension (9), our study did not find any co – morbidities of patients in the study to be significant predictors of this reaction. This could be due to the differences in proportions of patients that presented with these co- morbidities.

In line with most previous studies (11, 13), our results also demonstrated that age was not significantly associated with the occurrence of this reaction. Elderly patients are more prone to develop Type A ADR as compared to SK induced hypotension which is a Type B ADR as unlike Type A ADR, it is not related to dose or its pharmacological action (25, 26). Nevertheless, irrespective of age, all patients must be closely monitored during SK therapy.

Our study have also confirmed the findings of previous studies(8,11) that reported gender differences is not associated with the occurrence of SK induced hypotension thus highlights that this reaction is different in many aspects compared to other ADRs as gender differences have been associated with the development of ADRs in general (25,26,27).

Our study also proved that interventions that was given to manage this reaction was effective as all patients were able to complete their thrombolysis with SK although there was a delay due to withholding SK infusion during hypotensive episode. Most patients required an addition of a vasopressor to increase the blood pressure after given fluid resuscitation. In contrary, other studies have reported that only a small number of patients required vasopressor to recover blood pressure (9, 11). This could be due to differences in institutional policy on management of SK induced hypotension and also the response of interventions may differ between patients.

There were a few limitations of the present study. The first limitation is due to the retrospective nature of the study, we could not obtain information on interventions that in current practice could have been instituted based on different magnitude of blood pressure reductions. Due to this, there could be differences in the actual pattern of drop in blood pressure and its management strategies. Another limitation that our study had is the interventions strategies done could not be analyzed in detail to give a clearer understanding on the choice of the interventions chosen. Information such as the exact timing the interventions were started and stopped were not possible to be obtained. This was attributed to the design of the study which was retrospective and thus dependent on the existing documentations of these interventions.

Despite the limitations, this study was able to provide a valuable insight on the occurrence of SK induced hypotension. The prevalence data analyzed in this study gives a reflection on the burden of this adverse reaction

towards fibrinolytic therapy with SK in general. Appropriate steps can be taken to prepare in advance based on information on the pattern of occurrence of this reaction. This is important as any delay can be detrimental. Apart from this, a change in current practice is possible as risk stratification among STEMI patients that presented with inferior MI can be done by weighing the benefit and risk of giving SK to these group of patients. To further explore the association between location of MI and the occurrence of this reaction, a prospective study comparing patients that were given SK and other fibrinolytics would be beneficial as the significance of hypotension due to SK can be determined and help provide valuable information that can guide in selecting a suitable agent for STEMI patients.

CONCLUSION

This study have given an overview on the overall occurrence of SK induced hypotension. The risk and benefit of developing SK induced hypotension should be assessed among inferior MI patients and effective strategies can be implemented to ensure SK treatment is safe to all STEMI patients.

DECLARATION

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This study was self-funded
Conflict of Interest
All authors declare no conflict of interest
Availability of Data
All data is available upon request
Consent for publication
All authors agreed with the submission and publication in this journal.
Authors' contributions
KM and AMR designed the study. KM and JN collected research data and carried out analysis. AMR supervised the study data collection and analysis and reviewed the manuscript.
All authors read and approved the final manuscript.

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Table 1: Baseline Demographic and Clinical Characteristics

Parameters	Frequency (n, %)
Gender	
Female	18 (9.8)
Male	165(90.2)
Age	
<65 years old	143(78.1)
≥65 years old	40(21.9)
Weight	
<50 kg	5(2.7)
≥50 kg	178(97.3)
Co morbidities	105(57.4)
Hypertension	84(45.9)
Diabetes Mellitus	66(36.1)
Chronic Heart Disease	23(12.6)
Asthma	15(8.2)
Dyslipidaemia	7(3.8)
Others	15(8.2)
No comorbidities	78(42.6)
Location of Myocadial Infarction	
Anterior MI	69(37.7)
Inferior MI	114(62.3)
Medications administered pre SK infusion	
Anticoagulant	171(93.4)
Fondaparinux	12(6.6)
Enoxaparin	
Antiplatelet	
Aspirin	1(0.5)
Aspirin +Clopidogrel	177(96.7)
Aspirin +Ticagrelor	5(2.7)

Table 2: Prevalence and Pattern of SK Induced Hypotension

Parameters	Mean ± SD
[a]ADR during SK infusion	53(29)
Hypotension	41(22.4)
Bleeding	9(4.4)
Rashes	2(1.1)
Arrhythmia	1(0.5)
No ADR	130(71)
Blood pressure pre SK infusion(mmHg)	
SBP(mmHg)	132.1 ± 20.8
[b]SBP during hypotension	82(18)
Drop of SBP during hypotension(mmHg)	49.7 ± 23.5

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[b]**Onset of Hypotension(minutes)**	15(13)
[b]**Duration of hypotension(minutes)**	15(10)
[a]**Duration of hypotension(minutes)**	
10 minutes	14(34.1)
15 minutes	12(29.3)
20 minutes	6(14.6)
25 minutes	3(7.3)
30 minutes	4(9.8)
35 minutes	1(2.4)
45 minutes	1(2.4)
[c]**Duration SK infusion prolonged(minutes)**	20.75 ± 13.5

a Frequency, n(%)
b Median(Interquartile Range)
c Mean ± SD

Table 3: Univariate Analysis for Risk Factors of SK Induced Hypotension

Variable	**SK Induced Hypotension (n, %)**		
	Yes	**No**	**p value[a] [x^2(df)]**
Gender			
Male	38	127	0.767(2 tailed)
Female	3	15	
Age			
<65 years old	33	110	0.680
≥65 years old	8	32	[0.170(1)]
Weight			
<50kg	2	3	0.312(2 tailed)
≥50kg	39	139	
Location of MI			
Anterior	22	47	**0.017**
Inferior	19	95	[5.729(1)]
Co morbidities			
Hypertension			
Yes	18	66	0.771
No	23	76	[0.085(1)]
Diabetes Mellitus			
Yes	15	51	0.937
No	26	91	[0.006(1)]
Chronic Heart Disease			
Yes	7	16	0.323
No	34	126	[0.976(1)]

Asthma/COPD			
Yes	4	11	0.747(2 tailed)
No	37	131	
Dyslipidaemia	3	4	**0.188(2 tailed)**
Yes	38	138	
No			

[a]Statistical calculations were done using chi-squared test, Fisher Exact Test (for variable –gender, weight, dyslipidemia and asthma.

Table 4: Multivariate Analysis Regarding Predictor Variable for Development of SK Induced Hypotension

Variable	B	OR	p value	95% CI
Inferior MI	0.850	2.34	**0.018**	1.155 - 4.743
Comorbidity – Dyslipidaemia	0.993	2.7	0.231	0.560 – 13.02

Backward LR multiple logistic method applied.
No interactions and multicolinearity detected
Hosmer Lemeshow Test $\chi^2 = 3.459$, df = 7, p = 0.840, overall classification table = 77.6%, and are under ROC curve (60.3%) was applied to test the model fitness B – Regression coefficient; OR – Odds Ratio; CI- Confidence Interval.

Figure 1: Frequency of Interventions Used to Manage SK Induced Hypotension