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Prospective Study

Feasibility and Efficacy of Delayed Pharmacoinvasive Therapy for ST- Elevation Myocardial Infarction

Delayed pharmacoinvasive strategy in acute STEMI

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Abstract

BACKGROUND

ST-elevation myocardial infarction (STEMI) refers to a clinical syndrome that features symptoms of myocardial ischemia with consequent ST-elevation on electrocardiography and an associated rise in cardiac biomarkers. Rapid restoration of brisk flow in the coronary vasculature is critical in reducing mortality and morbidity. In patients with ST segment elevation myocardial infarction who could not receive primary percutaneous coronary intervention on time, pharmacoinvasive strategy (thrombolysis with timely percutaneous coronary intervention within 3-24 h of initiation) is an effective option.

AIM

To analyze role of delayed pharmacoinvasive strategy in the window period of 24-72 h after thrombolysis.

METHODS

This was a physician-initiated, single-center prospective registry between January-2017 and July-2017 which enrolled 337 acute ST segment elevation myocardial infarction patients with partially occluded coronary arteries. Patients received routine pharmacoinvasive therapy (percutaneous coronary intervention within 3-24 h of thrombolysis) in one group and delayed pharmacoinvasive therapy (percutaneous coronary intervention within 24-72 h of thrombolysis) in another group. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 days of the procedure. The secondary endpoint included, major bleeding as defined by Bleeding Academic Research Consortium (BARC) classification, angina, and dyspnea within 30 days.

RESULTS

Mean age in both the groups was comparable (55.1 ± 10.1 years *vs* 54.2 ± 10.5 years, *P* = 0.426). Diabetes was 20.2% and 22.1% in routine & delayed groups, respectively. Smoking rate was 54.6% and 55.8% in routine and delayed groups, respectively. Thrombolysis was initiated within 6 h of onset of symptoms in both groups (*P* = 0.125). The mean thrombolysis to percutaneous coronary intervention time in routine and delayed group was 16.9±5.3 h and 44.1±14.7 h, respectively. No significant difference was reported for occurrence of measures clinical outcomes in both groups within 30 days (8.7% *vs* 12.9%, *P* = 0.152). Univariate analysis of demographic characteristics and risk factors for patients who reported major adverse cardiac and cerebrovascular events in both the groups didn't report any significant correlation. Secondary endpoints such as angina, dyspnea, and major bleeding were non-significantly different between routine and delayed groups.

CONCLUSION

Delayed percutaneous coronary intervention pharmacoinvasive strategy in a critical diseased but not completely occluded artery beyond 24 h in patients, who have been timely thrombolyzed seems a reasonable strategy.

Key Words: Coronary artery disease; ST-elevation myocardial infarction; Primary percutaneous coronary intervention; Pharmacoinvasive strategy; Thrombolysis; Atherosclerosis

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Core Tip: Primary PCI is the gold standard strategy for acute STEMI. But in real world scenario, pharmacoinvasive strategy with PCI within 3 to 24 h after successful

thrombolysis has been proven to be a viable alternative In absence of primary PCI . In resource poor countries, we often encounter patients who present to interventionist beyond 24 h of thrombolysis. Our study aims to analyse safety and feasibility of this delayed pharmacoinvasive PCI approach in patients presenting 24-72 hrs of thrombolysis.In this single centre registry, we enrolled 337 patients of acute STEMI and were into 2 groups. First was routine pharmacoinvasive arm who presented within 3 to 24 h of successful thrombolysis and second group was delayed pharmacoinvasive arm who presented within 24 to 72 h of successful thrombolysis and underwent PCI to non occluded IRA.Our study found no significant difference in primary end point at 30 days which was major adverse cardiac and cerebrovascular events. Secondary end points of angina, dyspnoea and major bleeding also did not differ significantly.Our study affirms safety and feasibility of delayed pharmacoinvasive PCI in patients who present late 24-72hrs after successful thrombolysis.

INTRODUCTION

ST-elevation myocardial infarction (STEMI), a potentially lethal diagnosis, refers to a clinical syndrome that encompasses symptoms of myocardial ischemia with consequent ST-elevation on electrocardiography and an associated rise in cardiac biomarkers. Rapid restoration of brisk flow in the coronary vasculature is critical in reducing mortality and morbidity. Primary percutaneous coronary intervention (PCI) is the global standard of care method for patients presenting with acute STEMI.[1,2] However, the practicality of all patients reaching the PCI-capable center within one hour is a challenge. Thus, in patients with acute STEMI who cannot get primary PCI in a timely manner, pharmacoinvasive strategy is considered as an effective and viable option.[3,4] This is particularly true in developing nations where this delay often crosses the golden period of 24 h as the burden of disease is exponentially increasing and limited availability of resources. The famous OAT-trial (Occluded Artery Trial), failed to show any advantage of performing PCI (beyond 72 h) + optimal medical therapy compared to optimal medical therapy alone.[5]

So, in the present study we analyzed a novel concept of 'delayed pharmacoinvasive therapy' in acute STEMI patients with partially occluded coronary vasculature who had received thrombolysis within first 12 h of symptoms onset and underwent PCI in a window period of 24-72 h; and compared both routine and delayed pharmacoinvasive strategies in such patients.

MATERIALS AND METHODS

This was a physician-initiated, single-center prospective registry which enrolled STEMI patients who were thrombolyzed within 12 h of acute event and subsequently underwent PCI between January-2017 and July-2017. The study protocol was approved by Institutional Review Board and was performed in accordance with Declaration of Helsinki. The written informed consent was received from patient or from patient designees before enrollment.

The enrolled patients with STEMI either received at peripheral hospitals, thrombolyzed and referred to us; or else were directly admitted to our hospital after the golden hour of primary PCI, thus received thrombolysis. For various nonspecific reason, some of them could not undergo PCI within 3-24 h of initiation of thrombolytic therapy. The common reasons for this delay were financial constraints and imbalance between the service seekers and providers which doesn't support 24 h functioning of cath-lab, even in tertiary care centers. The period of 24-72 h has remained a grey area for the decision of primary PCI in the literature but is one of the usually encountered strategy in low resource clinical setup and used in many centers with PCI, if vessels are still found to be occluded in angiography. We called this group as delayed pharmacoinvasive group. To evaluate the effectiveness of this strategy, we compared the results with the cohort who underwent routine pharmacoinvasive therapy (thrombolyzed within 12 h of symptoms onset followed by PCI within 3-24 h initiation of thrombolysis). The groups were not randomized. Stated simply, Group 1 (Routine) represented those patients undergoing PCI < 24 hrs of symptoms onset and Group 2 (Delayed) consisted of those subjects undergoing PCI between 24-72 hrs of symptom onset.

Patients who underwent primary PCI were excluded from the study. Other exclusion criteria included contraindication for thrombolysis or patients presenting beyond window period for thrombolysis, totally occluded arteries on angiogram within 24-72 h.

Clinical Endpoints and Definitions:

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 days that included composite of death, rehospitalization due to reinfarction and congestive heart failure, target vessel revascularization and stroke. The secondary endpoint included individual primary endpoints, major bleeding as defined by Bleeding Academic Research Consortium classification, angina and dyspnea within 30 days. The impact of time of thrombolysis to PCI on the clinical outcome (< 24 h; 24-48 h and 48-72 h) was also assessed.

Statistical Analysis

The statistical review of this study was performed by a biomedical statistician from King George's Medical University. All the data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows version 20.0; Chicago, IL, USA). The categorical and continuous variables were summarized as frequency (percentage) and mean value ± standard deviation, respectively. The difference between two groups was verified using Chi-square test for categorical variables and independent sample t-test for continuous variables considering $p < 0.05$ as statistically significant.

RESULTS

The Flow chart of study patients is demonstrated in **Figure 1**. Among 880 STEMI patients presented at our tertiary care center in the given period, 337 patients were divided into two groups i) 183 patients in the routine group who underwent PCI with 3-24 h of initiation of thrombolysis, and b) 154 patients in the delayed group who underwent PCI with 24-72 h of initiation of thrombolysis.

Demographic characteristics of the study cohorts (routine group *vs* delayed group) are compared in **Table 1**. Mean age in both the groups was comparable (55.1 ± 10.1 years *vs* 54.2 ± 10.5 years, $P = 0.426$) with a predominance of male patients in both the group

(87.4% in routine group and 89.6% in delayed group). Occurrence of anterior wall ST-segment elevation myocardial infarction and non-anterior wall ST-segment elevation myocardial infarction were almost equally distributed in the routine and delayed groups (53.6% *vs* 57.1% and 46.4% *vs* 42.9%; *P* = 0.509, respectively). In both the groups, around 58% patients had single vessel disease while 42% patients had multiple vessel disease. A statistically significant difference in mean left ventricular ejection fraction between two groups was noted (routine: 46.9 ± 4.7 and delayed: 45.8 ± 4.5; *P* = 0.034).

In both the routine and delayed groups, thrombolysis was initiated within 6 h of onset of symptoms (5.2 ± 3.4 h *vs* 5.8 ± 4.5 h, *P* = 0.125). The mean thrombolysis to PCI time was 16.9 ± 5.3 h in routine group while it was 44.1 ± 14.7 h (an average 27 h late) in delayed group.

The clinical outcomes within 30 days of the procedure in both the groups are depicted in **Table 2**. The primary endpoint i.e MACCE was reported in 16 (8.7%) patients in routine group and in 20 (12.9%) patients in the delayed group (*P* = 0.152). Angina occurred in 4 (2.2%) patients in routine group and in 1 (0.6%) in delayed group (*P* = 0.381). Dyspnea occurred in 6 (3.3%) and 5 (3.2%) in routine and delayed group, respectively (*P* = 0.99).

To analyze the effect of time of thrombolysis to PCI on clinical outcomes, we further divided delayed group into two subgroups: i) thrombolysis to PCI time 24 - ≤48 h (*n* = 96) and ii) 48 - 72 h (*n* = 58) and was compared with routine group (thrombolysis to PCI time <24 h; *n* = 183). However, no statistically significant difference in measured clinical outcomes among all the three groups was observed (**Table 3**).

Univariate analysis of demographic characteristics and risk factors for patients who reported MACCE in both the groups are outlined in **Table 4**. A significant correlation was reported between Killip class-2 with the occurrence of primary outcomes in routine group (odd ratio: 4.59, CI: 1.08-19.40).

DISCUSSION

Primary PCI within one hour of symptoms onset is the standard of care strategy in acute STEMI.[1,6] However, the real world scenarios are not always ideal thus decision making in such cases is a challenge for interventional cardiologists.[7-10] As per guidelines, pharmacoinvasive therapy (thrombolysis with PCI within 3-24 h) is recommended as an effective option in patients with acute STEMI who could not receive primary PCI within this golden hour.[6] Furthermore, there is a lacuna in the literature regarding the role of PCI, in patients who present in a window of 24-72 h of thrombolysis. This period is critical and the benefits of reperfusion of partially occluded artery must be balanced against the potential harm from procedure-related complications, myocardial injury because of distal embolization of athero-thrombotic debris, and loss of recruitable collateral flow to other coronary territories.[11,12] In our study, we compared effectiveness of routine (PCI within 24 h of thrombolysis) and delayed (PCI within 24-72 h of thrombolysis) pharmacoinvasive therapies and the results stated no statistically significant difference in the clinical outcome between two therapies within 30 days of the procedure.

Almost a decade ago OAT-trial (Occluded Artery Trial) was published to test the hypothesis that whether opening a totally occluded infarct related artery, 3-28 days following acute STEMI, will improve the clinical outcome or not. The results of that trial cautioned about a trend towards excess non-fatal re-infarction when PCI was performed in stable patients with totally occluded infarct related artery, 3 to 28 days after STEMI, and did not show any reduction in major cardiovascular events during a mean follow-up of 3 years among these patients.[5,13] Furthermore, in an analysis from the Melbourne Interventional Group registry of 4307 patients with STEMI who underwent PCI, no mortality hazard was reported where PCI was delayed beyond the first 24 h but was performed within the index admission. However, they have not defined/specified the index admission in terms of time/hours.[14]

A meta-analysis of ten randomized controlled trials on timing of PCI in non-STEMI patients showed no reduction in death or re-infarction rate in early *vs* delayed intervention. However, recurrent ischemia and length of stay were significantly

reduced with an early invasive strategy.[15] In non-STEMI cases a delayed invasive approach is recommended, with an early invasive strategy within 24 hours in high-risk patients and a delayed invasive strategy within 72 hours in intermediate risk patients.[16] As randomized controlled trials of these kinds are difficult to plan for STEMI patients, decisions must be based on observational studies or clinical registries. Recently, a randomized controlled trial was published for transient STEMI in which the outcomes of a STEMI-like approach (with an immediate invasive strategy) were compared with a non-STEMI like approach (with a delayed invasive strategy) and the results showed no difference in clinical outcomes.[17]

PCI in any scenario after 72 h is not recommended as it can be more detrimental than beneficial to vascularize the myocardium which is already dead.[18] In the present study, the mean symptom onset to angiography time was 22.0 ± 6.6 hours and 49.4 ± 15.5 hours in routine and delayed group, respectively. Contrary to this in the reported literature these time windows are significantly less.[3,19] Notably, it is difficult to compare the triage and referral facilities between developed and developing countries. Delayed presentation was one of the most important factors in our study determining the poor primary outcomes as compared to western data. The delay in reaching to STEMI care hospital in our country is multifactorial: i) due to delay in recognition of chest symptom by patients themselves, ii) due to unavailability of electrocardiogram machine at peripheral health care centers, iii) due to incompetency in diagnosing and taking decision for referral to higher centers by the health care provider, and iv) due to poor transportation services. However, in our opinion these loopholes in our systems are not too difficult to handle. The lag time for patient presentation can be reduced by creating public awareness regarding symptoms of acute coronary syndrome, educating the grass root level health care providers, ensuring the availability of an electrocardiogram machine at peripheral health care centers, and strengthening the ambulance services. Increasing the number of cath-labs and their working hours by increasing the number of work force will also prevent the procedural delays.

The primary outcomes i.e, MACCE within 30 days was reported in 8.7% in routine group and 13.6 % in the delayed group (P = 0.152). The STEMI patients undergoing primary PCI have witnessed a wide range of MACCE (1.6% to 23.3%) in 30 days, in various studies and variation depends on the baseline risk factors of the study population and pharmacological intervention prior to PCI.[20-22] Furthermore, in our cohort Killip class was the most important predictor for worse outcomes among all the clinical parameters analyzed by univariate analysis. Killip class II patients had larger infarct and poorer left ventricular function as compared to Killip class I and it is a well-recognized fact that the outcome of STEMI with high Killip class (≥ class II) is poor.[23,24] Male sex and left ventricular ejection fraction >45% were the other two parameters which reported moderate significance in predicting the outcomes.

Ours is a first of its kind study to clearly document the useful role of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) in patients with acute STEMI, which is extremely important and practical in low resource high burden settings.

Limitations

There were few limitations of our study. First, we enrolled a comparatively small number of patient population and shorter duration of the study. As randomized controlled trials are difficult to conduct in these subjects because of ethical and legal issues, keeping in mind our preliminary results which support delayed pharmacoinvasive therapy in a specified group of population, prospective registries must be encouraged to conclude further. Second, despite a prospective design we did not use cox proportional hazard model which has been shown have more statistical power than logistic regression model in cross sectional studies.[25] However, when the follow up is short and event rates are low (as in our study) both methods may be comparable.[26] Third , we did not evaluate the psychological impact of a delayed PCI or the Post Traumatic Stress Disorder symptoms during the extra waiting period. Fourth, despite a high rate of smoking at baseline data regarding persistent smoking at 30 days

was not available. However, counselling for smoking cessation was provided to all smokers as a protocol.

CONCLUSION

The results of present study specifically established that the clinical outcomes of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) are comparable to routine pharmacoinvasive (3-24 h of initiation of thrombolysis) in patients with acute STEMI. Delayed PCI (24-72 h following thrombolysis) in critical diseased but not completely occluded arteries, which have been timely thrombolysed, seems a reasonable strategy in acute STEMI patients.

ARTICLE HIGHLIGHTS

Research background

ST elevation MI (STEMI) when untreated is a potentially fatal condition and timely primary percutaneous coronary intervention (PCI) is the key to improve outcomes.

Research motivation

In developing countries, despite multiple guidelines and interventions the primary PCI coverage in STEMI remains low in clinical practice. PCI within 24 h of thrombolysis (pharmacoinvasive approach) has emerged as a viable alternative to Primary PCI.However, due to logistic and financial reasons patients in developing world may undergo PCI late (>24 hrs) after thrombolysis.

Research objectives

This study aimed to analyze the safety and feasibility of delayed pharmacoinvasive strategy in the window period of 24-72 h after thrombolysis.Group 1 (Routine) represented those patients undergoing PCI < 24 hrs of symptoms onset and Group 2

(Delayed) consisted of those subjects undergoing PCI between 24-72 hrs of symptom onset.

Research methods

This was a single center and prospective registry at a tertiary care center.The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 days of the procedure.

Research results

Among 337 patients of STEMI who underwent thrombolyis,there was no difference in measured clinical outcomes (MACCE) at 30 days between routine pharmacoinvasive and delayed pharmacoinvasive groups (8.7% *vs* 12.9%, P = 0.152).The mean thrombolysis to percutaneous coronary intervention time in routine and delayed group was 16.9±5.3 h and 44.1±14.7 h, respectively.

Research conclusions

Delayed percutaneous coronary intervention pharmacoinvasive strategy in a critical diseased but not completely occluded artery beyond 24 h in patients, who have been timely thrombolyzed seems a reasonable strategy.

Research perspectives

Late PCI after thromobolysis in STEMI is common in developing world due to logistic and financial reasons. This study demonstrates the safety and feasibility of such delayed pharmacoinvasive PCI lending credibility to this approach utilized in daily practice.

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