ORIGINAL ARTICLE

Comparison of no-reflow phenomenon after percutaneous coronary intervention for acute myocardial infarction between smokers and nonsmokers

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Background: No-reflow phenomenon after percutaneous coronary intervention (PCI) in patients with acute ST-segment-elevation myocardial infarction (STEMI) is relatively common and has therapeutic and prognostic implications. Cigarette smoking is known as deleterious in patients with coronary artery disease (CAD), but the effect of smoking on no-reflow phenomenon is less investigated. The aim of this study was to compare no-reflow phenomenon after percutneous coronary intervention for acute myocardial infarction, between smokers and non smokers. **Materials and Methods:** A total of 141 patients who were admitted to Chamran Hospital (Isfahan, Iran) between March and September, 2012 with a diagnosis of STEMI, enrolled into our Cohort study. Patients were divided into current smoker and nonsmoker groups (based on patient's information). All patients underwent primary PCI or rescue PCI within the first 12-h of chest pain. No-reflow phenomenon, thrombolysis in myocardial infarction (MI) flow, and 24-h complications were assessed in both groups. **Results:** A total of 47 current smoker cases (32.9%) and 94 (65.7%) nonsmoker cases were evaluated. Smokers in comparison to nonsmokers were younger (53.47 ± 10.59 vs. 61.46 ± 10.55, $P < 0.001$) and they were less likely to be hypertensive (15.2% vs. 44.7%, $P < 0.001$), diabetic (17% vs. 36.2%, $P < 0.05$), and female gender (4.3% vs. 25.5%, $P < 0.01$). Angiographic and procedural characteristics of both groups were similar. 9 patients died during the first 24-h after PCI (4.3% of smokers and 6.4% of nonsmokers, P: 0.72). No-reflow phenomenon was observed in 29.8% of current smokers and 31.5% of nonsmokers ($P = 0.77$). **Conclusion:** No-reflow phenomenon or short-term complications were not significantly different between current smokers and non smokers.

Key words: Cigarette smoking, no-reflow phenomenon, primary percutaneous coronary intervention, thrombolysis in myocardial infarction flow

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INTRODUCTION

Although considerable evidences have demonstrated that percutaneous coronary intervention (PCI) is the most advantageous and rewarding reperfusion strategy available in patients with acute ST-segment-elevation myocardial infarction (STEMI),[1-3] but they fail to restore optimal myocardial reperfusion in a sizeable portion of patients, mostly because of no-reflow phenomenon.[4] No-reflow is defined as reduced coronary reperfusion (failure to restore thrombolysis in myocardial infarction [TIMI] flow grade 3)[5] without any arterial obstruction, dissection, or spasm in angiography.[6] The incidence of this phenomenon is present in 10-54% of the procedures depending on the characteristics of the studied population and the method used for its diagnosis, and it is associated with an adverse clinical outcome with greater short and long-term progression to heart failure and increased mortality.[7-9] Several authors have established a significant association between this phenomenon, and plasma levels of different markers[10-14] or with certain features of atherosclerotic plaque visualized by Intra Vascular Ultra Sonography.[15,16] Other studies have shown that the combination of clinical variables and procedural findings is useful to identify this group of patients.[17] One of these clinical variables is cigarette smoking.

Tobacco smoking is a well-established preventable risk factor for the development and progression of coronary artery disease (CAD) and is strongly related to cardiovascular causes' morbidity and mortality; but several recent studies showed that smokers have less no-reflow phenomenon after PCI in the setting of acute STEMI.[18] This phenomenon, often termed the smoker's

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paradox,[19] presumably exists because smokers are usually younger and they have fewer cardiovascular risk factors and their infarct lesions have a greater thrombotic component with relatively less atherosclerotic plaque.

Due to increasing number of smokers, especially among women and young adults in Iran and lack of sufficient studies about the effect of smoking on no-reflow phenomenon, we undertook this study to assess the relationship between cigarette smoking and postprocedural TIMI flow grade, no-reflow phenomenon and short-term outcomes.

MATERIALS AND METHODS

Study population

A total of 141 patients who were admitted to Chamran Hospital (Isfahan, Iran) between March and September of 2012 with a diagnosis of STEMI, enrolled into our Cohort study. The diagnosis of STEMI was established in the presence of chest pain lasting for 20 min associated with electrocardiographic changes (new ST elevation at the J point in at least 2 contiguous leads of ≥2 mm [0.2 mV] in men or ≥1.5 mm [0.15 mV] in women in leads V_2-V_3 and/or of ≥1 mm [0.1 mV] in other contiguous chest leads or the limb leads or new or presumably new left bundle branch block).[20] We excluded patients with restenosis after stenting, coronary artery bypass graft failure, severe heart failure or cardiogenic shock, important systemic disease, or serum creatinine >2.5 mg/dl. We also excluded patients who took streptokinase (SK) and obtained successful results. The ethical Committee of the Isfahan University of Medical Sciences reviewed and approved this study (ethical code: 392317).

Smoking status

According to self-reported smoking status, participants were categorized as smokers and nonsmokers. Any patient who had smoked 10 cigarettes/day within the year preceding the index procedure was considered a smoker. The rest of patients were considered as nonsmoker. Thus, nonsmokers included those patients who had never smoked and those who had quit smoking 1-year before the index procedure (former smokers).

Data collection, angiographic evaluation and clinical follow-up

In the beginning, study procedure was explained to subjects and informed consents were obtained from them. Then, a questionnaire containing demographic data (age and gender), history of diseases (diabetes mellitus, stroke, hypertension, CAD, and hyperlipidemia), and SK prescription was completed. Blood samples were obtained before angiography.

Within the first 12-h of chest pain, the subjects underwent angiography and then primary PCI or rescue PCI if they had chest pain and/or persistent ST-segment elevation despite receiving SK. In order to perform angiography, Seldinger method was applied by 6 French catheters. The results of angiography including the involved artery, position and extent of stenosis were recorded for each patient. After receiving a 70 IU/kg dose of stat heparin, PCI was applied using Seldinger method by 7 French catheter. PCI was done in an infarct-related artery (IRA) and the interventionist selected the stent number and size based on the involved artery and plaque length and diameter. The size of catheter balloon was determined by a skilled operator who simultaneously viewed a cine angiogram. Angiography was performed after PCI to assess TIMI flow, and no-reflow phenomenon, and the results were recorded for all patients. No-reflow was defined as post-PCI TIMI grade 0, 1, or 2 flow in the absence of mechanical obstruction. Normal reflow was defined as TIMI grade 3 flow. Patients were transferred to coronary care unit after PCI. All patients received 600 mg of clopidogrel and 325 mg of aspirin stat prior to PCI. They were also prescribed a daily 325 mg of aspirin and 75-150 mg of clopidogrel following PCI.

The complications, including death, reinfarction, bleeding, arrhythmia and cerebrovascular accident, during the first 24-h after PCI were recorded.

Statistical analysis

In order to analyze the collected data, descriptive statistics (percentages and mean ± standard deviation) was applied. Differences between groups stratified by smoking status were tested by the Chi-square tests (Fisher's exact test if needed) for dichotomous variables and the independent *t*-test for continuous variables. Mann-Whitney nonparametric test was performed to evaluate TIMI flow. We also used this test to compare platelet count between groups because of abnormal distribution. Then, differences in no-reflow phenomenon and 24-h outcomes between smokers and nonsmokers were assessed. Results were adjusted for age, gender, diabetes, hypertension, history of CAD and the extent of stenosis by logistic regression analysis. $P < 0.05$ were considered as statistically significant. All analyses were performed using SPSS for Windows 16.0 (IBM Corporation, Chicago).

RESULTS

The baseline characteristics of both groups are summarized in Table 1. Among the total number of 141 patients, 47 patients (32%) were smokers, and 94 (65%) were nonsmokers. All patients in the smoker group were a heavy smoker (≥10 pack/year). Nonsmokers were 8 years older ($P < 0.001$) and a larger proportion of nonsmokers were women ($P < 0.01$). In addition, major co-existing conditions such as hypertension ($P < 0.001$), and diabetes mellitus ($P < 0.05$) were more prevalent among nonsmokers.

There were no significant differences in hematocrit (HCT), platelet (Plt) count and left ventricle ejection fraction in both groups. Rate of SK prescription in both groups was similar.

There were modest differences in angiographic features between smokers and nonsmokers [Table 2]. Primary PCI was performed nearly at the same rate between smokers and nonsmokers (P = 0.34). Culprit lesion localization was almost the same between two groups. One stent was implanted in most of the patients (80.85% of smokers and 81.91% of nonsmokers, P = 0.59) but in a small subset of patients, according to the interventionist opinion two or three stent were implanted in IRA. The angiographic efficacy of the intervention measured as a proportion of patients with final TIMI 3 flow in the culprit vessel was high in both groups, without any significant differences (P = 0.32).

Table 3 shows major adverse cardiac events (MACE) during the first 24-h after PCI. MACE such as death, arrhythmia and reinfarction during the first 24-h after PCI were slightly lower in the smoker group, but did not show any statistical significance.

Multivariable analysis was performed to identify independent relationship between smoking status and no-reflow phenomenon. Age, gender, diabetes, hypertension, history of CAD and extent of stenosis were tested for multivariable analysis. Smoking status, when adjusted for these variables by logistic regression analysis, did not possess any predictive value in terms of postPCI TIMI flow and no-reflow phenomenon (odds ratio [OR] = 1.68; 95% confidence interval [CI]: 0.68-4.10, P = 0.25).

DISCUSSION

Despite widespread awareness of smoking deleterious effect, it remains the single largest preventable cause of cardiovascular morbidity and premature death in developed countries.[21] In the Interheart trial investigating 27089 participants from 52 countries, current smoking was associated with an almost 3-fold greater risk of nonfatal acute myocardial infarction (MI) compared with never smoking.[22] In the present study, we assessed the impact of smoking on no-reflow phenomenon after PCI in STEMI patients.

We found significant differences in baseline clinical characteristics between smokers and nonsmokers undergoing PCI. Smokers, despite having lower incidence of diabetes mellitus and hypertension (P = 0.019 and 0.01 respectively), require PCI 8 years earlier than nonsmokers (P = 0.001). However, once smokers underwent successful PCI, the first 24-h in-hospital outcomes were similar to

Table 1: Baseline demographics and clinical status onadmission

Variables	Smokers (n = 47)	Nonsmokers (n = 94)	P
Age (years±SD)	53.47±10.59	61.46±10.55	<0.001
Gender			
Female (%)	4.3	25.5	0.002
Male (%)	95.7	74.5	
Diabetes (%)	17	36.2	0.02
Hypertension (%)	15.2	44.7	0.001
Previous CAD (%)	8.5	19.1	0.10
Hyperlipidemia (%)	39.1	37.2	0.83
SBP (mmHg)	121.14±17.9	122.21±23.16	0.84
DBP (mmHg)	76.43±12.16	74.40±12.51	0.36
HCT (%)	41.32±5.48	42.60±3.74	0.14
Plt (10^3/mm^3)	207±50	205±52	0.91
LVEF (%)	39.89±10	40.75±9.7	0.65
SK prescription (%)	44.7	47.9	0.72

CAD = Coronary artery disease; DBP = Diastolic blood pressure; HCT = Hematocrit; LVEF = Left ventricular ejection fraction; MI = Myocardial infarction; Plt = Platelet; SBP = Systolic blood pressure; SK = Streptokinase; SD = Standard deviation

Table 2: Angiographic and procedural characteristics of the analyzed groups

Variables	Smokers (n = 47)	Nonsmokers (n = 94)	P
Indication for PCI (%)			
Rescue PCI	44.7	47.9	0.34
Primary PCI	55.3	52.1	
Stenosis (%)			
Cut-off	44.7	56.4	0.19
90-99	40.4	33.0	0.45
70-90	14.9	10.6	0.46
Localization of culprit lesion (%)			
RCA	29.8	29.8	0.95
LAD	65.9	67.0	
LCX	4.3	3.2	
PostPCI TIMI flow (%)			
0-1	14.9	13.9	0.32
2	14.9	17.6	
3	70.2	68.5	
No-reflow phenomenon (%)	29.8	31.5	0.77

LAD = Left anterior descending artery; LCX = Left circumflex artery; PCI = Percutaneous coronary intervention; RCA = Right coronary artery; TIMI = Thrombolysis in myocardial infarction

Table 3: MACE during the first 24-h after PCI

Events	Smokers (n = 47)	Nonsmokers (n = 94)	P
CVA (%)	0	0	–
Death (%)	4.3	6.4	0.72
Reinfarction (%)	0	1.1	0.48
Arrhythmia (%)	2.1	5.3	0.64
Bleeding requiring transfusion (%)	0	0	–

CVA = Cerebrovascular accident; MACE = Major adverse cardiac event; PCI = Percutaneous coronary intervention

nonsmokers (P = 0.6). Sherif *et al*. studied 4660 patients for 1-year after PCI, and showed that short-term complications were similar in both groups of patients.[23] In contrast to our results, Sukiennik *et al*. found higher unadjusted mortality rates after PCI among nonsmokers during hospitalization (2.4% for smokers compared with 4.6% for nonsmokers, P = 0.0532).[24] Weisz *et al*. analyzing the data obtained in the randomized Cadillac trial found the lowest mortality in current smokers, intermediate in former smokers, and highest in nonsmokers after 30 days and 1-year.[19] However, after a multivariate correction for differences in baseline variables, current smoking status was no longer protective against mortality. Furthermore, part of these apparently contradicting results might be explained by differences in the definition of smoking status and the concomitant therapies. Surprisingly we observed no case of bleeding requiring transfusion in our study. Probably because our patient had lesser risk factors for bleeding such as female sex, chronic renal failure, systolic blood pressure <100 and old age. Also, because heparin was not prescribed after PCI.

No-reflow is one of the major problems in patients with STEMI who undergo primary PCI and may limit the benefits of recanalization of the IRA. It is known that angiographic no-reflow is strongly correlated with morbidity and mortality in acute MI.[7,8,25-27] The rate of no-reflow phenomenon in our study was 30.6%, which was consistent with previously published no-reflow rates. We found no relationship between smoking and angiographic no-reflow (P = 0.77). Similarly, Hong *et al*. study on plaque component on 190 acute coronary syndromes (ACS) patients demonstrated no difference in no-reflow between smokers and nonsmokers (P = 0.7).[16] But, several previous reports have suggested that smokers have a more effective reperfusion. Data from Albertal *et al*. showed that postprocedural TIMI flow grade and TIMI frame were better in smokers, whereas myocardial blush grade was similar between both groups. Percentage of complete (>70%) ST-segment resolution (STR) at 60 min was higher in active smokers than nonsmokers (76.4% vs. 50%, P = 0.002). Multivariate logistic regression analysis identified active smoking as an independent predictor of complete STR at 60 min (OR = 3.47; 95% CI: 1.48-8.14; P = 0.004).[28] Ndrepepa *et al*. showed that among 1140 patients with STEMI undergoing primary PCI, smokers had less no-reflow phenomenon (P = 0.04). Univariable and multivariable logistic regression models were used to identify the correlates of the no-reflow after primary PCI.[7] This could be explained by healthier coronary artery risk factor profile, less extensive atherosclerotic disease and hence, smaller plaque burden in smokers rather than nonsmokers. Elevated Plt, fibrinogen, and HCT levels are also encountered in active smokers, indicating hypercoagulable state promoting vascular thrombosis. Therefore, coronary obstructions in patients who smoke may be more of a thrombogenic origin than atherosclerotic, so they are more susceptible to thrombolysis, either pharmacological or mechanical, compared to nonsmokers.[28] On the other hand, when there is a significantly greater thrombus burden, thrombi tend to fragment with balloon dilatation, which can lead to distal embolization and no-reflow phenomenon.[8] So maybe better result in previous studies is because of widespread use of anti-Plt agents. Desai *et al*. found that clopidogrel reduced the rate of closed IRA or death/MI before angiography in the Clarity-TIMI 28 trial, which was especially marked among those who smoked ≥10 cigarettes/day. Similarly, clopidogrel was significantly more effective in reducing the rate of cardiovascular death, MI, or urgent revascularization through 30 days among those who smoked ≥10 cigarettes/day compared to those who did not. Probably, enhanced Plt activation induced by smoking makes the effect of clopidogrel more pronounced in smokers, in addition to improved pharmacokinetics of clopidogrel in smokers.[29]

Study limitations

There were several limitations to this study. First, the potential bias from misclassification of smoking status may exist because of the possible inaccurateness of a patient's reporting of smoking status. Second, all participants were from a single high-volume coronary treatment center, which would restrict the generalization of our findings. Third, the diagnosis of no-reflow was made considering only the epicardial flow. It is better to consider complementary diagnostic methods such as STR 3-h after reperfusion and the evaluation of myocardial blush grade to increase sensitivity.[30] But, the quality of our coronary angiogram did not allow adequate assessment of myocardial blush score in some patients, so we used conventional TIMI flow grading system. Forth, female participants constituted a small number of our smoker patient. Finally, we followed patients for a short period, so the impact of smoking on MACE is not estimated precisely.

However, within these limitations, we believe that our work will stimulate more research to verify our results and explore the pathophysiology of adverse outcomes in different smoking status of patients undergoing PCI.

CONCLUSION

There was no significant difference in no-reflow phenomenon and MACE during the first 24-h after PCI among smokers and nonsmokers. The survival advantage in some other studies is not a consequence of smoking status *per se* making the commonly used term "smoker's paradox" misleading. This may be fully explained by the younger age of smokers, their more favorable clinical characteristics and the less extensive coronary atherosclerosis. In fact, smoking contributes to the occurrence of ACS at a younger age and

no convincing evidence concerning a protective role of smoking in the interventional setting exists. Finally, bearing in mind the results of primary and secondary prevention trials clearly indicating beneficial effects of a nonsmoking lifestyle and smoking cessation, any form of smoking should be strongly discouraged.

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AUTHOR'S CONTRIBUTION

HS contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. FDT contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HZ contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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