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Does Adjunctive Prophylactic Intracoronary Infusion of Low Dose Alteplase Prevent No-Reflow Phenomenon During Primary Percutaneous Coronary Intervention?

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Original Article

Abstract

INTRODUCTION: Primary percutaneous coronary intervention (PPCI) is the gold standard approach to restore blood flow in ST-segment elevation myocardial infarction (STEMI); however, the no-reflow phenomenon as a potential complication of PPCI can worsen the outcomes. It has been hypothesized that adjunctive prophylactic intracoronary infusion of low-dose fibrinolytic might improve the PPCI outcomes; however, this theory is a matter of debate. The current study aims to investigate the value of adjunctive prophylactic intracoronary low-dose alteplase to prevent the no-reflow phenomenon in patients with STEMI.

METHOD: This case-control study was conducted on 80 STEMI patients who underwent PPCI. The patients were assigned into the case group who were intervened by 10 mg adjunctive intracoronary alteplase immediately at the end of the balloon angioplasty (n=40) and controls (n=40) who underwent conventional PPCI only. The angioplasty-associated outcomes including final TIMI score, need for no-reflow treatment, ST-segment resolution, post-PPCI complications, and death were compared between the groups.

RESULTS: Alteplase use was accompanied by significantly improved final TIMI flow scores (P-value<0.001) and fewer requirements for no-reflow treatments (P-value<0.001); however, it did not improve the ST-segment resolution (P-value=0.491). The mortality rate and post-angioplasty complications did not differ between the groups (P-value>0.05).

CONCLUSION: Based on the findings of this study, adjunctive infusion of low-dose intracoronary alteplase during PPCI could not efficiently prevent the no-reflow phenomenon. Although the final TIMI flow and need for post-stenting no-reflow treatment improved, ST-segment resolution did not occur dramatically. Given that, this approach requires further investigations and should be considered cautiously.

Keywords: ST-elevation myocardial infarction, Tissue activator plasminogen, Alteplase, No-reflow phenomenon, Case-control studies

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Introduction

Coronary heart disease, as the final consequence of the atherosclerotic process, is a significant cause of mortality worldwide [1]. Globally, cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity, affecting about one-third of annual deaths. However, its distribution is not balanced worldwide, and its incidence is considerably higher among low-

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to-moderate income communities [2,3].

ST-segment elevation myocardial infarction (STEMI) is an event that occurs due to a sudden occlusion of an epicardial coronary artery following an atherosclerotic plaque rupture, leading to thrombus formation [4]. The primary goal in the approach to STEMI is to effectively and rapidly restore the blood flow in the ischemic myocardial tissue, which can be achieved by either timely performed primary percutaneous coronary intervention (PPCI) or a pharmacologic strategy consisting of thrombolysis to save the diseased myocardium and decrease mortality. However, according to the American Heart Association guidelines, PPCI is remarkably superior to the latter [5].

No-reflow or slow flow is one of the most conflicting challenges in the management of STEMI via PPCI, occurring in 20% of the cases due to large clots, myocardial salvage, or depressed left ventricular ejection fraction [6]. Moreover, atherothrombotic debris might be embolized from the infarct-related artery during PPCI, which contributes to microvascular obstruction. Regardless of the mechanical microvascular obstruction, the release of proinflammatory mediators and vasoconstrictors can deteriorate post-PPCI reperfusion by causing microvascular vasospasm, interstitial edema, and further cellular injury. The larger a thrombus is, the more severe distal embolization on myocardial tissue can occur [7,8].

On the other hand, reperfusion can paradoxically exacerbate myocardial injury due to edema resulting from reperfusion injury, which subsequently leads to microvessel occlusion following external compression. The primary factors in reperfusion injury are platelets, which form microthrombi plugs in the microvasculature. Additionally, platelet-to-neutrophil aggregation has a proinflammatory effect, promoting pro-inflammatory leukocyte infiltration and vasoconstriction [9,10].

Various pharmacologic strategies, including the use of vasodilators such as nitrates, adenosine, or verapamil, have been proposed to manage the no-reflow phenomenon. However, there is no effective strategy to prevent no-reflow during PPCI [11]. A new hypothesis has been proposed in favor of adjunctive infusion of low-dose intracoronary fibrinolytic therapy, which could theoretically prevent microvascular damage and the no-reflow phenomenon. However, the evidence in this regard is limited and controversial [8]. The primary goal of the current study is to investigate the value of adjunctive prophylactic intracoronary low-dose alteplase to prevent the no-reflow phenomenon in patients with STEMI.

Materials and Methods

Study population

The current case-control study was conducted on 80 patients admitted due to STEMI to undergo PPCI at the Shahid Chamran Cardiovascular Center affiliated with Isfahan University of Medical Sciences from February 2021 to January 2023.

The study protocol, primarily designed based on the Helsinki declaration, was proposed to the Ethics Committee of Isfahan University of Medical Sciences and approved via code number IR.MUI.MED.REC.1401.413. The study protocol was explained to the patients or their legal guardians, they were reassured regarding the confidentiality of their personal information, and they signed written consent for participation in the study.

The patients with STEMI who had the proximal-to-middle main epicardial coronary arteries (left anterior descending, right or left circumflex coronary arteries) involvement in the PPCI and whose interval between the onset of symptoms and PPCI to restore the perfusion was less than 6 hours were included in the study. The exclusion criteria were Rentrop scores of 2 or 3 in the involved epicardial artery, any contraindication for fibrinolytic use, and reluctance for participation in the study.

Intervention

All the patients underwent PPCI from the femoral/radial arteries using a modified Seldinger technique. Those who were

allocated to the case group received 10 mg intracoronary alteplase (Boehringer Ingelheim, Germany) immediately at the end of the balloon angioplasty. In the next step, stenting was done for all cases. All the steps were similar between the cases and controls except for the prophylactic infusion of low-dose intracoronary alteplase as an adjunctive therapy in the cases.

Data collection

Demographic (age and gender), habitual (smoking), medical, clinical, and laboratory information of the studied population were gathered in the study checklist. The medical data included chronic diseases (hypertension, diabetes mellitus, and hypercholesterolemia) and medications (aspirin, clopidogrel, and statins). Hypertension was defined as the history of anti-hypertensive medications use or the SBP≥140 mmHg, DBP≥90 mmHg or both. Using blood sugar-controlling agents, insulin injection or oral agents, and the medical data compatible with increased blood sugar in the range of diabetes mellitus definition was considered diabetes mellitus. The use of lipid-lowering agents or cholesterol above 200 mg/dl was determined as hypercholesterolemia [12].

On-arrival vital signs (heart rate (HR), systolic and diastolic blood pressure (SBP and DBP)) and laboratory data (hemoglobin, platelet count, and serum creatinine) were recruited from the medical records.

The other clinical manifestations included angioplasty-related data of the infarcted related coronary artery (LAD, LCX, and RCA) or saphenous vein graft (SVG) in patients with the history of coronary artery bypass grafting (CABG), primary thrombolysis in myocardial infarction score (TIMI), thrombus grade based on Rentrop score [13], and the performance of post-dilation with NC.

Primary outcome

The primary outcomes of the study were to investigate post-angioplasty final TIMI score, requirement for no-reflow phenomenon treatment, ST-segment resolution, and post-PPCI complications incidence. Successful ST-segment resolution was defined as a downward deviation of more than 70% toward the isoelectric line in the electrocardiogram within 60 minutes of index interventions [13].

TIMI flow grading was assessed as the following:

- 0: No penetration of contrast in the infarct-related vessel,
- 1: Penetration of some contrast beyond the obstruction but no perfusion in the distal coronaries,
- 2: Perfusion in the whole infarct-related vessel, but with delayed flow,
- 3: Full perfusion of the infarct-related vessel and normal flow [14].

The assessed complications included the incidence of major bleedings (intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and gross hematuria), requirement for blood transfusion, in-hospital stent thrombosis, and death.

Statistical analysis

The collected data was entered into the Statistical Package for Social Sciences (SPSS Inc. PASW statistics for window Chicago) version 24. Categorical variables were presented in absolute numbers and percentages, while continuous variables were presented as mean±standard deviation. Chi-square or Fisher's exact tests were used to compare the categorical data. Continuous variables were compared using an independent t-test. A P-value less than 0.05 was considered the level of significance.

Results

In this study, data from 80 patients with STEMI were collected. The patients predominantly consisted of males (88.75%) and had a mean age of 60.67±10.31 years old. The patients were divided into two equal groups; the case group underwent PPCI plus adjunctive infusion of low-dose intracoronary alteplase (n=40), and the control group underwent conventional PPCI only (n=40).

Table 1. Demographic, habitual and medical characteristics

Variables	Case group (n=40)	Control group (n=40)	P-value
Demographic characteristics			
Age (years), mean±standard deviation	59.00±10.35	62.35±10.28	0.153*
Gender (male), n (%)	35(87.5)	36(90.0)	0.723**
Habits			
Smoking (yes), n (%)	15(37.5)	14(35.0)	0.816**
Chronic medical history, n (%)			
Hypertension	27(67.5)	21(52.5)	0.171¥
Diabetes mellitus	15(37.5)	17(42.5)	0.648**
Hypercholesterolemia	13(32.5)	12(30.0)	0.809**
Drug history, n (%)			
Aspirin	8(20.0)	11(27.5)	0.431**
Clopidogrel	1(2.5)	3(7.5)	0.615¥
Statins	6(15.0)	8(20.0)	0.556**

*t-test **Chi-Square ¥Fisher's Exact

Table 1 displays the demographic, habitual, and medical characteristics of the studied groups. Based on this table, the patients were similar in terms of the mentioned categories (P-value>0.05).

The groups studied by the authors were statistically similar in terms of the periprocedural variables, including the involved epicardial territory (P-value>0.05), the primary TIMI flow (P-value>0.999), thrombus grade (P-value=0.579), and the practice of post-dilation with NC (P-value=0.260). Additional data included on-arrival heart rate (P-value=0.995), SBP (P-value=0.167), and DBP (P-value=0.057), as well as laboratory data including hemoglobin (P-value=0.287), platelet count (P-value=0.068), and serum creatinine (P-value=0.659). Detailed information is demonstrated in Table 2.

Table 2. Angiographic, on-admission vital signs and laboratory data

Variables		Case group (n=40)	Control group (n=40)	P-value
Angiographic characteristics				
Involved epicardial territory/ graft, n (%)	**LAD**	15(37.5)	17(42.5)	0.648**
	LCX	0 (0)	2(5)	0.494¥
	RCA	24(60.0)	18(45.0)	0.179**
	SVG	1(2.5)	3(7.5)	0.615¥
Primary TIMI flow grade	**0**	37 (92.5)	37 (92.5)	-
	1	3(7.5)	3(7.5)	
Thrombosis Rentrop score	**3**	4(10.0)	2(5.1)	0.579**
	4	8(20.0)	6(15.4)	
	5	28(70.0)	31(79.5)	
Post angioplasty dilatation with N C		15(37.5)	20(50.0)	0.260*

Variables	Case group (n=40)	Control group (n=40)	P-value
On-admission vital signs			
Heart rate (per minute), mean±standard deviation	80.40±18.36	80.18±16.77	0.955*
Systolic blood pressure (mmHg), mean±standard deviation	134.10±25.21	126.10±26.09	0.167*
Diastolic blood pressure (mmHg), mean±standard deviation	84.88±18.40	77.40±16.12	0.057*
On-admission laboratory data			
Hemoglobin (mg/dl), mean±standard deviation	14.83±2.69	14.24±2.17	0.287*
Platelet count (per microliter), mean±standard deviation	213.48±78.29	185.24±51.75	0.068*
Creatinine (mg/dl), mean±standard deviation	1.22±0.30	1.25±0.38	0.659*

LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery, SVG: saphenous vein graft
*t-test **Chi-Square ¥Fisher's Exact

Table 3 shows the primary outcomes of PPCI intervention with/ without adjunctive low-dose intracoronary alteplase infusion. Based on this table, alteplase use was accompanied by significantly higher final TIMI flow scores (P-value<0.001) and fewer requirements for no-reflow treatments (P-value<0.001); however, it could not lead to the dramatically ST-segment resolution (P-value=0.491). The mortality rate and post-angioplasty complications did not differ between the groups (P-value>0.05).

Table 3. Post-angioplasty outcomes and complications

Variables		Case group (n=40)	Control group (n=40)	P-value
Post-angioplasty outcomes				
Post-angioplasty TIMI flow, n (%)	**0**	0 (0)	0 (0)	<0.001**
	1	0 (0)	1(2.5)	
	2	19(48.7)	2(5.0)	
	3	20(51.3)	37(92.5)	
Requirement for no reflow treatment, n (%)		6 (15)	21(52.5)	<0.001*
ST-segment resolution, n (%)		23(57.5)	26(65.0)	0.491*
Post-angioplasty complications, n (%)				
In Hospital Stent Thrombosis		0 (0)	0 (0)	-
Intracranial hemorrhage		0 (0)	0 (0)	-
Gastrointestinal bleeding		0 (0)	0 (0)	-
Gross hematuria		0 (0)	0 (0)	-
Blood transfusion requirement		0 (0)	0 (0)	-
Death		0(0)	0 (0)	-

*Chi-Square **Fisher's Exact

Discussion

The primary aim of the current study was to investigate the usefulness of adjunctive infusion of low-dose intracoronary fibrinolytic to prevent the no-reflow phenomenon in patients undergoing PPCI due to STEMI. As the potential confounding factors affecting

the angioplasty outcomes, the demographic, habitual, medical, clinical, on-arrival vital signs, laboratory parameters, and primary angiographic findings were similar between the groups studied by the authors. Given that, the results of the study might be logically attributed to the applied approaches only. Accordingly, the authors found that prophylactic infusion of low-dose alteplase could not result in a remarkable superior response to revascularization.

The hypothesis emphasis on intracoronary fibrinolytic use during PPCI has been raised since the late 1990s when researchers used intracoronary t-PA for thrombolysis and represented controversial and confusing data; however, they also represented promising outcomes regarding the successful blood flow restoration; they were concerned about the dosage to minimize the potential complications [15-17]. Nevertheless, due to the promising data in this issue, further investigations on diverse agents and dosages went on. Ibrahim and colleagues represented significantly improved left ventricular longitudinal function through Doppler imaging and better blood flow considering TIMI flow grading in the patients undergoing post-PPCI intracoronary alteplase infusion with the low dose of 0.3 mg/kg. They followed the patients for 6 months through cardiac magnetic resonance imaging which favored the intervention via alteplase [18]. The logic by which the studies favoring intracoronary alteplase use immediately after PPCI refers to the ability of fibrinolytic for thrombus dissolution and improvement in blood perfusion to the injured myocardial cells in more distal parts. This theory has been enforced considering a significant decrease in troponin levels of the patients with appropriate microvascular perfusion [18].

However, some of the other authors have firmly defied against the use of intracoronary fibrinolytics, for instance, alteplase, considering the outcomes that were in contrast with the primary goal of using this agent. For instance, Maznyczka et al. conducted a study in which the risk of microvascular obstruction not only did not decrease, but also increased and they opposed its routine use after a PPCI for patients with STEMI [19]. The other researchers who have not supported intracoronary fibrinolytic use claimed that it is not beneficial for the patients, but might potentially increase the risk of adverse events. McCartney et al. conducted a study on 440 patients with STEMI undergoing PPCI plus intracoronary 10-20 mg alteplase infusion. They represented no reduction in microvascular obstruction as well as an insignificant decrease in the incidence of major adverse cardiovascular events including cardiac death, nonfatal MI, and unplanned hospitalization for heart failure[13]. Similarly, the investigation by Maznyczka and colleagues on STEMI patients who were allocated to three groups of placebo, low dose (10 mg), and high dose (20 mg) alteplase declared no difference in microvascular myocardial function considering TIMI score, index of microcirculatory resistance, and resistive reserve ratio measured immediately after PPCI [20]. Those who oppose this strategy have reversal theories. They claim that the baseline TIMI flow status is directly associated with the response to fibrinolytic. Accordingly, lower TIMI scores indicating more inappropriate blood flow can potentially lead to ineffective delivery of the drug to microcirculation. In this regard, an investigation has shown that intracoronary alteplase administration in the patients with TIMI flow ≤2 was associated with increased microvascular obstruction as well as myocardial hemorrhage; while those with TIMI flow 3 well-responded to the drug. The reduced antegrade blood flow might potentially lead to higher local alteplase concentrations which is considered to increase the risk of myocardial hemorrhage [21]. On the other hand, in circumstances of slow microvascular flow, the procoagulant effects of alteplase might be augmented, thereby promoting microvascular thrombosis and worsening microvascular obstruction [22].

In summary, as represented above, the data regarding the adjunctive infusion of low-dose intracoronary fibrinolytic use immediately after

PPCI is controversial. Each of the groups, those favoring versus opposing alteplase use, have their own logics. Nevertheless, data on this issue are inconclusive and show the necessity of further investigations.

Limitations

The small sample population is the major limitation of our study. On the other hand, cohort design of study could provide better knowledge. Further studies are strongly recommended.

Conclusion

Based on the findings of this study, adjunctive intracoronary infusion of low-dose alteplase applied immediately after PPCI could efficiently prevent from no-reflow phenomenon; however, ST-segment resolution did not occur convincingly. Given that, even by negligible adverse effects, this approach requires further investigations and should be considered cautiously.

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Conflict of interest

No Conflict of interest

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