Statin use and morbidity outcomes in septic shock patients: a retrospective cohort study

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Abstract

***Objective*: The purpose of this study is to determine the association between statin use and septic shock morbidity.**

***Design*: A retrospective, single center chart review.**

Location: Intensive care unit of an urban tertiary care hospital.

***Patients and participants*: Convenience sample of 150 patients diagnosed with septic shock in the hospital intensive care unit (ICU).**

***Intervention*: The cohort of subjects on statin therapy prior to ICU admission was compared to the cohort that was not on prior statin therapy. The primary morbidity outcome between the two groups was duration of vasopressor support.**

***Results*: Mean duration of vasopressor support was 233±SE 94 hours in the statin group and 126±SE 20 hours in the non-statin group (p=0.269). ICU length of stay was 12 days in the statin group and 11 days in the non-statin group (p=0.600). Hospital length of stay was 44 days in the statin group and 39 days in the non-statin group (p=0.851). ICU mortality and hospital mortality was not statistically different between the two groups.**

***Conclusion*: Prior statin use was not associated with decreased duration of vasopressor support or morbidity in septic shock patients. Conversely, there were trends towards worse outcomes in patients on statins prior to admission.**

Key words: Sepsis, statins, HMG CoA Reductase inhibitors.

Introduction

Sepsis is a significant burden on the health care system and is among the top ten leading causes of death in the United States. (1) The incidence of sepsis is rising substantially due to an aging population, increasing resistance among microorganisms, higher prevalence of immunocompromised patients, increasing number of patient comorbidities and more high risk surgeries being performed. One in four cases of sepsis progresses to severe sepsis or septic shock, conditions characterized by organ dysfunction and hypotension. (2) Septic shock carries a high mortality rate, adversely affects quality of life after hospital discharge and is a significant financial burden to the health care system.

The cornerstones of treatment in sepsis are fluid resuscitation, broad spectrum antibiotics, and other adjunctive therapies. (2) It is postulated that HMG CoA Reductase inhibitors, or "statins", have additional benefit and mechanisms beyond their cholesterol-lowering properties, a characteristic

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known as pleiotropy. (3) The pleiotropic effects of statins include modulation of tissue factor expression, reduction of coagulation activity and anti-inflammatory activity. Many retrospective and cohort trials have shown that statins are associated with reduced morbidity and mortality in various infections including bacteremia and pneumonia. (3) The postulated mechanism of the benefit of statin use in sepsis include decreasing sepsis related inflammation, oxidative stress, endothelial dysfunction, and coagulation. (4) Thus, statins may be novel therapeutic agents in the prevention and treatment of sepsis because they target a number of pathways that are deregulated during the sepsis process.

Several retrospective studies have shown a mortality and morbidity reduction in septic or infected patients on statin therapy. (3) There has been only one study that has specifically considered statins in patients diagnosed with sepsis, whereas the majority of studies studied other infectious states such as pneumonia or bacteremia. (5) Although there is evidence that demonstrate the benefits of statins, there are some studies that show no effect of statins on morbidity or mortality and even one study that shows a negative effect of statins on mortality in patients with infections. (3) There is no study to date that studies the effect of statins in septic shock patients. Septic shock, characterized by signs of organ dysfunction despite fluid resuscitation and requiring vasopressor support, carries the highest rate of morbidity and mortality of the sepsis continuum. The purpose of our study is to determine whether statin use is associated with positive outcomes in septic shock and to investigate the benefits of statins in this high risk population.

Methods

A retrospective, convenience sample of 150 patients was selected from the medical records of all patients admitted to the intensive care unit (ICU) of St. Paul's Hospital with the diagnosis of septic shock. All patients who were diagnosed with septic shock and received vasopressor support for at least 24 hours while in the ICU were included. Patients with unknown medical history were excluded. A retrospective chart review was to determine whether statins were prescribed prior to ICU admission along with other baseline and demographic data. The medical records were also reviewed to determine duration of vasopressor support. The primary endpoint was duration of vasopressor support between statin and non-statin groups. The secondary endpoints were ICU length of stay, hospital length of stay, ICU mortality, and hospital mortality. Research ethics approval was granted by the Providence Health Care Research Ethics Board of the University of British Columbia.

The data were collected on a standardized data collection form and transferred to a Microsoft Excel spreadsheet. Categorical variables were analyzed using the Chi-square test and continuous variables were analyzed using the independent samples t test. Linear regression was performed to account for baseline differences between the 2 groups. Statistical analysis was performed using SPSS Version 9 for Windows. No external funding was secured for this study.

Results

A convenience sample of 150 ICU patients who were diagnosed with septic shock and on vasopressor support between July 2006 and March 2008 was retrospectively identified. Of 150 septic shock patients, 40 patients were taking statins prior to ICU admission and 110 patients were not. Patient characteristics and results are listed in **Table 1**. In the statin group, 30% of patients admitted to the ICU continued with their statin treatment during the duration of their ICU stay. Mean age was 67-year-old in the statin group and 53-year-old in the non-statin group. 73% of patients in the statin group were male versus 59% in the non-statin group.

The primary endpoint, duration of vasopressor support, was 233±SE 94 hours in the statin group and 126±SE 20 hours in the non-statin group (p=0.269) (**Table 1**). There was no difference in the length of ICU and hospital stay between the statin group and the non statin group. ICU mortality and hospital mortality was similar between the two groups as well. Linear regression did not show a significant difference in the primary endpoint between the statin and non-statin cohort after adjusting for disparate, baseline patient characteristics.

Discussion

Contrary to previous studies done with statin use and sepsis outcomes, this study did not show a morbidity benefit with

prior statin use in a high risk, septic shock population. It would be intuitive that if statin users had better outcomes in previous sepsis studies, then a more critically ill population of septic shock patients would derive similar if not greater benefit from statin use. However, the results of this study illustrate the exact opposite, that statin use had no influence and may even be deleterious for patients in septic shock.

Possible confounders in this study are the retrospective nature of this study and the imbalance of baseline characteristics between the two groups. Of note, the statin group were predictably older and had a higher incidence of comorbidities such as diabetes mellitus, chronic kidney disease, and coronary artery disease. Having more comorbidities in the statin group may have biased this group to worse outcomes compared to the non statin group. This hypothesis is supported by our results, as the statin group, with more cardiac comorbidities had a trend towards worse outcomes compared to the non statin group. We accounted for the disparate baseline patient characteristics and its influence on the results by performing a linear regression but a significant difference in the primary outcome between the 2 groups was not found. It is possible that statin use served as a marker for more severely ill patients, rather than contributing towards the outcome of interest in this study.

Another explanation to the neutral results seen with statin use in our study is that our cohort of septic shock patients had a high morbidity and mortality rate. Given the severity of their illness, it is possible that any intervention at this stage of the sepsis continuum would provide minimal benefits. Thus, the benefits of statins in sepsis may be most beneficial during the early phases of sepsis related inflammatory and dysregulation processes. Septic shock represents a stage where there is significant inflammatory, procoagulant and deregulatory processes occurring and that intervention at this stage may be less beneficial.

All studies done to date regarding statin use and sepsis related outcomes have been retrospective in nature, thus only an association can be demonstrated. A prospective, randomized trial is needed to establish a causal relationship between statin use and sepsis outcomes. Future retrospective studies in this area may consider propensity matching of patients to achieve better balanced baseline patient characteristics in the study arms.

Conclusion

Our study showed no significant difference in duration of vasopressor support in septic shock patients between statin users and non statin users. There were trends towards worse outcomes in septic shock patients on statins compared to non statin users, which contradicts previous data.

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Table 1. Patient characteristics on admission to the ICU and outcomes

	Statin group (n=40)	Non-statin group (n=110)	p
Mean age (years)	67	53	<0.001
Male sex (%)	73	59	<0.001
Number of days ventilated	11	9	0.615
SOFA score	11	11	0.569
Lowest pH within 24h of admission	7.2	7.0	0.159
Highest WBC count within 24h of admission (giga/l)	19	20	0.802
Highest serum creatinine within 24h of admission (μmol/l)	207	170	0.136
Lowest systolic blood pressure within 24 hours of admission (mmhg)	79	77	0.355
Lowest diastolic blood pressure within 24 hours of admission (mmhg)	40	40	0.685
Lowest PaO2 within 24 hours of admission (mmHg)	82	71	0.015
Diabetes mellitus (%)	42	13	
Chronic dialysis (%)	8	5	
Chronic kidney disease (%)	40	16	
Peripheral vascular disease (%)	23	4	
Immunocompromised (%)	15	27	
Coronary artery disease (%)	80	9	
Stroke (%)	5	2	
Intravenous drug use (%)	13	33	
Mean duration of vasopressor support (hours)±SE	233±94	126±20	0.269
ICU length of stay (days)	12	11	0.600
Hospital length of stay (days)	44	39	0.851
ICU mortality (%)	33	35	0.817
Hospital mortality (%)	48	43	0.605

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