Characteristics and Outcomes of Patients with Vasoplegic Versus Tissue Dysoxic Septic Shock

Sarah A. Sterling[1], **Michael A. Puskarich**[1], **Nathan I. Shapiro**[2], **Stephen Trzeciak**[3], **Jeffrey A. Kline**[4], **Richard L. Summers**[1], and **Alan E. Jones**[1]

[1]Department of Emergency Medicine, University of Mississippi School of Medicine, Jackson, MS

[2]Departments of Emergency Medicine and Vascular Biology, Beth Israel Deaconess Medical Center, Boston, MA

[3]Departments of Emergency Medicine and Medicine, Cooper University Hospital, Camden, NJ

[4]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN

Abstract

Background—The current consensus definition of septic shock requires hypotension after adequate fluid challenge or vasopressor requirement. Some patients with septic shock present with hypotension and hyperlactatemia >2mM/L (tissue dysoxic shock), while others have hypotension alone with normal lactate (vasoplegic shock).

Objective—To determine differences in outcomes of patients with tissue dysoxic versus vasoplegic septic shock.

Methods—Pre-planned secondary analysis of a large, multi-center randomized control trial. Inclusion criteria were suspected infection, 2 or more systemic inflammatory response criteria, and systolic blood pressure <90 mmHg after a fluid bolus. Patients were categorized by presence of vasoplegic or tissue dysoxic shock. Demographics and sequential organ failure assessment (SOFA) scores were evaluated between the groups. The primary outcome was in-hospital mortality.

Results—A total of 247 patients were included, 90 patients with vasoplegic shock and 157 with tissue dysoxic shock. There were no significant differences in age, race, or gender between the vasoplegic and tissue dysoxic shock groups. The group with vasoplegic shock had a lower initial SOFA score than did the group with tissue dysoxic shock (5.5 vs. 7.0 points, p=0.0002). The primary outcome of in-hospital mortality occurred in 8/90 (9%) of patients with vasoplegic shock compared to 41/157 (26%) in the group with tissue dysoxic shock (proportion difference 17%, 95% CI 7–26%, p<0.0001; log rank test p = 0.02). After adjusting for confounders, tissue dysoxic shock remained an independent predictor of in-hospital mortality.

Conclusion—In this analysis of patients with septic shock we found a significant difference in in-hospital mortality between patients with vasoplegic versus tissue dysoxic septic shock. These findings suggest a need to consider these differences when designing future studies of septic shock therapies.

Keywords

sepsis; septic shock; hyperlactatemia; lactate; mortality

Contact Information: Alan E. Jones, MD, Research Director, Department of Emergency Medicine, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216, aejones@umc.edu.

Introduction

Sepsis is the tenth leading cause of death in the United States (US) with mortality rates for severe sepsis estimated to be 30% or higher.[1] Severe sepsis has also been estimated to be the primary cause for at least 500,000 emergency department (ED) visits annually in the US, with average ED stay times of almost 5 hours.[2] The current consensus definition of overt septic shock requires suspicion of infection and systemic inflammation associated with persistent hypotension after adequate fluid challenge or a vasopressor requirement.[3] Furthermore, hyperlactatemia has been shown to be a predictor of mortality in sepsis that is independent of organ failure and shock, with even modest elevations in lactate (2–4 mmol/ L) having an impact on clinical outcomes.[4,5] The objective of this study was to determine if there are differences in clinical characteristics and outcomes among patients with vasoplegic septic shock, defined as overt shock and a normal lactate, as compared to patients with tissue dysoxic septic shock, defined as overt shock and an elevated lactate >2 mM/L.

Methods

Study Design

We conducted a secondary analysis of a recently completed, large, multi-center randomized control trial.[6] The objective of the trial was to evaluate the non-inferiority of lactate clearance versus central oxygen saturation (ScvO2) as a marker of adequate oxygen delivery during early quantitative resuscitation of septic patients in the ED.

The methodology of the trial was previously reported.[6] In short, the trial was conducted at Carolinas Medical Center, Charlotte, NC, Beth Israel Deaconess Medical Center, Boston, MA, and Cooper University Hospital, Camden, NJ and occurred between January 2007 and January 2009. The Institutional Review Board at each institution (090602A) approved the study, and all participants or their surrogate provided written informed consent. The trial was registered on Clinicatrials.gov identifier NCT00372502.

Patients presenting to participating EDs with septic shock were consecutively enrolled or were eligible for enrollment if they were older than 17 years old, had confirmed or suspected infection, two or more systemic inflammatory response criteria, and systolic blood pressure <90 mmHg after a 20mL/kg rapid volume challenge or a whole blood lactate concentration of > 4 mmol/L. Patients were excluded from participation if they were pregnant, had any primary diagnosis other than sepsis, an expected surgical requirement within six hours of diagnosis, an absolute contraindication to chest or neck central venous catheterization, cardiopulmonary resuscitation, or advanced directive orders that would conflict with the study procedure. Once enrolled, patients were randomized to 1 of 2 study groups. While in the ED, each group had a structured quantitative resuscitation protocol, which has been previously described and published. [6] The ScvO2 group (N=150) was resuscitated by directing therapy required to meet threshold values of central venous pressure, mean arterial pressure, and central venous oxygen saturation (ScvO2). The lactate clearance group (N=150) had similarly targeted goals in central venous pressure, mean arterial pressure, and then lactate clearance (decrease in lactate of at least 10% over at least 2 hours) instead of ScvO2 as a measure for adequate oxygen delivery. Protocols were followed until all endpoints were met or a maximum time of 6 hours was reached. The results of this study confirmed the primary hypothesis of non-inferiority, with a 6% (95% confidence intervals −3 to 14%) in-hospital mortality difference between the two study groups.[6] A total of 300 patients were randomized, 53 of whom demonstrated an elevated lactate and normotension, and were therefore excluded from the present analysis. This group of patients has been analyzed and the results published previously[7], and were outside the scope of the current analysis given the focus on patients with hypotension in sepsis.

Data Analysis

For the present study, we categorized patients enrolled in the trial into one of two groups, vasoplegic shock or tissue dysoxic shock, as previously defined. Patient demographics and clinical characteristics were evaluated between the two groups using t-tests, Mann-Whitney-U, and chi-squared tests, as appropriate. The primary outcome of in-hospital mortality was evaluated using proportion differences and Kaplan-Meier curve with log rank test. In order to assess for potential confounding, we conducted a logistic regression model using in-hospital mortality as the dependent variable. Candidate variables were chosen based on known predictors of mortality, such as age and degree of organ dysfunction, and those variables found to be different between groups in the bivariate analysis, and maintained in the multivariate model if p < 0.10 to maintain the event to independent variable ratio of approximately 8–10:1.[8] The model was refined using reverse stepwise elimination. Model fit was determined using Hosmer and Lomeshow's goodness of fit test. All statistical tests were two sided with p<0.05 considered significant. Data were analyzed using STATA (10.0, StataCorp, College Station, TX) or StatsDirect statistical software (StatsDirect 2.7.7, Cheshire, England).

Results

A total of 247 patients were included in this study. 90 (36%) patients met criteria for vasoplegic shock versus 157 (64%) with tissue dysoxic shock. Patient demographics and initial clinical characteristics are shown in Table 1. There were no significant differences in demographics between the vasoplegic and tissue dysoxic shock groups. The group with vasoplegic shock had a lower initial SOFA score (5.5 points) than the group with tissue dysoxic shock (7.0 points) (p=0.0002).

The primary outcome of in-hospital mortality occurred in 49/247 (20%) patients, including 8/90 (9%, 95% CI 4 to 17%) in the vasoplegic shock compared to 41/157 (26%, 95% CI 19 to 34%) in the tissue dysoxic shock group (proportion difference 17%, 95% CI 7–26%, p<0.0001). Figure 1 shows survival to hospital discharge curve for the two groups using a Kaplan-Meier format. A significant difference in survival between the two groups was noted (log rank test p = 0.02.) Additionally, we found significant differences in ICU and hospital length of stay and multiple organ failure between the groups (Table 3).

To attempt to control for potential confounding, we developed a logistic regression model using in-hospital mortality as the dependent variable. The final model including age, total Sequential Organ Failure Assessment score at enrollment, treatment with norepinephrine versus other vasopressors, and shock type (vasoplegic versus tissue dysoxic shock). Increasing age and SOFA score were associated with adverse outcome, while choice of norepinephrine versus other vasopressors was associated with improved outcomes in the multivariate model. The adjusted odds ratio to predict in-hospital mortality for tissue dysoxic was 3.0 (95% CI 1.3–7.2). The final model demonstrate goodness of fit by the method of Hosmer and Lomeshow (p = 0.83).

Discussion

In this study we sought to evaluate the differences in outcome for patients with vasoplegic shock and tissue dysoxic shock. Our results indicate a significant difference in mortality between the two groups and that the presence of tissue dysoxic shock is an independent predictor of in-hospital mortality, even after accounting for potential confounding variables between cohorts. These results highlight the importance of potentially considering these subgroups of shock differently, particularly during enrollment into clinical trials where

homogeneous populations are necessary to decrease the likelihood of random error and maintain the power to detect differences between study groups.

In this study, we evaluated only patients with septic shock by consensus definition and categorized those patients as having a normal lactate or an elevated lactate. In clinical practice, patients with persistent hypotension would be treated similarly, with fluids, vasopressors and inotropic agents, regardless if lactate levels were elevated or normal. Thus the implications of our results for clinicians are more prognostic than therapy changing. However, for the clinical trialist, these results could potentially impact the design of inclusion criteria for trials and may serve to ensure less heterogeneity in septic shock populations.

Previous authors have questioned if patients with sepsis-induced hypotension and a normal lactate should be considered septic shock.[9] Hernandez et al examined the addition of hyperlactatemia to the consensus definition of septic shock citing significant differences in mortality between septic shock patients without an elevated lactate compared to those with an elevated lactate (7.7% and 42.9%, respectively). These authors went on the question if hypotension without lactate elevation should even be considered septic shock. In follow-up of their initial study, Hernandez and colleagues evaluated the outcomes and microcirculatory profiles of septic shock patients with and without hyperlactatemia. They again found significant differences in mortality and microcirculatory blood flow in patients with sepsis-induced hypotension and a normal lactate when compared to those with an elevated lactate.[10]

Our findings confirm these findings and suggest a differential prognosis for patients with biochemical evidence of tissue dysoxia as opposed to just vasoplegia without evidence of tissue dysoxia. In the previous study by Hernandez et al, patients were evaluated with serial lactates during the pre-ICU and ICU resuscitation periods, and patients with any abnormal lactate measurement during that time were included in the hyperlactatemia subgroup.[9] Our study grouped Emergency Department patients based on initial lactate levels and further shows inherent differences apparent on presentation, despite disease course or resuscitation efforts.

Additionally, previous research by Puskarich et al.[7] evaluated the outcomes of the varying presentations of septic shock. In that study, cryptic shock (suspected infection with a lactate greater than 4 mmol/L and normotension) and overt shock (suspected infection and persistent hypotension) had similar in-hospital mortality rates of 20% and 19%, respectively. Our study extends these findings to further show that there are significant differences within the overt shock group when incorporating lactate as a variable.

Our study does have some important limitations. The initial study took place at experienced hospitals that perform high volumes of acute sepsis resuscitations and thus have resources that may not be available at other hospitals, so the results of this study may not be generalizable. Also, patients were placed into 1 of 2 treatment groups with different protocols in the initial study. The ScvO2 treatment group's protocol did not target lactate clearance, which has been associated with worse outcomes versus lactate non-clearance and discordance from ScvO2 optimization.[11] However, both treatment groups had protocols with similar goals and outcomes and both the vasoplegic and tissue dysoxic shock groups had similar rates of achieving their pre-defined resuscitation goals (Table 2), mitigating this potential concern. Furthermore, when added to the multivariate model, treatment arm did not impact the results of our study. Finally our study can only draw associations and cannot show cause and effect.

Conclusion

In this analysis, we found a significant difference in in-hospital mortality between vasoplegic and tissue dysoxic septic shock groups. These findings suggest a need to consider such outcomes when designing future studies of septic shock therapies.

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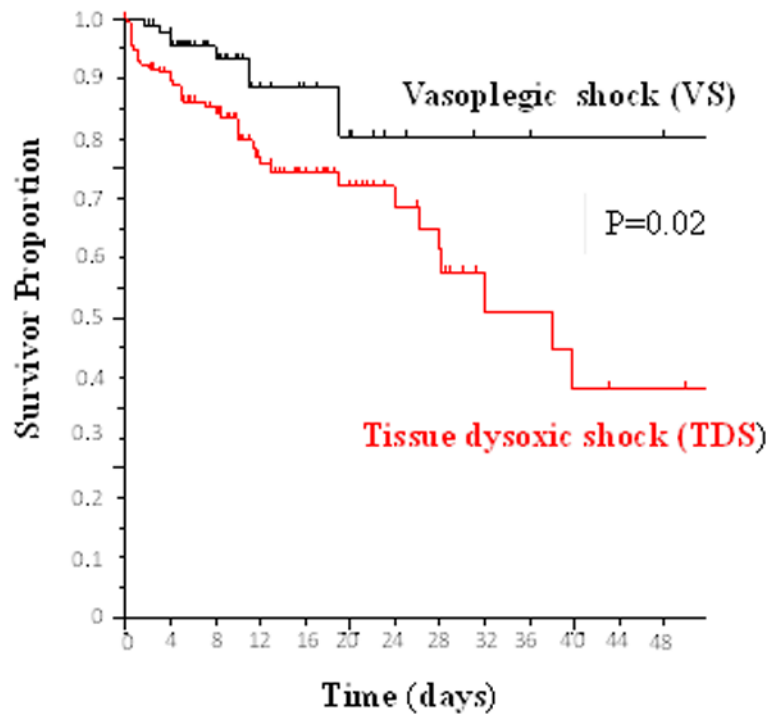
Figure 1.

Table 1

Patient demographics and clinical characteristics

Variable	VS group (N=90)	TDS group (N=157)	P value
Age *	58 (47–71)	61 (51–93)	0.21
Sex (%)			
Male	47 (52)	90 (57)	0.51
Female	43 (48)	67 (43)	
Race (%)			
Caucasian	53 (59)	83 (53)	0.43
Black American	24 (27)	61 (39)	
Hispanic	10 (11)	11 (7)	
Other	3 (3)	2 (1)	
Disease Severity *‡			
SOFA score	5.5 (4–7)	7.0 (4–10)	0.0007
Comorbidities (%)			
Diabetes mellitus	18 (20)	58 (34)	0.009
Hypertension	44 (49)	90 (57)	0.25
Congestive heart failure	17 (19)	20 (13)	0.26
Peripheral vascular disease	7 (8)	17 (11)	0.58
History of MI	11 (12)	13 (8)	0.43
Chronic steroid use	10 (11)	21 (13)	0.75
Human immunodeficiency virus	9 (10)	14 (9)	0.96
End stage renal disease	4 (4)	15 (10)	0.23
Chronic obstructive pulmonary disease	13 (14)	28 (18)	0.61
Suspected Source of Infection			
Pneumonia	32 (36)	60 (38)	0.78
Urinary tract	26 (29)	40 (25)	0.77
Intra-abdominal	7 (8)	23 (15)	0.16
Vascular line	1 (1)	9 (6)	0.02
Skin/Soft tissue	11 (12)	17 (11)	0.90
Unknown	11 (12)	7 (4)	0.045

Abbreviations: VS = Vasoplegic Shock; TDS = Tissue Dysoxic Shock; SOFA = Sequential Organ Failure Assessment.

* Median (IQR)

‡ Disease severity scores calculated at time of enrollment

Table 2

Administered treatment and resuscitation endpoints

	VS group (N=90)	TDS group (N=157)	P value
Interventions			
Total fluids in ED (L)[*]	4.5 (3.1–6)	4.1 (3–5.3)	0.23
Steroids in 6 hours (%)	16 (18)	23 (15)	0.64
Vasopressors (%)			
Norepinephrine	43 (48)	99 (63)	0.03
Dopamine	18 (20)	30 (19)	>0.99
Resuscitation Goals Achieved After Interventions			
Central Venous Pressure	82 (91)	136 (87)	0.40
Mean Arterial Pressure	87 (97)	147 (94)	0.32

Abbreviations: VS = Vasoplegic Shock; TDS = Tissue Dysoxic Shock;

[*]Median (IQR)

Table 3

Patient Outcomes

Variable	VS group (N=90)	TDS group (N=157)	P value
In-hospital mortality (%) [+]	8 (9)	41 (26)	0.002
Length of Stay[*]			
ICU	2.6 (1.5–5)	4 (1.9–8.2)	0.009
Hospital	7 (5–10)	9 (5.1–17)	0.042
Hospital complications (%)			
Multiple organ failure	10 (11)	44 (28)	0.003
Care withdrawn	6 (7)	20 (13)	0.200

Abbreviations: VS = Vasoplegic Shock; TDS = Tissue Dysoxic Shock;

[+] Primary study end point

[*] Median (IQR)