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Clopidogrel and ischemic stroke outcomes by smoking status: Smoker's paradox?

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ABSTRACT

Background and purpose: Active smokers with myocardial infarction were shown to have enhanced benefit with clopidogrel compared with aspirin. Whether this "paradox" exists in ischemic stroke patients is unknown. We aimed to investigate whether smoking status has a differential impact on the efficacy of clopidogrel vs. aspirin in patients with non-cardioembolic strokes.

Methods: This single-center study retrospectively assessed 1792 non-cardioembolic ischemic stroke patients discharged from January 2013 to October 2014, and followed for 12 months. Patients were categorized as current-smokers and never-smokers. Primary outcome was a composite of secondary ischemic stroke, myocardial infarction and all-cause death. Secondary outcome was secondary ischemic stroke.

Results: 1066 patients were current-smokers and 726 were never-smokers. Compared with never-smokers, current-smokers had significantly higher rates of ischemic stroke (4.3% vs. 1.2%; adjusted OR: 3.60, 95%CI: 1.50–8.64, p = 0.004). Regarding the primary outcome, among smokers, rates showed a lower trend in clopidogrel vs. aspirin groups (3.7% vs. 6.4%; adjusted OR 0.57, 95%CI: 0.31–1.07, p = 0.08), but no difference among never-smokers (2.1% vs. 1.0%; adjusted OR: 1.67, 95%CI: 0.47–5.89, p = 0.42). Similarly, among smokers, trending lower rates for recurrent ischemic stroke were observed in clopidogrel vs. aspirin group (3.1% vs. 5.0%; adjusted OR: 0.60, 95%CI: 0.31–1.18, p = 0.14); but no difference between the two groups among never-smokers (1.7% vs. 1.0%; adjusted OR 1.36, 95%CI: 0.36–5.52, p = 0.65).

Conclusions: Smoking is a major risk factor for recurrent stroke in our retrospective non-cardioembolic ischemic stroke cohort. Active-smokers trend toward better cardiovascular outcomes when on clopidogrel. This finding needs to be confirmed in a prospective cohort.

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1. Introduction

The interaction between cigarette smoking and cardiovascular outcomes is complex [1]. On one hand, cigarette smoking influences the inception and progression of atherosclerosis [2] and poses hazards to cardiovascular and cerebrovascular systems which can trigger thrombotic complications including myocardial infarction (MI), ischemic stroke (IS), and cardiovascular death [3]. However, several recent studies observed reduced recurrence of cardiovascular events and an improved survival in smokers with antithrombotic therapy after an index cardiovascular event, a phenomenon called "smoker's paradox" [4,5]. This observation has been postulated to be due to cytochrome P450 (CYP) 1A2 and B6 induction by cigarette smoking leading to increased clopidogrel active metabolite and enhanced platelet inhibition [6].

While a smoker-clopidogrel paradox has been observed among cardiovascular patients, little is known about whether this paradox exists in ischemic stroke patients. The objective of this study was to assess whether smoking status has a differential clinical impact on the efficacy of clopidogrel vs. aspirin among recent ischemic stroke patients.

2. Methods

2.1. Subjects

We retrospectively reviewed the prospectively maintained stroke registry of a single medical center (Xuanwu Hospital) comprising

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1910 non-cardiogenic ischemic stroke patients consecutively discharged from between January 2013 to October 2014, who were prescribed clopidogrel (75 mg/day) or aspirin (100 mg/day) after their index events. In the local protocol, subjects were not prescribed either of these agents if they met any of the following criteria: known allergy or intolerance to aspirin or clopidogrel; active bleeding or bleeding tendency; any bleeding within last 6 months; dyscrasia and malignancy, simultaneous use of other antithrombotic drugs (oral anticoagulants, dipyridamole, ticlopidine, or cilostazol), platelet count $<100 \times 10^6$/L during admission, liver disease with baseline hepatic enzymes >2.5 times the upper limit of normal during admission. The study was approved by the local institutional review board.

Patients were categorized as current smokers, former smokers and never-smokers according to their smoking status which was ascertained and recorded on the medical records at hospital admission for the indexed event. Current smokers were defined as persons smoking at least 1 cigarette per day during the month before hospital admission. Never-smokers were defined as those who had never smoked [7]. As the former smoker is not easy to defined and its impact on cardiovascular events is not well defined, the study excluded 118 patients who had smoked previously and stopped >1 month before the stroke hospitalization. As a result, there were two groups for the purpose of this analysis: current smokers vs. never-smokers.

2.2. Clinical outcomes assessment

All participants had standard assessments of demographic characteristics, medical history and clinical outcomes per local clinical stroke protocol. Per protocol, stroke patients were evaluated at the time of admission, and were continuously assessed every month until 12 months post-stroke. Primary outcome was a composite of secondary IS, MI and all-cause death. The secondary outcome was secondary IS alone. In addition, we compared safety profiles of clopidogrel vs. aspirin on the cumulative bleeding events (major or minor, including mucocutaneous hemorrhage, gastrointestinal bleeding, and intracranial hemorrhage, et al.) during the 12-month period according to smoking status.

2.3. Statistical analysis

We performed two-tailed *t*-tests for continuous variables and chi-squared tests for categorical variables. A Mann-Whitney *U* test was performed for the variables that were not normally distributed. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated and stratified by the smoking status. Adjusted OR and 95% CI were calculated using a logistic regression model. We adjusted age, sex, hypertension, diabetes, hyperlipidemia and prior coronary heart disease. p value <0.05 was considered as statistical significance. Statistical analyses were conducted with SPSS statistical software, version 22.0 (Chicago, IL, USA).

3. Results

3.1. Study population

A total of 1792 patients were included in this study, of which 1066 (59.5%) were classified as "current smokers" and 726 (40.5%) as "never smokers". The baseline characteristics and clinical outcomes of the patients were reported by smoking status in Table 1. Compared with never smokers, current smokers were relatively younger, more frequently male, more likely to have a history of hyperlipidemia. Current smokers had significantly higher rates of secondary IS [46 (4.3%) vs. 9 (1.2%), p = 0.000], MI [10 (0.9%) vs. 1 (0.1%), p = 0.034] and bleeding events [21 (2.0%) vs. 3 (0.4%), p = 0.005] than never-smokers. In both unadjusted and adjusted model, current smokers had an increased risk of secondary IS compared with never smokers at statistically significant level [3.59 (1.75–7.39) vs. 3.60 (1.50–8.64)]. Table 2 shows both unadjusted and adjusted ORs for other clinical outcomes according to the smoking status.

Table 1
Baseline demographics and clinical outcomes by smoking status.

	Current smokers (n = 1066)	Never-smokers (n = 726)	p-Value
Demographics			
Age (yr, mean ± SD)	58.68 ± 11.60	62.78 ± 13.56	0.000
Male (%)	95.4	43.8	0.000
Clinical History (n, %)			
Hypertension	682 (64.0)	494 (68.0)	0.075
Diabetes	304 (28.5)	227 (31.3)	0.211
Hyperlipidemia	469 (44.0)	264 (36.4)	0.001
Prior coronary heart disease	132 (12.4)	104 (14.3)	0.233
Medication (n, %)			0.210
Aspirin	683 (64.1)	486 (66.9)	
Clopidogrel	383 (35.9)	240 (33.1)	
Primary outcome (n, %)			
Secondary ischemic stroke	46 (4.3)	9 (1.2)	0.000
Myocardial infarction	10 (0.9)	1 (0.1)	0.034
All-cause death	2 (0.2)	0	0.518
All primary events	58 (5.4)	10 (1.4)	0.000
Safety endpoint (n, %)			
Bleeding events	21 (2.0)	3 (0.4)	0.005

3.2. Impact of smoking status on outcomes: clopidogrel vs. aspirin

Of the current smokers, 683 patients were treated with aspirin and 383 patients were treated with clopidogrel. In never-smokers, 486 subjects were prescribed with aspirin and 240 subjects with clopidogrel. In the never-smokers, aspirin-treated patients were younger, less frequently to have a history of hypertension compared with clopidogrel-treated patients. Table 3 shows the baseline characteristics and clinical outcomes of patients according to clopidogrel or aspirin treatment stratified by the smoking status. Regarding the primary outcome, for smokers, rates were numerically lower in clopidogrel vs. aspirin groups [14 (3.7%) vs. 44 (6.4%); adjusted OR 0.57, 95% CI: 0.31–1.07, p = 0.080], but more congruent among never-smokers [5 (2.1%) vs. 5 (1.0%); adjusted OR 1.67, 95% CI: 0.47–5.89, p = 0.424]. Similarly, for the outcome of secondary IS alone, among smokers, relatively lower rates were observed in the clopidogrel vs. aspirin group [12 (3.1%) vs. 34 (5.0%); adjusted OR 0.60, 95% CI: 0.31–1.18, p = 0.138]; but a less pronounced difference between clopidogrel vs. aspirin was observed among never-smokers [4 (1.7%) vs. 5 (1.0%); adjusted OR 1.36, 95% CI: 0.36–5.52, p = 0.651]. The rates of bleeding events were similar in the clopidogrel vs. aspirin group among both current smokers [9 (2.3%) vs. 12 (1.8%); adjusted OR 0.94, 95% CI: 0.08–10.48, p = 0.959] and never-smokers [1 (0.4%) vs. 2 (0.4%); adjusted OR 1.73 95% CI: 0.55–3.19, p = 0.526] (Fig. 1).

4. Discussion

The primary findings in this study are as follows: 1) Of patients with non-cardioembolic ischemic strokes, current smokers experienced an increase in the primary composite clinical outcome of secondary IS, MI, and all-cause death in 12 months after indexed event, compared with never-smokers; 2) Of smokers, There is a trend of lower composite vascular events in clopidogrel-treated patients as compared with the aspirin-treated patients, whereas no such trend was observed in never-smokers; 3) No significant difference was observed between antiplatelet agents and smoking status for bleeding events.

Cigarette smoking is a strong independent risk factor for all-cause mortality and recurrent ischemic events [2], therefore, smoking cessation is a recommended treatment with strong evidence for secondary prevention of atherosclerotic vascular disease [8].

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