Original Article

On-shelf Streptokinse EnsuRes More Favorable In-hospital Outcome after Acute STEMI (OSTRIC trial) - A Single Centre Randomized Controlled Trial

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Abstract:

Introduction: The burden of CAD is increasing at a greater rate in South Asia than in any other region globally. Among them acute ST elevation myocardial infarction (STEMI) is one of the leading causes of death and disability. Major aspect of treatment of acute STEMI is reperfusion of the infarct related artery. Delay in reperfusion is associated with higher mortality and morbidity rates. While primary percutaneous coronary intervention (PCI) is the preferred mode of reperfusion, only few patients can get this form of reperfusion within recommended timelines. On the other hand, thrombolysis is easily available, economical and evaluated in several clinical studies. Thrombolysis is an important reperfusion strategy, especially when primary PCI cannot be offered to STEMI patients, with a time dependent fashion.

Methods: This randomized controlled trial was conducted in the department of Cardiology of National Institute of Cardiovascular Diseases since January 2016 to June 2018. Objective of the study was to find out the outcomes of acute STEMI patients after getting on-shelve or purchased Streptokinase (STK). Initially there was no free supply of STK in our hospital as it is an expensive drug, later on fund was arranged and STK was made available at free of cost by the hospital authority. Total 300 patients fulfilling inclusion and exclusion criteria were included in the study. Group I: 150 patients received on-shelf STK when it was made free by the authority and Group II: 150 patients received purchased STK when it was not available at free of cost. Study populations were analyzed for LVF, Cardiogenic shock, MACE (re-infarction, stroke and death) and duration of hospital stay.

Results: The mean age of the study population in group I and II were 53.88 ± 14.51 vs. 57.18 ± 15.28 years (p= 0.46). Mean door to injection time in group I and II were 25.51 ± 7.9 vs. 70.36 ± 16.6 minutes (p=<0.001). ST segment resolution was significantly higher in on-shelf STK group then purchased group which were 109 (72.7%) vs. 92 (61.3%), p=0.03. Considering the in-hospital outcome we found that in group I and group II LVF (killip III/IV) was 10 (6.7%) vs. 23 (15.3%) , Cardiogenic shock was 11 (7.3%) vs. 24(16%) , re-infarction was 9(6%) vs. 13 (8.7%) , Stroke was 6 (4%) vs. 8 (5.3%) and death was 12 (8%) vs. 23(15.3%). Among them LVF (killip III/IV), Cardiogenic shock and Death were significantly higher in group II (p=0.02, 0.01 and 0.04 respectively). Major adverse cardiac events (MACE) included re-infarction, Stroke and death, were significantly higher in group II [27 (18%) vs. 44(29.3), p= 0.02]. Mean hospital stay was significantly higher in group

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II (6.05 ± 1.81) then group I (5.33±1.26), (p=<0.001). Multivariate logistic regression analysis showed hypertension (p=.025) and door to injection time (p=.002) were statistically significant predictors for in-hospital major advance cardiac events (re-infarction, stroke and death) after streptokinase therapy.

Conclusion: Despite the strength of evidence based medicine pertaining to the benefits of primary PCI in STEMI, treatment options in Bangladesh are often dictated by resources, logistics, availability and affordability. In our country, not many hospitals offer primary PCI services round the clock. So thrombolysis by streptokinase it the potential reperfusion strategy in our context. In our study it has been found that on-shelf Streptokinase significantly reduce door to injection time which ultimately reduce cardiovascular mortality and mortality and also significantly reduce hospital stay. Hospitals intended to treat acute STEMI patients should have on-shelve Streptokinase to reduce door to injection time which affect the in-hospital outcome by reducing significant cardiovascular mortality and morbidity.

Key words: STEMI, Thrombolytic Therapy, Streptokinase, In-Hospital Outcome

Introduction:

CVD is the number one killer worldwide.[1,2] According to the heart disease and stroke statistics 2016 update by the American Heart Association, heart disease and stroke continue to be the top two killers worldwide. As of 2013, 31% of all deaths were from CVD, with 80% occurring in low- and middle-income countries. The burden of CVD, especially the CAD is increasing at a greater rate in South Asia than in any other region globally. The prevalence of CVD in India has been estimated to be nearly 3% in 2000, and upto10% in recent years, indicating rising prevalence.[3,4] The health care in Bangladesh is the reflection of mixed economy. Only 20% of the population has the affordability to take proper medical care either with government supported schemes or private insurance. In this scenario, it is not difficult to understand the challenges in delivery of modern evidence based management of STEMI to the majority of the population.[5]

Acute ST elevation myocardial infarction (STEMI) is one of the leading causes of death and disability. It generally occurs due to sudden occlusion of a coronary artery by formation of thrombus at the site of fissured or ruptured atherosclerotic plaque.[6] Major aspect of treatment of acute STEMI is reperfusion of the infarct related artery. Reperfusion therapy aims at restoration of antegrade flow in the occluded infarct related artery, which reduce infarct size and improves clinical outcome.[7] The management of acute STEMI has rapidly evolved worldwide during the last two decades. Despite global agreement on most issues related to the management of STEMI, wide discrepancies exist in implementation of Western guidelines in most of the developing world. The need has been felt that every country and society should adopt the existing scientific data, in combination with local limitations and strengths, and develop protocols that work best in their community.

Selection of reperfusion strategy in STEMI the prompt restoration of antegrade flow is the core aim. Delay in reperfusion is associated with higher mortality and morbidity rates. Timely reperfusion results in better myocardial salvage and preservation of left ventricular function. Despite recent advances in pharmacological and interventional reperfusion strategies, timely reperfusion still remains suboptimal in patients with STEMI. While primary percutaneous coronary intervention (PCI) is the preferred mode of reperfusion by most guidelines, only few patients with STEMI can avail this form of reperfusion within recommended timelines. On the other hand, thrombolysis is easily available, economical and evaluated in several clinical studies but fraught with dangers of re-occlusion of infarct related artery (IRA). Initial timely thrombolysis followed by early PCI to improve the patency rates, labeled as pharmaco-invasive (PI) strategy, is an attractive option of reperfusion in STEMI and may bridge the gaps in systems of care.

There are currently three reperfusion strategies recommended worldwide. Primary PCI is the preferred reperfusion strategy in patients with STEMI, provided it can be performed within guideline mandated time-frame, by an experienced team.[8] Primary PCI produces higher rates of IRA patency, TIMI 3 flow, and lower rates of recurrent ischemia, re-infarction, emergency repeat revascularization procedures, intracranial haemorrhage and death.[9] Randomized clinical trials have repeatedly shown that primary PCI is superior to thrombolysis, when performed in a timely manner, in high-volume, experienced centres.[10,11] Primary PCI results in TIMI 3 flow of IRA in over 90% of patients.[12] PCI related delay of >60 min negates any mortality benefit compared to immediate thrombolysis.[13]

Thrombolysis is an important reperfusion strategy, especially when primary PCI cannot be offered to STEMI patients, with a time dependent reduction in mortality and morbidity rates within 12 h after symptom onset. Thrombolytic therapy has greater benefit in patients treated within 1 h of symptom onset, with a sharp drop off after 3 h. Thrombolysis prevents

approximately 30 early deaths per 1000 patients treated within 6 h after symptom onset.[14]

Thrombolysis is currently the most practiced form of reperfusion method in Bangladesh. The earlier studies examined thrombolytics, initially with streptokinase (STK) and subsequently with tissue plasminogen activator (tPA) and its analogs. A meta-analysis of thrombolytics showed that this was a good way of reperfusion with improved outcomes across subsets except in those presented beyond 12 h of symptom onset.[14] Benefit from thrombolytic therapy in patients with STEMI who present more than 12 h after symptom onset has not been established, although consideration should be given in patients with on-going chest pain, with large myocardium at risk or hemodynamic instability, if primary PCI is not available.

Fibrin specific agents have some advantages over streptokinase, but are more expensive and not widely available. However, the final decision of choice of thrombolytic agent is at the discretion of the treating physician and the patient's choice. Pharmaco-invasive (PI) strategy PI strategy consists of early thrombolysis followed by either rescue PCI for patients with failed thrombolysis, or non-urgent coronary angiography to determine the need for additional revascularization within 3–24 h.[15,16] It differs from a 'facilitated' approach which consists of an immediate PCI following fibrinolysis and has shown adverse outcomes.[17]

Streptokinase is cheap, easily available and is the most frequently used thrombolytic agent in Bangladesh. Most of the hospitals of the country do not keep Streptokinase. in their shelf and it kills time to collect it from outside. Considering all points we designed this study to find out in-hospital outcomes of on-shelf and purchased Streptokinase.

Materials and methods:

This randomized controlled trial was conducted in the department of Cardiology of National Institute of Cardiovascular Diseases since January 2016 to June 2018. Objective of the study was to find out the outcomes of acute STEMI patients after getting on-shelf or purchased Streptokinase. In Bangladesh most of the patients purchase STK, as it is an expensive drug it is not kept on the shelf. In our hospital initially there was no free supply of STK later on fund was arranged and STK was made available at free of cost by the hospital authority. Total 300 patients fulfilling inclusion and exclusion criteria were included in the study. Group I: 150 patients received on-shelf STK when it was made free by the authority and Group II: 150 patients received purchased STK when it was not available at free of cost. Inclusion criteria were age >18 and <80, clinical and ECG diagnosis of acute STEMI, presented within 12 hours of onset of chest pain) and exclusion criteria were uncontrolled hypertension, old myocardial infarction, post PCI or CABG, cardiomyopathies, valvular heart disease, congenital heart disease, severe co morbidities i.e. CVD, CKD. ST segment resolution considered significant when it is reduced by 50% from the baseline. Study populations were analyzed for LVF, Cardiogenic shock, MACE (re-infarction, stroke and death) and duration of hospital stay. Informed written consent were taken from all patients.

Statistical Methods:

Data obtained from the study were analyzed and significance of differences were estimated by using statistical methods. Variables were analyzed by chi-square test, t-test where applicable. Multivariate logistic regression analysis was done. P value $p < 0.05$ were considered as significant. Statistical analyses were performed with SPSS, version 20.0 (SPSS Inc).

Results and discussion:

The mean age of the study population in group I were 53.88 ± 14.51 years and group II were 57.18 ± 15.28. There was no statistical difference (p= 0.46). Age group 41-60 years were height in both group, group I were 64 (42.7%) and group II were 60 (40%) (Table 1). Although ischaemic heart disease develops on average 7–10 years later in women compared with men, MI remains a leading cause of death in women. Acute coronary syndrome (ACS) occurs three to four times more often in men than in women below the age of 60 years, but after the age of 75, women represent the majority of patients.[7]

Male patients were 70.7% and 66.7% in group I & II respectively. Female patients were 29.3% and 33.3% in group I and II respectively with no statistical difference (p= 0.43). Risk factors analysis of our study population showed hypertension were 56 (27.3%), diabetes were 47 (31.3%), smoking were 41 (27.3%) in group I and hypertension were 60(40%), diabetes were 49 (32.7%) and smoking were 39 (26%) in group II with no statistical difference (p= 0.63, 0.80 and 0.79 (Table I).

Several recent studies have highlighted a fall in acute and long-term mortality following STEMI in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention.[18,19,20]

Among the study population it was observed that mean door to injection time were 25.51 ± 7.9 minutes in group I and it was 70.36 ± 16.6 minutes in group II. Mean door to injection time were significantly lower in on-shelf STK group then purchased STK group which is three times lower

(p=<0.001) (Figure II). If the reperfusion strategy is fibrinolysis, the goal is to inject the bolus of fibrinolytics within 10 min from STEMI diagnosis. This time is selected based on the median time from randomization to bolus recorded in the STREAM trial, which was 9 min.[21] In previous ESC STEMI guidelines,[22] the target time was 30 min, but this was calculated from FMC (as opposed to STEMI diagnosis). STEMI diagnosis should occur within 10 min from FMC.

There are several features of successful thrombolysis. ST segment resolution along with relieve of chest pain and hemodynamic improvement are prominent. In our study it has been found that ST segment resolution was significantly higher in on-shelf STK group then purchased group which were 109 (72.7%) vs. 92 (61.3%) respectively with p=0.03. patients with failed thrombolysis was treated by additional Injection Low molecular heparin. As the time elapsed thrombus become organized and resist lyses. For this reason the early thrombolytic is administered the early ST segment resolution occur.

In our study it has been found that acute extensive anterior MI were highest in groups I which was 69 (46%) followed by Antero septal 27 (18%), Inferior 24 (16%), Inferior+ RVI 19(12.7%) and High lateral 11(7.3%) on the other hand acute extensive anterior MI were also highest in groups II which was 74(49.3%) followed by Inferior 27 (18%), Antero septal 24 (16%), Inferior+ RVI 15 (10%) and High lateral 10 (6.7%) with no statistically significant difference between groups (p= 0.98) (Table III).

Considering the in-hospital outcome in our study we found that in group I significant arrhythmia was 12(8%), LVF (killip III/IV) was 10 (6.7%), Cardiogenic shock was 11 (7.3%), re-infarction was 9(6%), Stroke was 6 (4%) and death was 12 (8%) whereas in group II significant arrhythmia was 10(6.7%), LVF (killip III/IV) was 23 (15.3%), Cardiogenic shock was 24(16%), re-infarction was 13 (8.7%), Stroke was 8 (5.3%) and death was 23(15.3%). Among these variables LVF (killip III/IV), Cardiogenic shock and Death were significantly higher in group II (p=0.02, 0.01 and 0.04 respectively) (Table IV). Patients having primary PCI also had lower rates of heart failure, mechanical complications, and cardiac arrest compared with fibrinolysis and no reperfusion (P < 0.05). The rates of hemorrhage stroke (0.3%, 0.6%, and 0.1%) and other major bleeding (3.0%, 5.0%, and 3.1%) were similar in the primary PCI, fibrinolysis, and no reperfusion group (P > 0.05).[21]

In our study Major adverse cardiac events (MACE) included re-infarction, Stroke and death, were significantly higher in group II [27 (18%) vs. 44(29.3) , p= 0.02]. Poor in-hospital outcome prolonged mean hospital stay. Mean hospital stay was significantly higher in group II (6.05 ± 1.81) then group I (5.33±1.26), (p=<0.001). Multivariate logistic regression analysis showed hypertension (p=.025) and door to injection time (p=.002) were statistically significant predictors for in-hospital major advance cardiac events (re-infarction, stroke and death) after STK therapy (Table V).

Table-I

Baseline characteristics of the study population (N-300)

Variables	On-shelf STK (n=150)n (%)	Purchased STK (n=150)n (%)	P value
Age (yrs)	53.88 ± 14.51	57.18 ± 15.28	0.46
Male	106 (70.7)	100 (66.7)	0.43
Female	44 (29.3)	50 (33.3)	
Hypertension	56 (37.3)	60 (40)	0.63
Diabetes	47 (31.3)	49 (32.7)	0.80
Smoking	41 (27.3)	39 (26)	0.79
Door to injection time (min)	25.51 ± 7.9	70.36 ± 16.6	<0.001
ST resolution	109 (72.7)	92 (61.3)	0.03

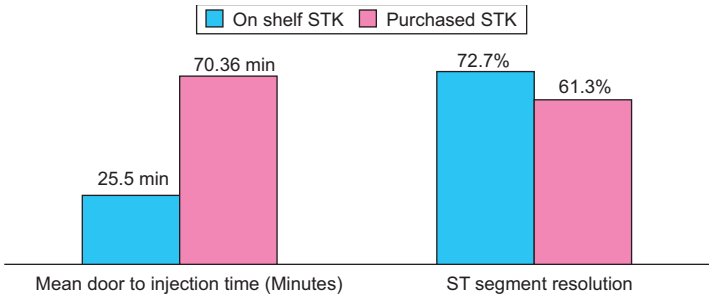

Fig.-1: *distribution of study population according to mean door to injection time and ST segment resolution.*

Table-II

Age distribution of the study population (N=300)

Age group	On-shelf STK (n=150)n (%)	Purchased STK (n=150)n (%)	P value
≤40	38(26)	27 (18)	
41-60	64(42.7)	60 (40)	0.25
61-80	42(28)	56(37.3)	
>80	5(3.3)	7(4.7)	

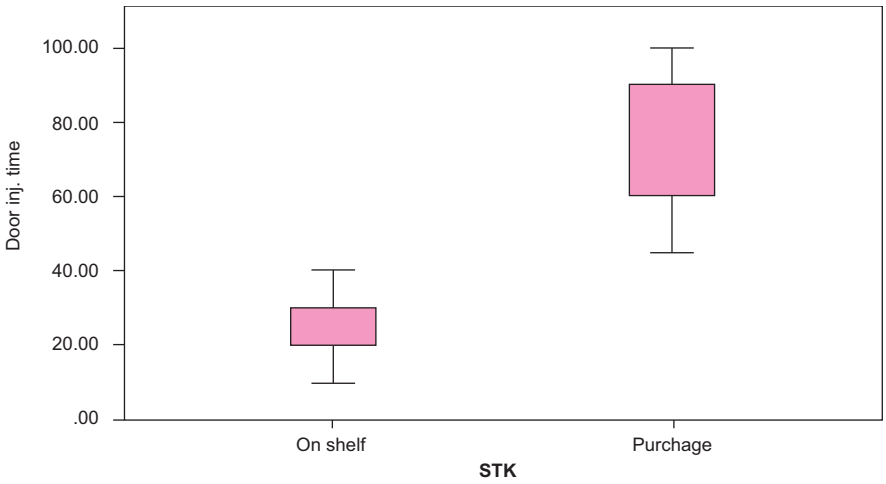

Fig.-2: *Box whisker plot showing mean door to injection time difference between groups.*

Table-III

Distribution of the study population according to ECG diagnosis (N=300)

Variables	On-shelf STK(n=150) n (%)	Purchased STK (n=150)n (%)	P value
Extensive Anterior	69 (46)	74(49.3)	
Antero septal	27 (18)	24 (16)	
High lateral	11(7.3)	10 (6.7)	0.98
Inferior	24 (16)	27 (18)	
Inferior+ RVI	19 (12.7)	15 (10)	

Table-IV

Distribution of the study population according to in-hospital outcome (N=300)

Outcome	On-shelf STK (n=150)n (%)	Purchased STK (n=150)n (%)	P value
Significant arrhythmia	12(8)	10(6.7)	0.54
LVF (Killip III/IV)	10 (6.7)	23 (15.3)	0.02
Cardiogenic shock	11 (7.3)	24(16)	0.01
Hospital stay (days)	5.33±1.26	6.05 ± 1.81	<0.001
MACE	27 (18)	44(29.3)	0.02
Re-infarction	9(6)	13 (8.7)	0.37
Stroke	6 (4)	8 (5.3)	0.58
Death	12 (8)	23(15.3)	0.04

Table-V

Multivariate logistic regression analysis for Major adverse cardiac events (MACE)

Variables	B	S.E.	Wald	df	p	Exp(B)
Age	.005	.011	.251	1	.616	1.005
Male sex	.384	.357	1.157	1	.282	1.468
HTN	.689	.308	5.007	1	.025	.502
DM	.305	.358	.726	1	.394	.737
Smoking	.472	.367	1.656	1	.198	.623
Antero septal MI	.186	.470	.156	1	.693	1.204
Door to Inj. time	.036	.012	9.414	1	.002	.965
ST resolution	.234	.325	.519	1	.471	.791

Discussion:

Acute ST elevation myocardial infarction (STEMI) is one of the leading causes of death and disability. Wide discrepancies exist in implementation of western guidelines in most of the developing world. Primary PCI is the preferred mode of reperfusion by most guidelines but in Bangladesh it is very difficult to ensure. When a patient with acute STEMI reach to coronary care unit it takes time to counsel patient and relatives about treatment options. There are several options according to time of arrival and mode of presentation. If patients present within 12 hours there are two options, one is Primary percutaneous intervention (PPCI) and another one is fibrinolysis. In our country cardiac care hospital with PPCI facilities are very limited, so large group of population are out of PPCI coverage.

On the other hand fibrinolytic therapy is alternative to PPCI as treatment option for acute STEMI patients which is cheap, available at affordable cost all over the country. STK can be given in any hospital with coronary care unit facilities thus immediate and prompt administration of STK should be ensured at every cardiac care hospital. After administration of STK there is option for Pharmaco-invasive therapy for selected cases. After advised for STK for the patients it has been observed that there is undue delay. Several factors playing role for this delay such as 1.literacy level of our population is poor, 2. Delay in decision making 3. Instant cash money may not be available in the pocket, 4. It may not be available at nearby pharmacy, 5. If available may not be preserved at proper way, 6. Price may be higher, 7. Advised drug brand may not be available 8. Supply may be hampered due to some other causes.

Aim of our study was to find out the outcomes of acute STEMI patients after getting on-shelf or purchased Streptokinase. In Bangladesh most of the patients purchase STK, as it is an expensive drug it is not kept on the shelf. In our hospital initially there was no free supply of STK later on fund was arranged and STK was made available at free of cost by the hospital authority. As door to injection time is an established predictor of post STEMI outcome, if we can cut down the time by shelving STK in the CCU it will definitely bring better outcome. In our study it was observed that mean door to injection time were 25.51 ± 7.9 minutes in group I and it was 70.36 ± 16.6 minutes in group II. Mean door to injection time were significantly lower in on-shelf STK group then purchased STK group which is three times lower (p=<0.001) (Figure II). As a result In our study it has been found that ST segment resolution was significantly higher in on-shelf STK group then purchased group which were 109 (72.7%) vs. 92 (61.3%), p=0.03. The better the early reperfusion the better the outcome. In our study we found that in on shelf STK group LVF (killip III/IV) was 10 (6.7%), Cardiogenic shock was 11 (7.3%), Stroke was 6 (4%) and death was 12 (8%) whereas in purchased group LVF (killip III/IV) was 23 (15.3%), Cardiogenic shock was 24(16%), Stroke was 8 (5.3%) and death was 23(15.3%). Among these variables LVF (killip III/IV), Cardiogenic shock and Death were significantly higher in group II (p=0.02, 0.01 and 0.04 respectively) (Table IV). MACE were significantly higher in group II [27 (18%) vs. 44(29.3), p= 0.02]. Poor in-hospital outcome prolonged mean hospital stay. Mean hospital stay was significantly higher in group II (p=<0.001). Shortened hospital stay reduce treatment cost which ultimately lessen this huge economic burden both for the government as well as of the patients. As it is evident that on shelf STK ensure early reperfusion which ultimately positively affect better outcome. As most of our STEMI patients are being treated by STK, provision should be there to keep on shelf STK in all the CCUs of the country both government and private hospitals to reduce cardiovascular morbidity and mortality.

Conclusion:

Timely delivery of reperfusion therapy (whether pharmacological or mechanical) in patients with STEMI is more important than the choice of therapy and the entire emphasis should be to deliver reperfusion therapy to a patient

of STEMI as rapidly as possible. Moreover, despite the strength of evidence based medicine pertaining to the benefits of primary PCI in STEMI, treatment options in Bangladesh are often dictated by resources, logistics, availability and affordability. In our country, not many hospitals offer primary PCI services round the clock in the urban areas and this inadequacy is pronounced more in rural areas where penetration of medical care is modest at best. In our study it has been found that on-shelf Streptokinase significantly reduce door in injection time which ultimately reduce cardiovascular mortality and mortality and door to injection time is proved to be one of the predictor for major adverse cardiac events.

Recommendations

Despite recent advances in pharmacological and interventional reperfusion strategies, timely reperfusion still remains suboptimal in patients with acute STEMI in Bangladesh. Initiation of reperfusion therapy varies, mandating uniform guidelines across the country. The right reperfusion strategy should be timely, effective, complete, safe and easily accessible. Hospitals intended to treat acute STEMI patients should have on-shelve Streptokinase to reduce door to injection time which effect the in-hospital outcome by reducing significant cardiovascular mortality and morbidity.

Conflict of interest- None.

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