Implications of Statin Use on Vasopressor Therapy in the Setting of Septic Shock

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Abstract

Background: Pleiotropic anti-inflammatory and immunomodulatory effects of statins have been associated with improved outcomes in the critically ill population. **Objective:** To evaluate the implications of prior statin use on the duration of vasopressor therapy in the setting of septic shock. **Methods:** This was a retrospective, multicenter study of adult patients who were diagnosed with septic shock. Patients were included if they were treated with any vasopressor for greater than 6 hours from the time of admission. The primary outcome was to compare the duration of vasopressor therapy in patients with septic shock with and without previous statin exposure. **Results:** A total of 88 statin-exposed cases and 205 unexposed controls were included in the analysis. Despite 92% of statin-exposed patients being reinitiated on therapy within 24 hours, the duration of vasopressors did not differ between groups (44 hours, statin group vs 53 hours, control group, $P = .51$). There were also no mortality differences between the statin group and the controls (40% vs 47%, $P = .27$). **Conclusions:** Long-term statin exposure does not impact the duration of vasopressor therapy in septic shock. The lack of differences in clinical outcomes supports the concept that sepsis involves pro- and anti-inflammatory pathways as well as other nonimmunologic pathways. Results lend further credence to the recent conceptualization of sepsis, with complications leading to organ dysfunction caused not primarily due to inflammatory responses but by a dysregulated response to infection.

Keywords

statins, septic shock, vasopressors, sepsis

Introduction

Sepsis is a complex disease state considered to be associated with an intense inflammatory response. The extent of this inflammation is a reflection of widespread activation of host defense mechanisms in response to invading microorganisms. The course of sepsis releases mediators of multiple inflammatory cascades marked by activation of cytokines, leukocytes, and complement systems in an effort to combat microbial toxins.¹ This inflammatory pathway is termed systemic inflammatory response syndrome (SIRS). Historically, sepsis has been defined as SIRS plus signs and symptoms of infection. Severe sepsis is when an infection results in acute organ dysfunction. This diagnosis is made in approximately 750 000 patients annually with an associated mortality rate of 40%.^{2–4} The progression of severe sepsis to septic shock results in a 40% to 70% mortality rate. These patients have hypotension refractory to fluid resuscitation and require vasopressors to maintain organ perfusion.^{1–3}

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in cholesterol biosynthesis, and are used first line for hyperlipidemia. However, statins have other biochemical effects on human

physiology in addition to lowering total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglycerides.^{4,5} Anti-inflammatory and immunomodulatory roles have been proposed as mechanisms of mortality reduction including inhibition of the effects of tumor necrosis factor α (TNF- α), reactive oxygen species (ROS), and nuclear factor κ B (NF- κ B).⁴ Other pleiotropic effects of statins that have been identified are improved endothelial function, plaque stabilization, and reduced thrombogenicity.^{6,7,8} Due to the vasodilatory mechanism behind septic shock, statin effects on inflammatory modulators may provide a protective effect on endothelial damage, thereby supporting the prevention of sepsis progression.⁹

A number of studies have evaluated the effects of statin therapy in sepsis.^{10–15} A systematic review evaluating statins

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in sepsis reported a reduction in mortality associated with statin users.¹³ One prospective cohort analysis found that statin therapy improved 28-day survival in patients with severe sepsis-associated acute respiratory distress syndrome (ARDS) with significantly more vasopressor-free days compared with those without statin therapy.¹⁴ In contrast, Zechmeister et al were not able to identify a statistically significant decrease in the duration or dose of vasopressor use in patients with septic shock. However, a nonsignificant trend toward decreased mortality was identified.¹⁵ Due to this variability in the literature, the purpose of this study was to evaluate the implications of statin use on the duration of vasopressor therapy in the setting of septic shock in patients exposed to statin therapy prior to admission.

Methods

Study Design and Patient Population

Patients for this multicenter, retrospective cohort analysis were identified through a medical record query of International Classification of Diseases, Ninth Revision (ICD-9) codes for septic shock (785.52/ICD-9). The definition of septic shock used to enroll patients was based on the 2012 “Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock.”¹⁶ The University of Louisville Hospital is a level I trauma center and academic medical center, while Jewish Hospital is a large tertiary referral center. This study was approved by the institutional review board at both facilities. Patients at both institutions were included if they were age 18 years or greater, presented with septic shock, and were treated with a vasopressor for at least 6 hours. Those who were exposed to statin therapy prior to admission were compared with those with no prior exposure. Patients were excluded if they had a contraindication to statins, were pregnant, or were incarcerated. Each facility utilized a protocol for sepsis management which specified appropriate antibiotics for administration.

Baseline characteristics included age at admission, weight, body mass index (BMI), gender, race, smoking history, and presenting source of infection. Certain preexisting conditions deemed to contribute to inflammation were determined a priori and were also collected: coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), stroke, diabetes mellitus (DM), transplant, human immunodeficiency virus (HIV), and cancer.

Outcomes

The primary outcome of this study was to compare the duration of vasopressor therapy in patients with and without statin exposure in the setting of septic shock. Secondary outcomes included intensive care unit (ICU) and hospital lengths of stay, in-hospital mortality, admission sequential organ

Figure 1. Flowchart of patient population analyzed.

failure assessment (SOFA) scores, number of vasopressors required, time to first dose of antimicrobials, days of antimicrobial therapy, and steroid use. The number of vasopressors required and its correlation to hospital mortality were also examined.

Statistical Analysis

Continuous data were tested for normality. Due to lack of normality, a nonparametric Wilcoxon 2-sample test was used. Hospitalization data and mortality were described as medians and interquartile ranges (IQRs) or counts and percentages, based on the class of data (continuous or categorical, respectively). Differences between groups for categorical measures were tested using chi-square tests or Fisher's exact test. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina) with a significance level of $P \leq .05$.

Results

A total of 88 statin therapy cases and 205 unexposed controls were identified from January 2013 through June 2015 and included for analysis (Figure 1). Testing determined that stratified analyses were not required for the 2 institutions included. Statin-exposed patients were older, less likely to be current smokers, and more likely to have the following pre-existing conditions: CAD, stroke, and DM. There were no differences noted in end-organ dysfunction (Table 1).

Vasopressor Therapy

The duration of vasopressor use did not differ in patients with septic shock based on prior statin exposure (Table 2). There were more outliers among patients without exposure to statins (0-32 vs 0-14 days). The number of vasopressors

Table 1. Comparison of Baseline Characteristics, Preexisting Conditions, and End-Organ Dysfunction.

	Cases (n = 88)	Controls (n = 205)	P value
Patient characteristics			
Median (range) age, y	61.5 (18.0)	55.0 (17.0)	<.001
Median (range) weight, kg	84.1 (28.1)	81.4 (31.0)	.17
Median (range) BMI	28.9 (11.0)	27.1 (10.0)	.19
Male, n (%)	52 (59.1)	115 (56.1)	.70
Race, n (%)			.56
White	59 (67.0)	144 (70.2)	
Black	22 (25.0)	40 (19.5)	
Other	7 (8.0)	21 (10.2)	
Current Smoker, n (%)	24 (27.3)	81 (39.5)	.047
Source of infection, n (%)			
Pneumonia	42 (47.7)	91 (44.4)	
Urinary tract infection	14 (15.9)	34 (16.6)	
Other	32 (36.4)	80 (39)	
Preexisting conditions, n (%)			
CAD	26 (29.5)	13 (6.3)	<.001
CHF	18 (20.5)	29 (14.1)	.22
COPD	25 (28.4)	39 (19.0)	.09
Stroke	12 (13.6)	10 (4.9)	.01
DM	42 (47.7)	42 (20.5)	<.001
Transplant	0 (0.0)	2 (1.0)	>.99
HIV	1 (1.1)	5 (2.4)	.67
Cancer	17 (19.3)	42 (20.5)	.87
Median (range) end-organ dysfunction			
SOFA score	10 (5)	10 (6)	.40
CPK units/L	610 (20)	238 (918)	.42
AST units/L	110 (14)	68 (125)	.32
ALT units/L	48 (6)	39 (57)	.83

Note. P values <.05 were considered statistically significant. BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HIV = human immunodeficiency virus; SOFA = sequential organ failure assessment; CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 2. Duration of Vasopressor Use and Number of Vasopressors Required.

Vasopressor use	Cases (n = 88)	Controls (n = 205)	P value
Median (range) duration, h	44 (65.0)	53.0 (63.0)	.51
Number required	n (%)	n (%)	.08
1	58 (65.9)	108 (52.7)	
2	16 (18.2)	61 (29.8)	
3	14 (15.9)	36 (17.6)	

Note. P values <.05 were considered statistically significant.

did not differ based upon exposure to statins ($P = .08$); however, there was a significant association between the number of vasopressors required and an outcome of death ($P < .001$). The majority of patients were ordered norepinephrine as a first line vasopressor (87%).

Hospital Length of Stay and Mortality

Neither ICU nor hospital length of stay differed by prior statin exposure ($P = .07$ and $P = .81$, respectively), although

there was a nonsignificant trend toward decreased length of ICU stay in the statin group (Table 3). The median ICU length of stay was 5 days (IQR = 6 days) for the statin group and 6 days (IQR = 10 days) for the control group. The median hospital length of stay was 8 days (IQR = 12 days) and 10 days (IQR = 16 days) for the statin group compared with the control group. There were no differences in mortality (40% in the statin group vs 47% in the control group, $P = .27$) or days to death (approximately 5 days each, $P = .45$) by exposure to statins.

Table 3. Comparison of In-Hospital Mortality in Relation to Number of Vasopressors Used.

Number of vasopressors required	In-hospital mortality (n = 131)	Alive at discharge (n = 162)	P value
Number required	n (%)	n (%)	<.001
1	47 (35.9)	119 (73.5)	
2	46 (35.1)	31 (19.1)	
3	38 (29.0)	12 (7.4)	

Note. P values <.05 were considered statistically significant.

Table 4. Time to First Dose and Duration of Antimicrobial Use and Characterization of Steroid Use.

	Cases (n = 88)	Controls (n = 205)	P value
Time to first dose of antimicrobial, mean (standard error)			
Hours	6.1 (5.7)	10.8 (3.7)	.48
Median (range) antimicrobial usage			
Duration, days	5 (6.0)	5 (6.0)	.85
Steroid use, n (%)			
Yes	30 (34.5)	66 (32.5)	.78

Note. P values <.05 were considered statistically significant.

Other Measures

Duration of antimicrobial therapy was a median of 5 days in both groups ($P = .85$). There was no difference in time to first dose of antimicrobial or steroid use between the 2 groups ($P = .48$ and $P = .78$, respectively; Table 4). Patient-specific statin exposure was as follows: atorvastatin (n = 38), lovastatin (n = 4), pravastatin (n = 12), rosuvastatin (n = 12), and simvastatin (n = 23). Ninety-two percent of statin-exposed patients were reinitiated on statin therapy within 24 hours of admission. Fourteen control patients (6.8%) were started on statin therapy during their hospital stay.

Discussion

The results of this study suggest that previous statin exposure has no impact on the duration of vasopressor therapy in patients who present with septic shock. Previous studies have been inconsistent regarding the effects of statin therapy on vasopressor use. Mansur et al demonstrated a significant increase in vasopressor-free days in patients with previous statin exposure categorized as having severe sepsis-associated ARDS.¹⁴ In contrast, Zechmeister et al were unable to show any decrease in the duration of vasopressor therapy in patients with statin continuation on admission.¹⁵ Data provided by the current study suggest that statins do not impact the duration of vasopressor therapy in patients presenting with septic shock.

Also significant is that the current study compared prior statin exposure with no prior statin exposure rather than simply focusing on the continuation of statin therapy. In contrast, both Mansur et al and Zechmeister et al assessed statin effects by comparing continuation versus noncontinuation of statin therapy on admission.^{14,15} That is, these studies only

compared the short-term effects of statins by assessing statin administration on admission. We sought to understand the long-term effects of statin exposure. Fortunately, for the purposes of our research focus, statins were continued on admission in all but 7 of the patients in the case group. As a result, we were able to compare prior statin exposure and continuation on admission with no statin exposure, with no significant differences found. Both the long-term and short-term effects of statins appear to suggest no medical benefit from augmenting the duration of vasopressor requirement in patients presenting with septic shock.

Not surprisingly, patients in the statin group were more likely to have CAD, prior stroke, and DM. Statins thus do not seem to provide a protective effect in septic shock for those patients who have an indication for use. Heterogeneity between the 2 groups could possibly have contributed to a lack of significant outcomes. Future studies with more homogenous groups in regard to age, gender, smoking status, and preexisting conditions could potentially further refine our knowledge regarding the impact of statins on the duration of vasopressor therapy.

Recently the *Journal of the American Medical Association* published Sepsis-3, a new definition of sepsis and septic shock. This new definition asserts that sepsis is defined by life-threatening organ dysfunction caused by a dysregulated host response to infection. Previous definitions of sepsis have focused almost exclusively on inflammation. This is a concept that has not been shown to be sufficiently sensitive or specific.¹⁷ More recent data now recognize that sepsis involves activation of both pro- and anti-inflammatory responses as well as other nonimmunologic pathways such as cardiovascular dysfunction and alterations in coagulation.^{17,18} Statins have been shown to have pleiotropic anti-inflammatory effects. The positive outcomes these agents have allegedly demonstrated in sepsis and septic shock have been attributed to these properties. The findings of no difference in this study in any outcome measure including duration of vasopressor therapy, mortality, length of ICU or hospital stay, and end-organ dysfunction support the theory behind the new sepsis definition, which places less emphasis on the inflammatory cascade in response to infection.

This study was limited by its retrospective design and use of ICD-9 codes to identify the study population. Another limitation was the time to first dose of antimicrobials in each

group despite sepsis protocols at both institutions calling for their immediate administration. While not directly associated with the primary outcome of this study, evidence has linked increased time to antimicrobial therapy with higher rates of mortality.¹⁹ In addition, case patients were identified utilizing home medication reconciliation documentation. Some patients did not have documented home medications, and inconsistencies were sometimes noted between the physician-provided home medication list and the list entered into the electronic medical record. This could potentially skew the results if patients were misclassified based on statin exposure. Due to the retrospective nature of this study, adherence to statin therapy could not be accurately assessed. This could confound the results as duration and consistency of previous statin exposure could have varied among patients in the case group.

Conclusion

Despite previous reports, the results of this study indicate that long-term statin exposure does not impact the duration of vasopressor therapy in patients presenting with septic shock. In addition, statins do not affect mortality, length of ICU or hospital stay, initial SOFA scores, duration of antibiotic use, or steroid use in the setting of septic shock. The lack of significant differences between groups in this study supports the concept that sepsis involves both pro- and anti-inflammatory pathways as well as other nonimmunologic pathways. Our results lend further credence to the most recent conceptualization of sepsis, with complications of this disease state leading to life-threatening organ dysfunction caused not primarily due to inflammatory responses but by a dysregulated host response to infection.

Declaration of Conflicting Interests

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