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Research Brief

Angiographic outcomes in STEMI patients receiving fibrinolysis with guideline directed optimal antithrombotic therapy

Shazia Durdana [a], Mohammad Azharuddin Malik [b, *], Asif Hasan [b], M.U. Rabbani [b]

[a] Department of Medicine, Aligarh Muslim University, Aligarh, Uttar Pradesh, India
[b] Department of Cardiology, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

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ABSTRACT

STEMI is a major public health problem requiring timely reperfusion. Fibrinolysis remains prevalent reperfusion strategy where timely primary percutaneous coronary intervention (PCI) cannot be performed. Adjunctive antithrombotic agents are of utmost importance for maximizing the benefit of fibrinolysis. This prospective study evaluates the angiographic outcomes in STEMI patients receiving fibrinolysis with optimal antithrombotic therapy and reported TIMI 3 flow rates of 33.8% and 41.5% for streptokinase and reteplase respectively, that were significantly higher than various prior studies. This data reiterates the utility of thrombolysis in resource limited settings.

1. Introduction

STEMI remains a major public health problem despite the advances in diagnosis and management. Timely reperfusion of the infarct-related coronary artery using fibrinolysis or percutaneous coronary intervention (PCI) is central to optimal STEMI treatment, minimizing myocardial damage, preserving left ventricular function, and decreasing morbidity and mortality.[1] However, limited resources, affordability issues, and inadequate transportation facilities to PCI-capable hospitals prevent the PCI from becoming default reperfusion strategy, thus, making fibrinolysis the prevalent reperfusion strategy. Multitude of clinical trials have been conducted so far which demonstrated that earlier fibrinolytic administration, improves myocardial salvage, preserves left ventricular mechanical function and subsequently leads to significant mortality reduction, thus, favoring key role of pharmacological reperfusion in acute treatment of STEMI.[2–4] Key component of the pharmacological "cocktail" is fibrinolytic therapy, but adjunctive antithrombotic agents are of utmost importance for maximizing and maintaining the benefit of dissolving the occlusive coronary artery thrombus as demonstrated by various prior studies.[5–7] However, in previous studies, antiplatelet agents or anticoagulants were either not used together consistently or if at all these agents were used, then they were in suboptimal dosing. This study attempts to unfold the relationship between successful fibrinolysis and angiographic parameters on the background of routine loading with dual antiplatelet therapy (DAPT) and optimal anticoagulation with heparin.

2. Method

The objective of this observational study was to assess angiographic success of thrombolysis in terms of angiographic TIMI 3 flow and TMP 3 grade in context of routine loading with DAPT and heparin in patients (>18 years age) presenting with STEMI (according to Third universal definition of MI)[8] from January 2018 to December 2019. Patients presenting with NSTEMI, or with STEMI but having contraindications to thrombolysis or refusing consent for reperfusion therapies were excluded from the study. DAPT and anticoagulant therapy were administered to every patient as per current AHA guidelines[9] followed by reperfusion therapy in the form of either thrombolysis or primary PCI depending upon the availability and feasibility. Keeping in view the superiority of enoxaparin over unfractionated heparin, enoxaparin was administered as a preferred anticoagulant to every patient prior to thrombolysis and then, for duration of index hospitalization.[10] Only patients who ultimately underwent thrombolysis were enrolled for the study with exclusion of patients who underwent primary PCI. Choice of thrombolytic to be used was left at physician's discretion after informed discussion with patient. Relief of chest pain after thrombolysis was assessed by visual analog scale and repeat ECG was done at 90 min after the administration of thrombolytic agent

* Corresponding author.
E-mail address: malikazharuddin@gmail.com (M.A. Malik).

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Table 1
Baseline characteristics of patients in relation to the thrombolytic agent used.

CHARACTERISTICS	Overall	Streptokinase (n = 59)	Reteplase (n = 41)	P-Value
Mean age	54.89 ± 11.19	54.76 ± 10.89	55.07 ± 11.76	0.892
Angina duration[a]				
Upto 3 h	38% (n = 38)	30.5% (n = 18)	48.8% (n = 20)	0.064
<6 h	75% (n = 75)	71.2% (n = 42)	80.5% (n = 33)	0.361
6–12 h	23% (n = 23)	25.4% (n = 15)	19.5% (n = 8)	
>12 h	2% (n = 2)	3.4% (n = 2)	0% (n = 0)	
Mean angina duration (hours)	5.16 ± 3.99	5.71 ± 4.51	4.37 ± 2.99	0.098
Door-to-needle time (minutes)	20.2 ± 16.22	21.61 ± 16.54	18.17 ± 15.72	0.299
Relief of chest pain	74% (n = 74)	72.85% (n = 43)	75.6% (n = 31)	0.760
ECG settling	70% (n = 70)	66.2% (n = 39)	75.6% (n = 31)	0.308
Reperfusion arrhythmias	14% (n = 14)	8.5% (n = 5)	21.9% (n = 9)	0.056
Killip class				
KC-I	83% (n = 83)	81.4% (n = 48)	85.4% (n = 35)	0.163
KC-II	6% (n = 6)	8.5% (n = 5)	2.4% (n = 1)	
KC-III	8% (n = 8)	5.1% (n = 3)	12.2% (n = 5)	
KC-IV (Cardiogenic shock)	3% (n = 3)	5.1% (n = 3)	0% (n = 0)	
Guideline-based medications				
ACEIs	85% (n = 85)	84.7% (n = 50)	85.4% (n = 35)	0.932
β-Blocker	89% (n = 89)	89.8% (n = 53)	87.8% (n = 36)	0.750
Complications				
Access site hematoma	1% (n = 1)	0% (n = 0)	2.4% (n = 1)	0.498
Bleeding	2% (n = 2)	3.4% (n = 2)	0% (n = 0)	
Heart failure	3% (n = 3)	3.4% (n = 2)	2.4% (n = 1)	
Others (Shivering)	1% (n = 1)	1.7% (n = 1)	0% (n = 0)	
Cag timing after thrombolysis				
3–24 h	53% (n = 53)	52.5% (n = 31)	53.6% (n = 22)	0.136
>24–48 h	27% (n = 27)	20.3% (n = 12)	36.6% (n = 15)	
>48–72 h	6% (n = 6)	8.5% (n = 5)	2.4% (n = 1)	
>72 h	14% (n = 14)	18.6% (n = 11)	7.3% (n = 3)	
TIMI-3 Flow	37% (n = 37)	33.8% (n = 20)	41.5% (n = 17)	0.441
TMP-3 Grade	35% (n = 35)	33.8% (n = 20)	36.6% (n = 15)	0.782
LVEF				
<40%	17% (n = 17)	23.8% (n = 15)	5.4% (n = 2)	0.048
40-<50%	32% (n = 32)	31.7% (n = 20)	32.4% (n = 12)	
50% or more	51% (n = 51)	44.4% (n = 28)	62.2% (n = 23)	

Abbreviations: KC- Killip class; TIMI- Thrombolysis in Myocardial Infarction; TMP- TIMI Myocardial Perfusion; CAG-Coronary angiography; ACEIs- Angiotensin converting enzyme inhibitors; LVEF- Left ventricular ejection fraction.
[a] Angina duration- Represents time interval between onset of symptoms to presentation to casualty.

to look for settling of ECG changes (resolution of ST segment elevation by >50% in the index lead showing greatest degree of elevation on presentation) and development of reperfusion arrhythmias. Success of thrombolysis was assessed via measurement of angiographic parameters such as TIMI (Thrombolysis in Myocardial Infarction trial) flow grade classification and TIMI myocardial perfusion grade classification (TMP)[11,12] as shown in Videos 1–4. Statistical data were analyzed using SPSS software version 26. Categorical variables were compared by Chi-square test while continuous variables were compared using Student *t*-test and a 'p' value of less than 0.05 was significant.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ihj.2020.11.011

3. Results

100 patients were recruited in the study, with 90 (90%) males. Baseline characteristics of patients in relation to thrombolytic agent used, are shown in Table 1. Average age of study population was 54.89 ± 11.19 years. TIMI 3 flow was present in 37% (n = 37) patients while 35% (n = 35) patients achieved TMP 3 grade. Among patients thrombolysed with streptokinase, TIMI-3 flow was established in 33.8% (n = 20) patients and among patients thrombolysed with reteplase, TIMI 3 flow was present in relatively higher number of patients i.e. 41.5% (n = 17). Combined TIMI 2/3 flow rates were 93.2% and 85.4% with streptokinase and reteplase respectively. Similar trends were present in relation to the TMP grade, although these differences were statistically insignificant. Out of 41 patients thrombolysed with Reteplase, mortality was reported in 2.4% (n = 1) patients in comparison to Streptokinase with mortality rates of 3.4% (n = 2). In our study, patients with TIMI 3 flow were younger and had lesser duration of symptoms before presentation to the hospital than the patients with TIMI flow less than 3. Other characteristics and predictors of TIMI flow rates are detailed in Table 2.

4. Discussion

In this study, TIMI-3 flow rates and TMP-3 grades were reported in higher proportion of patients thrombolysed with reteplase as compared to streptokinase. However, these differences were statistically insignificant, and lack of significance could reflect insufficient study size to detect such a difference. Overall TIMI-3 flow rates as well as combined TIMI 2/3 flow rates were significantly higher than prior studies which were lacking in optimal antithrombotic therapies as evident from the data shown in Table 3.[13–15] This synergistic effect of antithrombotic therapies with thrombolysis improves outcomes in STEMI in terms of coronary artery patency. However, one should keep in mind, the potential imbalances in infarct-artery location as suggested by the study results shown in Table 2. TIMI grade 3 flow was achieved more frequently in patients with an infarct-related artery other than the LAD, attributable to the fact that myocardial territory of LAD being very large leads to extensive necrosis of myocardium that it supplies and contributes to worse outcomes. Thus, our current findings strongly support the utility of fibrinolysis in conjunction with optimal

Table 2
Characteristics and predictors of TIMI flow rates in the study population.

Characteristics	TIMI 3 Flow		P-Value
	No (n = 63)	Yes (n = 37)	
Age	55.81 ± 10.941	53.32 ± 11.605	0.286
Sex distribution			
Males	62.22% (56)	37.77% (34)	0.629
Females	70% (7)	30% (3)	
Risk factors			
HTN	30.1% (19)	40.5% (15)	0.290
Diabetes Mellitus	14.2% (9)	21.6% (8)	0.346
Smoking	52.3% (33)	40.5% (15)	0.253
Dyslipidemia	66.6% (42)	62.2% (23)	0.648
F/H/O CAD	11.11% (7)	24.3% (9)	0.082
Past H/O IHD and prior MI	11.1% (n = 7)	10.8% (n = 4)	0.963
Mean *angina duration	5.714 ± 4.469	4.216 ± 2.839	0.07
Angina duration upto 3 hours	36.5% (n = 23)	40.5% (n = 15)	0.688
Angina duration upto 1 hour	4.8% (n = 3)	13.5% (n = 5)	0.119
Killip class			
KC-1	77.7% (49)	91.8% (34)	0.22
KC-II	6.3% (4)	5.4% (2)	
KC-III	11.11% (7)	2.7% (1)	
KC-IV (Cardiogenic shock)	4.7% (3)	0% (0)	
Coronary angiography based ira			
LAD	60.3% (38)	32.4% (12)	0.025
LCx	9.5% (6)	18.9% (7)	
RCA	30.1% (19)	48.6% (18)	
Door-to-needle time			
Upto 30 min	88.9% (56)	89.1% (33)	0.324
31–60 min	11.1% (7)	8.2% (3)	
>60 min	0% (0)	2.7% (1)	
Thrombolytic agent			
Streptokinase	66.2% (39)	33.8% (20)	0.441
Reteplase	58.5% (24)	41.5% (17)	
One-year outcome			
Death	4.7% (3)	0% (0)	0.216
Recurrent angina	7.9% (5)	2.7% (1)	
Recurrent revascularisation	3.2% (2)	0% (0)	

Abbreviations: HTN- Hypertension; F/H/O CAD- Family history of Coronary artery Disease; LAD- Left anterior descending artery; LCx- Left circumflex artery; RCA- Right coronary artery. *Angina duration- Represents time interval between onset of symptoms to presentation to casualty.

Table 3
Comparison of TIMI 3 flow in current study and other studies.

TIMI 3 Flow	Our Study	GUSTO-I[13]	TIMI Trial(Phase-I)[14]	RAPID-II[3]
Streptokinase	33.8%	29% (Stk and S/C Heparin) 32% (Stk and I.V. Heparin)	18%	–
Reteplase	41.5%	–	34%	59.9%

TIMI 2/3 Flow	Our Study	Martin G.V. et al, 1988[15]	RAPID-II[3]
Streptokinase	93.2%	68.5%	–
Reteplase	85.4%	–	83.4%

Abbreviations: GUSTO-I- Global utilization of Streptokinase and tissue plasminogen activator for occluded coronary arteries; TIMI- Thrombolysis in Myocardial Infarction; RAPID–II– Reteplase (r-PA) vs Alteplase Patency Investigation During Acute Myocardial Infarction Study.

antithrombotic therapy for STEMI patients in contemporary primary PCI era when resource constraints exist.

5. Conclusion

This study reiterates the utility of thrombolysis in resource limited settings where mechanical reperfusion for STEMI cannot be performed in a timely manner. The outcomes are better as compared with historical controls when routine treatment with heparin and dual antiplatelet agents is given in conjunction with fibrinolysis. Thus, our study supports the pharmaco-invasive strategy for STEMI with fibrinolysis in conjunction with routine loading with dual antiplatelet therapy and anticoagulant and subsequent invasive assessment and PCI if needed, in areas where significant healthcare resource and infrastructure constraints exist.

Declaration of competing interest

None declared.

References

1. Gibson CM, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008 Dec 1;156(6):1035–1044.

2. Rovelli F, De Vita C, Feruglio GA, Lotto A, Selvini A, Tognoni G. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet*. 1986;1(8478):397–402.
3. Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation*. 1996 Sep 1;94(5):891–898.
4. Armstrong PW, Collen D, Antman E. Fibrinolysis for acute myocardial infarction: the future is here and now. *Circulation*. 2003;107(20):2533–2537.
5. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *J Am Coll Cardiol*. 1988 Dec;12(6 Supplement A):A3–A13.
6. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607–1621. https://doi.org/10.1016/S0140-6736(05)67660-X.
7. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352(12):1179–1189. https://doi.org/10.1056/NEJMoa050522.
8. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020–2035.
9. Levine GN, Bates ER, Bittl JA, et al. ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082–1115, 2016.
10. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006 Apr 6;354(14):1477–1488.
11. TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial: phase I findings. *N Engl J Med*. 1985 Apr 4;312(14):932–936.
12. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation*. 2000 Jan 18;101(2):125–130.
13. Gusto Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993 Sep 2;329(10):673–682.
14. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation*. 1987;76(1):142–154.
15. Martin GV, Sheehan FH, Stadius M, et al. Intravenous streptokinase for acute myocardial infarction. Effects on global and regional systolic function. *Circulation*. 1988 Aug;78(2):258–266.