Association between smoking and hospital mortality in myocardial infarction patients undergoing primary angioplasty

Associação entre tabagismo e mortalidade hospitalar de pacientes com infarto agudo do miocárdio submetidos à angioplastia primária

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ABSTRACT – Background: The association between smoking and better clinical outcomes in myocardial infarction patients undergoing fibrinolysis is known as the smoking paradox. The relation between smoking and clinical outcomes after primary angioplasty is controversial. The study aimed to assess the association between smoking and hospital mortality in patients admitted due to ST-segment elevation myocardial infarction submitted to primary angioplasty. **Methods:** A single-center registry including all patients submitted to primary angioplasty from January to July 2014. A comparative analysis was carried out of the baseline clinical, angiographic, and procedural characteristics between the groups of smokers and non-smokers. An exploratory analysis of the factors associated to hospital mortality was performed through univariate logistic regression. **Results:** A total of 193 patients were included; in that, 45% smokers, mean age 62±11.9 years. The groups were similar regarding the clinical, angiographic, and procedural characteristics, except for dyslipidemia and use of angiotensin converting enzyme inhibitors or angiotensin II receptor blocker that were higher in the group of smokers. Hospital mortality was 7.8%, and there was no association with smoking (p=0.346). The variables associated to hospital mortality were low ejection fraction (OR: 8.22; p=0.022), left main coronary artery lesion (OR: 7.72; p=0.003), creatinine ≥1.5mg/dL (OR: 40.80; p<0.001), final TIMI flow 0-1 (OR: 7.72; p=0.003) and age ≥75 years (OR: 4.18; p=0.010). **Conclusion:** There was no association between smoking and hospital mortality in patients submitted to primary angioplasty.

Keywords: Tobacco use disorder; Myocardial infarction; Percutaneous coronary intervention; Hospital mortality

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RESUMO – Introdução: A associação do tabagismo a melhores desfechos clínicos entre os pacientes com infarto agudo do miocárdio submetidos à fibrinólise é conhecida como paradoxo do tabagista. A relação entre tabagismo e desfechos clínicos após angioplastia primária é controversa. O estudo teve como objetivo avaliar a associação entre tabagismo e mortalidade hospitalar em pacientes admitidos por infarto agudo do miocárdio com supradesnivelamento do segmento ST submetidos à angioplastia primária. **Métodos:** Registro unicêntrico, que incluiu todos os pacientes submetidos à angioplastia primária no período de janeiro a julho de 2014. Foi realizada análise comparativa das características clínicas basais, angiográficas e do procedimento entre os grupos de tabagistas e não tabagistas. Foi feita análise exploratória dos fatores associados à mortalidade hospitalar, utilizando regressão logística univariada. **Resultados:** Foram incluídos 193 pacientes, sendo 45% tabagistas, com média de idade de 62±11,9 anos. Os grupos foram semelhantes quanto às características clínicas, angiográficas e do procedimento, exceto por dislipidemia e uso de inibidor da enzima conversora de angiotensina ou bloqueador dos receptores de angiotensina II maiores no grupo de tabagistas. A mortalidade hospitalar foi de 7,8%, e não houve associação com o tabagismo (p=0,346). As variáveis associadas à mortalidade hospitalar foram baixa fração de ejeção (RC: 8,22; p=0,022), lesão em tronco de coronária esquerda (RC: 7,72; p=0,003), creatinina ≥1,5mg/dL (RC: 40,80; p<0,001), fluxo final TIMI 0-1 (RC: 7,72; p=0,003) e idade ≥75 anos (RC: 4,18; p=0,010). **Conclusão:** Não houve associação

entre tabagismo e mortalidade hospitalar nos pacientes submetidos à angioplastia primária.

Descritores: Tabagismo; Infarto do miocárdio; Intervenção coronária percutânea; Mortalidade hospitalar

BACKGROUND

Smoking is associated with the development and progression of cardiovascular disease, and it increases by two to three fold the risk of coronary artery disease (CAD).^{1,2} In the Brazilian population, smoking has an estimated prevalence of 14.5%,³ and is a risk factor in almost half of acute myocardial infarction (AMI) patients.⁴⁻¹⁰

The association of smoking with better clinical outcomes in AMI patients undergoing fibrinolysis is known as the smoking paradox. This has been attributed to the heterogeneity of baseline clinical characteristics rather than to a beneficial effect of smoking.^{4,11-13} Some studies have explored the association between smoking and hospital mortality in patients undergoing primary angioplasty, and presented controversial results.^{6,8,10,14-17}

This study aimed to evaluate the association between smoking and hospital mortality in patients undergoing primary angioplasty.

METHODS

Study design and population

A single-center registry of all patients who underwent primary angioplasty for treatment of ST-segment elevation myocardial infarction (STEMI), from January to July 2014. Patients who self-declared being active smokers upon hospital admission were defined as smokers. Hospital mortality was defined as the occurrence of death during hospitalization up to 30 days after admission. The project was evaluated and accepted by the Ethics Committee of the organization (CAAE 47779915.0.0000.5039), and all principles of the Declaration of Helsinki of 1975 (revised in 2008) and norms of the resolution 466/2012 of the National Health Council were respected.

Inclusion and exclusion criteria

Patients older than 18 years, with ischemic time (defined as the elapsed time from onset of pain to the first contact with the emergency department of the hospital) of less than 12 hours, and with clinical and electrocardiographic diagnosis of STEMI were included. Patients who did not undergo diagnostic cardiac catheterization for any reason, and those who had other diagnoses after the procedure (Takotsubo, aortic dissection, AMI with normal coronary arteries and coronary vasospasm) were excluded.

Procedures

All patients followed the standard treatment flowchart of the organization, with administration of acetylsalicylic

acid and the second antiplatelet agent (600mg clopidogrel, 180mg ticagrelor, or 60mg prasugrel) at the discretion of the emergency cardiologist. The procedures were performed predominantly via the femoral artery, with administration of 70 to 100U/kg of unfractionated heparin during the intervention. Baseline clinical variables (demographic characteristics, risk factors for coronary disease, drug therapy, time of ischemia, and electrocardiographic pattern) and angiographic and procedural characteristics were collected. Patients were divided into smokers and non-smokers groups.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Science (SPSS), version 23.0 (IBM Corp. New York, USA). The normal distribution of continuous data was assessed by the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Data that presented normal distribution were expressed as mean and standard deviation and compared with the Student's *t* test. Continuous non-normal distribution variables were presented as median and interquartile ranges and were analyzed by the Mann-Whitney test. Categorical data were expressed as percentage or frequency. The Chi-squared test or Fisher's exact test was used for the categorical variables. Logistic regression analysis was used to assess the risk factors associated with the endpoint death. Statistical results were considered significant when $p < 0.05$ (bicaudal).

RESULTS

A total of 193 patients were included, of which 59 (30.6%) were female. The mean age was 62 ± 11.9 years. The mean time from onset of pain to hospital arrival was 342.6 ± 159.3 minutes. The prevalence of smoking was 45.1%. Table 1 presents the baseline clinical characteristics of the groups. There was higher prevalence of dyslipidemia (34.5% vs. 16.0%; $p = 0.003$) and lower use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) (97.7% vs; 84.9%; $p = 0.003$) among smokers. The other baseline clinical characteristics were similar.

The angiographic and procedural characteristics are presented in table 2. The pattern of single-, two-, and three-vessel disease was 38.8%, 34.7%, and 21.8%, respectively. The right coronary artery was the most frequently identified culprit artery (49.2%), followed by the left anterior descending artery (43.5%), and the circumflex artery (6.2%). There was one infarction due to occlusion of the left main coronary artery (LMCA) (0.5%), and one due to saphenous vein graft occlusion (0.5%). Nineteen patients (9.8%) had initial Thrombolysis in Myocardial Infarction (TIMI) flow grade 3; thrombus manual aspiration was used in 16.6% of cases, pre-dilation was performed in 71.5%, and the mean number of stents per patient was 1.3 ± 0.6 . In 14 patients (7.3%), angioplasty was performed without

Table 1. Clinical characteristics of the total population and of the groups smokers and non-smokers

Characteristic	Total (n=193)	Smokers (n=87)	Non-smokers (n=106)	p value
Age, years	62.3±13.0	62.3±11.9	62.2±13.9	0.974
Female	59 (30.6)	28 (32.2)	31 (29.2)	0.754
Hypertension	114 (59.1)	50 (57.5)	64 (60.4)	0.683
Diabetes mellitus	55 (28.5)	22 (25.3)	33 (31.1)	0.371
Dyslipidemia	47 (24.4)	30 (34.5)	17 (16.0)	0.003
Family history of CAD	45 (23.3)	21 (24.1)	24 (22.6)	0.807
Renal failure*	19 (12.0)	6 (6.9)	13 (12.3)	0.212
Ischemic time, minute†	342.6±159.3	347.3±156.8	338.7±161.9	0.970
ST-elevation pattern in ECG				0.230
Anterior	79 (40.9)	30 (34.5)	49 (46.2)	
Inferior	109 (56.5)	55 (63.2)	54 (50.9)	
Lateral	5 (2.6)	2 (0.02)	3 (0.03)	
Ejection fraction‡	0.52±0.12	0.54±0.12	0.50±0.12	0.120
Troponin, ng/mL	4,410±3,680	4,295±3,591	4,502±3,773	0.844
CKMB-mass, U/L	147.64±122.88	154.77±124.64	141.62±121.95	0.707
Antiplatelet agents				
AAS	190 (100.0)	87 (100.0)	103 (100.0)	-
Clopidogrel	76 (40.0)	33 (37.9)	44 (41.5)	0.593
Ticagrelor	137 (72.1)	64 (73.5)	73 (68.8)	0.680
Prasugrel	5 (2.6)	2 (0.02)	3 (0.03)	0.792
GP IIb/IIIa inhibitor	25 (13.2)	10 (11.5)	15 (14.1)	0.533
Anticoagulants				
UFH	18 (9.5)	10 (11.5)	8 (7.5)	0.382
Enoxaparin	138 (72.6)	64 (73.5)	74 (69.8)	0.791
Fondaparinux	40 (21.1)	20 (23.0)	20 (18.8)	0.547
ACEI or ARB	175 (92.1)	85 (97.7)	90 (84.9)	0.009
Beta-blocker	155 (81.6)	74 (85.0)	81 (76.4)	0.256
Statin	188 (98.9)	86 (98.8)	102 (96.2)	0.904
Nitrate	94 (49.5)	39 (44.8)	55 (51.9)	0.239

Results expressed as mean ± standard deviation or n (%). * The first serum creatinine level after admission was considered, ≥1.5 mg/dL; † time from onset of pain to admission at emergency room; ‡ value obtained from echocardiogram performed at 2 to 10 days after infarction. CAD: coronary artery disease; ECG: 12-lead electrocardiogram; CKMB: creatine-kinase iso-enzyme MB; ASA: acetylsalicylic acid; GP: glycoprotein; UFH: unfractionated heparin; ACEI: angiotensin converting enzyme inhibitors; BRA: angiotensin II receptor blockers.

Table 2. Angiographic and procedural characteristics of the total population and of the groups smokers and non-smokers

Characteristic	Total (n=193)	Smokers (n=87)	Non-smokers (n=106)	p-value
Lesion pattern				0.298
Single-vessel	75 (38.8)	38 (43.8)	37 (34.9)	
Two-vessel	67 (34.7)	31 (35.6)	36 (34.0)	
Three-vessel	42 (21.8)	15 (17.2)	27 (25.4)	
LMCA lesion	9 (4.7)	3 (3.4)	6 (5.7)	
Culprit lesion				0.508
LMCA	1 (0.5)	0 (0.0)	1 (0.9)	
Left anterior descending	84 (43.5)	34 (39.1)	50 (47.2)	
Circumflex	12 (6.2)	6 (6.9)	6 (5.7)	
Right coronary	95 (49.2)	46 (52.9)	49 (46.2)	
Surgical graft	1 (0.5)	1 (1.1)	0 (0.0)	
Coronary TIMI flow pre (target vessel)				0.431
TIMI 0	146 (75.6)	68 (78.2)	78 (73.6)	
TIMI 1	12 (6.2)	7 (8.0)	5 (4.7)	
TIMI 2	16 (8.3)	6 (6.9)	10 (9.4)	
TIMI 3	19 (9.8)	6 (6.9)	13 (12.3)	
Coronary TIMI flow post (target vessel)				0.988
TIMI 0	2 (1.0)	1 (1.1)	1 (0.9)	
TIMI 1	10 (5.2)	4 (4.6)	6 (5.7)	
TIMI 2	38 (19.7)	17 (19.5)	21 (19.8)	
TIMI 3	143 (74.1)	65 (74.7)	78 (73.6)	
Thrombus manual aspiration	32 (16.6)	13 (14.9)	19 (17.9)	0.579
Predilation	138 (71.5)	59 (67.8)	79 (74.5)	0.304

Results expressed by n (%). LMCA: left main coronary artery; TIMI: thrombolysis in myocardial infarction.

stent implantation. After primary angioplasty, 12 patients maintained final TIMI flow 0-1 (5.2%). There were no differences between smokers and non-smokers regarding the angiographic and procedural characteristics analyzed.

There was no difference in hospital mortality between smokers (5; 5.7%) and non-smokers (10; 9.4%) ($p=0.346$). The factors associated with hospital mortality were age ≥ 75 years, creatinine ≥ 1.5 mg/dL, ejection fraction $\leq 35\%$, LMCA lesion, and final TIMI flow grade of 0 or 1 (Table 3).

Tabela 3. Predictive factors of in-hospital mortality of myocardial infarction patients submitted to primary angioplasty

Factor	Odds ratio	95%CI	p-value
Smoking	0.58	0.19-1.78	0.346
Creatinine ≥ 1.5 mg/dL	40.80	9.51-174.97	<0.001
Ejection fraction $\leq 35\%$	8.22	1.36-49.56	0.022
LMCA lesion	7.73	2.01-29.70	0.003
Final TIMI flow 0-1	7.73	2.01-29.70	0.003
Age ≥ 75 years	4.18	1.41-12.38	0.010

DISCUSSION

The present registry showed no association between smoking and hospital mortality in patients undergoing primary angioplasty, contrary to the smoker's paradox. The main findings of the study were: no association between smoking and age at the time of AMI, with a mean age of 62.3 ± 13.0 years; long elapsed time between the onset of symptoms and admission to hospital, with a mean of 342.6 ± 159.3 minutes; high success rate of primary angioplasty (93.8%); the majority of patients were male; similar baseline characteristics between groups, statistically differing only in the use of ACE inhibitors or BRA (97.7% vs. 84.9%; $p=0.003$), and dyslipidemia (34.5% vs. 16.0%; $p=0.003$), higher among smokers; use of the main classes of the second antiplatelet agent, with a higher prevalence of ticagrelor (72.1%), followed by clopidogrel (40.0%) and prasugrel (5.0%).

The absence of association between smoking and other baseline clinical characteristics may justify the non-association between smoking and mortality. Currently, the estimated smoking prevalence in the Brazilian population is around 14%. In this registry, approximately half of MI patients were smokers, reinforcing the causal relationship between smoking and AMI risk in the current context.³

In a subanalysis of the HORIZONS-AMI study, Goto et al.⁴ evaluated the impact of smoking in STEMI patients who underwent primary angioplasty. They randomized more than 3,500 patients, of whom half were smokers. They found that mortality was lower in smokers, but this finding was not sustained after adjustment of variables.

Smoking patients, compared to non-smokers, were younger, more often men, had lower body mass index, and lower prevalence of hypertension, dyslipidemia, diabetes mellitus, renal failure and anemia on admission; they also had a higher platelet count and were less often in Killip class 2 upon hospital admission. These results are consistent with other studies. Weisz et al.⁶ published a subanalysis of the CADILLAC study, in which they showed that the mortality of STEMI patients treated with reperfusion is not related to smoking. In the Brazilian population, this association was studied by Curado et al.,¹⁸ through the analysis of 20,319 STEMI patients undergoing primary or salvage angioplasty, in the Brazilian National Registry of Cardiovascular Interventions (CENIC, <http://www.corehemo.net/>). Similar to the aforementioned studies, smoking did not show a protective effect after multivariate analysis, with the conclusion that the results were due to differences found in the clinical and angiographic characteristics between smokers and non-smokers. Addad et al.⁸ evaluated this association in a French population registry, including 688 patients, in which they found a prevalence of 70.1% of active smoking in AMI patients undergoing thrombolysis or primary angioplasty. Mortality was significantly lower among smokers in case of thrombolysis, compared to non-smokers (5.3% vs. 13.0%; $p=0.008$). However, in the primary angioplasty group, there was only a trend towards lower mortality among smokers (10.0% vs. 17.6%; $p=0.07$). After multivariate analysis, cardiogenic shock ($p<0.0001$), anterior wall AMI ($p=0.03$), and active smoking ($p=0.03$) remained as independent predictors of mortality in case of thrombolysis. These results show that baseline clinical differences, such as younger age at AMI presentation, lower prevalence of comorbidities and of risk factors in the smoking population with AMI, can explain the occurrence of the smoking paradox phenomenon, but there may be other factors that influence this association.

An important feature of this registry was that most patients used ticagrelor, whereas previous studies have used clopidogrel as the second antiplatelet agent.^{4,6,8,18} It is known that smoking has an effect on the pharmacodynamics of P2Y₁₂ receptor inhibitors. Smoking induces CYP1A2, one of the cytochrome P450 isoenzymes responsible for the activation of thienopyridines, influencing the antiplatelet efficacy of these drugs.¹⁹⁻²¹ Clopidogrel is the drug most studied in this context, but ticagrelor and prasugrel may also be influenced by this same mechanism.

Clopidogrel and prasugrel are inactive prodrugs, which bind irreversibly to the platelet P2Y₁₂ receptor, and inhibit platelet activation and aggregation by adenosine diphosphate (ADP),²² whereas ticagrelor is an active drug, which inhibits reversibly the P2Y₁₂ receptor, has a half-life of 12 hours, does not need hepatic metabolic activation, and is less influenced by cytochrome P450.²³ Gagne et al.²¹ published a meta-analysis in which clopidogrel was associated with a 25% reduction in major adverse cardiac and

cerebrovascular events in smokers, but only 8% in the non-smoker group. Subsequent evaluations of the TRITON-TIMI 38 and TRILOGY-ACS studies showed that prasugrel was more effective than clopidogrel in reducing cardiovascular risk in patients with acute coronary syndrome who were smokers, but not in non-smokers.^{19,24} Reduction in final TIMI flow grade 0 or 1, death, or recurrent AMI outcomes with the use of prasugrel and ticagrelor was 29% and 17% in smokers, and 8% and 11% in non-smokers, respectively, when compared to clopidogrel.²¹ This effect of smoking on these drugs may also influence the rates of bleeding complications associated with both thrombolytic and primary angioplasty, attenuating potential improvement in ischemic outcomes.²¹ Although the antiplatelet effect of the new P2Y₁₂ receptor inhibitors appears to be more intense in smokers, in the studied population, most of whom used ticagrelor as the second antiplatelet agent, no association with hospital mortality was observed.

A Brazilian study which evaluated the clinical profile of young AMI patients (<45 years) undergoing primary angioplasty showed that this population had a high prevalence of modifiable risk factors, notably smoking, which was present in 72.2% of patients studied.²⁵ Larsen et al.²⁶ published an analysis on AMI patients undergoing primary angioplasty, with age-stratified data, comparing the prevalence of smoking in the study population and in the general population. Smoking was present in 46.43% of studied population. Patients undergoing angioplasty were more likely to be smokers (OR 3.4; 95%CI 3.3-3.4), with greater probability of smoking in young patients (OR for age <35 years 11.4; 95%CI 10.0-12.8). Relative reductions by 10%, 50% and 75% in smoking are predicted to prevent 109, 544 and 815 cases of AMI, with the conclusion that smoking continues to be a powerful risk factor for AMI, especially in the younger population.

Some limitations of this study should be noted, such as a single-center setting that limits external validity; the non-availability of data about smoking load and time of smoking, which could interfere in the association between smoking and hospital mortality; and its observational nature, which limits the evaluation of causality, although, from an ethical point of view, it would be impossible to explore this association of causality through randomized trials.

CONCLUSION

There was no association between smoking and hospital mortality in patients undergoing primary angioplasty. Advanced age, renal dysfunction, left main coronary artery lesion, left ventricular dysfunction, and procedural failure were associated with higher mortality at 30 days.

SOURCE OF FINANCING

None.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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