

# MINUTES ARE MUSCLE AND DELAY IS DEATH

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## ABSTRACT

**Objective:** To determinetese the door to needle time (DNT) for thrombolysis of patients presenting with acute ST elevation myocardial infarction (STEMI) to emergency department, and its association with outcome of thrombolysis in terms of success and complications.

**Methodology:** This cross-sectional study was conducted in chest pain clinic of Cardiology Unit, Lady Reading Hospital, Peshawar from February to May, 2017. Total 724 patients presenting with acute STEMI, fulfilling the inclusion criteria were included in the study by consecutive sampling. Demographic details, door to needle time (DNT), symptom to door time (SDT) and post-thrombolysis complications were recorded on a predesigned proforma. Mean  $\pm$  S.D was calculated for continuous variables while frequencies and percentages were calculated for categorical data. Chi-square test was applied for association with a p value of  $<0.05$  as significant. Regression model was used to determinetese odd ratios (OR) with a p value  $<0.05$  as significant.

**Results:** Mean age of the patients was  $54.4 \pm 8.4$  years. Out of 724 patients, 50.8% were male with a mean SDT of  $362.1 \pm 92.1$  and DNT of  $34.42 \pm 39.31$  minutes. About 62.4% of patients were thrombolysed in less than 30 minutes, 27.1% in 30-60 minutes and 9.9% patients in  $>60$  minutes. Percentage of successful thrombolysis decreased from 80.53% to 67.1% and 66.6% with increasing DNT from  $<30$  minutes, 30-60minutes and  $>60$  minutes with a p-value  $<0.01$ . Complication rate increased from 33.4% to 51.53% and 70.83% with an increase of 0.48 times to 2.25 times and 2.92 times in OR for failed thrombolysis while moving from  $<30$  minutes to 30-60 minutes and  $>60$  minutes respectively (p  $<0.01$ ). Factors contributing to failure of thrombolysis included predisposing factors for coronary artery disease (CAD).

**Conclusion:** Morbidity and mortality in patients of acute STEMI decreases if DNT is  $<30$  minutes.

**Key Words:** Door to needle time, Symptom to door time, Thrombolysis

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## INTRODUCTION

Coronary artery disease is the top ranked cause of morbidity and mortality throughout the world<sup>1</sup>. However, early intervention to regain perfusion can reduce both mortality and morbidity. Strategies for reperfusion include percutaneous coronary intervention (PCI) and thrombolytic therapy after acute STEMI<sup>2</sup>. The maximum benefit of reperfusion is obtained when it is performed within the first hour of symptom onset. Delay of every hour in reperfusion results in 20% increase in hazard ratio (HR) of death<sup>3</sup>. Early restoration of coronary blood flow is linked with better outcomes in preserving the left ventricular function<sup>4, 5</sup>. Early reperfusion results in 17-25% reduction in 30-day mortality<sup>6, 7</sup>. Also, the late

mortality rate increases from 2.5% to 6.5% with increasing reperfusion time from 1 hour to 4 hours<sup>8</sup>. Randomized clinical trials illustrate that primary PCI is superior to thrombolytic therapy in reducing mortality, re-infarction and coronary artery bypass graft (CABG) surgery<sup>9, 10</sup>. In developing countries like ours where facilities for primary PCI are not available everywhere, thrombolytic therapy remains the gold standard treatment of acute STEMI. The rationale for thrombolysis after STEMI arises from fact that thrombus in coronary artery causes transmural infarction and thrombolytic agents can reopen the vessel. Rentrop et al<sup>11</sup> demonstrated that 80% of the clots can be lysed if thrombolysed in 4-6 hours resulting in optimal restoration of blood flow. Also the complication rates are reduced with timely reperfusion

after STEMI. As symptom to door time (SDT) is beyond the control of physicians in the emergency department, our goal should be to decrease the door to needle time (DNT). The American Heart Association (AHA) and American College of Cardiology (ACC) guidelines recommend a DNT of <30 minutes for thrombolysis in STEMI patients<sup>1</sup>. Achievement of this DNT is a marker for quality of care in hospitals<sup>12</sup>.

Our study aimed to determinate the DNT for patients presenting with STEMI and its effect on successful thrombolysis and post-thrombolysis complication rate.

## METHODOLOGY

This was a cross-sectional study conducted in chest pain clinic of Cardiology Unit, Lady Reading Hospital, Peshawar from January to May, 2017. A total of 724 patients of either gender and all age groups presenting with STEMI, new onset LBBB and posterior MI on ECG having SDT of <10 hours were included in the study. Patients with NSTEMI, delayed presentation, contra-indications to thrombolysis, pre-hospital thrombolysis, history of previous STEMI, cardiomyopathy, and arrhythmias were excluded from the study.

Streptokinase infusion (1.5 million IU given in one hour) was used for thrombolysis after STEMI. Successful thrombolysis was defined as more than 50% resolution of the sum of ST elevation 90 minutes after initiating the streptokinase infusion with resolution of chest pain

Data regarding demographic features, co-morbid conditions, SDT, DNT, indication for thrombolysis, result of thrombolysis (successful or failed) and immediate complications after thrombolysis i.e. within 24 hours of thrombolytic treatment were recorded in a pre-designed proforma and analyzed in SPSS version 20.0. Continuous variables like age, DNT were expressed in mean  $\pm$  S.D and categorical variables like gender, complication rates and factors resulting in delay of thrombolysis were calculated in frequencies and percentages. Data was stratified for door to needle time into 3 categories i.e. <30 minutes, 30 to 60 minutes and >60 minutes. Association of successful thrombolysis, failed thrombolysis and complications with different categories of DNT were measured with chi-square test. Binary logistic regression model was applied to calculate the OR for failed thrombolysis with DNT strata and various co-morbid conditions. P value of <0.05 taken as significant.

## RESULTS

The mean DNT was calculated to be  $34.42 \pm 39.21$  minutes and the mean SDT was  $382.1 \pm 92.1$  minutes in our study. About 452 (62.4%) patients had a DNT of <30 minutes, 196 (27.1%) had a DNT of 30–60 minutes and 72 (9.9%) had a DNT of >60 minutes. Baseline charac-

teristics of patients are given in Table 1.

Association of successful thrombolysis with DNT in different strata was calculated using chi-square test as shown in Table 3. There was a significant association between successful thrombolysis and DNT of <30 minutes and 30-60 minutes with a p value of <0.01 and 0.001 respectively. A DNT of >60 minutes was associated with poor outcomes with only 48 (66%) patients having successful thrombolysis (p value: 0.25).

Post thrombolysis complications within 24 hours included minor complications like gum bleeding and hematoma at injection site. The rates of complications were also significantly associated with DNT as shown in Table 4.

By increasing DNT to >60 minutes, the POR for failed thrombolysis increased by 2.92 times. Complication rates also increased from 37% to 69.4% as DNT increased from <30 minutes to >60 minutes respectively as shown in table 5.

Along with DNT various other co-morbid conditions increasing the risk of failed thrombolysis were studied and POR for each co morbid condition were calculated using regression model as shown in table 6.

Finally, various factors causing delay in thrombolysis were analyzed. Complete heart block being the first one followed by increased systolic blood pressure (BP) and unavailability of streptokinase (SK) in hospital pharmacy. (Figure 1)

## DISCUSSION

Successful resolution of STEMI grossly depends on timely thrombolysis. Severe ischemia leads to necrosis of myocardial cells in 20 minutes. So, the interval from sudden stop of blood flow to reperfusion is a critical factor<sup>13</sup>. Irrespective of the method used, early reperfusion is critical for damage control<sup>14,15,16</sup>. Reperfusion in first hour decreases mortality by 6.5%, falling to 3.7% in second hour, 2.6% after 6 hours, and ineffective after 12 hours<sup>17</sup>. TIMI II trial demonstrated that every hour delay raises fatality by 1%<sup>18</sup>.

In a recent study by Terkelsen et al, only 27% patients were thrombolysed in <30 minutes while 32% in <90minutes<sup>19</sup>. A meta-analysis from Nallamothu et al suggested that if that a delay of >60 minutes for PCI, thrombolysis should be the preferred strategy<sup>20,21</sup>.

The 2000-2001 Canadian Registry demonstrated that 63% of patients with STEMI failed to be thrombolysed in <30 minutes<sup>22</sup>. Another Canadian study QUEBEC in 2003 showed median DNT of 32 minutes in patients of STEMI<sup>23</sup>. Studies in India in 2015 showed only 27% patients of STEMI being thrombolysed in <30 minutes<sup>24</sup>. In a study conducted in Punjab Institute of Cardiol-

**Table 1: Demographic characteristics of patients and door to needle time**

Variables	Mean $\pm$ S.D	Frequency (%age)
Age (in years)	54.4 $\pm$ 8.4	---
Male	---	368 (50.8%)
Female	---	352 (49.2%)
Diabetes Mellitus	---	296 (40.9%)
Hypertension	---	436 (60.2%)
Smoking	---	304 (42%)
Family History of CAD	---	240 (33.1%)
Dyslipidemia	---	250 (33.5%)
Family History of HTN/DM	---	301 (41.8%)
Door-To-Needle Time (in minutes)	34.42 $\pm$ 39.21	---
<30 minutes	---	452 (62.4%)
30 – 60 minutes	---	196 (27.1%)
>60 minutes	---	72 (9.9%)

**Table 2: Indications for thrombolysis**

Types of MI		
Anterior MI	---	105 (14.5%)
Antero-lateral MI	---	226 (31.2%)
Antero-Inferior MI	---	24 (3.3%)
Inferior MI	---	93 (12.8%)
Infero-lateral MI	---	68 (9.4%)
Infero-Posterior MI	---	80 (11%)
Inferior + RV MI	---	48 (6.6%)
Lateral MI	---	24 (3.3%)
High lateral MI	---	28 (3.9%)
Posterior MI	---	16 (2.2%)
New onset LBBB	---	12 (1.7%)

MI: Myocardial Infarction, LBBB: Left bundle branch block, RV: Right ventricle.

**Table 3: Association between successful thrombolysis and DNT strata**

DNT: Categories	Successful	Failed	x <sup>2</sup> -value	P-value
<30 minutes:	364(80.5%)	88(19.5%)	16.29	<0.01
30-60 minutes:	132(67%)	64(33%)		
>60 minutes:	48(66%)	24(34%)		

gy Lahore, 46.2% patients with STEMI had DNT of >30 minutes<sup>25</sup>. Another study in Armed Forces Institute of Cardiology, Rawalpindi illustrated that 70% of their patients were thrombolysed in <30 minutes<sup>26</sup>. Our results are comparable to this study and far better than the rest. In our study, we managed to thrombolysed 62.4% of our patients with STEMI in <30 minutes, 27.1% in 30 – 60 minutes and only 9% in >60 minutes. Previously a study conducted in 2010 in Lady Reading Hospital by Jabbar et al<sup>27</sup>, only 7.1% patients with STEMI were

thrombolysed in <30 minutes. This indicates a significant improvement in the level of care provided by our hospital since 2010.

In our study, we had seen the association of successful thrombolysis with DNT. The earlier the thrombolysis, the more successful is thrombolysis. Odds of failed thrombolysis increased from 0.48 to 2.25 and 2.92 times for thrombolysis being delayed from <30 minutes to 30-60 minutes and >60 minutes respectively. Also the

**Table 4: Frequency of complications with comparisons in dnt strata**

VARIABLES	DNT<30minutess:	DNT30-60minutess:	DNT>60minutess:	X2 p-value
Total number	456	196	72	
Stroke	4(0.8%)	4(2.04%)	4(5.5%)	<0.01
LVF	138(30.2%)	87(45.3%)	39(54.1%)	<0.01
Arrhythmia	27(5.9%)	31(15.8%)	22(30.5)	<0.01
Cardiogenic Shock	17(3.7%)	33(16.6%)	30(41.6%)	<0.01
Heart block	24(5.2%)	20(10.2%)	12(16.6%)	<0.01
VSR	5(1%)	2(1%)	3(4.1%)	<0.01
Death	23(5.04%)	40(20.4%)	21(29.1%)	<0.01
Minutesor complications	170(37.2%)	97(49.4%)	50(69.4%)	<0.01

LVF: Left ventricular failure, VSR: Ventricular septal rupture

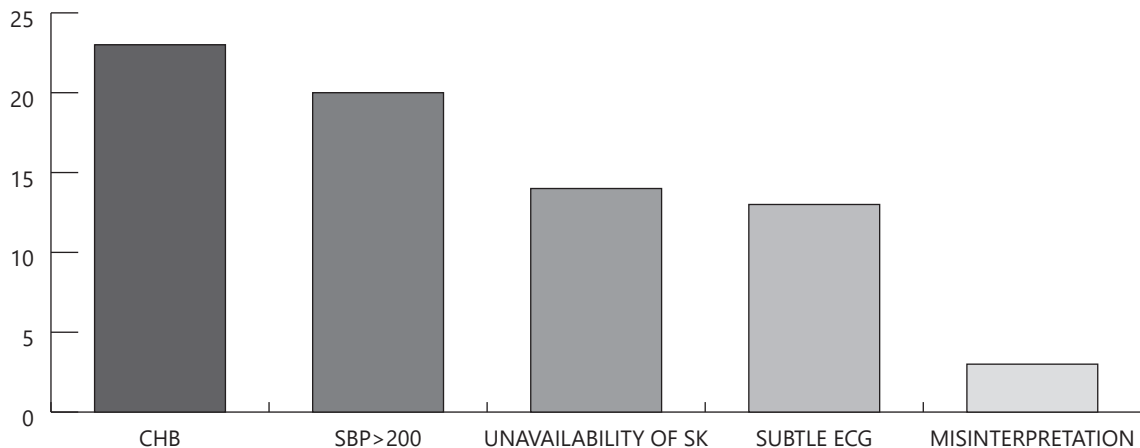
**Table 5: Stratified analysis for POR and complication rates**

DNT	ODDS OF FAILED THROMBOLYSIS			
	POR	Exp(PR)	CI(Exp.PR)	P-value
<30 minutes	0.48	0.68	0.21-1.09	0.610
30-60 minutes	2.25	1.71	1.29-2.13	<0.01
>60 minutes	2.92	2.10	1.47-2.79	<0.01

**Table 6: POR for failed thrombolysis with different co morbid conditions**

DNT	Risk of failed thrombolysis		
	POR	Exp-PR	P-value
AGE	0.030	0.623	0.194
SEX (MALE)	1.17	1.111	0.041
DM	3.79	1.693	<0.01
HTN	0.81	1.017	0.047
SMOKING	1.78	0.995	<0.01
FHX OF CAD	0.65	0.537	0.221
DYSLIPIDEMIA	1.01	0.983	0.051
NAFLD	2.97	1.71	<0.01

**Figure 1: Factors causing delay in thrombolysis**



complication rates increased from 37% to 49% and 70% for <30, 30-60, and >60 minutes respectively. Various other co-morbid conditions were also studied for their effect on failed thrombolysis. Diabetes mellitus, smoking and NAFLD being the most important one. Another important aspect of our study was that we analyzed different factors causing delay in thrombolysis and increasing DNT. Complete heart block needing temporary pacemaker installation was the most frequent cause of delay, followed by high B.P (>200 mmHg SBP) in which cases patients were thrombolysed after stabilization.

## CONCLUSION

Morbidity and mortality in patients of acute STEMI and complications of thrombolysis decrease with decreasing DNT. Moreover, complications of thrombolysis increase with co morbidities and risk factors for CAD.

The level of care can further be improved by overcoming the factors causing delay in thrombolysis by providing up to date facilities in chest pain clinic.

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### CONTRIBUTORS

MSJ and SBK conceived the idea, planned the study and drafted the manuscript. ZUZ, SAH helped in acquisition of data and did statistical analysis. AMG supervised the whole process and critically reviewed the manuscript. All authors contributed significantly to the submitted manuscript.