



## Evaluation of Associated Risk Factors in Patients with Failed Thrombolysis Determined by Bedside Non-Invasive Findings and Their Comparison - an Observational Study

### KEYWORDS

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### ABSTRACT

Acute coronary syndrome is divided into ST Segment Elevation Myocardial Infarction(STEMI), Non ST Segment Elevation Myocardial Infarction(NSTEMI) and Unstable Angina. In our setting fibrinolysis still remains the most preferred approach to STEMI. An ICU study to determine whether fibrinolytic therapy performed in patients with STEMI was successful or unsuccessful by using non-invasive bedside findings, and if it was a failed thrombolysis, to compare the associated risk factors seen in these patients with failed thrombolysis at our centre with cases at other worldwide centers. 94 patients were studied over a span of one and a half years, and included male and female patients of all age groups. 37 patients had a failed lysis and 57 had a successful lysis. All the patients received a loading dose of thrombolytics. Patients presenting with Acute MI at an early window period, Killip Class I or a low Trop T of <0.03ng/dl did not reduce the risk of a failed thrombolysis. Majority of the patients in the Failed thrombolysis group did not have a family history or past history of CAD. Failed thrombolysis was more in the 40-60 yrs age group. More Silent MIs were seen in Failed thrombolysis group. Failed thrombolysis group had more complications.

### Introduction:

According to the last WHO study identifying the 10 leading causes of deaths in the world, by broad income group, in the year 2008, ischemic heart disease stood out first in the list with 7.25 million deaths per year at a high percentage of 12.8. The influence of acute coronary syndrome particularly Myocardial Infarction (MI), is on the increase despite the immense number of awareness programs launched and advanced interventions on the play, to put them on hold. Henning et al(1) also determine which was better and to look into the possible risk factors involved and drugs used. In this large study, which compared 1572 patients with acute MI done over a period of almost 4 years, patients who had MI with ST-segment elevation were randomly assigned to fibrinolysis or primary angioplasty. It included patients from 24 referral hospitals and the participating hospitals served 62 percent of the Danish population. It was demonstrated that angioplasty was superior to fibrinolysis and a look at their associated risk factors in both cases were studied and compared, percentage of death and reinfarction, disabling stroke was also looked into. Gershlick et al(2) took a detailed look at the patients in whom reperfusion fails to occur after thrombolytic therapy for acute MI. Conservative therapy with repeat thrombolysis was compared with Rescue PCI. A multi-center trial in the United Kingdom involving 427 patients with ST-segment elevation myocardial infarction in whom reperfusion failed to occur (less than 50 percent ST-segment resolution) within 90 minutes after thrombolytic treatment were randomly assigned to repeated thrombolysis (142 patients), conservative treatment (141 patients), or rescue PCI (144 patients). Within a span of 5 yrs, candidates were evaluated at 35 centers. Adults 21 to 85 years of age were eligible for inclusion if they had re-

ceived any licensed thrombolytic agent for MI with ST segment elevation within 6 hours of the onset of chest pain and if reperfusion had then failed to occur, as judged by the predetermined 90-minute ECG (less than 50 percent resolution in the lead with previous maximal ST-segment elevation). Patients assigned to repeated thrombolysis received a fibrin-specific thrombolytic agent (alteplase or reteplase, according to the physician's choice) and intravenous heparin. Low-molecular-weight heparin (LMWH) was not used in the first 24 hours. The rate of event-free survival among patients with failed thrombolysis treated with rescue PCI was 84.6 percent, as compared with 70.1 percent among those receiving conservative therapy and 68.7 percent among those undergoing repeated thrombolysis. There were no significant differences in mortality from all causes. Event-free survival after failed thrombolytic therapy was significantly higher with rescue PCI than with repeated thrombolysis or conservative treatment. Rescue PCI should be considered for patients in whom reperfusion fails to occur after thrombolytic therapy.

### Materials and methods:

An ICU study to determine whether fibrinolytic therapy performed in patients with STEMI (presenting to our hospital within a window period of 9 hours), was successful or unsuccessful by using non-invasive bedside findings, and if it was a failed thrombolysis, to compare the associated risk factors seen in these patients with failed thrombolysis at our centre with cases at other worldwide centers, presented in published literature. From January 2010 to July 2011, 94 adults who fulfilled the criteria for thrombolysis, both successful and failed were included in this study.

The aim of this ICU study was to determine whether fibi-

nolytic therapy done in patients with STEMI (presenting to our hospital within proper time) was successful or unsuccessful by using non-invasive bedside findings, and if it was a failed thrombolysis, to compare the associated risk factors seen in such patients at our centre with failed thrombolysis at the worldwide centers in the above published literature. 94 patients were studied over a span of one and a half years, and included male and female patients of all age groups. The main aim of the study was to look into failed thrombolysis and the common associated risk factors in these particular cases. Of the 94 cases looked into, 37 patients had a failed lysis and 57 had a successful lysis. A detailed study into the age, gender, risk factors such as smoking, H/o diabetes, dyslipidemia (Total Cholesterol, HDL and LDL), hypertension and past and family history of coronary artery disease were carried out. Infarct localization, Killip class, Hb level and multiple lytic agents used were all looked into. Presentation (classical/silent, on weekdays/weekends), window period, pre-medication used, use of LMWH, whether thrombolysis was successful or failed (determined using non-invasive methods), development of complications (which included heart block and ventricular tachycardia), cardiac markers (which included Trop T, CPKMB, CPK) and survival rate at the end of 12 hrs postthrombolysis, were the other characteristics considered. All the patients received a loading dose of chewable aspirin 325 mg, clopidogrel 300mg, atorvastatin 80mg prior to thrombolysis along with LMWH (enoxaparin according to body weight mostly or fondaparinux 2.5mg). Along with tenecteplase which was given according to the body weight, first dose of enoxaparin was given half intravenous and half sub cutaneous as evidenced by trials. Beta blockers were added only in selective cases of Inferior Wall MI, and in most all cases of Anterior Wall MI. Parenteral nitroglycerin (NTG) was used in patients with ongoing chest pain and adequate blood pressure; others were given oral nitrates. Angiotensin converting enzyme inhibitors (ACEI) was added accordingly. Patients presenting with pulmonary edema were treated with parenteral furosemide, other anti-failure, decongestive and supportive care.

Decision to thrombolysed was made if patient presented within the correct window period, with ST elevation on ECG, ongoing chest pain, and finally if the patient did not have any contraindications. Thrombolytic agents were selected according to the affordability, heart wall involved and blood pressure or Re MI. In patients presenting with Inferior Wall MI with right ventricular infarction or cardiogenic shock, Tenecteplase was the first preference for lysis as it does not have antigenic property, nor causes a fall in blood pressure further in the already hypotensive patient. Thrombolysis was done only at the emergency or at the ICU with bedside monitor and defibrillator with trained personal and life saving drugs on standby. All routine labs, including sugar levels and cardiac enzymes were sent at the time of admission. Serial ECGs were taken at the time of admission, repeated at 60 minutes, 90 minutes, 6 hrs and 12 hrs routinely. Insulin was started in patients with high sugars. In patients with persistent chest pain and ST elevation at the end of 90 minutes, tirofiban without loading dose was considered. In failed thrombolysis with hemodynamic instability at occasions rescue angioplasty was done, TPI / IABP was used. Majority of the patients routinely underwent angiogram after stabilizing and stenting or revascularization subsequently.

#### Results:

A total of 94 patients and their satisfying criteria were studied. Of the 94 patients who presented with acute MI,

only 7 were of the female gender. Out of the 37 cases of failed thrombolysis in our study, only 3 belonged to the female gender. In our study, MI was seen as early as 40 yrs and above. Failed and successful thrombolysis was seen maximum in the age group 40-60 yrs. In our study, there were 7 individuals belonging to <40 yrs, and all of them had a successful thrombolysis. Majority of patients in the Successful thrombolysis group came within 1-3 hrs of onset of chest pain, followed by the 3-6hrs group. In successful thrombolysis, early window period mattered. In the Failed thrombolysis group, majority came in the 1-3 hrs group and 6-9hrs group. However, in the Failed thrombolysis group, presentation at an early window period did not show much difference. The "p value" was found to be 0.317 and was not statistically significant. Only 32 of the 94 patients who came with MI were smokers. Of the 37 patients with failed thrombolysis, only 13 were smokers; thus failed thrombolysis was seen more in non smokers. The "p value" was found to be 0.857 (<0.05 for statistical significance) and was not statistically significant. Of the 37 patients who came with MI and had a failed thrombolysis, 25 were diabetics. The "p value" was found to be 0.151 and was not statistically significant. In our study, in both Successful and Failed thrombolysis group, hypertensives were less as compared to diabetes. Of the 57 patients in the Successful lysis group, only 22 were hypertensives, whereas in the Failed thrombolysis group, of the 37 patients only 14 were hypertensive. The "p value" was found to be 0.941 and was not found to be statistically significant. Of the 94 patients who sustained MI, only 28 patients had past history of CAD. The "p value" was found to be 0.651 and was not statistically significant. Of the 37 patients with failed thrombolysis, only 5 had family h/o CAD. The "p value" was found to be 0.354 and was not statistically significant. Anterior Septal MI was the highest among infarctions in both Successful and Failed thrombolysis groups. The "p value" was <0.354 and was not statistically significant. Successful thrombolysis was seen maximum (44 patients) in Killip class I group. Failed thrombolysis was also seen maximum (20 patients) in killip class I group. Of the 10 patients admitted in Killip IV, 6 patients had failed thrombolysis. The p value was 0.132 and was not statistically significant. Of the 57 patients who had successful thrombolysis, 55 of them presented to the hospital with classic pain. Of the 7 patients who came with silent MI, 5 of them had failed thrombolysis. The "p value" was found to be 0.071 and was not statistically significant. Streptokinase was used more than tenecteplase at our centre, probably due to price factor. Tenecteplase was used in 41 of the 94 patients. Both streptokinase and tenecteplase did not have any superiority over each other in successful or failed Thrombolysis. The "p value" was found to be 0.503 and was not statistically significant. Of the 37 patients in the Failed thrombolysis group, 6 developed ventricular tachycardia and 5 developed complete heart block. The "p value" was found to be 0.014 and was not statistically significant. Of the 37 patients in the Failed thrombolysis group, 36 did not have ST resolution post lysis where as all the 57 patients in the Successful thrombolysis group had good ST resolution. It was statistically significant. Of the 94 patients in the study, only 5 had documented AIVR or reperfusion arrhythmia of which 4 patients belonged to the Successful lysis group. The "p value" was found to be 0.362 and was not statistically significant. Of the 37 patients with failed thrombolysis, 18 had a Trop T of <0.03 ng/dl. Highly elevated Trop T of >2.0ng/dl, was seen in 13 cases out of 94. The "p value" was found to be 0.446 and was not statistically significant. Successful Thrombolysis was 57 or 60.64%. Failed Thrombolysis was 37 or 39.36%.

The "p value" was found to be 0.000 and was statistically significant. At 12 hours, 8 (8.602%) of the 94 patients died, of which 5 belonged to the Failed thrombolysis group. The "p value" was found to be 0.170 and was not statistically significant. The mean total cholesterol of 28 of the 37 patients in the Failed thrombolysis group was 176.11. These patients had a mean LDL of 163.29 as compared to 128.19 in the Successful thrombolysis group. In 34 of the 37 patients in the Failed thrombolysis group in whom hemoglobin was checked, the mean value was 12.624g/dl, and in the Successful thrombolysis group it was 13.076g/dl in the 54 patients compared.

#### Discussion:

patients who presented with acute MI in total, only 7 were of the female gender. Of the 37 cases of failed thrombolysis in our study, only 3 belonged to the female gender. In all the Western literatures compared, majority (about 70-80%) of patients who presented with acute MI and had failed thrombolysis were also males. In our study, MI was seen in patients of age as early as 40 yrs and above, whereas in the Western literature(3), most of the studies had age limits starting from 50 yrs and above for MI; thus showing that in our set up MI presents approximately about 10 years earlier. Failed and successful thrombolysis was seen maximum in the 40-60 yrs age group. In our study, there were 7 individuals belonging to <40 yrs and all of them had successful thrombolysis. Majority of the patients in the Successful thrombolysis group came within 1-3 hrs of onset of chest pain, followed by the 3-6hrs group. In successful thrombolysis, presentation at an early window period of 1-3 hrs helped the outcome of the thrombolysis to be successful. In the Failed thrombolysis group, majority of the patients came in the 1-3 hrs group and 6-9hrs group. However in the Failed group, presentation at an early window of 1-3 hrs period did not show much difference. Irrespective of the early window period, the thrombolysis was not a success. This was contradictory to the statement in many Western literatures(4) which states that, presentation at an early window period favors successful thrombolysis. According to our study it is concluded that the most likely cause for patients presenting in a early window period, having failed thrombolysis may be due to the fact, that majority of the patients in the failed thrombolysis group in our study were diabetics. The western population had fewer Diabetics. Only 32 of the 94 patients who came with MI were smokers. Of the 37 patients with failed thrombolysis only 13 were smokers; thus failed thrombolysis was seen more in non smokers. In the Western literature (5) compared, however, majority of the patients with failed thrombolysis were smokers and it was the third main risk factor after male sex and age group in their study. Of the 37 patients who came with MI and had a failed thrombolysis, 25 were diabetics. Unlike in the Western literatures(6) compared where smoking and hypertension were seen as a more common risk factor than diabetes, whereas in our set up; diabetes was seen as the major risk factor for MI after male sex and age group. In our study, in both the Successful and Failed thrombolysis group, hypertensives were less as compared to diabetics. In the Successful lysis group, of the 57 patients only 22 were hypertensive, whereas in the Failed thrombolysis group, of the 37 patients only 14 were hypertensive. In the Western literature(7) compared, hypertension was a major risk factor for MI. In their Failed thrombolysis group, it was a more common risk factor than diabetes. Of the 94 patients who sustained MI, only 28 patients had past history of CAD. In the Western literature compared, patients with failed thrombolysis who had a past h/o CAD were about <15%, where as

it was almost double in our set up, ie. 12 (32.4%) of 37 patients who had failed thrombolysis had a past history of Coronary Heart Disease. Of the 37 patients with failed thrombolysis, only 5 had a family h/o CAD. None of the Western literatures compared(8), included family history in the study. Anterior Septal MI was the highest among infarctions in both Successful and Failed thrombolysis group. Similarly, in the Western countries too, Anterior Septal MI was more common compared to other infarctions. Successful thrombolysis was seen maximum (44 patients) in Killip class I group. Failed thrombolysis was also seen maximum (20 patients out of 37) in killip class I group. Of the 10 patients admitted in Killip IV, 6 patients had failed thrombolysis. In the Western literature most of the patients with failed thrombolysis presented in Killip II or above. In our study majority of the failed thrombolysis belonged to Killip class I, which was again contradictory to the Western literature(9) which stated that a low Killip class has better chance for successful thrombolysis and survival. Here again it is attributed that the most likely cause for patients presenting in Killip class I, having more failed thrombolysis in our study may be due to the fact, that majority of the patients in failed thrombolysis group in our study were diabetics. The western population had fewer Diabetics. Successful thrombolysis was seen more in weekdays. Failed thrombolysis was seen more in weekends. In the Western literature (10) also, delay in presentation was seen more during weekends. Of the 57 patients who had successful thrombolysis, 55 of them presented to the hospital with classic pain. Of the 7 patients who came with silent MI, 5 of them had failed thrombolysis. In the Western literature the above characteristic was not compared. Streptokinase was used more than Tenecteplase at our centre, probably due to price factor. Tenecteplase was used in 41 of the 94 cases. Both streptokinase and Tenecteplase did not have any superiority over each other in successful or failed thrombolysis. In Killip Class III and IV, Tenecteplase was preferred due to fibrin specificity and to avoid hypotension. In the cases presented in the Western literature fibrin specific thrombolytics were preferred. Of the 37 patients in the Failed thrombolysis group, 6 developed ventricular tachycardia and 5 developed complete heart block. In the Successful thrombolysis group of 57 patients, only 5 had complications, of which 4 had complete heart block and 1 had ventricular tachycardia. In the Western literature the above characteristic was not compared. Of the 37 patients in the Failed thrombolysis group, 36 patients did not have ST resolution post lysis, where as all the 57 patients in the Successful thrombolysis group had good ST resolution. ST resolution was used as a non invasive, bed side marker of failed thrombolysis in majority of the Western studies compared. Of the 37 patients in the Failed thrombolysis group, 32 patients had ongoing chest pain, post thrombolysis. Persistence of pain post thrombolysis was used as a non invasive, bed side marker of failed thrombolysis in majority of the Western studies compared. Of the 94 patients in the study, only 5 had documented AIVR or reperfusion arrhythmia; of which 4 belonged to the Successful lysis group. It is believed that in our study more patients had AIVR during or post thrombolysis, but was not documented due to its short run or other causes. AIVR is also one of the criteria used in the Western literature to clinically identify a successful lysis. Of the 37 patients in the Failed thrombolysis group, 18 patients had a Trop T of <0.03 ng/dl. Highly elevated Trop T of >2.0ng/dl, was seen in 13 of the 94 cases in the study, of which only 6 belonged to the Failed lysis group. This observation means that even with a normal Trop T level, the thrombolysis could be unsuccessful, and with a higher Trop T level the thrombolysis could

turn out to be successful. Trop T was not used as a characteristic in any of the compared Western studies. CPK/CP-KMB levels were higher in the Failed thrombolysis group. Of the 37 patients in the Failed thrombolysis group, in 30 patients in whom the levels were measured, the mean value accounted to 2819.80/208. In the Western literature the above characteristic was not compared. At 12 hours post thrombolysis, 8 (8.6%) of the 94 patients died due to complications, in which 5 belonged to the Failed thrombolysis group. Unlike in our study, death was documented 30 days post lysis or intervention, in 2 of the Western studies compared. Of the 37 patients in the Failed thrombolysis group, the mean total cholesterol of 28 patients was 176.11. Patients in the Failed thrombolysis group had a mean LDL of 163.29 as compared to 128.19 in the Successful thrombolysis group. This again stresses the necessity of lower LDL levels by most of the Western literature. Of the 37 patients in the Failed thrombolysis group, in 34 patients in whom hemoglobin was checked, the mean value was 12.624g/dl, and in the Successful thrombolysis group it was 13.076g/dl in the 54 patients compared. Haemoglobin levels did not play much role as a risk factor for CAD in our study. In the Western literature the above characteristic was not compared.

#### Conclusions:

In our study, in patients presenting with Acute MI at an early window period, Killip Class I or a low Trop T of

<0.03ng/dl did not reduce the risk of a failed thrombolysis. This could most likely be due to the fact that many patients with failed thrombolysis also had diabetes as discussed earlier. Majority of the patients in the Failed thrombolysis group did not have a family history or past history of CAD. Failed thrombolysis was more in the 40-60 yrs age group. More Silent MIs were seen in Failed thrombolysis group. Failed thrombolysis group had more complications which included mostly ventricular tachycardia or Complete Heart Block. In our study male population had more failed thrombolysis. None of the 7 male patients aged below 40 yrs who presented with MI had a failed thrombolysis in our study. Five of the Eight patients who died at the end of 12 hrs in this study belonged to the Failed thrombolysis group. In our study, Anterior wall associated MIs had more events of failed thrombolysis than Inferior wall associated MIs. Diabetics were more in the Failed thrombolysis group. Failed thrombolysis was more in non smokers and non hypertensives. Failed thrombolysis group patients had a significantly higher mean LDL level. Failed thrombolysis was noticed to be more during the weekends as compared to week days, in our study.

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