ARTÍCULO ORIGINAL

Tabaquismo y su Asociación con Mortalidad Intrahospitalaria en Pacientes con Ictus Hemorrágico.

Cigarette Smoking And Its Association With In-Hospital Mortality In Hemorrhagic Stroke Patients.

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Resumen

Antecedentes: El fumar es un factor de riesgo tradicional claramente identificado con un mayor riesgo de desarrollar accidente cerebrovascular (ACV). A pesar de existir un riesgo más elevado de desarrollar ACV, algunos reportes han demostrado que pacientes ya hospitalizados con diagnóstico de ACV hemorrágico tienen una mortalidad intrahospitalaria menor a sus pares no fumadores, situación conocida como la paradoja del tabaquismo. **Objetivos**: El objetivo de este estudio es analizar la mortalidad Intrahospitalaria de Pacientes con Accidente Cerebrovascular Hemorrágico entre aquellos pacientes fumadores versus los no fumadores. **Métodos y resultados**: Este estudio epidemiológico observacional analítico de casos y controles incluyó a todos los pacientes con diagnóstico de accidente cerebrovascular hemorrágico incluidos en el "Registro de Accidentes Cerebrovasculares de Florida" entre el año 2008 y 2012. Entre los 21.013 pacientes diagnosticados con accidente cerebrovascular hemorrágico, el 10,9% de los pacientes fueron fumadores. Se utilizaron modelos multivariables para estimar la tasa de probabilidad ajustada de mortalidad intrahospitalaria en fumadores versus no fumadores. El tabaquismo se asoció con una menor mortalidad hospitalaria en pacientes hemorrágicos. (UOR = 0,71 frente a AOR = 0,75). Como se observa en las tablas, muchos de los factores de confusión, la hipertensión, IMC> 40, y la hiperlipidemia, tuvieron asociación significativa después del modelamiento estadístico mientras que otros factores como el sexo, la raza, el tipo de seguro de salud y la presencia de diabetes no tuvieron una asociación estadísticamente significativa. La diferencia entre las tasas de probabilidad no ajustadas y ajustadas para el tabaquismo (0,71 frente a 0,75 respectivamente) indica que no hay presencia de factores de confusión sustanciales por edad y otras variables de control. **Conclusiones**: Entre los pacientes hospitalizados por accidente cerebrovascular hemorrágico, el tabaquismo es un factor de riesgo para el desarrollo del mismo, especialmente en pacientes jóvenes, incluso entre aquellos con pocos factores de riesgo vascular, sin embargo, la asociación persistente con menor mortalidad intrahospitalaria después de los análisis ajustados probablemente represente otra confusión no medida, aunque no se puede excluir un efecto biológico del tabaquismo. Se necesitan más estudios clínicos basados en la población para explorar las variables que contribuyen a los resultados en estos pacientes.

Palabras clave: Tabaquismo, mortalidad, ictus, enfermedad cerebrovascular.

Abstract

Background: Smoking is a well-known reversible risk factor associated with acute ischemic stroke (AIS), however, some data showed that in-hospital mortality rates among smoker's patients with hemorrhagic stroke is lower when compared with non-smokers patients. The objective of this analysis was to assess in-hospital patient mortality rate between smokers and non-smokers patients with confirmed diagnosis of hemorrhagic stroke. **Methods and Results:** We analyzed all the data from patients diagnosed with hemorrhagic stroke that were registered in the Florida Stroke database from 2008-2012. Among the 21,013 patients diagnosed with hemorrhagic stroke, 10.9% of patients were smokers. A Multivariable model was used to estimate the adjusted odds ratio of in-hospital mortality rate in smokers versus non-smokers. Smoking was associated with lower in-hospital mortality in hemorrhagic patients. (UOR= 0.71 vs. AOR= 0.75). Other risk factors like hypertension, BMI>40 and hyperlipidemia, remained significantly associated after modeling, and some others like gender, race, health insurance coverage, and diabetes became insignificant. The difference between unadjusted and adjusted odds ratios for smoking (0.71 versus 0.75) indicates no presence of substantial confounding by age and other control variables. **Conclusions:** Among patients hospitalized for hemorrhagic stroke, smoking is a risk factor for early age of onset, even among those with few vascular risk factors. The persistent association with lower in-hospital mortality after adjusted analyses probably represents other unmeasured confounding, although a biological effect of smoking cannot be excluded. Further clinical and prospective population-based studies are needed to explore variables that contribute to outcomes in these patients.

Keywords: Smoking, mortality, stroke, cerbrovascular disease.

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Introduction

Despite our understanding of cerebrovascular accident also known as stroke, mortality due to it remains high, representing one of the most important causes of death in world.[1] In the United States, more than 700,000 strokes that caused more than 165,000 deaths occur each year.[2] Worldwide, stroke is the 2nd leading cause of death representing more than 10% of all the causes of fatalities by 2016.[3] Deaths due to stroke are either reported prior to the arrival of the patients to the hospitals as well as during the period of hospitalization.[4] Several reasons have been linked with an increase of developing stroke, including traditional risk factors such as smoking, diabetes, obesity or sedentarism as well as not traditional risk factors like vitamin D deficiency or altitude exposure.[5] Smoking as a major risk factor for stroke, causes endothelial dysfunction increasing the risk of thrombosis, incrementing the chances of occluding arteries or veins.[6] Approximately 30% of deaths due to coronary artery disease (CAD) are associated to smoking.[7] Smoking also nearly doubles the risk of an acute ischemic stroke.[8] Cigarette smoking is the most common preventable cause of any vascular disease.[4] Clinical practice guidelines recommend smoking cessation, especially to survivors of stroke, transient ischemic attack (TIA), MI, and other vascular diseases; yet 18-35% of survivors smoke.[7]

Smoker's paradox was first introduced two to three decades ago after observing that smokers experienced decreased mortality following an acute MI, when compared to non-smokers.[9] There are other types of paradoxes, for instance obesity and gender paradox have been reported in stroke survivor patients.[10-12] Smoking and its association with acute ischemic stroke have been studied more extensively relative to hemorrhagic stroke. As mentioned above, a smoker's paradox exists possibly because, in smokers, acute ischemic stroke occurs on average 10 years earlier that in non-smokers.[4] There could be a collective effect of younger age, lower clinical risk profiles, and possibly more aggressive treatment that result in a better prognosis in patients who smoke.[9,12,13]

One study in elderly Chinese patients who smoke showed that cigarette smoking was associated with a higher mortality risk of hemorrhagic stroke and both its major subtypes, i.e. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), based on a large community-based sample and a sufficient follow-up period.[14] However, a protective effect was observed in patients with intracranial hemorrhage (ICH) a type of stroke that had not been addressed in previous studies.[15] Although previous reports have shown that the association between cigarette smoking and hemorrhagic stroke is weak and inconsistent. This report is focused on the association between smoking vs. non-smoking, and the occurrence of in-hospital mortality after a hemorrhagic stroke. No studies have been performed to study the association of smoking and in-hospital mortality in hemorrhagic stroke patients in Florida to our knowledge.

Methods

Population: A secondary data analysis of the Florida Stroke Registry was conducted in those patients who were hospitalized with a diagnosis of stroke from 2008 to 2012. Stroke was defined according to the International Classification of Diseases 10th edition (ICD-10) discharge codes. The total numbers of patients with stroke reached 333,367 and from those patients, 21,013 were diagnosed with intracerebral hemorrhage (ICD-10) code 431, intracranial hemorrhage).

Smoking: The study population was divided in two groups based on their smoking status. Information about smoking status was obtained from the medical record by using ICD-10 codes as well. Both groups were current those patients that were currently smokers (any cigarette use within the year preceding the stroke) versus nonsmokers patients (either never smokers or those who had been abstinent for >1 year prior to stroke). The available data does not distinguish between the 2 subtypes of nonsmokers.

Outcome: The primary outcome of interest for this study was in-hospital mortality, which was defined as patients who died during their stay at the hospital or those who survived and were discharged.

Control variables: Control variables were selected based on an extensive literature review. Demographic factors were self-reported and those included sex and race (white, African American, and all other races were included as other). Insurance status was self-reported and patients were divided into commercial insurance and non-commercial insurance. Non-commercial medical insurance included Medicare, Medicaid, worker's compensation, TriCare, State/Local government insurance, non-payment, commercial liability coverage, and any other form. Clinical factors such as hypertension, diabetes mellitus, hyperlipidemia, and morbid obesity (BMI>40 or BMI<40) were recorded via ICD-10 codes and were used in the data set accordingly.

Statistical Analysis: Statistical analyses were performed using the software SPSS version 24. Patient demographics and clinical variables were analyzed for both cohorts. Percentages were used for categorical variables and medians with interquartile ranges for continuous variables. Categorical data were analyzed by Pearson $\chi 2$ and continuous data by Wilcoxon rank sum test. Logistic regression models were used to compute odds ratios (ORs) and Confidence Intervals (CI) for factors associated with in-hospital mortality in hemorrhagic stroke patients.

Multivariable logistic regression analysis was employed to adjust for potential confounding effect of each one of the control variables, on the estimation of the OR of in-hospital mortality between smokers and non-smokers.

Results

In the Florida Stroke Registry, there were 333,367 records of patients that were diagnosed with a stroke. We limited the age group to patients >= 18 years old, resulting in 300,000 patients. Among them, 21,013 patients were diagnosed with hemorrhagic stroke according to appropriate ICD-10 code (intracranial hemorrhage). Prevalence of smoking in our study population was (2285/21013) and overall in-hospital all causes mortality was (4591/21013). The overall prevalence of smoking was 10.9%. The overall in-hospital all causes mortality was 21.8%. Data on demographics, comorbidities, and in-hospital mortality were collected and analyzed.

Table 1 shows that in this cohort, smokers were substantially younger than those who do not smoke. Younger smokers were also mostly African American men, with hypertension, and overweight (BMI>40). They were also less likely to have a history of diabetes mellitus, and

Table 1. Characteristics of Hemorrhagic Stroke Patients in the Florida Stroke Registry and their Smoking Status.

Characteristics	Smoking No (N= 18728) N (%)	Smoking Yes (N= 2285) N (%)	p value
Age (years)			<0.001
< = 50	10.1	25.3	
51 - 60	13.7	31.4	
61 - 70	17.0	23.6	
71 - 80	26.9	13.9	
> 80	32.2	5.8	
Gender			<0.001
Male	50.0	59.1	
Female	50.0	40.9	
Race			<0.001
Black or African American	19.3	25.1	
White	74.9	69.9	
Other	5.8	5.1	
Health insurance coverage			<0.001
Commercial	9.8	12.7	
No Commercial	90.2	87.3	
BMI(kg/m2)>40			0.110
No	92.2	91.2	
Yes	7.8	8.8	
Diabetes Mellitus			<0.001
No	70.7	78.6	
Yes	29.3	21.4	
HTN			<0.001
No	93.7	90.9	
Yes	6.3	9.0	
Hyperlipidemia			<0.001
No	63.8	71.1	
Yes	36.2	28.9	

BMI-Body Mass Index; HTN-Hypertension

Table 2. Characteristics of Hemorrhagic Stroke Patients in the Florida Stroke Registry and their In-Hospital Mortality Status.

Characteristics	In-hospital mortality Alive (N= 16422) N (%)	In-hospital mortality Death (N= 4591) N (%)	p value
Smoking			<0.001
No	77.6	22.4	
Yes	83.0	17.0	
Age			<0.001
< = 50	81.5	18.5	
51 - 60	80.3	19.7	
61 - 70	79.8	20.2	
71 - 80	75.4	24.6	
> 80	77.1	22.9	
Gender			0.006
Male	78.9	21.1	
Female	77.4	22.6	
Race			0.003
Black or African American	79.7	20.3	
White	77.6	22.4	
Other	80.4	19.6	
Health insurance coverage			0.028
Commercial	80.0	20.0	
No Commercial	77.8	22.2	
BMI >40			<0.001
No	77.7	22.3	
Yes	83.4	16.6	
Diabetes Mellitus			0.03
No	78.0	22.0	
Yes	79.3	20.7	
HTN			<0.001
No	77.8	22.2	
Yes	83.0	17.0	
Hyperlipidemia			<0.001
No	75.9	24.1	
Yes	82.7	17.3	

BMI-Body Mass Index; HTN-Hypertension

hyperlipidemia. Smokers carried commercial insurance more often than non-smokers.

Table 2 shows that only 17.0% of smokers who were diagnosed with hemorrhagic stroke died during their stay as compared with 22.4% of nonsmokers. In-hospital mortality was increased in patients who were >70 years old, white race, with a BMI<40. Patients who had a history of hypertension, hyperlipidemia, and diabetes mellitus were associated with lower mortality. Patients with in-hospital mortality more commonly carried non-commercial insurance.

A multivariate analysis was performed to assess for any confounding that might have altered the results. The potential confounders that were analyzed included age, gender, race (African American, white, other), health insurance coverage (commercial vs. non-commercial), morbid obesity (BMI>40), diabetes mellitus, hypertension, and hyperlipidemia.

Table 3. Bivariate Logistic Regression Model of Factors Significantly Associated With In-Hospital Mortality in Hemorrhagic Stroke.

Characteristics	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Smoking				
No	Reference			
Yes	0.71 (0.63-0.79)	<0.001	0.75 (0.67-0.85)	<0.001
Age				
< = 50	Reference			
51 - 60	1.08 (0.95-1.24)	0.242	1.09 (0.94-1.26)	0.243
61 - 70	1.12 (0.98-1.27)	0.095	1.12 (0.97-1.28)	0.132
71 - 80	1.43 (1.27-1.61)	<0.001	1.33 (1.16-1.52)	<0.001
> 80	1.31 (1.16-1.47)	<0.001	1.12 (0.98-1.29)	0.096
Gender				
Male	0.91 (0.91-0.98)	0.006	0.96 (0.89-1.02)	0.193
Female	Reference			
Race				
Black or African American	0.88 (0.81-0.96)	0.004	1.13 (0.95-1.33)	0.172
White	Reference			
Other	0.84 (0.73-0.98)	0.027	1.20 (1.02-1.40)	0.024
Health insurance coverage				
Commercial	Reference			
No Commercial	1.14 (1.01 -1.30)	0.028	1.09 (0.96-1.23)	0.194
BMI >40				
No	Reference			
Yes	0.69 (0.61-0.79)	<0.001	0.81 (0.71-0.94)	0.005
Diabetes Mellitus				
No	Reference			
Yes	0.92 (0.86-0.99)	0.030	0.97 (0.90-1.05)	0.494
HTN				
No	Reference			
Yes	0.72 (0.62-0.83)	<0.001	0.78 (0.67-0.91)	0.001
Hyperlipidemia				
No	Reference			
Yes	0.66 (0.61 -0.71)	<0.001	0.64 (0.59-0.69)	<0.001

BMI-Body Mass Index; HTN-Hypertension

Smoking was associated with lower in-hospital mortality in hemorrhagic patients. (UOR= 0.7, 95% CI, 0.6-0.8). After adjusting for age, gender, race, health insurance coverage, BMI > 40, diabetes mellitus, hypertension and hyperlipidemia, the magnitude of the association remained almost the same (OR= 0.75, 95% CI, 0.67-0.85). As observed in the tables, many of the confounders, hypertension, BMI>40, and hyperlipidemia, remained significantly associated after modeling, and some others like gender, race, health insurance coverage, and diabetes became insignificant.

Discussion

This study investigates if there is an association between smoking and in-hospital mortality in patients admitted with hemorrhagic stroke and registered in the Florida Stroke Registry from the years 2008-2012. Our analysis showed a decrease in in-hospital mortality in smokers when compared to non-smokers, resulting in an OR=0.71 and after adjusting for confounders, the OR=0.8 (95% CI, 0.67- 0.85). There was no significant increase in the odds ratio after adjusting for all the potential confounders leading us to conclude that smoking by itself is potentially a protective factor. Although smoking in this case is considered a protective factor, we highly recommend against the use cigarettes because of the hazardous effects of smoking that are manifested as the occurrence of stroke in patients' years earlier than might otherwise have occurred.

A "smoker's paradox" was observed in ischemic stroke by previous studies conducted by Ali et al. (2013, 2015).[4,16] Edjoc et al.[15] observed a protective effect in patients with intracranial hemorrhage (ICH) patients, a finding not present in previous studies. Our study reports lower in-hospital mortality in hemorrhagic stroke in smoker's patients, being this a novel finding because no previous studies have assessed in-hospital mortality of hemorrhagic patients to our knowledge. The pathophysiology behind this occurrence is unknown. It could be due to chronic changes in vasomotor tone that might lead to preconditioning in smokers, as well as the development of improved small vessel cerebral collaterals and better cerebral perfusion.[17-18] It could be hypothesized that chronic long term hypercapnia or relatively low but persistent hypoxia might trigger angiogenesis.[5,19] Metabolic changes to in the brain might limit the initial injury and influence stroke progression and mortality.[12,16]

As incidental findings we observed that patients with hypertension, morbid obesity and hyperlipidemia had lower in-hospital mortality. The expectation would be that patients with comorbidities would have a higher chance of in-hospital mortality. These findings are counterintuitive, suggesting that besides the so-called "smoking paradox", there could be other paradoxes, deserving further research.[10,11]

The Strengths of our study include an extensive database in the Florida Stroke Registry, a well collected dataset the include demographic, socioeconomic and clinical relevant data. This study had some important limitations. One of the limitations was that there is no severity scale for Stroke, which prevents us from properly evaluating patients with different severities of stroke. Another limitation is the unknown amount of cigarettes smoked by patients during their lifetime, or if they were former smokers, as the database reports only if they were smokers or non-smokers according to the patients themselves. There was also no report of pre-admission mortality, or post-hospital follow-up in patients who were still alive. Therefore, our recommendation would be to perform a study on mortality of patients with hemorrhagic stroke after 6 months and 12 months.

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