IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
August 2021 Vol.:22, Issue:1

The Smoker's Paradox in Patient with Acute Coronary Syndrome: A Systemic Review

IJPPR
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An official Publication of Human Journals
ISSN 2349-7203
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Submitted: 25 July 2021
Accepted: 31 July 2021
Published: 30 August 2021

Keywords: Acute coronary syndrome, smoker's paradox, cardiovascular disease, acute myocardial ischemia

ABSTRACT

Acute Coronary Syndrome (ACS) is a term that describes a range of clinical syndromes associated with acute myocardial ischemia resulting from an imbalance between myocardial oxygen demand and supply. Smoking is an established risk factor of cardiovascular disease yet unlike non-smokers, smokers are expected to have lower mortality after acute coronary syndrome. This is termed as "smoker's paradox". This manuscript performs a systemic review of literature to find the existence of paradox.

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INTRODUCTION

Tobacco smoking is well-established potent risk factor of acute myocardial infarction (AMI) and premature death[1. Reduction of smoking is one of the most important ways that the society can prevent disease. But paradoxically, smokers have decreased mortality following AMI, compared to non smokers. Various studies have established that smokers with AMI are younger than non-smokers, they tend to have fewer comorbidities, and have fewer concomitant cardiovascular risk factors. Recent advancement in antiplatelet, antithrombotic, and interventional therapy, as well as the use of a sociomedical approach to reduce delays in medical access, have effectively reduced mortality rates after acute myocardial infraction. Considerable evidence in the literature suggests that habitual cigarette smokers have lower unadjusted mortality rates following acute myocardial infarction (AMI), a phenomenon often termed 'smoker's paradox'[2-4].The etiology of "smoker's paradox", during which smokers have a far better prognosis than non-smokers in AMI, is believed to flow from less damage to microvascular function after primary coronary intervention, and smokers have a slightly higher incidence of AMI with a higher grade of inflammation, without severe coronary atherosclerosis. There has been great interest in this controversy over the past decades. Some suggest that the paradoxical favourable outcome is due to the more 'thrombotic' nature of MI in smokers as oppose to atherosclerotic in non-smokers and hence, better reperfusion response after thrombolysis[5. However, others argue that smokers were younger at the onset with better baseline prognostic factors like lower rate of diabetes and hypertension among others. Nevertheless, there is no universally accepted satisfactory explanation for this. Thus, the existence of "smoker's paradox" has been focused in this article.

METHODS

SEARCH STRATEGY

The necessary articles for the review were collected using online publications via PubMed, NCBI, Medline, Medscape, Embase, Embase classic. The data collected from medline is from a time period of 2001 to 2021 written in English, and the other online data collection sites are also used during this time period. Various keywords where used to collect the detailed data such as: myocardial infraction, ST segement elevation angina, ST segment elevation myocardial infarction, non ST segment elevation myocardial infarction, cytokines inflammation, long term adverse effects.

In this review, the full text of the related publications was obtained and analysed in order not to miss any relevant articles. Titles and abstracts are also reviewed, and the review is prepared based on the full analysis.

INCLUSION AND EXCLUSION CRITERIA

- Studies of patients hospitalised for acute coronary syndrome (ACS), including the previous WHO criteria for AMI and the more recent definition of ACS, including ST-elevation myocardial infraction [STEMI], Non-ST-elevation myocardial infraction [NSTEMI] and unstable angina pectoris [UAP] [6,7].

- A clear definition of smoking status into current, former and non- smokers, including baseline characteristics of each group with age as a minimum. In case former smokers weren't defined separately, a minimum requisite was that they had to be defined and characterised either as smokers, non-smokers or per definition were excluded from the analysis.

- The length of follow-up reports and included a minimum of hospital mortality.

- Only English-language original articles were included.

- The studies containing > 100 smokers and > 100 non-smokers were included.

- Studies reporting only post-discharge mortality were excluded.

SMOKING STATUS

Information about smoking status was obtained from the patients at the time of admission. Current smokers were considered as those who reported smoking cigarettes at entry to the studies. Only those who had never smoked were considered as non smokers. Patients with smoking history of less than a month, ex-smokers were excluded.

SMOKING- A MYTH OR TRUTH

- It is proposed that smokers also have an enhanced response to clopidogrel therapy [8-18].

- It has been noted that smokers suffer more out-of-hospital death, thus creating a selection bias when assessing in-hospital mortality[18-24].

- Smokers are younger, hence fewer risk factors Most studies that reported this paradox is from the pre-thrombolytic and thrombolytic era and smokers known to have a higher thrombotic burden, which could cause a heightened response to thrombolysis [25-26].

- and comorbidities and are more aggressively treated, and this could contribute to their better prognosis[27-30].

Despite all this evidence, there are still contemporary studies that show smoking to be an independent predictor of outcome.

Erland Aune et.al identified 17 different studies meeting all the inclusion criteria. The Superior Yield of the New strategy of Enoxaparin, Revascularization and GlY co-protein IIb/IIIa inhibitors (SYNERGY) trial, which is presented by two publications, one demonstrating crude mortality rates [31] and another adjusted mortality rates. Five studies were considered as a contemporary population of ACS and mainly included patients according to the diagnostic criteria from 2000[32]. The other studies were based upon patients included according to the WHO criteria[33]. The follow-up time for 17 included studies varied from in-hospital to three years. Out of six studies within-hospital follow-up, two registries show "smoker's paradox"[34]. Four out of six studies with follow up between one month to six months found evidence for the paradox, whereas none of the five studies that followed patients for one year or more did so[35,36].

Randomised controlled trials (RCT) in STEMI treated with percutaneous coronary intervention (PCI)

In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, 2,082 patients with STEMI undergoing primary PCI were randomised to either angioplasty or stenting with or without abciximab[30] Although current smokers had a lower crude death rate, the adjusted analysis didn't find a lower mortality than that of non-smokers.

RCT in patients treated with fibrinolysis for STEMI

Both the International Tissue Plasminogen Activator/ Streptokinase Mortality Trial [37,38] and the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial [39] demonstrated higher adjusted mortality rates among non-smokers, that supporting smoker's paradox. For the latter study, no such effect was

observed within the angiographic substudy of 2,437 patients. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Micardico (GISSI-2) trial [40] included patients with the same factorial study design as the international study, but they did not demonstrate any reduced adjusted in-hospital mortality for smokers compared with newer-smokers.

RCT of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) subjected to invasive management

In the SYNERGY trial, patients with NSTE-ACS were randomised to enoxaparin or unfractionated heparin and then undergone coronary angiography and PCI or coronary artery bypass grafting (CABG). The crude death rate after one year was similar among smokers and non-smokers. In the adjusted analysis, there was a significant mortality excess among smokers and non-smokers, supporting the undesirable effect of current smoking at baseline.

Multi-centre post-AMI studies from RCTs

The TRAndolapril Cardiac Evaluation (TRACE) study consisted of 2,606 patients aimed to determine whether patients with left ventricular dysfunction post AMI would benefit from long-term treatment with trandolapril vs. placebo [41.] In a study of 6,676 AMI patients subjected for participation in the TRACE study, the long-term mortality was very lower among smokers than either ex- or non-smokers. In spite of this, the adjusted analysis didn't give any evidence for the existence of smoker's paradox [42].

The Optimal Trial In Myocardial Infarction with the Angiotensin Antagonist Losartan (OPTIMAAL) study of patients with AMI and heart failure for randomised treatment with captopril vs. losartan[43]. The unadjusted mortality rate among current smokers was 17% lower than among non-smokers, but this reduced risk was eliminated after adjustment of age and other factors.

Molstad conducted a study on 484 unselected AMI patients between 1982 and 1984 [10]. The three-month death rate among current smokers was only one-third of that among ex- and never-smokers.

Bettencourt et al. [34] and Gaspar et al. [35] included consecutive patients with ACS and couldn't verify the existence of the smoker's paradox. In the latter study, the adjusted analysis indicates higher six-month mortality rate among current and former vs. never-smokers.

The Analysis del Retraso en el Infarcto Agudo de Miocardio (ARIAM) registry from Spain included patients with AMI and UAP admitted to a CCU/Intensive Care Unit (ICU) [44]. In patients with AMI, the CCU/ICU mortality was nearly one-third among smokers than non-smokers. The adjusted OR for smokers was significantly in favour of the paradox.

The Investigation, Busqueda Específicay Registro de Isquemia Cooronaria Aguda (IBERICA) registry included patients between 25 and 74 years of aged with AMI. Within this registry, smokers had a decreased adjusted 28-day mortality rate than the non-smokers[45].

The Global Registry of Acute Coronary Events (GRACE) included patients diagnosed with ACS. In an analysis of 19,325 patients, the in-hospital mortality rate among smokers was just half of that among those who never-smokes. There was no significant difference in adjusted OR for current smokers compared with never-smokers. These results were consistent in all subgroups of the ACS population studied (STEMI, NSTEMI and unstable angina).

Possible explanation for smoker's paradox

The possible explanations for the reported paradoxical findings can be categorised either due to systematic errors, residual confounding or different pathogenesis: the latter, therefore, represents a true effect of smoking. Systematic errors would include publication bias. The declining frequency of papers reporting the "smoker's paradox" during the last decade supports our argument that the paradox was the results of skewed reports during the 1980s to 1990s. Another systematic error could be that smokers with an acute cardiac event could have a greater case fatality before admission to hospital than non-smokers[46]. Those admitted alive to the hospital would, therefore, already represent the survivors. Adjustment for age and co-morbidity did reduce the magnitude of the smoking effect in many of the studies, but not all. Part of the remaining effect would be due to residual confounding, both because of measurement errors in the co-factors and lack of information about risk factors. The six studies supporting a smoker's paradox have included STEMI patients, with fibrinolysis the dominant reperfusion strategy. This may indicate that there are slight differences within the pathogenesis of the acute coronary event in smokers as compared to non-smokers. It has previously been shown that smokers with STEMI have improved myocardial perfusion after fibrinolysis compared to non-smokers, despite adjustment for differences in age and co-morbidities [47,48]. Tobacco smoking is additionally related to increased levels of circulating fibrinogen and tissue factor. This suggests a more fibrin-rich thrombus in smokers with STEMI which leaves them more amenable to fibrinolytic therapy and thus, an improved

survival rate. All these explanations may operate in unison to contribute to the observation that smokers perform better than non-smoker after an AMI.

STUDIES FAVOURING THE PARADOX

RANDOMISED TRIALS

International Tissue Plasminogen Activator/Streptokinase Mortality Trial and GISSI-2 [39] had a similar design and enrolled STEMI patients within the same time period. A "smoker's paradox" was observed in the International study, whereas only a non-significant trend for better outcome for smokers was demonstrated in GISSI2. These two studies bring forward the matter of the classification of former smokers. In the International study, the OR for six-month mortality was presented for never-smokers vs. current + former smokers, while the contrasting GISSI-2 only reported in-hospital mortality in current vs. never-smokers. In the GUSTO-1 study, 40,599 patients were included in an analysis of 30-day mortality in relation to smoking status. To the simplest of our knowledge, it is during this study that idea of the smokers paradox is first coined. Although not stated expressively within the abstract of the first article, the results from the adjusted analysis were significantly in favour of the paradox within the overall population studied. The abstract refers to the adjusted OR among 2,431 patients subjected to the angiographic substudy, among which the paradox was not apparent.

STUDIES NOT SUPPORTING THE PARADOX

RANDOMISED TRIALS

In TRACE, some different confounders to those used in the thrombolytic studies were included, with the study recruiting screenees for a randomised trial[42]. The study population that was screened for entry into TRACE is representative of unselected AMI patients admitted to hospital alive with an AMI. On the other hand, OPTIMAAL included highly selected patients with AMI and heart failure [43]. The percentage of patients given fibrinolysis was 54% in OPTIMAAL screenees and 39% in TRACE screenees, as opposed to 100% in the fibrinolytic trials. In the more recent CADILLAC trial, in which, patients were selected to undergo primary PCI for STEMI, the paradox could not be verified. This suggests that the possible existence of a smoker's paradox does not extend into the invasive era. In SYNERGY, the only randomised trial including NSTE-ACS with patients scheduled for invasive management, a significantly increased adjusted HR for one-year mortality in current vs. never-smokers was found.

Registries, both the Israeli[50] and Hellenic registries included hospitalised patients with AMI in the fibrinolytic era. Similar to NRMI 2, IBERICA and ARIAM, the mortality rate was compared among current vs. non-smokers, with the results contradictory. It is possible that the number of patients was too small to register the differences noted in the three larger registries. The GRACE registry was the only study to include patients based upon the current definition of ACS and included in-hospital invasive procedures as a covariate. Neither in the total population of nearly 20,000 patients, nor in the subgroups of patients with STEMI, NSTEMI, could the existence of the paradox is verified. Single centre studies, in neither of the two single centre studies from Portugal could the paradox be demonstrated, with one showing a non-significant increase in odds ratio for current vs. non-smokers for six-month mortality (in keeping with the findings from SYNERGY). In the study of NSTEMI patients, a significant interaction between treatment strategy and smoking at admission was observed, showing a statistically significant effect of smoking on mortality. However, due to the statistically significant interaction between cohort and smoking, the effect of smoking differed between cohorts. Smokers in the conservative cohort had a statistically higher adjusted mortality than non-smokers. In the study, smokers received a particular clinical benefit from an early invasive strategy[51], and there was no statistically significant differences between mortality for smokers as compared to non-smokers in the invasive cohort. Accordingly, there was no evidence for the existence of a smoker's paradox in the study.

DISCUSSION

In a systematic search, there will always be a conflict between completeness and accuracy. Here a wide search was performed and tested the initial search for possible omissions according to the known important publication cannot exclude the possibility of having omitted relevant important studies. In that context, two recent studies that didn't meet our inclusion criteria are of interest. They address the important smoking interaction of clopidogrel. Desai et al. presented data from 3,427 STEMI patients and found that the beneficial effect of clopidogrel was especially pronounced among those who smoked ≥ 10 cigarettes per day. The study by Bliden et al. of 259 patients undergoing elective stenting shows that clopidogrel induced increased platelet inhibition and lower aggregation as compared with non-smokers. The design of those studies, however, didn't leave the exploration of the existence of the "smoking paradox". Due to expected variations in the definition of nonfatal cardiovascular events as well as the sub-classification of fatal events,

this overview does not explore possible associations between smoking status and events other than total mortality. In addition, the overview doesn't include any mechanistic studies.

The “smoker’s paradox” was predominantly observed in AMI patients selected consistent with the WHO criteria. During that period, fibrinolysis was the dominant reperfusion strategy for such patients. The paradox, however, hasn’t been demonstrated in additional recent studies using routine early invasive management. As such, it might encourage smoking cessation instead of counting on the “positive effects” of smoking. Current smokers with ACS were younger and more frequently males, who had fewer risk factors and comorbidities, more benign clinical presentation and fewer complications, and received more aggressive treatment. These differences completely explained the lower in-hospital and one-year mortality initially observed in current smokers. But, in our population, we didn't find a true smoker’s paradox. Besides, the apparent benefit was only seen within the subset of patients with STEMI, while differences in overall characteristics were less marked in other sorts of ACS and no benefit in mortality was seen. Nevertheless, the study is only limited to immediate outcome. Smoking status posts myocardial infarction and its effect on future outcome wasn't assessed. Currently, the general evidence from the literature remains in favour of non-smokers, especially for future outcome and post coronary revascularisations.

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