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Original Article

Pharmacoinvasive Therapy in Treating Acute STEMI Patients in Covid-19 Era

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Abstract

Background: *Treating acute ST segment elevated myocardial infarction (STEMI) patients by primary PCI (pPCI) has dramatically fallen globally in covid era as there is chances of potential threat of spreading COVID among the non-COVID patients. Thereby, thrombolysis of acute STEMI patient in grey zone till COVID RT PCR report to come, was the mode of treatment of acute myocardial infarction patient in our hospital. We have carried out this prospective observational study to see the outcomes of thrombolysis and subsequent intervention.*

Methods: *STEMI patient who presented to our emergency department with chest pain and ECG and hs-Troponin-I evidenced acute STEMI, were enrolled in the study. Total 139 patients enrolled (Male:120, Female :54); average age for Male: 54 yrs., female was: 56yrs. All patients were admitted in the grey zone of CCU where thrombolysis was done. COVID-19 patients were excluded from intervention and managed conservatively. Covid Negative patients were kept transferred to CCU green zone. On average 2.1 days after Fibrinolysis, elective PCI carried out. Data analysis from 48 patients who underwent pharmacoinvasive therapy was done.*

Results: *Among the study population, Covid-19 positive was in 11 (7.9%) patients and Covid-19 was negative in 128 (92.1%) patients. Primary PCI was performed in 7 (5.03%) patients. Rest of the patients were managed by Pharmacoinvasive therapy. Thrombolysis by Tenecteplase (TNK) was done in 89 (64%) patients, and by Streptokinase in 25 (17.9%) patients, 18 (12.9%) patients did not receive any thrombolysis due to late presentation. Chest pain to needle time was 7.2 ±12.7hrs., thrombolysis to balloon time was 117.5 ±314.8hrs. More than 50% stenosis resolution observed in 20 (41.6%) patients, chest pain resolution within one hour of thrombolysis observed in 21 (43.8%) patients. Ten (20.8%) patients developed. Door to needle time was 30 mins. Total, 88 stents were deployed in 83 territories. CABG was recommended for 7 (5.03%) patients. Stented territory was LAD 37 (45.7%) and RCA 32 (39.5%) and LCX 12 (14.8%).*

Conclusion: *In the era of COVID-19, in this prospective cohort study, on acute STEMI patient management, we found that pharmacoinvasive therapy, reduced patients' symptoms and ST resolution occurred partially.*

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Introduction:

In the late December 2019, an outbreak of corona virus diseases 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV 2) occurred in Wuhan China.[1] ST segment elevation myocardial infarction (STEMI) remains a leading cause of death worldwide.[2] In the era of COVID-19, Pharmacoinvasive therapy is the most recommended treatment modality in patient with acute STEMI.[3] Its benefit depends on rapidly achieving first medical contact-to- device times within 90-120 min. Delayed reperfusion results in larger myocardial infarction, increased risk of heart failure, shock and no survival advantage

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compared with fibrinolytic therapy. The sooner the coronary flow is reestablished, the less myocardial necrosis, ventricular dysfunction, and mortality.[4]

There is also evidence that early PCI after thrombolytic therapy improves outcomes especially in patients without reperfusion criteria. The Pharmacoinvasive strategy is defined as thrombolytic therapy combined with rescue PCI (in failed thrombolysis), or PCI within 2 to 24 hrs. after thrombolysis (in successful thrombolysis).[5,6] This strategy is particularly important in patients who can't meet the 120-minute objective. STREAM trial suggested a benefit in patients who could not get PPCI done within 60 minutes.[7]

COVID-19 pandemic inevitably poses severe challenge to the emergent care of STEMI Patients, as the regional STEMI-networks was reorganized to assist COVID-19 and screening and infection control to prevent spread of nosocomial infection may substantially defer primary PCI.[8,9]

American college of cardiology's interventional council and Society of cardiovascular angiography and intervention issued statement of management of STEMI in COVID-19 and continues to primary PCI as standard treatment.[10]

In contrast, Chinese society of Cardiology recommended strategy of thrombolysis over pPCI due to concerns of resource allocation, as well as challenge in transfer of patients to facilitate that perform pPCI.[11]

Aim of our present study to see the benefit or outcomes of pharmacotherapy either by TNK or STK and subsequently rescue PCI of infarct related artery in STEMI patients. In our present study, all STEMI patients were thrombolized by TNK or STK in grey zone irrespective of COVID-19 RT PCR results. COVID-19 positives were kept on conservative management in COVID-19 dedicated area. COVID-19 negative subsequently underwent coronary angiography and subsequently revascularization either by PCI according to the nature of culprit lesion or Coronary artery bypass graft (CABG).

Methods:

We conducted this prospective study, at our center, a tertiary care hospital opens round the clock 24/7 for primary PCI services for STEMI patient admitted from March 8, 2020, to April 30, 2022, Patient were admitted in grey zone of CCU from ED, where Pharmacoinvasive therapy either by Streptokinase or Tenecteplase done. Covid-19 test was sent. COVID-19 positive cases were relocated to dedicated COVID-19 ward and managed medically. COVID-19 negative cases were scheduled for coronary angiogram and subsequent intervention either by PCI or CABG were carried out. Patients with no history of COVID-19 exposure or any symptoms, and whom primary PCI were deemed necessitate, were sent from ED to Cath lab. Later, the COVID-19 test of these group of patients, found negative.

Protocol:

The diagnosis of STEMI was established by a typical history of chest pan, diagnostic ECG changes and serial; elevation of cardiac biomarkers.[24] Blood samples drawn pre-PCI. Primary PCI performed in patients with ongoing symptoms <12 hrs. in duration. Complications like cardiogenic shock or need for IABP, need for emergent CABG, mechanical ventilation or heart failure episodes treated conservatively, clinically significant arrhythmia requiring pacemaker or major bleeding requiring blood transfusion and were excluded from study. All data were summarized and displayed as mean +/- standard deviation and in percentage.

Results:

In this global perspective of COVID-19 pandemic, Pharmacoinvasive strategies to treating STEMI patient at our center were studied. Total 139 patient (F 19: Male 120) with acute STEMI were studied. Average age for female was 56 yrs vs. male 54 yrs. COVID-19 test was carried out on all patients., among them, COVID-19 positive in 11 (7.9%) patients and managed conservatively in dedicated COVID-19 ward. Primary PCI was performed in 7 (5.4%) patients. Rest was managed by Pharmacoinvasive therapy either by TNK or STK. Thrombolysis by Tenecteplase in 89 (64%), Streptokinase in 25 (17.9%) patient, 18 (12.9%) patients did not receive any thrombolysis due to late presentation. Later, elective PCI was carried out on an average of 2.1 days after thrombolysis.

Table-I
Profile of patient

	Male	Female
Number	120	19
Age (yrs.)	54.3±11.0	56.7±11.7
SBP (mmHg)	120.0±18.0	128.0±17.0
DBP (mmHg)	74.0±13.0	76.0±6.7
No Risk Factor	2.4±1.0	1.9±0.6

Data: Mean ± SD

Table-II
Serum Troponin-I, Creatinine and HbA1C level, LVEF

	Male	Female
hs-Troponin I (pg/ml)	16656.6±20950.6	12109.7±16608.3
S. Creatinine (mmol/L)	1.28±0.4	0.79±0.2
HbA1C (%)	8.34±1.6	8.05±1.5
LVEF (%)	41.4±9.4	48.8±13.

Data: Mean ± SD

Table-III
Average size of Stent used

		Length (mm)	Diameter(mm)
LAD	M	32.7±11.1	3.04±0.5
	F	30.8±22.5	3.0±0.4
RCA	M	38.0±18.2	3.04±0.4
	F	16.5±4.9	2.75±0.4
LCX	M	31.1±9.5	3.08±0.5

Data: Mean ± SD

Table-IV
Serum Lipid Profile

	Male	Female
TC (mmol/L)	196.9±55.9	206.5±18.8
TG (mmol/L)	181.5±96.3	300.0±131.8
HDL (mmol/L)	36.4±9.2	26.4±6.6
LDL (mmol/L)	124.1±47.3	128.5±17.7

Data: Mean ± SD

Table 1. Shows the profile of studied patients in this prospective observational study. In the studied population average ages are (male 54.3+ 11.0 vs female 56.7+11.6 year.). COVID-19 test was carried out on all STEMI patients. Table 2. Showed that high Sensitivity troponin-I were more released in male than female (male 16,656.6 vs female 12,109.7), LVEF (male 41.4% vs Female 48.8%) and HbA1C (male 8.3% vs female 8.05%). Table 3. Showed average size of stent used, male required long size stent than female. Table 4. showed average lipid profile, female patient having higher cholesterol than male. Common CAD risk factors; as shown in Fig 1., that 41% (57) were hypertensive, 38.9% (54) were Diabetic, 36% (50) were dyslipidemia, Smoker 32.3% (45) and FH positive for CAD were 27.3% (38) and hypothyroidism 1.4% (2). According to the involvement of myocardium infarction as shown in Fig 2., that STEMI diagnosis of Ant Wall MI 46.8% (65), Inferior Wall MI 52.5% (73), high lateral MI 0.7% (1). Figure 3., showed the percentage distribution of management or recommendation at presentation to ED, were Pharmacoinvasive therapy by Tenecteplase done in 64.1% (89), Streptokinase in 17.9% (25) patient, Primary PCI 5.07% (7) patient, 12.9% (18) patient did not receive any thrombolysis due to late presentation. As shown in Figure 4, Showed common stented territory LAD 45.6% (37), RCA 40.7% (33) and LCX 13.5% (11). Figure 5. Showed the Percentage distribution of recommendation after coronary angiogram, were for PCI in 58.9% (82), CABG 5.1% (7%) patient and 2.8% (4) patient kept on medical management. CAG not done in 28.1% (39) patient as patient defer the procedure, some of them were Covid positive. Death in 5.1% (7) patient due to shock. defer PCI 1 (3.3%) and medical management 3 (10%) patients. Total, 88 stents were deployed in 83 territories of 83 patients. As shown in Figure 6, Different type stents used; Everolimus 61.4% (54), Sirolimus 25% (22), Progenitor cell with sirolimus 2.3% (2) and Zotarolimus 11.4(10%). Fig 7. Showed chest pain duration, chest pain to contact time, chest pain to needle time, thrombolysis to needle time and door to needle time among 48 patients from the study. Figure 8., showed the 50% plaque resolution, disappearances of chest pain within 1 hr of thrombolysis, LVF and death due to shock.

Discussion:

According to current ST-segment elevation myocardial infarction (STEMI) guidelines, primary PCI remains the preferred reperfusion strategy for STEMI as long as it can be performed in a timely and expert fashion.[12,2] However, timely

access to pPCI remain a significant challenge given logistic constrains and system delays which mitigate prompt access to such care.

Acute ST Elevated MI (STEMI) is the leading cause of death from cardiovascular diseases in Bangladeshi patient population. Thrombolysis is the key mode of practices as emergent initial management in mostly, even though many of the patients are not receiving it either due to patient ignorance's, unwillingness to visit doctor and to some extent financial constrain is the key factors. In many of the district level hospitals, unfortunately, due to the absence of CCU care and lack of adequate support services, treating acute STEMI patients by thrombolysis is far beyond the reach of patients.

Access time to emergent management of STEMI either by thrombolysis or by primary PCI (pPCI) where Cath lab facilities exist are crucial for our patient population. Streptokinase is the most available thrombolytic agent in our country and is widely used. Recently, Tenecteplase, though available, may not be used widely because of high price. Many of these patients might develop acute LVF and life-threatening arrhythmia and may die before reaching the hospital. We found sub-study of 48 patients, that chest pain to contact time was 3.7 hrs. and chest pain to needle time was 3.5 hrs.

Globally many patients primarily present to a non-PCI capable hospital requiring transfer to a percutaneous coronary intervention (PCI) site. In this context 40% to 75% do not achieve guideline recommended metrics of 120 mins with pPCI.[13] In the STREAM (strategic reperfusion early after Myocardial infarction) trial, Pharmacoinvasive approach by early fibrinolysis coupled with timely PCI provided similar 30-day outcomes and 1 year mortality.[14]

Half-dose Tenecteplase in those >75yrs obviated major bleeding and intracranial hemorrhages rates and in a large real-world registry was associated with improved 1-year clinical outcomes compared with pPCI without differences in major bleeding or intracranial rates.[15]

Covid-19 is a rapidly spreading disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) affecting millions globally and kills million as well. STEMI rates have declined globally in Covid era, perhaps partly because of patients unwilling to access the emergency medical system or risk hospital exposure to Covid-19. Those presenting hospitals without PCI-capability are not receiving the benefit of pre-hospital cardiac catheterization laboratory activation because it has been suspended.[16]

Emergency department (ED) evaluations are prolonged with additional screening for Covid-19. Transfer from ED to catheterization laboratory is complicated by the risk of additional staff exposure and delays in preparation with personal protective equipment. As frequency and duration of pPCI delays for reperfusion therapy increase, fibrinolytic therapy and Pharmacoinvasive strategy offer a logical, effective, and safe alternative while decreasing risk of Covid-19 exposure risk for healthcare workers.

The European Society of Cardiology and the American College of cardiology / American Heart Association[17-18] STEMI guidelines recommend fibrinolytic therapy and Pharmacoinvasive strategy for hospitals if timely pPCI cannot be performed. Fibrinolytic therapy more frequently aborts myocardial infarctions in early presenter compared with pPCI, requires less personnel, and avoids time-to-treatment delays. Approximately, three quarters of fibrinolytics patients will achieve infarct artery reperfusion, thus allowing for delayed angiography in stable patients those with Covid-19 positive.

In our present study, patient received fibrinolytics either TNK or STK. Sub-study data comprised of 34.5% (48) patient from 139 total patient, we found that almost 50% are not achieving complete reperfusion with ST resolution. Subsequent coronary angiogram was carried out. Finally, complete revascularization was done by rescue PCI of infarct related artery.

Those presenting by 12 hours after symptom of acute onset of STEMI, mortality is reduced by pharmacological reperfusion therapy by fibrinolytic, antiplatelet, and antithrombotic.[19] Primary PCI reduces the rate of reinfarction, stroke and mortality compared with fibrinolytic therapy.[20] Therefore, many centers with PCI capable adapted pPCI[3] as their primary preferred reperfusion strategy.

Early administration of fibrinolytic therapy in the ambulance (which is not yet practiced in our country) reduces mortality compared with after arrival hospital administration.[21] In our country, early thrombolysis is not yet practiced due to absence of efficient skilled paramedics. In the CAPTIM trial (Comparison of Angioplasty and prehospital thrombolysis trial) which randomized to prehospital fibrinolysis or primary PCI, patient presenting <2 hrs. after the onset of symptom had outcomes when randomized to prehospital fibrinolytic therapy as good or even better (e.g., reduced cardiogenic shock) than those with to undergo pPCI.[22] In this trial, rescue PCI and in-hospital PCI rates were 26% and 60%. In the ASSENT-4 (Assessment of the safety and Efficacy of New Treatment Strategy) trial[23] randomized to receive prehospital full dose Tenecteplase-facilitated PCI or primary PCI, had similar outcomes those to CAPTIM trial.

Thus, in patient presenting early <2-3 hrs. after symptom onset, pre-hospital fibrinolysis with a policy of liberal rescue PCI can aid in to achieve mortality of <4%, similar to those of Primary PCI.[24] The utility of rescue angioplasty for STEMI was debated during the 1990s and in 2000 received conceptual support when it showed patients with TIMI 0-1 flow had better outcomes after rescue PCI than conservative management.[25] The decision of rescue PCI , time is of the essence and the non-invasive evaluation of reperfusion needs to be performed quickly at bedside. Early studies using intracoronary Streptokinase in STEMI patients described four features of associated with recanalization of IRA: relief of chest pain, development of reperfusion arrhythmia, resolution of ST elevation and rapid release of biochemical markers.[26]

The degree of ST recovery has been shown to be associated with patency and flow in the IRA with >70% ST recovery associated with 90-95% of achieving patent IRA.[27] Sigle lead ST segment has been found to be as good as multilead measurement. ST resolution is an imperfect discriminator of TIMI 2 or TMI 3 flow with 50% patients patient with persistent ST elevation has patent IRA at angiography. Thus, the ST resolution failure may indicate failure of perfusion at myocyte or microvascular level and in these group of patient persistent ST elevation associated with more extensive myocardial damage and a higher long-term mortality.[28]

In patients with ST -elevation myocardial infarction (STEMI) timely reperfusion is of paramount importance. The choice between primary PCI or intravenous fibrinolytic agents depends on time to effective treatment delivery, availability, and total ischemic time.[29] Although pPCI is the preferred strategy according to clinical guidelines[2,30], limited resources, lack of infrastructure, challenges to achieve timely pPCI have fostered patients to receive significantly less reperfusion therapies in low to middle income countries.[31]

The Pharmacoinvasive (PIs) strategy is based on widespread availability of fibrinolysis and relative simplicity of its administration to restore myocardial blood flow totally or partially, coupled with cardiac catheterization and clinically appropriate PCI delivered urgently for patients with failure to reperfusion or rescheduled in those with successful reperfusion. Randomized clinical trials [32-33] and observational trial[15] have shown similar efficacy and safety of PIs compared with pPCI. PIs considered a reasonable alternative when pPCI not delivered on a timely basis.

Time to reperfusion remains a key modifiable determinant of mortality in STEMI.[34] Despite the symptom onset to start of pharmacological reperfusion treatment remains largely unchanged with a median 2.5 to 3 hours in the developmental country where emergency fibrinolysis can be done on ambulance.[35] The single bolus fibrinolytic drug Tenecteplase has facilitated the treatment of acute myocardial infarction, with efficacy equivalent to alteplase for 30 day and 1 year mortality and with the added benefit of less systemic benefit except elderly pat of >75yrs whom half dose recommended.[36]

In our present study, STEMI patients were admitted in grey zone with prior testing of Covid RT PCR and thrombolysis by STK or Tenecteplase. After thrombolysis, patients with Covid Positive RT PCR were sent to Covid dedicated ward and 3-4 weeks later their CAG and angioplasty were done accordingly. Negative RT PCR underwent Coronary Angiogram. Most of the patients showed

partial recanalization and subsequently angioplasty done by drug eluting stent with TIMI IIII distal flow.

Sub-study of our present observational cohort, comprises 48 patients (M:40; F8), chest pain duration, chest pain to contact to hospital, chest pain to needle time of thrombolysis and thrombolysis to balloon time was addressed. Average chest pain duration was 3.7 hrs., chest pain to contact time 3.3 hrs., chest pain to needle time was 7.2 hrs. and thrombolysis to balloon time 28.4 hrs. during Covid era, Pharmacoinvasive therapy constitutes thrombolysis by STK or TNK followed by rescue PCI on next day in Covid RT PCR negative cases is the set protocol of management of STEMI patient in our hospital. Chest pain to balloon time was more than 24 hrs. Also, some of the patients developed LVF, so PCI was delayed till recovery from LVF.

Among the 48 patients we found 50% stenosis resolution occurred only in 41.6% (20) patients, chest pain resolution in 43.8% (21) patients, indicating that not all patients benefitted by thrombolysis. Therefore, our strategies to treat by subsequent rescue PCI, is an additional alternative to complete revascularization in a proportionate percentage of acute STEMI patients.

We have found that Pharmacoinvasive therapy is the most beneficial mode of treating STEMI in our population in Covid-19. It does help to isolate Covid -19 positive cases, thus helping in preventing the spread of COVID-19. Reduction of symptoms of chest pain and thrombolysis by pharmacological treatment either by STK or TNK may help in reduction of STEMI complication. In all patients, complete thrombolysis was not achieved, and the reason is not known to us. Thus, quite a proportionate number of patients after initial thrombolysis, 59.7% (83) patients needed complete revascularization by rescue PCI by implanting Second / Third generation Drug Eluting Stents (DES) of the culprit artery.

Cardiovascular manifestation of Covid 19 is complex. Patients may present as STEMI, myocarditis simulating a STEMI presentation, stress cardiomyopathy, non-ischemic cardiomyopathy, coronary spasm or myocardial injury without a documented type I or Type 2 AMI.[37] The Covid-19 phase is not over. Every day, we found Covid positive STEMI patients receiving pharmaco-therapy in our grey zone. Thus, Pharmacoinvasive therapy remains the main and key stay of treatment of Acute STEMI in our population.

Regarding thrombolysis therapy, we have not achieved satisfactory goal to thrombolysis all STEMI patients in our District level hospital, whereas it is limited in medical college hospital, dedicated cardiovascular institutes only. Our specialist doctor should come forward, especially in managing all acute STEMI patients instead of referring them to tertiary care center. By giving loading doses of aspirin with Clopidogrel or Ticagrelor and statin; in some instances, Low Molecular weight heparin or Un-fractionated heparin, will not warranted to avoid STEMI associated life threatening arrhythmia or LVF before reaching the referred hospital.

We need prompt patient counselling and to respond to the first call from a patient or relative for chest pain. Also, we need to train our paramedics, so in ambulance pharmacotherapy can be given before reaching the hospital for invasive therapy. Even though Cardiac Cath labs are available mostly in capital city, many in the divisional city and medical college hospital, not sufficient to provide invasive means of treating acute STEMI. Collectively, we need to focus to develop a common consensus to a greater percentage of patients to provide pharmaco therapy in treating acute STEMI, thus saving lives, and avoiding life threatening complications.

Conclusion:

We have found that Tenecteplase failed to provide complete thrombolysis in acute STEMI cases and subsequent rescue PCI was mandated to ensure complete revascularization. Thus, considering our socioeconomic condition, quite a significant percentage of the studied patients, TNK may be an extra financial burden, particularly those who underwent subsequent rescue PCI.

Conflict of Interest - None.

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