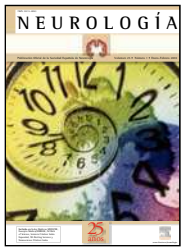
Neurología. 2011;**26(3)**:150-156

NEUROLOGÍA

www.elsevier.es/neurologia



ORIGINAL ARTICLE

Previous statins treatment and risk of post-stroke infections

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Received on 20th April 2010; accepted on 22th July 2010

KEYWORDS
Stroke;
Statins;
Complications;
Infections

Abstract
Introduction: Clinical and laboratory studies have attributed an inmuno-supressor effect to the statins. Furthermore, the administration of simvastatin in the acute onset of stroke has been associated with an increased infection frequency. Our objective is to assess the influence of statins previous treatment on infection after ischemic stroke.
Patients and methods: Observational study of patients with ischaemic stroke hospitalised in a Stroke Unit. Demographic data, vascular risk factors, stroke severity, stroke subtype and previous statins treatment were evaluated. The following infections were registered: pneumonia, urinary tract infection, pseudomembranous colitis and sepsis. The patients were classified into two groups, depending on previous statin treatment.
Results: A total of 2045 patients were included (1165 were male, aged 69.05±12.5 years). Of these, 306 (15%) patients were receiving statins prior to stroke. These patients had more frequently arterial hypertension, DM, peripheral arterial disease and hypercholesterolaemia than the patients who were not treated with statins (P<0001). There was no statistically significant difference between overall in-hospital infection frequency between patients treated with statins and those with no statins treatment, (11.8% vs. 13%), nor in individual infection type: pneumonia (7.8% vs. 10.2%), urinary tract infection (4.2% vs. 2.8%), pseudomembranous colitis (0.3% vs. 0.7%) and sepsis (2.6% vs. 4.4%). In the atherothrombotic stroke subtype, statins were associated with a lower frequency of sepsis (unadjusted OR, 0.949; 95%CI; 0.928-0.971).
Conclusions: Previous treatment with statins does not appear to influence the frequency of in-hospital infections in patients with ischaemic stroke.

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PALABRAS CLAVE
Ictus;
Estatinas;
Complicaciones;
Infecciones

Tratamiento previo con estatinas y riesgo de complicaciones infecciosas tras un infarto cerebral agudo

Resumen
Introducción y objetivo: Diversos estudios clínicos y experimentales atribuyen un efecto inmunosupresor a las estatinas y la administración de simvastatina en la fase aguda del ictus se ha asociado a mayor frecuencia de infecciones durante el ingreso. Nuestro objetivo es comprobar si el consumo previo de estatinas influye en la aparición de complicaciones infecciosas intrahospitalarias tras un infarto cerebral (IC).
Pacientes y métodos: Estudio observacional incluyendo pacientes con IC ingresados en la Unidad de Ictus. Se analizan: datos demográficos, factores de riesgo vascular, gravedad al ingreso, subtipo etiológico de infarto cerebral y consumo previo de estatinas. Se ha estudiado la aparición de las siguientes complicaciones infecciosas durante la hospitalización: neumonía, infección urinaria, colitis pseudomembranosa y sepsis de cualquier origen agrupando a los enfermos en dos grupos: pacientes que previamente tomaban o no estatinas.
Resultados: Se incluyeron 2.045 pacientes (1.162 varones) con edad media de 69,05 años (DE 12,5). El 15%(306 pacientes) tomaba estatinas previamente al IC. Dichos pacientes presentaban con mayor frecuencia que los que no lo hacían ($p < 0,0001$) antecedente de HTA, DM, arteriopatía periférica e hipercolesterolemia. La frecuencia de infección intrahospitalaria fue similar en ambos grupos, tanto evaluada de manera global (11,8%vs 13%, $p = 0,643$) como al analizar cada una de las infecciones separadamente. En el subgrupo de IC aterotrombótico, las estatinas se asociaron con una menor frecuencia de sepsis (OR no ajustado 0,949, IC 95%[0,928–0,971]).
Conclusiones: El tratamiento previo con estatinas parece no influir en la frecuencia de complicaciones infecciosas intrahospitalarias tras un IC agudo.

Introduction

Cerebrovascular disease is the number two killer in Spain and the leading cause of death among women.[1] Infections during hospitalizations of the patients often their increase mortality, as well as prolonging their convalescence.[2,3] Furthermore, numerous studies[2,4,5] have proven that the presence of post-stroke infection is independently associated with a worse functional prognosis. This datum is even more important, since post-stroke infections and, in particular, pneumonia are the most common complications in patients who have suffered a cerebral infarction.[3] The possible physiopathological mechanisms involved in the association between developing infections and poorer patient prognosis are hypoxia, hypotension, and fever associated with infections, as well as the immobilization and delay in beginning rehabilitation that these complications can cause.

It has been reported that, in addition to their lipids-lowering effect, statins also have anti-inflammatory, anti-oxidant, endothelium-stabilizing, and immunomodulating effects.[6-9]. The data regarding the clinical repercussions of this last-named effect are contradictory: on the one hand, it has been indicated that patients who take statins have a lower risk of developing sepsis[10,11] than those who do not. On the other hand, a higher proportion of infections has been observed among people who take statins during the acute phase of the stroke,[12] as well as a higher rate of statin-related infections in the week leading up to the stroke.[13]

Our objective is to analyze whether prior treatment with statins impacts the frequency of infectious complications during the period of hospitalization following an acute CI.

Methods

Study design

An observational study of consecutive patients cared for at the Stroke Unit of the Neurology Department at a university teaching hospital was carried out. Patients with a final diagnosis of CI between January 2001 and December 2008 were selected, excluding transient ischemic attacks and brain hemorrhages.

The patients were cared for in the Emergency Room by the neurologist on duty and those who met the following criteria were later transferred to the Stroke Unit: patients with acute stoke of less than 48 hours of evolution, without any age limit. The presence of irreversible brain damage, dementia, prior dependence rated by means of the Modified Rankin Scale as being greater than 2, life-threatening concurrent illnesses, or acute head trauma were criteria for not admitting the patients to the Stroke Unit.

For the purposes of the study, the patients cared for were categorized into two groups depending on previous statin

administration (the Statins Group (SG) or the Non-Statin Group (NSG). The SG stayed on the previous treatment at the same dose during their stay in hospital. In those who were not on statin treatment, a statin was introduced after the first 48-72 h following the cerebral ischemic event, depending on the type of stroke and the result of the plasma lipid profile, according to the clinical guidelines currently in force. As of 2006, following the publication of the SPARCL study[14] atorvastatin treatment was initiated at a dose of 80 mg in cases of lacunar or aterothrombotic CI after 48-72 hours.

Variables analyzed

The presence of the following complications during the period of hospitalization was analyzed: pneumonia (presence of symptoms suggestive of pneumonia [dyspnea, fever, mucopurulent expectoration] and/or crackling on lung auscultation, with radiological evidence of condensation in the pulmonary parenchyma), urinary tract infections (UTI) (presence of symptoms [dysuria, pollakiuria, choluria], and alterations in urine sediment with leukocyturia and urine culture positive for nitrites), pseudomembranous colitis (clinical criteria and detection of toxins A or B in feces or identification of the germ on coproculture), and sepsis (presence of 2 or more of the following conditions: temperature over 38°C, heart rate greater than 90 bpm, respiratory rate greater than 20 bpm or pCO_2 greater than 32 mm Hg, leukocytosis greater than 12,000/mm^3 or less than 4,000/mm^3 or more than 10% band neutrophils and evidence of infection documented with positive cultures). Other systematic complications analyzed were: acute coronary syndrome, pulmonary thromboembolism, respiratory failure, and multiorgan failure

Patients' demographic data (age and gender); vascular risk factors (diabetes mellitus, high blood pressure, dyslipemia, atrial fibrillation, valve disease, peripheral arteriopathy, smoking, alcoholism, other toxic substances, prior stroke, and prior TIA) were recorded. The etiological stroke subtype were analyzed following the criteria of the Cerebrovascular Disease Study Group of the Spanish Society of Neurology.[15] aterothrombotic infarction, cardioembolic infarction, lacunar infarction, infarction of unusual cause, and infarction of undetermined etiology. The severity at the time of admission was studied by means of the Canadian Stroke Scale: for the purposes of the analysis an CSS ≤ 6 was considered to represent moderate-severe stroke and CSS > 6, a mild stroke.[16] Likewise, prior treatment with antiaggreggants, anticoagulants, angiotensin-converting enzyme inhibitors (ACEI), calcium antagonists, beta-blockers, angiotensin II receptor antagonists (ARA-II), and diuretics. Intrahospital mortality was also analyzed.

The following were included as neurological complications: evolving cerebral infarctions (worsening of the neurological functions that occurs between 1-72 hours after the onset of the stroke and that is not due to the presence of another cause), cerebral oedema (symptoms and signs suggestive of brain oedema such as diminished consciousness or clinical symptoms of intracranial hypertension that is confirmed on computerized tomography [CT]), hemorrhagic transformation (appearance of bloody content in the area of the CI), hydrocephalus (ventricular dilation generally due to obstruction of cerebrospinal fluid), recurring stroke (appearance of new symptoms or focal neurological signs that are compatible with a new stroke and that cannot be accounted for by the previous stroke), increased volume of the infarction (growth of CI evidenced on imaging tests), and the presence of convulsions within the context of the stroke in non-epileptic patients, including early seizures at the time the CI was beginning.

Statistical analysis

The qualitative data are expressed as absolute frequencies and percentages, whereas the quantitative data are expressed as the mean, median, and standard deviation (SD) (minimum, maximum).

In the comparison between the two groups of patients, the qualitative variables were analyzed using the chi-square test or Fisher's exact test and the quantitative variables were analyzed using Student's t test or by means of non-parametric techniques. Statistical significance was set at α=0.05.

In order to study which factors were associated with the appearance of infections during hospitalization, a step-wise, multivariate, logistics regression model was developed. This model included the variables that, having sufficient number of cases, presented a level of statistical significance of 0.20 or less in the univariate analysis. The data were prospectively included in a database (Excel 2003, Microsoft Inc.) and analyzed using the SPSS 15.0 statistical analysis software package (SPSS Inc.).

Results

Two thousand forty-five (2,045) patients (1,162 males and 883 females) were included with a mean age of 69.05 years (minimum=16 years, maximum=98 years) and a median of 72 years (SD 12.5). Fifteen percent (15%; 306 cases) were taking statins prior to the stroke. The patients who were on prior treatment with statins were older (70.8±9.1 vs. 68.7±13, p<0.005) (median SG: 73 years of age, median NSG 72 years of age) and presented a higher incidence of high blood pressure (79.1% vs. 68.7%, p<0.0001), diabetes mellitus (39.9% vs. 25%, p<0.0001), dyslipemia (87.6% vs. 19.9%, p<0.0001), ischemic heart disease (33.7% vs. 9.8%, p<0.0001), peripheral arteriopathy (8.8% vs. 5.1%, p=0.008), prior stroke (18% vs. 11.6%, p=0.002), and prior transient ischemic attack (9.5% vs. 5%, p=0.002) than those who were not taking statin treatment at the time of the CI (table 1). There were fewer smokers in the SG (13.7% vs. 24.7%, p<0.0001). With respect to the treatments they were taking prior to their stroke, a larger proportion of patients in the SG was seen to be taking: platelet antiaggreggants (52% vs. 23%, p<0.0001), ACEI (29.4% vs. 16.1%, p<0.0001), ARA-II (10.8% vs. 6.6%, p=0.008), beta-blockers (24.5% vs. 9.5%, p<0.0001), and calcium antagonists (15% vs. 9.5%, p=0.004).

However, there were not significant differences as regards gender, presence of atrial fibrillation, cardiac valve disease, alcohol use and use of other toxic substances, prior use of

Table 1 Demographic data, vascular risk factors, prior treatments, stroke characteristics and evolution according to prior treatment with statins

	Statins (n=306)	No statins (n=1739)	p
Demographic data			
Age (mean±SD (range); median)	70.8±9,1 [38.88]; 73	68.7±13 [16.98]; 72	0.005
Males	176 (57.5%)	986 (56.7%)	0.799
Vascular risk factors			
High blood pressure	242 (79.1%)	1.058 (60.8%)	<0.0001
Diabetes mellitus	122 (39.9%)	434 (25%)	<0.0001
Dyslipemia	268 (87.6%)	346 (19.9%)	<0.0001
Atrial fibrillation	53 (17.3%)	267 (15.4%)	0.383
Ischemic heart disease	103 (33.7%)	170 (9.8%)	<0.0001
Cardiac valve disease	23 (7.5%)	101 (5.8%)	0.248
Peripheral vascular disease	27 (8.8%)	88 (5.1%)	0.008
Prior stroke	55 (18%)	202 (11.6%)	0.002
Prior TIA	29 (9.5%)	87 (5%)	0.002
Tobacco	42 (13.7%)	430 (24.7%)	<0.0001
Alcohol	29 (9.5%)	237 (13.6%)	0.053
Other toxic substances	0 (0%)	10 (0.6%)	0.375
Prior treatment			
Anticoagulant	102 (5.9%)	24 (7.8%)	0.185
Platelet antiaggreggant	159 (52%)	400 (23%)	<0.0001
ACEI	90 (29.4%)	280 (16.1%)	<0.0001
ARA-II	33 (10.8%)	114 (6.6%)	0.008
Beta-blockers	75 (24.5%)	128 (7.4%)	<0.0008
Ca antagonists	46 (15%)	166 (9.5%)	0.004
Diuretics	57 (18.6%)	289 (16.6%)	0.408
Stroke etiological subtype			
Aterothormbotic	80 (26.1%)	395 (22.7%)	0.190
Cardioembolism	84 (27.5%)	443 (25.5%)	0.466
Lacunar	106 (34.6%)	587 (33.8%)	0.763
Undeterminado	42 (13.8%)	301 (17.3%)	0.127
Unusual	2 (0.7%)	39 (2.2%)	0.076
Severity of CI			
Canadian Stroke Scale ≤6	82 (26.8%)	499 (28.7%)	0.497
Evolution of the CI			
Neurological complications	39 (12.7%)	243 (14%)	0.653
Systemic complications	47 (15.4%)	286 (16.4%)	0.675
Infections	36 (11.8%)	226 (13%)	0.643
Mortality	22 (7.2%)	155 (8.9%)	0.378

TIA: transient ischemic attack; ARA-II: angiotensin-II receptor antagonist; Ca antagonists: calcium antagonists; SD: standard deviation; CI: cerebral infarction; ACEI: angiotensin converting enzyme inhibitors.

anticoagulants and diuretics, severity on admission (CSS≤6), etiological subtype, neurological complications, systemic complications, overall infection rates, or mortality (table 1).

In the multivariate logistics regression model, we found that being older (OR: 1.037, 95%confidence interval: [1.02-1.05]) and having a more severe stroke (CSS≤6)(OR: 7.38, 95%CI: [5.33-10.21]) were associated with a higher rate of intrahospital infection (table 2). By etiological subtypes, the CI of undetermined origin was associated with a higher rate of intrahospital infection (OR: 1.5, 95%CI: [1.08-2.10]). A significantly lower risk of infection was observed in lacunar infarctions (OR: 0.13, 95%CI [0.06-0.29])(table 2).

When analyzing each infectious complication separately, no significant differences were found with respect to frequency according to previous statin treatment in the cases of pneumonia (SG 7.8%, NSG 10.2%), UTI (SG 4.2%, NSG2.8%), sepsis (SG2.6%, NSG4.4%), or pseudomembranous colitis (SG 0.3%, NSG 0.7%) (table 3).

However, the exploratory analysis of infections by etiological subgroups of CI found that in patients with CI of

Table 2 Stepwise, multivariate, logistics regression model of factors associated with intrahospital infectious complications following stroke

	Raw OR			Adjusted OR		
	OR	95%CI	p	OR	95%CI	p
Statins	0.89	0.61-1.29	0.552	–	–	–
Age	1.05	1.03-1.06	<0.0001	1.037	1.02-1.05	<0.0001
Being female	1.32	1.02-1.71	0.034	–	–	–
High blood pressure	1.22	0.92-1.61	0.169	–	–	–
Ischemic heart disease	1.75	1.252-2.44	0.002	–	–	–
Diabetes mellitus	1.36	1.03-1.80	0.028	–	–	–
Atrial Fibrillation	2.23	1.64-3.03	<0.0001	–	–	–
Smoking	0.58	0.41-0.82	0.002	–	–	–
Previous TIA	0.62	0.32-1.21	0.198	–	–	–
Platelet antiaggreggants	1.31	1.04-1.82	0.022	–	–	–
Anticoagulants	1.39	0.85-2.26	0.181	–	–	–
Diuretics	1.25	0.90-1.74	0.186			
Ca antagonists	1.39	0.94-2.06	0.089	–	–	–
Aterothrombotic CI	1.35	1.01-1.81	0.039	–	–	–
Cardioembolic CI	1.85	1.40-2.43	<0.0001	–	-	–
Lacunar CI	0.05	0.02-0.10	<0.0001	0.13	0.06-0.29	<0.0001
CI of undetermined origin	2.48	1.84-3.33	<0.0001	1.50	1.08-2.10	0.015
Severe strokea	12.78	9.36-17.46	<0.0001	7.38	5.33-10.21	<0.0001

TIA: transient ischemic attack; Ca antagonists: calcium antagonists; CI: cerebral infarction.
[a]Score ≤ 6 on the Canadian Stroke Scale at the time of admission.

aterothrombotic origin, the SG did not present a single case of sepsis. No other significant difference in the development of infectious complications was encountered according to the etiological subtypes of CI (table 4).

Discussion

Many clinical studies have been conducted in recent years that have examined the presence of infection in relation to prior status use in any number of diseases: chronic kidney failure in hemodialysis,[11] diabetes,[17] acute coronary syndrome, ischemic stroke, and in patients hospitalized to undergo a revascularization procedure.[18] In all of these studies, there were fewer cases of sepsis[11,18] and pneumonia.[17] Our study is the first of these characteristics to be carried out exclusively in stroke patients. From the results it can be inferred that taking statins does not affect the appearance of infection following hospitalization due to stroke. However, a lower rate of sepsis has been observed in association with taking statins as an exploratory finding, albeit only in cases of CI of aterothrombotic origin. This discovery would be in line with studies that have suggested that statins exert a protective action against sepsis.[11,18-21] It is possible that this results has more to do with endothelial stabilization and reduction in serum cholesterol, as well as the statin-induced collateralization and angiogenesis,[22] but not with their immunomodulating action.

Table 3 Intrahospital infectious complications according to prior treatment with statins

	Prior treatment with statins	
	Yes	No
Pneumonia	24 (7.8%)	177 (10.2%)
Urinary tract infection	13 (4.2%)	49 (2.8%)
Sepsis	8 (2.6%)	77 (4.4%)
Pseudomembranous colitis.	1 (0.3%)	13 (0.7%)

Different experimental studies maintain that the beneficial effect derived from statins in cerebrovascular disease is not due only to their lipid-lowering effect, but also to their anti-inflammatory and immunosuppressant pleiotropic actions.[6-9] These effects are due to the fact that mevalonate synthesis is blocked and mevalonate is a precursor of several isoprenoids in charge of cell signaling in the inflammatory response. In this regard, statins decrease the release of cytokines and acute phase reactants, limit endothelial cell activation, and improve endothelial function.

Most of the studies have looked at the effect of prior statin treatment and there are few studies that focus on the administration [of statins] in the acute phase of the CI. In a recent study,[12] a higher infection rate was seen in patients in whom simvastin was used during the acute phase of the stroke. These data appear to be inconsistent with the beneficial effect that statins have shown on the course of CI, both when administered prior to the stroke[23-25] as

Table 4 Infectious complications according CI etiological subtype

	Statins (n=306)	No statins (n=1739)	p
Aterothrombotic CI			
Pneumonia	7 (7.2%)	46 (47.4%)	0.453
Urinary tract infection	6 (6.2%)	16 (16.5%)	0.181
Sepsis	0 (0%)	20 (20.6%)	0.033
Pseudomembranous colitis	0 (0%)	2 (2.1%)	1
Cardioembolic CI			
Pneumonia	9 (6.6%)	74 (54%)	0.167
Urinary tract infection	3 (2.2%)	14 (10.2%)	0.742
Sepsis	3 (2.2%)	28 (20.4%)	0.326
Pseudomembranous colitis	0 (0%)	6 (4.4%)	0.596
Lacunar CI			
Pneumonia	0 (0%)	1 (11.1%)	1
Urinary tract infection	0 (0%)	6 (66.7%)	0.598
Sepsis	0 (0%)	1 (11.1%)	1
Pseudomembranous colitis	1 (11.1%)	0 (0%)	0.153
Undetermined CI			
Pneumonia	8 (7.1%)	53 (46.9%)	0.819
Urinary tract infection	4 (3.5%)	12 (10.6%)	0.118
Sepsis	5 (4.4%)	26 (23%)	0.562
Pseudomembranous colitis	0 (0%)	5 (4.4%)	1
Unusual CI			
Pneumonia	0 (0%)	4 (50%)	1
Urinary tract infection	0 (0%)	2 (25%)	1
Sepsis	0 (0%)	2 (35%)	1
Pseudomembranous colitis	0 (0%)	0 (0%)	

well as afterwards.[12,14] The timing for statin treatment initiation following stroke must be established, although that lies beyond the scope of the objectives set forth for this study.

With respect to the rate of infectious complications, we recorded slightly fewer cases of pneumonia (SG: 7.8% and NSG: 10.2%) and of urinary tract infections (SG: 2.8% and NSG: 4.2%) in our study in comparison with other studies.[4] This may be accounted for by the fact that from the very beginning of patient recruitment, dysphagia rating protocols were used[26] and, for the most part, urinary catheters were used intermittently and as per protocol, restricting their use to those patients with acute urinary retention.

Our study has some limitations. It is an observational study based on consecutively admitted stroke patients. Only a small number of infectious complications during hospitalization were assessed. In addition, the type of statin, duration of treatment prior to the CI, adherence to statin treatment or dose were taken into account. On the other hand, we found fewer infectious complications in our sample in comparison with other studies,[4] which implies greater difficulty in finding statistically significant differences.

In conclusion, prior treatment with statins does not appear to influence the rate of intrahospital infectious complications following an acute stroke.

Conflict of interest

The authors state that there are not conflict of interest.

Acknowledgements

The authors would like to thank the Biostatistics Department of the Hospital Universitario La Paz.

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