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The Association of Prior Statin Use in Septic Shock Treated With Early Goal Directed Therapy

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sepsis; septic shock; early goal directed therapy; statins

INTRODUCTION

Sepsis is a common, lethal, and expensive health care problem. In the United States approximately 215,000 deaths are attributed to sepsis annually (1). More people die annually of sepsis than of lung and breast cancer combined. This results in over 380,000 ICU admissions yearly, and an enormous economic burden of over 17 billion dollars (1). The incidence of sepsis is estimated to be increasing steadily at 1.5% annually, with over 1.1 million cases per year by 2020 (1). Despite this, all drug trials, save one, to date have failed to show a reduction in mortality (2). Our current therapeutic armamentarium is limited and

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inadequate and consists of early recognition and goal oriented resuscitation, early administration of appropriate antibiotics, source control, along with the selective use of stress dose corticosteroids, and recombinant human activated protein C (rhAPC) (3-7). A novel therapeutic intervention or drug therapy in sepsis could save thousands of lives and millions of dollars. Given the high mortality of severe sepsis and septic shock, coupled with the lack of effective drug therapy, the testing of new agents remains of paramount importance.

Early goal directed therapy (EGDT) describes an algorithmic and goal oriented approach to the resuscitation of severe sepsis and septic shock, with the aim of correcting tissue hypoxia and improving cellular bioenergetics. The results of the initial trial showed a substantial improvement in mortality, which has been reproduced in multiple centers (8-18). Despite this, the morbidity and mortality of severe sepsis and septic shock remains unacceptable. Statins, or 3-hydroxy-methyl-glutaryl coenzyme A reductase inhibitors, were introduced in the 1980s. They are primarily used to favorably alter cholesterol and lipid metabolism and reduce the risk of death from cardiovascular events. However, statins also exert a wide ranging effect on inflammatory and immune cascades (20-32). Published data on anti-inflammatory and immune-modulatory effects of statins suggest they may reduce mortality risks associated with unchecked immune response to selected infection (20-32). However, there are no data to suggest that statin therapy may improve outcome above and beyond that associated with EGDT.

This study was designed to investigate whether prior statin use was associated with improved clinically relevant outcomes, including mortality, mechanical ventilation (MV) days, ICU length of stay (ILOS), and hospital length of stay (HLOS) in patients with severe sepsis or septic shock treated with EGDT. Although prior statin use has been associated with improved outcomes in patients with severe sepsis and septic shock, it is not known if prior statin use is associated with an incremental benefit in the subset of septic patients who receive EGDT. We hypothesized that patients on statin therapy prior to presentation may have improved outcomes above and beyond that provided by an early and goal oriented approach to resuscitation.

METHODS

This was a single center retrospective cohort study conducted in a large, urban, academic teaching hospital, with an annual Emergency Department (ED) census of approximately 56,000 patients and a 30 bed medical-surgical intensive care unit (ICU). The study protocol was approved by the local institutional review board with waiver of informed consent.

Data were collected on 91 consecutive patients who presented between February 2005 and May 2008 in severe sepsis or septic shock and received EGDT. The trigger for EGDT at our institution is: systolic blood pressure (BP) less than 90mmHg or mean arterial pressure (MAP) less than 65mmHg despite a crystalloid challenge of 20 to 30cc/kg, or initial serum lactate concentration greater than 4 mmol/L. All patients age 18 years and older with the above criteria were considered eligible for the study. For the purpose of this study, patients were divided into two groups: statin group and non statin group. Data were collected on patients identified via the Surviving Sepsis Campaign Chart Review database and linked to the Project IMPACT database electronically. Primary data collection was done by two abstractors (MG and CS). CS has had extensive experience and training in database management and chart review. MG was trained in the data retrieval process prior to study initiation. Variables were defined prior to data extraction and placed in standardized format during the data collection process. Regular meetings and monitor of data collection were performed and the chart reviewers were blinded to study hypothesis. The following data was

collected with respect to the statin group and non statin group: age, gender, race, source of infection, clinical and laboratory variables required for the determination of the Acute Physiology and Chronic Health Evaluation (APACHE II) score (on a scale from 0 to 71, with higher scores indicating more severe organ dysfunction) and Sequential Organ Failure Assessment (SOFA) score (on a scale of 0 to 24, with higher scores indicating more severe organ dysfunction), total intravenous fluids (IVF) administered, initial lactate level, estimate time to central venous pressure goal (CVP8ET), and achievement of central venous mixed oxygen saturation (ScvO₂) higher than 70%.

The primary outcome measure was mortality and secondary outcomes included MV days, ILOS, and HLOS. The statin group and non statin group were compared by the Pearson chi square and Fisher's exact test to test for statistical significance. Statistical significance was defined as a $p < 0.05$.

RESULTS

There were 91 patients analyzed in this retrospective cohort study. Patients (18 of 91) were taking a statin prior to presentation. Eighty-seven patients presented from the Emergency Department, with the remaining four presenting from the hospital ward prior to ICU admission. There were no significant differences in baseline characteristics between the statin and no statin groups (Table 1). The most common sources of infection were lung, urinary tract, and abdomen, with no statistical significance between the two groups. Multiple infectious sources were present in only 12 patients. Mean lactate at presentation was 5.61 mmol/L in the statin group and 5.76 mmol/L in the non statin group ($p = 0.817$). Baseline illness severity was similar between the two groups, as the statin group had an initial mean APACHE II score of 21.46 compared with 20.29 in the non statin group ($p = 0.301$) and an initial mean SOFA score of 6.55 in the first 6 hours compared with an initial SOFA score of 7.12 in the non statin group ($p = 0.249$). With respect to the resuscitation and treatment variables, there were no significant differences between the mean values of two groups either (Table 2).

Fewer patients in the statin group (44.4%) required mechanical ventilation as compared to the non statin group (54.8%). Patients requiring mechanical ventilation had fewer MV days in the statin group (7.29 days vs. 8.49 days, $p = 0.026$). There was a trend toward improved ILOS in the statin group as compared to the non statin group (4.89 days vs. 7.15 days, $p = 0.077$), as well as HLOS (14.44 days vs. 17.94 days, $p = 0.065$). Mortality in the statin group was 22.2% vs. 39.7% in the non statin group ($p = 0.273$) (Table 3).

DISCUSSION

Sepsis induced tissue hypoperfusion and the progressive circulatory shock that can accompany have excessively high mortality rates. Pathophysiologic changes are very complex and include inflammation, immune paralysis, apoptotic cell death, mitochondrial dysfunction, and microcirculatory derangements. The changes on a macrocirculatory level are well chronicled and include components of hypovolemic, distributive, cardiogenic, and obstructive shock, with increased venous capacitance, low arteriolar tone, increased pulmonary vascular resistance, and myocardial dysfunction (19). Despite the recent advances in understanding the pathophysiology of sepsis, therapeutic interventions to improve outcome have been relatively sparse. In the 1980s and 1990s, the increased understanding of the underlying mechanisms of sepsis led to the testing of various drugs targeting the septic cascade. This led to around 70-80 clinical trials, resulting in multiple phase III studies with the most promising agents. Unfortunately, trials of novel drug strategies, excluding one, have fallen short (2).

It is difficult to ascertain the etiology of failed drug therapy in sepsis. Given the fact that sepsis induces such broad effects on cellular physiology, it is not surprising that agents targeting a narrow pathophysiologic window have failed. Statins have been described in the literature to exert influence over multiple pathways commonly altered in sepsis. The effects of inflammation and immune modulation have been well chronicled (20-32). Human studies also point to a possible therapeutic role for statins in sepsis. Taken together, these published reports show an association between statin use and improved outcome in bacteremia (33), sepsis (34-39), infected Emergency Department patients (40-43) pneumonia (44,45,47-49), lung injury (46), and multi organ failure (50). As no well conducted randomized controlled trials exist, these results must be interpreted in context of their limitations.

Given these findings, statin therapy may be a viable option for treatment of severe sepsis and septic shock in the Emergency Department setting. Most existing literature points to the beneficial effects of statin premedication, which is an uncontrollable factor when a patient presents to the hospital. Based on the above inflammatory and immune modulating effects of statins, as well as the above cited clinical outcomes, we believe that a pathophysiological rationale exists in favor of administering acute statin therapy as well. The current study is the first to look at statin therapy in the setting of EGDT. Similar to previous trials (44-49), the data did show benefit in pulmonary function, as there was a significant reduction in mechanical ventilation days between the two groups. While not reaching statistical significance, statin therapy was associated with a trend toward improved outcomes with respect to ICU and hospital length of stay, as well as mortality.

Several limitations of this investigation exist. The retrospective design and chart review have inherent limitations. Due to difficulties in defining prior statin use retrospectively via database and chart review, it is possible that crossover existed between the two groups. The exposure to statins is subject to misclassification bias. Despite standardized treatment at our institution for both groups, undetected treatment differences may have existed. These differences may have affected outcome and would otherwise be best controlled in a prospective randomized control trial design. While not statistically significant, there were trends in differences between the two groups with respect to sex and racial demographics. It is possible that outcome differences could be attributed to these imbalances. Although a robust amount of data for septic patients is captured at our institution, it is possible that unaccounted data could have affected the results and introduced bias. A power analysis could not be conducted prior to the study, as the data used was what was available to the authors at the time. These facts, combined with the relatively small sample size in this trial make drawing conclusions more difficult based on this trial alone.

CONCLUSION

This retrospective cohort study of severe sepsis and septic shock patients treated with EGDT did show an association of prior statin use with decreased mechanical ventilation days and a trend in improvement in other clinically relevant outcomes. The results of our study, within the context of the limitations as cited above, have some similarities with previous data in this arena. To our knowledge this is the first trial to examine an association of statin use with outcomes in severe sepsis patients treated with EGDT. Given the complex pathophysiology of sepsis and the pleiotropic effects of statins, it is difficult to elucidate where the benefit in statin therapy is driven from. It is possible that the beneficial effects of statins do not serve to improve outcome above and beyond that from a well conducted, quantitative resuscitation strategy. However, the trends in this study suggest that a larger trial would have shown benefit, similar to previous trials. The results of this trial, combined with previous data should serve as hypothesis generating for future prospective randomized controlled trials in this arena.

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Table 1

Baseline Characteristics

Variable	Statin (n = 18)	No Statin (n = 73)	P Value
Age	67.3 (42-87)	59.2 (25-88)	0.102
Sex (%)			
Female	11 (61.1%)	27 (37%)	0.108
Male	7 (38.9%)	46 (63%)	
Race (%)			
White	11 (61.1%)	31 (42.5%)	0.467
Black	6 (33.3%)	30 (41.1%)	
Hispanic	1 (5.6%)	11 (15.1%)	
Other	0	1 (1.1%)	
Source of Infection			
Pneumonia	6	18	0.554
Urinary	10	23	0.099
Abdomen	1	16	0.177
Skin	2	13	0.726
Wound	2	3	0.260
Lactate (mmol/L) (SD)	5.61 (4.02)	5.76 (3.36)	0.817
APACHE II (SD)	21.46 (10.71)	20.29 (8.73)	0.301
SOFA (SD)	6.55 (3.50)	7.12 (4.45)	0.249

*
SD: Standard deviation

Table 2

Resuscitation Variables

Variable	Statin	No Statin	P value
First Vasoactive Medication	11 (73.3%) NE 4 (26.7%) DA 0 (0%) Dob	46 (85.2%) NE 5 (9.3%) DA 3 (5.6%) Dob	0.153
Fluids Total (L)			
0-6 Hours (SD)	5.22 (3.46)	4.45 (2.69)	0.692
6-72 Hours (SD)	11.47 (7.32)	15.4(8.45)	0.503
CVP 8 ET (minutes) (SD)	625.7 (85.58)	561.3 (77.27)	0.624
ScvO ₂ >70%	>24 hours <24 hours Not Obtained	1 13 4	8 45 18

NE, Norepinephrine. DA, Dopamine. Dob, Dobutamine. CVP 8 ET, Estimated time to achievement of CVP 8mmHg

* SD: Standard deviation

Table 3**Patient Outcomes**

Variable	Statin (n=18)	No Statin (n= 73)	P value
MV (%) Days	8 (44.4%) 7.29	40 (54.8%) 8.49	0.026
ILOS (days)	4.89	7.15	0.077
HLOS (days)	14.44	17.94	0.065
Mortality # (%)	4 (22.2%)	29 (39.7%)	0.273

MV, Mechanical Ventilation. ILOS, ICU Length of Stay, HLOS, Hospital Length of Stay