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Clinical paper

A history of smoking is associated with improved survival in patients treated with mild therapeutic hypothermia following cardiac arrest[☆]

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ABSTRACT

Objectives: To assess the association between smoking and survival with a good neurologic outcome in patients following cardiac arrest treated with mild therapeutic hypothermia (TH).
Methods: We conducted a retrospective observational study of a prospectively collected cohort of 188 consecutive patients following cardiac arrest treated with TH between May 2007 and January 2012. Smoking status was retrospectively collected via chart review and was classified as “ever” or “never”. Primary endpoint was survival to hospital discharge with a good neurologic outcome and was compared between smokers and nonsmokers. Logistic regression analysis was used to assess the association between smoking status and neurologic outcome at hospital discharge; adjusting for age, initial rhythm, time to return of spontaneous circulation (ROSC), bystander CPR, and time to initiation of TH.
Results: Smokers were significantly more likely to survive to hospital discharge with good neurologic outcome compared to nonsmokers (50% vs. 28%, $p = 0.003$). After adjusting for age, initial rhythm, time to ROSC, bystander CPR, and time to initiation of TH, a history of smoking was associated with increased odds of survival to hospital discharge with good neurologic outcome (OR 3.54, 95% CI 1.41–8.84, $p = 0.007$).
Conclusions: Smoking is associated with improved survival with good neurologic outcome in patients following cardiac arrest. We hypothesize that our findings reflect global ischemic conditioning caused by smoking.

1. Introduction

The harmful effects of cigarette smoking on public health are well established.[1] Although cigarette smokers have a higher probability of experiencing an acute coronary syndrome, they also have a lower unadjusted mortality rate following an acute myocardial infarction (AMI).[2–4] This phenomenon was recognized 25 years ago and was termed the “Smoker’s Paradox”.[5,6] Some studies attribute this observation to younger age and fewer co-morbidities in patients who smoke.[4,7–9] However, other studies have shown that the association between smoking and improved outcome persists after adjusting for these variables.[10–13] Since the introduction of the term “smoker’s paradox”, it remains unclear if there is a direct causal relationship between a history of smoking and reduced mortality following AMI.

Little is known regarding the potential mechanisms that underlie the association between smoking and improved outcomes following AMI. Smoking causes low-levels of hypoxia in diffuse tissue beds,[14,15] which may result in a greater tolerance of more severe, acute hypoxic injuries and attenuation of reperfusion injury. This effect, known as ischemic conditioning,[16] has been demonstrated in numerous experimental models and has been shown to be both neuroprotective[19] and cardioprotective.[17–21] Reperfusion and reperfusion injury following AMI share many features of the reperfusion injury that occurs in cardiac arrest, albeit diffuse tissue beds are involved in the setting of cardiac arrest. Given the physiologic similarities and the previously described relationship between smoking and improved outcomes following AMI, we hypothesized that a history of smoking may be associated with improved outcomes following cardiac arrest in patients treated with mild therapeutic hypothermia (TH).

To the best of our knowledge, the effect of smoking has never been studied in patients following cardiac arrest. The aim of the

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study was to determine if a history of smoking is associated with improved survival with good neurologic outcome in patients following cardiac arrest treated with mild TH.

2. Methods

We conducted an observational study of a prospectively collected cohort of 188 consecutive patients following cardiac arrest who underwent mild TH in the cardiovascular care unit of an academic tertiary care hospital between May 2007 and January 2012. All cardiac arrest survivors, age 18 years or older, who were unresponsive or comatose after return of spontaneous circulation (ROSC) were eligible for the TH protocol. Brainstem reflexes (i.e. cough, gag, corneal) as well as pathologic/posturing movements were permissible. Exclusion criteria for TH included: spontaneous awakening with purposeful movement, known or suspected pregnancy, known terminal illness or limited life expectancy, do not resuscitate (DNR) orders, initial body temperature less than 34 °C (93.2 °F), recent major head/facial trauma, cardiac arrest due to traumatic injury, and estimated time from arrest to ROSC of greater than 60 min. Relative exclusion criteria included known bleeding diathesis or ongoing bleeding, and when another cause of coma was present such as drug intoxication or pre-existing coma. The majority of the study patients were transferred from community emergency departments or directly to our institution from multiple emergency medical service (EMS) systems with unique pre-hospital protocols. Patients meeting TH criteria were generally cooled with external icepacks and/or chilled intravenous saline en route. Post-cardiac arrest patients determined by their treating physician to be suitable for TH were cooled to a target temperature of 33 °C (±1 °C) using an active surface cooling device (Arctic Sun, Medivance, Louisville, CO) for 24 h following the approximated time of ROSC. Target temperature was defined as the time a patient's core temperature reached 34 °C. After external cooling, all patients were actively rewarmed at 0.25 °C/h until normothermic (36 °C).[22]

Following approval from the institutional review board, data were collected on all patients following cardiac arrest. In addition to baseline demographics, initial rhythm, time to ROSC, occurrence of bystander cardiopulmonary resuscitation (CPR), presence of shock at admission (defined as a SBP <90 or use of vasopressors), and Cerebral Performance Category (CPC) score at hospital discharge and follow up were collected. ROSC was estimated by retrospective review of the electronic chart and EMS "run sheets" and was defined as the time the patient was found pulseless to ROSC. Time to initiation of TH and time to reach target temperature were both calculated from time of ROSC. Time of initiation of cooling was defined as the time at which any cooling method was applied, either at our hospital or prior to arrival at our facility; commonly used methods included cold saline infusion, application of ice packs, or the application of our external cooling device.

Smoking status was retrospectively classified as "ever" or "never". Patients were considered to be smokers if they were ever labeled as a smoker in the electronic medical record by a healthcare professional at any time, including during the index admission or during previous clinic visits or hospitalizations. The definition did not consider the amount smoked, or for former smokers the time since quitting. Patients were considered to be nonsmokers if they were labeled as a nonsmoker on the index admission and had never previously been labeled as a smoker in the medical record. Patients for whom smoking status was unknown, defined as never specifically mentioned in the electronic medical record, were excluded from this analysis. 82 patients were included prior to implementation of our CODE ICE standardized protocol, 56 (69%) were smokers. 106 patients were included after implementation of CODE ICE, 39 (39%) were smokers. Patients were considered to be previously healthy if they did not have a known chronic medical condition prior to cardiac arrest. Chronic medical conditions included coronary artery disease, congestive heart failure, arrhythmia, hypertension, chronic obstructive lung disease (COPD), chronic renal failure (CKD), neurologic disease, liver failure, disseminated malignancy, alcohol/drug abuse, obesity (BMI > 35), and insulin dependent diabetes mellitus (DM).

The primary endpoint was survival to hospital discharge with a good neurologic outcome. Neurologic outcome was assessed using the CPC score, with a "good" outcome defined as a score less than or equal to 2. The CPC score was developed as a measure of central nervous system function after cardiac arrest and has become the most commonly used outcome tool for this purpose.[23–25]

Descriptive statistics are presented as the median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. Wilcoxon rank sum test and Pearson Chi-square test were used to compare the baseline characteristics between smokers and non-smokers. Logistic regression analysis was used to assess the association between smoking status and neurologic outcome at hospital discharge while adjusting for age, initial rhythm, time to ROSC, bystander CPR, and time to initiation of TH. Another logistic model was fit to assess the association between smoking status and neurologic outcome with adjustment for the same set of covariates as well gender and comorbidities via a propensity score. A similar analysis was again done to analyze survival with good neurologic outcome in smokers and non-smokers at a median follow-up of 3 months. Odds ratios with 95% confidence intervals are presented. All tests were two-tailed, with a significance level of 5%. All statistical analyses were performed using open source R statistical software (version 2.15.1, Vienna, Austria).

3. Results

Of 188 consecutive patients considered for inclusion, smoking status was determined in 181 patients (96%). Table 1 displays a comparison of baseline characteristics. Non-smokers had shorter times to initiation of TH (160 vs. 240 min, $p = 0.01$), shorter time to reach target temperature (320 vs. 450 min, $p < 0.01$), and spent more time at target temperature (21.0 vs. 17.0 h, $p < 0.01$). No statistically significant difference in age, gender, past medical history, initial rhythm following ROSC, sepsis, or shock on admission between smokers and non-smokers was observed.

The overall in-hospital mortality rate was 60% (108/181). Of the 181 patients, 110 (61%) had poor and 71 (39%) had good CPC neurologic status at time of discharge. Fig. 1 displays clinical outcomes based on smoking status. Smokers were significantly more likely to survive to hospital discharge with good neurologic outcome compared to nonsmokers (50% vs. 28%, $p = 0.003$). In addition, Fig. 1 compares outcomes in relation to CPC score for smokers versus non-smokers at both hospital discharge and at follow-up. At a median of 3 months follow-up, results were similar to hospital discharge: more smokers had a CPC score of 1–2 and more non-smokers had a CPC score of 3 or greater.

Multivariable analysis was performed to assess the relationship between smoking history and clinical outcome. After adjusting for age, initial rhythm, time to ROSC, bystander CPR, and time to initiation of TH, a history of smoking was independently associated with increased odds of neurologically intact survival at the time of hospital discharge (OR 3.54, 95% CI 1.41–8.84, $p < 0.01$) (Table 2a) (Fig. 2). Sensitivity analysis using a propensity score for smoking while also adjusting for other potentially important co-variables demonstrated a similarly significant independent association between smoking and a good neurologic outcome at hospital discharge (OR 3.82, 95% CI 1.43–10.24, $p < 0.01$) (Table 2b).