Statin Medication Use and Nosocomial Infection Risk in the Acute Phase of Stroke

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Goal: Statins have immunomodulatory and peripheral anti-inflammatory properties that are independent of their lipid-lowering action. Whether these properties reduce the risk for developing poststroke infection is debated in clinical literature. We estimated the risk for developing nosocomial poststroke infection based on statin exposure in patients aged 18 or older hospitalized for ischemic stroke. *Materials and Methods:* A consecutive sample of acute care hospital electronic medical records was retrospectively analyzed. Patients were assigned to the exposed cohort either when statin use preceded infection or statin medication was used, but no infection developed. The unexposed cohort included patients not on statins or initiating statins after infection developed. The association of statin exposure with infection was examined with conditional logistic regression adjusted for poststroke infection risk factors. Cochran–Mantel–Haenszel analyses examined the association of statin exposure and infection status within strata of binary predictor variables that increased infection risk. *Findings:* Up to 1612 records were analyzed: 1151 in the exposed cohort and 461 in the unexposed cohort. Infection developed in 20% of the statin-exposed patients and in 41% of the statin-unexposed patients ($P < .001$). Exposure to statins reduced odds for developing nosocomial infection by 58% over no exposure (adjusted odds ratio = .418, $P < .001$). Statins lowered the infection risk for both sexes, patients with a nasogastric tube, and patients with dysphagia ($P < .05$). Statins did not change infection risk for patients with endotracheal intubation. *Conclusions:* In patients with ischemic stroke and without endotracheal intubation, statin medications were associated with reduced risk of nosocomial infections. **Key Words:** Infection—ischemic stroke—statin—risk factors.

Introduction

Infections are common in the acute phase of recovery from stroke.[1-3] Infection rates in the immediate poststroke period have been reported as high as 30% in patients with ischemic or hemorrhagic stroke, with the incidence of infection increasing to 45% in more complex patients receiving care in the intensive care unit.[3] Approximately 75% of poststroke infections occur within the first 72 hours of hospital admission,[4] with pneumonia and urinary tract infection (UTI) being the most commonly occurring nosocomial infections.[3] Infections are a leading contributor to poor functional outcome, increased hospital length of stay (LOS), and elevated morbidity and mortality in stroke.[3,5]

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Risk factors associated with nosocomial poststroke infection include advanced age,[5,6] female sex specific to UTI,[7,8] global stroke severity,[5] invasive stroke-related procedures (central venous catheterization,[5] urinary catheterization,[8] endotracheal intubation,[9,10] and nasogastric tube feeding[11,12]), and dysphagia.[9,13,14] Laboratory and clinical evidence also supports central nervous system injury-induced immunodepression as a significant contributing factor to systemic infections in the first days after cerebral ischemia.[5,15-17] Among the established features of stroke-induced immunodepression are increased levels of stress hormones and anti-inflammatory cytokines,[17] decreased numbers of circulating lymphocytes,[18] and a decreased capacity to release tumor necrosis factor-α in stimulated monocytes.[19] Although immunodepression after stroke is thought to limit detrimental autoimmune response in the brain, this response is believed to leave the patient vulnerable to systemic infection.[16]

Understanding the association between therapeutic agents commonly used in the acute phase of recovery from stroke and the development of poststroke infection is of benefit. For example, statin medications (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are among the most commonly used medications for secondary prevention of ischemic stroke.[20-23] Several observational studies in nonstroke patient populations have reported a protective effect for statins in that prior use results in reduced risk for developing an infection.[24-27] These results are interpreted to indicate that immunomodulation and peripheral anti-inflammatory properties are among the beneficial pleiotropic actions of statins that may inhibit a proinflammatory environment favoring infection. Prehospitalization use of statins has been associated with reduced risk of poststroke pneumonia in acute ischemic stroke patients who received thrombolysis.[28] Additional evidence from an animal model of stroke suggested that simvastatin treatment significantly inhibited bacterial growth in the lungs and blood of C57B16 mice.[29] By contrast, a meta-analysis of randomized controlled trials evaluating the prophylactic use of statins in patients with a variety of diagnoses concluded that statins did not reduce the risk of infection.[30] This meta-analysis included a single randomized trial of patients with ischemic stroke receiving statin medication prophylactically which revealed a nonsignificant effect in favor of statin use to prevent infection.[31] Conversely, a prospective cohort study in patients with ischemic stroke reported a nonsignificant increase in unadjusted infection risk with statin exposure either before-and-during hospitalization or by hospitalization day 3.[32] Similarly, a prospective cohort study of statin use initiated after ischemic stroke reported no significant increase over placebo in odds of infection at 90 days post stroke; however, other risk factors for infection were not controlled in determining risk.[33] Based on conflicting evidence in the literature, firm conclusions about the association between statin use and development of infection after ischemic stroke are elusive, a conclusion supported by a recent meta-analysis that included several of the aforementioned human trials.[34] This meta-analysis illustrated a small but nonsignificant effect size favoring reduced infection risk with statin use. This conclusion is understandable given the variability in timing of statin exposure relative to evidence of infection in the studies included in the review.

In the present study, we estimated the risk for developing poststroke infection based on statin use during the acute hospital stay for ischemic stroke. In contrast to previous studies, we were careful to determine whether initiation of statin medications preceded infection or not. Our analyses considered both the univariate association of statins and infection risk, and the association of statins with incidence of infection when other poststroke infection risk factors, such as advanced age, patient sex, stroke severity, intubation, catheterization, and dysphagia, were controlled. It was hypothesized that statin exposure would be associated with a decreased risk for developing nosocomial infection when other factors known to elevate infection risk were controlled.

Materials and Methods

Study Subjects

Patient-level data were obtained from electronic medical records of a large urban acute care hospital with Primary Stroke Center Certification. Institutional review board approval including an HIPAA (Health Insurance Portability and Accountability Act) Waiver was obtained to extract the medical record data for patients admitted with a primary or secondary diagnosis of stroke between January 1, 2009, and March 31, 2013. Data for the present study were part of a larger retrospective dataset examining infection risk in all types of stroke.

Eligible cases met the following inclusion criteria: consecutive admissions 18 years of age or more with a diagnosis of spontaneous ischemic stroke. Ischemic stroke was identified by ICD-9 (International Classification of Diseases, Ninth Revision) codes 433.xx, 434.xx, and 436.xx as the first or second diagnosis. To assure sufficient time for any medications to be administered or infections to be detected during the stay, patients with stays of 24 hours or less were excluded; this included patients who expired within 24 hours of admission (n = 22), were discharged home within 24 hours of admission (n = 122), were transferred to hospice care within 24 hours of admission (n = 2), were discharged to another acute facility or subacute facility within 24 hours of admission (n = 9), or left against medical advice within 24 hours of admission (n = 3). To ascertain only incident nosocomial infections, cases were excluded if there was a record of antibiotic use in the home medication list obtained at admission (n = 192) or if code V58.62 was present (n = 0), indicating current use of antibiotics. Cases were also excluded if any of the