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Vitamin C in the treatment of septic shock

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ABSTRACT

Objective: To assess the efficacy of improving outcomes of septic shock treatment with the addition of Vitamin C to standard treatment compared to standard therapy alone. To assess whether or not Vitamin C has a favorable outcome in the treatment of septic shock in terms of decreasing duration of vasopressor usage, reducing duration of intensive care unit (ICU) stay, and improving mortality.

Design: Systematic literature review.

Methods: Searches were conducted in PubMed and Google Scholar using the terms ascorbic acid, sepsis, septic shock, and vasopressors. In PubMed the following filters were used: humans only, clinical trials, studies within the past 10 years. Studies that used Vitamin C for the treatment of septic shock and measured the duration of vasopressor usage, total duration of ICU stay, and mortality were included in the review.

Results: All three studies showed a statistically significant reduction in the duration of vasopressor dependency with the addition of Vitamin C to the standard treatment of septic shock. There were conflicting results on the effects on mortality and duration of ICU stay.

Conclusion: The addition of Vitamin C may decrease the duration of vasopressor usage in the treatment of septic shock. Additional higher-powered studies are needed to determine the effects of Vitamin C on mortality and duration of ICU stay.

INTRODUCTION

Sepsis is a major public health concern affecting 1.5 million Americans annually and resulting in 250,000 deaths per year.[1] It is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[2] Patients with suspected sepsis can present with fever, tachycardia, hypotension, and leukocytosis. The most common sites of infection leading to sepsis include the lungs, abdomen, pelvis, and urinary tract.[3] A diagnosis of sepsis is often based upon clinical features combined with blood cultures indicating an infection. Systemic inflammatory response syndrome (SIRS) criteria is commonly used to identify patients with suspected sepsis. Table 1 illustrates the criteria for SIRS.

Sepsis progresses to septic shock when there is evidence of organ dysfunction and tissue hypoperfusion as evidenced by hyperlactemia or failure to respond to fluid resuscitation. As the infection progresses there is massive systemic vasodilation due to the release of bacterial endotoxin, resulting in distributive shock. Because of this massive vasodilation, vasopressors are required in septic shock to maintain a mean arterial pressure ≥65 mmHg.[4] Vasopressors are a group of medicines that cause vasoconstriction and are used to treat severely low blood pressure. Commonly used vasopressors include epinephrine, norepinephrine, and dobutamine, which work on adrenergic receptors. Potential harms related to extended duration of vasopressor usage include potentially fatal tachyarrhythmias and severe vasoconstriction leading to peripheral limb ischemia and critical limb ischemia.[5]

The Sequential Organ Failure Assessment (SOFA) score is the primary scoring system used to assess organ dysfunction and failure in septic patients. A high SOFA score reflects increasing organ dysfunction. Table 2 illustrates criteria used to calculate a SOFA score. Patients with a SOFA score ≥2 who require vasopressors and have a lactate of >2 mmol/L have a predicted mortality of 40%.[2] Higher SOFA scores are associated with increased morbidity and mortality in septic patients. The current treatment for septic shock includes admission to the ICU and subsequent resuscitation of the vasculature with intravenous (IV) fluids and vasopressors. Empiric treatment with antibiotics to cover all likely pathogens is started promptly after the diagnosis of sepsis. Despite this intensive treatment, the in-hospital mortality rate for septic patients is near 30%.[1]

Clinical studies have revealed that septic patients often present with hypovitaminosis C due to increased oxidative stress from infection. Oxidative stress in sepsis is due to an imbalance between antioxidant defense effectiveness and reactive species generation. This results in a build up of oxidants in the cell which impairs the mitochondria's ability to utilize oxygen, ultimately leading to cell and tissue hypoxia.[6] The enzymes involved in the synthesis of endogenous norepinephrine and vasopressin require ascorbate as a cofactor for optimal activity.[7] Thus, it is thought that supplementing patients in septic shock with high doses of vitamin C will improve hemodynamic instability, the need for exogenous vasopressin, and potentially decrease overall mortality. The aim of this review is to evaluate the effects of supplementing patients in septic shock with Vitamin C on the duration of vasopressor usage, mortality, and the length of ICU stay.

The Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following:

- Temperature >38 degrees C or <36 degrees C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or PaCO2 <32 torr
- WBC >12,000 cell/mm, <4,000 cells/mm, or >10% immature (band) forms

Table 1. SIRS clinical criteria used to determine risk for sepsis[8]
WBC= white blood cells

	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory PaO2/FIO2,mmHg	>400	≤400	≤300	≤200	≤100
Coagulation Platelets x 10^3/ul	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dl	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70	Dop ≤5 or dob (any dose)	Dop >5, epi ≤0.1, or norepi ≤0.1	Dop >15, epi >0.1, or norepi >0.1
CNS Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL Or urine output, mL/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

Table 2. Sequential organ failure assessment criteria from Jones et al.[9] *Dop=dopamine. Dob=dobutamine. Epi=epinephrine. Norepi=norepineprine.*

PICO

Population: Individuals in the ICU with septic shock
Intervention: Vitamin C plus standard septic shock therapy
Comparison: Standard septic shock therapy
Outcome: Vasopressor duration, mortality, duration of ICU stay

CLINICAL QUESTION

Among individuals in the ICU with septic shock, does Vitamin C plus standard septic shock therapy as compared to standard septic shock therapy alone reduce the duration of vasopressor dependency, improve mortality, and reduce the duration of the ICU stay?

METHODS

In September of 2017, a literature review search was conducted using PubMed and Google Scholar to identify studies that evaluated the use of Vitamin C for the treatment of sepsis. The following search terms were used: "ascorbic acid" and "sepsis". Within PubMed, these two words identified 149 articles. Next, restrictions were added to exclude articles that were not written within the last 10 years, which narrowed the search to 77 articles to be screened. Of these 77 articles, 67 were excluded because they were either not human studies or not clinical trials. The remaining 10 articles were narrowed down to 2 articles based on outcomes measuring duration of vasopressor usage and mortality.

An additional literature review search was done using Google Scholar with the terms mentioned previously in addition to "septic shock" and "vasopressor". This search yielded 1200 results. Only articles written within the last 10 years were included which narrowed the results to 636. Within Google Scholar, the articles were sorted by date and did not include citations or patents, which resulted in two articles to be reviewed. The other article was not included as it was not a clinical trial.

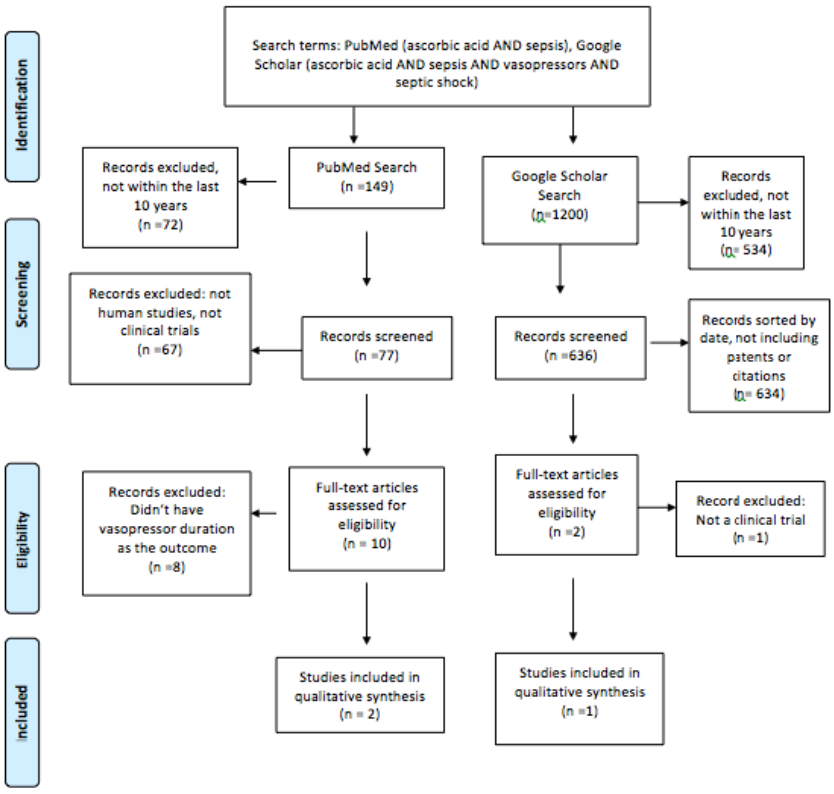

Figure 1. PRISMA flow diagram depicting the literature review resulting in the three studies evaluated[10]

An overview of the studies included in the review can be found in Table 3. The three articles included in this literature review examined the use of Vitamin C in the treatment of septic shock. All three studies measured the duration of vasopressor dependency, overall mortality, and the duration of the ICU stay.

RESULTS

Overview of Studies Included in Review			
	Study 1: Marik et al	Study 2: Zabet et al	Study 3: Habib et al
Year published	2016	2016	2017
Sample Size	94	28	100
Journal	CHEST journal	Journal of Research in Pharmacy Practice	International Journal of Microbiology & Advanced Immunology (IJMAI)
Study Design	Retrospective before-after	Double-blinded Randomized controlled trial	Randomized controlled trial
Duration of Study	7 months	17 months	Not specified
Efficacy Outcomes	Hospital mortality, Duration of vasopressor use; duration of ICU stay	Primary - Vasopressor dose and duration, Secondary - Duration of ICU stay, 28 day mortality	Duration of Vasopressor use; ICU stay length; Duration of mechanical ventilation; Need for renal replacement therapy; Mortality
Treatment Groups	Vitamin C treatment protocol n=47 Standard treatment n=47	Vitamin C treatment protocol n=14 Standard treatment n=14	Vitamin C treatment protocol n=50 Standard treatment n=50

Table 3. Overview of studies included in this review

Study 1 - Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Marik et al.[11]

Objective: The purpose of this study was to compare the outcomes and clinical course of septic patients treated with a regimen of intravenous vitamin C, hydrocortisone, and thiamine compared with standard treatment of patients with sepsis.

Study Design: This study was an Electronic Health Record (EHR) based retrospective before and after study performed at Sentara Norfolk General Hospital. The primary outcome measure of this study was hospital survival. The secondary outcome measure included duration of vasopressor therapy. There were 94 total cases analyzed in this study. Between January 2016 and July 2016, 47 patients with a primary diagnosis of sepsis or septic shock were treated with an experimental vitamin C protocol (Table 8). The control group consisted of 47 patients admitted to the same ICU between June 2015 and December 2015 using the same inclusion and exclusion criteria (Table 4). The authors stated there were no significant changes in ICU protocols, referral patterns, or patient populations between the time period during which the control group and the vitamin C treatment group were observed. The only difference stated to exist between treatment and control groups is the addition of the vitamin C treatment protocol (Table 8). However, certain patients in the control period were noted to have been treated with hydrocortisone (50 mg every 6 hours) per guidelines or a physician's discretion.

The diagnoses of severe sepsis and septic shock were based upon the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions. The search for patient cases for each group was performed using the hospital's EHR system using the inclusion and exclusion criteria (Table 4).

The standard management of a patient in septic shock consisted of empiric broad spectrum antibiotics, which were adjusted as culture results were returned and the patient's clinical picture changes. Norepinephrine was the vasopressor of choice for vasopressor strategy and was titrated to achieve a mean arterial pressure (MAP) of greater than 65 mmHg. If norepinephrine proved insufficient to achieve adequate MAPs, vasopressin, phenylephrine, or epinephrine was used.

Study Design (Marik)	
Inclusion Criteria	Exclusion Criteria
Patients admitted to ICU with primary diagnosis of severe sepsis or septic shock with a procalcitonin of ≥ 2ng/ml.	Patients < 18, pregnant patients, patients with limitations of care

Table 4. Inclusion and exclusion criteria for the Marik et al study

Study Results: The patients in the treatment group had a significantly reduced mortality (8.5%) when compared with the control group (40.4%, $p < 0.001$). The duration of vasopressor administration required to maintain a MAP of 65 mmHg or higher was significantly shorter in the vitamin C treatment group (18.3 hours) than the control group (54.9 hours, $P<0.001$). No statistically significant difference was noted between groups in the length of ICU stay. The report states that patients in the vitamin C treatment group could be predictably weaned off vasopressors 2-4 hours after beginning vitamin C treatment.

Study Critique: There are a number of drawbacks to how this study was conducted. Primarily the before-and-after study design is considered non-experimental due to the high likelihood that the control and experimental groups lack equivalency of conditions. This is in part due to the control and treatment trials taking place during different periods of time. While an attempt was made to ensure that conditions were the same for both periods of time, there may be subtle differences in the ICU that went undetected. A before-and-after study does provide useful evidence of the effectiveness of an intervention but lacks the ability to test efficacy. Another significant weakness of this study is the lack of blinding. The individuals administering the vitamin C treatments were not blinded and neither were the researchers accessing the EHR retrospectively.

The unblinded nature of this study design casts suspicion of bias on the part of the personnel administering the medications and charting the resultant patient response. The treatment regimen of vitamin C, corticosteroids, and thiamine presents a problem for assessing the clinical efficacy of vitamin C as an isolated factor. For the purposes of investigating the clinical usefulness of vitamin C compared to existing standard treatments, this study falls a bit short due to the trials having been conducted during different time periods and the confounding presence of hydrocortisone and thiamine in the treatment group. Nevertheless, this study does present intriguing data and certainly adds clinical research data to an evolving area of active research.

Study 2 - Effect of high-dose ascorbic acid on vasopressor requirement in septic shock. Zabet et al. [12]

Objective: The purpose of this study was to evaluate the effects of high dose vitamin C on hemodynamic parameters in surgical patients who meet septic shock criteria.

Study Design: This study is a double blind randomized controlled trial performed in the ICU of Imam Khomeini Hospital in Tehran, Iran. This study was specifically looking at post surgical patients presenting with septic shock.

The treatment of septic shock in the ICU during the course of this study followed recommendations by the Surviving Sepsis Campaign.[13] Crystalloid fluids were used for fluid resuscitation to maintain arterial pressures. Norepinephrine was the vasopressor of choice to maintain mean arterial pressure of over 65 mmHg when fluid resuscitation alone was insufficient. Antibiotic treatments were administered per hospital recommendations. Continuous IV fentanyl administration was used as the sedation protocol.
The primary outcomes measured were the dose and duration of vasopressor therapy required for each patient. The duration of ICU stay and 28 day mortality were secondary outcomes. Many demographic and laboratory data were collected initially to demonstrate equivalency between the treatment and control groups. In addition to standard demographic information, the researchers included a medical history of pre-existing diseases, the cause of ICU admission, and extensive laboratory and test results such as electrolyte levels, blood urea nitrogen, and serum creatinine. Initial Acute Physiology and Chronic Health Evaluation II (APACHE II) and SOFA scores were calculated using laboratory data and vital signs.

Patients who met inclusion criteria (Table 5) were separated into either the treatment or control group using permuted block randomization. This method of randomizing individuals in a clinical trial involves taking a series of blocks from which an equal number of patients is assigned to randomly. The block randomization in this study consisted of seven blocks of four patients each for a total of 28 patients (14 in each group). No patients

were excluded during the trial. The diagnosis of septic shock was based upon the definition provided by the Surviving Sepsis Campaign and the following criteria:

1. Presence of systemic inflammatory response (Table 1)
2. Suspected or proven infection
3. Presence of sepsis induced organ dysfunction (refer to SOFA score criteria, Table 2)

The Vitamin C treatment group received 25 mg/kg Vitamin C in 50 ml of dextrose 5% solution IV over 30 minutes every 6 hours for 72 hours (Table 8). The control group received a 50 ml IV infusion of dextrose 5% over 30 minutes. These treatments were mixed in the pharmacy. Researchers, patients, and those caring for the patients were all blinded to who was receiving the treatment or placebo.

Study Design - Zabet et al	
Inclusion Criteria	Exclusion Criteria
• 18-65 years old • Postoperative surgical patients with diagnosis of septic shock • Demonstrated need for vasopressors	• Concomitant use of other antioxidants • Corticosteroid administration • Any contraindication for high-dose ascorbic acid

Table 5. Inclusion criteria for the Zabet et al study. No exclusion criteria was explicitly stated in this study.

Study Results

Demographics: No statistically significant difference was noted between treatment and control groups for demographic data or clinical characteristics. SOFA and APACHE II scores, laboratory tests, and hemodynamic status were all statistically equivalent between groups during patient enrollment in this study.

Treatment efficacy: Duration of vasopressor therapy was significantly lower in the Vitamin C treatment group when compared with control ($P = 0.0007$). The 28-day mortality was significantly lower in the Vitamin C treatment group ($P = 0.009$). No statistically significant difference was noted between treatment and control groups for length of ICU stay. The mean required vasopressor doses were lower for the Vitamin C group (7.44 mcg/min) than for the treatment group (13.79 mcg/min, $p = 0.004$).

The article compared the treatment and control groups on numerous demographic and clinical features. APACHE II and SOFA scores were also calculated for patients in each group prior to treatment. No statistical significant difference was found between groups on any of these measures.

Study Critique: This study is a well-designed, double blind, randomized controlled trial. Researchers and those caring for the patient were effectively blinded. The inclusion criteria is clear, however exclusion considerations are not explicitly stated. The plethora of demographic and clinical data that the researchers compared to show equivalency between the treatment and control groups does serve to greatly strengthen this study. The primary drawback of this study is the low number of enrolled participants with 14 patients per group. This study would benefit immensely from increased power. With a low number of participants in this study there is an increased possibility of a type 2 error. An additional drawback to this study was the short duration of the intervention. A longer course of Vitamin C treatment beyond the 72 hours used in this study is certainly worth further investigation. Baseline serum Vitamin C levels are not measured in this trial. The authors of

this study do point out that it would be beneficial to obtain baseline Vitamin C levels in patients prior to therapy. A final note is that only postsurgical patients diagnosed with septic shock are included in this study. Post surgical patients with septic shock are a subset of all patients with septic shock. It is useful to assess this population specifically, however there is a possibility that these results are not applicable to all patients with septic shock.

Study 3- Early adjuvant IV Vitamin C treatment in septic shock may resolve the vasopressor dependence. Habib et. al.[14]

Objective: The purpose of this study was to evaluate the role of early intravenous high doses of Vitamin C, compared to standard treatment alone, as adjuvant therapy in patients with septic shock. The primary outcomes investigated were the duration of time on vasopressors, duration of ICU stay, days of mechanical ventilation, and need for renal replacement therapy. ICU-mortality was a secondary outcome.

Study design: This was a randomized controlled trial with a total of 100 patients conducted in the intensive care unit (ICU) in Alexandria University hospital in Egypt. The 100 patients were randomized using the even odd randomization technique to receive either conventional treatment with adjuvant Vitamin C (n=50) or conventional treatment alone (n=50). Inclusion and exclusion criteria for the study can be found in Table 6.

Upon admission to the ICU, patients in the Vitamin C group received 1.5g intravenous Vitamin C (ascorbic acid, Cevarol) every 6 hours until discharge from the hospital. The primary outcomes measured were the need for organ supportive measures including duration of vasopressor usage, mechanical ventilation and renal replacement therapy and also the length of ICU stays. The secondary outcome measured was in-ICU mortality. All patients were followed up from the day of enrollment until the day of discharge. The SOFA score was evaluated on day 1 of admission and every day thereafter until discharge or death.

Study Criteria - Habib et al	
Inclusion Criteria	**Exclusion criteria**
· Males and females >18 years of age · Admitted to the critical care department · Diagnosis of septic shock as defined by the 3rd International Consensus Definition for Septic Shock[2] · At least one positive blood culture	· Pregnant and lactating mothers · History of oxalate nephrolithiasis · Glucose- 6-phosphate dehydrogenase G6PD deficiency · Paroxysmal nocturnal hemoglobinuria · Hereditary hemochromatosis were · Any other type of shock state or patients with mixed type of shock

Table 6. Inclusion and exclusion criteria for the Habib et al study.

Study Results

Demographics: Of the 50 patients receiving intravenous Vitamin C therapy, the average age was 42.78 with 28 males and 22 females. The control group was comprised of 30 males and 20 females with an average age of 41.7 years. The SOFA scores were calculated prior to treatment with no statistically significant difference between the treatment group and control group. Mean arterial pressure, heart rate, respiration rate, and temperature were also documented for each group with no statistically significant difference between the two groups.

Treatment efficacy: The primary end point for the Habib et al study was the duration of vasopressor usage for septic patients in the ICU. Patients in the treatment group were on vasopressors for an average of 2.30 ± 1.2 days compared to the control group, which were on vasopressors for an average of 6.50 ± 2.57 days. The difference in duration of vasopressor usage between the two groups was statistically significantly significant with a p value of 0.001.

The total number of days spent in the ICU was an additional primary endpoint. Patients in the treatment group spent an average of 10.00 ±5.50 days in the ICU, with the median being 12 days. The control group spent an average of 14.10 ±6.47 days in the ICU with a median duration of 16 days. The difference in ICU stay was statistically significant with a P value of 0.04.

Other primary endpoints evaluated were the total days requiring mechanical ventilation and the need for renal replacement therapy. For the Vitamin C group, average time spent on mechanical ventilation was 4.60±2.08 days and the need for renal replacement therapy occurred in 30% of the group. In the control group the average duration of mechanical ventilation was 7.87±3.01 days with a need for renal replacement therapy occurring in 26%. There was no statistically significant difference between the groups for either measure, with a p value of 0.187 for mechanical ventilation and a p value of 0.412 for renal replacement therapy.

The secondary endpoint for the study was ICU mortality. There was no statistically significant difference between the treatment group and control group for mortality, with a p value of 0.138. Of the 50 patients in the treatment group, 12 eventually died of sepsis related complications resulting in a mortality rate of 24%. In the control group, 18 patients died resulting in a mortality rate of 36%.

Study Critique: Strengths of this study included randomization of participants, minimal demographic variation between the two groups, and a relatively large sample size. The randomization of the two groups resulted in no statistically significant differences with regards to their demographics, baseline vital signs, and initial lab work. Although 100 patients is not a large sample size by most standards, this is a large study size compared to other similar studies evaluating the use of Vitamin C in sepsis treatment. However, the authors did not mention power calculations, which contributes to the limitations of the study.

The researchers attempted to address confounding variables between the two treatment groups in their results section. They explicitly stated that there was no statistically significant difference between the two groups in the source of the patient's sepsis. However, the p value they used for this calculation was p=0.088, which is not statistically significant. Additionally, the author claims that cultures in both groups most commonly grew out gram-negative organisms, with a p value of 0.551. The author did not

address how different sources of sepsis and different causative organisms may impact the severity of septic shock and the effectiveness of the Vitamin C protocol.

Perhaps the largest weakness of the study was that baseline Vitamin C levels were not obtained prior to therapy. This introduces the possibility that the control group had collectively lower baseline levels of Vitamin C, accounting for the longer duration of vasopressors and longer ICU stay. For future studies, baseline levels of Vitamin C should be obtained prior to therapy in order to compare pre and post levels of Vitamin C with the treatment outcome.

In this study, SOFA scores were used in the baseline workup and to evaluate the trends throughout the course of the patient's illness. The author did not include these scores in the research article. In addition to vasopressor duration and mortality, a comparison between the trends of the SOFA scores of the treatment group and the control group should be a consideration for future studies in order to have objective evidence to assess patients' improvement.

An additional weakness of the study is that it was not blinded, which introduces the potential for bias in the evaluation of the outcomes. While Vitamin C in low doses is considered a benign therapy in most patients, the authors did not address potential harms of large doses of Vitamin C therapy in septic shock. Renal failure and chronic kidney disease impair the body's excretion of Vitamin C and can lead to the build up of insoluble oxalate which can accumulate and cause failure in multiple organs throughout the body. In future studies, the outcomes of Vitamin C use in patients with renal failure should be studied.[15] Lastly, the author does not define what the conventional sepsis treatment is at the hospital. He states that the hospital protocol for sepsis treatment was used, however, the exact sepsis protocol should be defined in order to optimize reproducibility of the study.

Study	Group	Duration of Vasopressor Use (hours)	p	Length of ICU Stay (days)	p	Mortality	p
Marik 2016	Control	54.9 (±28.4)	< 0.001	4 (4-10)	N/A	19 (40.4%)	< 0.001
	Ascorbic Acid Group	18.3 (±9.8)		4 (3-5)		4 (8.5%)	
Zabet 2016	Control	71.57 (±1.6)	= 0.0007	20.57 (±13.04)	= 0.85	9 (64.28%)	= 0.009
	Ascorbic Acid Group	49.64 (±25.67)		21.45 (±10.23)		2 (14.28%)	
Habib 2017	Control	156 (±64.68)	= 0.001	14.10 (±6.47)	= 0.04	18 (36%)	= 0.138
	Ascorbic Acid Group	55.2 (±28.8)		10.0 (±5.5) days		12 (24%)	

Table 7. Duration of vasopressor use, length of ICU stay, and mortality outcome data for each of the studies.

Study	Vitamin C protocol	Control
Marik	• IV Vitamin C 1.5gm every 6 hours for 4 days • IV Hydrocortisone 50mg every 6 hours for 7 days • IV Thiamine 200mg every 12 hour for 4 days	Standard ICU treatment of severe sepsis and septic shock.
Zabet	25 mg/kg IV ascorbic acid every 6 hours for 72 hours	Standard treatment plus placebo
Habib	1.5 gm IV ascorbic acid every 6 hours in first 24 hours after ICU admission plus conventional sepsis treatment	Conventional sepsis treatment

Table 8. Vitamin C treatment protocols for each of the studies assessed. For each of the studies, the Vitamin C treatment occurred as an adjunct to standard treatments. Marik et al performed the control and treatment phases of study at separate times. Zabet et al used a placebo to perform a double blind randomized controlled trial.

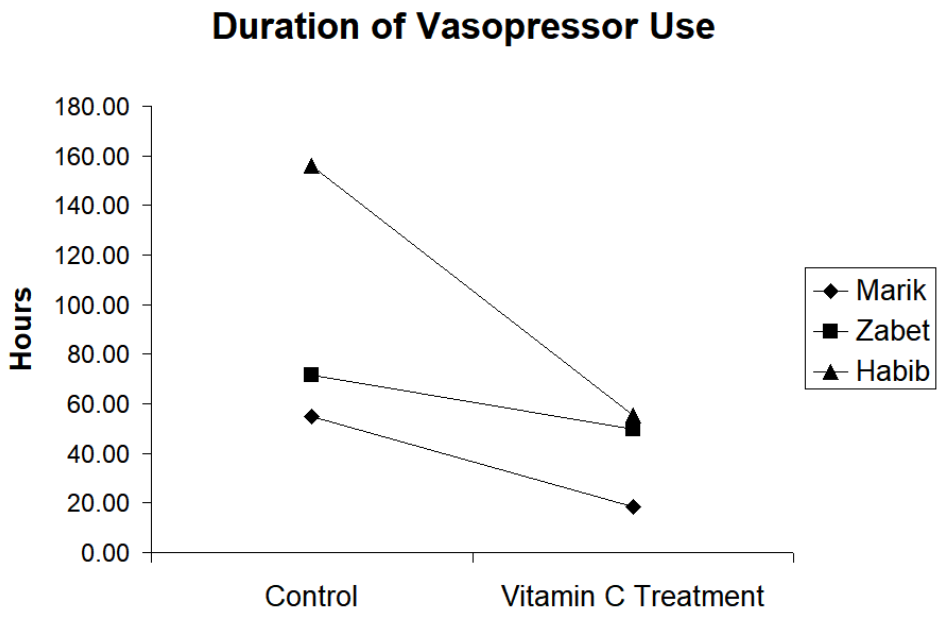

Figure 2. Duration of vasopressor use outcome data for all three studies assessed in this review. All three studies showed a statistically significant reduction in the duration of vasopressor use ($P < 0.05$).

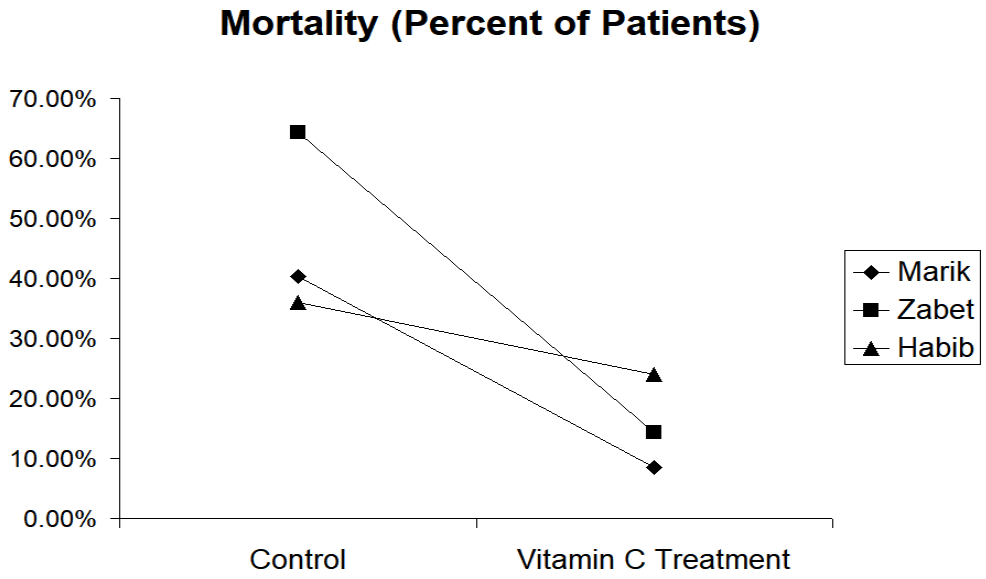

Figure 3. Mortality outcome data for all three studies assess in this review. Marik et al and Zabet et al both showed a statistically significant decrease in mortality ($P < 0.05$). Habib et al failed to show a statistically significant decrease in mortality.

Number Needed to Treat			
Zabet	Died	Survived	**NNT = 2**
Vitamin C Treatment Group	2	12	
Control Group	9	5	
Habib	Did Not Survive	Survived	**NNT = 8**
Vitamin C Treatment Group	12	38	
Control Group	18	32	
Combined Studies Overall	Did Not Survive	Survived	**NNT = 5**
Vitamin C Treatment Groups	14	50	
Control Groups	27	37	

Table 9. Number needed to treat based on mortality data for each study and the combined number to treat. The Marik et al study was not included due to study design.

DISCUSSION

Sepsis is the result of a systemic infection and is a major health concern with considerable associated morbidity and mortality. The massive vasodilatory response to the infection results in poor perfusion of organs and tissues leading to multi organ system damage. Current therapies are aimed at treating the infection in addition to maintaining adequate perfusion. This is accomplished by using broad-spectrum antibiotics, fluid resuscitation, and vasopressors to maintain a mean arterial pressure of greater than 65 mmHg. Recently there has been interest in the addition of Vitamin C to the standard treatment of septic shock. The aim of this review was to investigate the role of Vitamin C in the treatment of septic shock by analyzing three recent studies that compared Vitamin C usage to standard treatment. Each of these studies compared the efficacy of adding Vitamin C to standard treatments by using vasopressor requirements, length of ICU stay, and mortality as comparable outcomes. An overview of the findings of the studies in this review is provided in Table 3.

All three studies demonstrated a significant reduction in vasopressor dependency within the Vitamin C treatment group. This outcome is not surprising as ascorbic acid is a cofactor for the enzymes involved in the synthesis of endogenous vasopressors. Sepsis results in significant oxidative stress resulting in a reduction of Vitamin C levels and therefore a reduction in the synthesis of norepinephrine and vasopressin. This is a

significant finding, however, based on these articles alone it is unclear whether the reduction in vasopressor dependency is associated with a decrease in mortality.

There was conflicting evidence among the studies regarding the duration of ICU stay and reduction of mortality in the Vitamin C treatment group. Marik et al and Zabet et al found that the addition of Vitamin C to standard sepsis treatment resulted in a statistically significant reduction in mortality, with p values of 0.001 and 0.009 respectively. Although Marik et al. did show a statistically significant reduction in mortality, due to the low power of the study and it's quasi-experimental design, it is difficult to determine the validity of this result. Habib et al found no statistically significant difference in mortality with the addition of Vitamin C, with a p value of 0.138. These conflicting results could be due to the low power of all three studies.

The most notable limitation to this review is the low power within each of the studies. The small sample size in these trials and lack of significant randomized controlled trials on this topic are likely due the lack of knowledge about adverse effects associated with the addition of Vitamin C in septic shock. A recent Phase 1 safety trial was conducted in 2014 by Fowler et al to examine the safety of Vitamin C in the treatment of sepsis. The results found by this trial demonstrated that the addition of Vitamin C in septic shock was safe and well tolerated with no adverse events.[16] With these results and the promising results found in the three studies in this review, there will hopefully be larger randomized controlled trials conducted in the future to reveal more conclusive outcomes for the use of Vitamin C therapy in septic shock.

Number needed to treat (NNT) is a metric used to assess the impact of a therapy. It is the number of patients that must be treated for one patient to benefit from the therapy over a specified time. Calculated from mortality data in Table 9, the NNT for the Zabet et al study was 2. This means that for every 2 patients with septic shock treated with the regimen in Table 8 for 72 hours, there was a patient who had a reduced 28 day mortality. For the Habib et al study, the NNT was 8, meaning that for every 8 patients treated with the regimen in Table 8 for 24 hours after ICU admission, there was a patient who had reduced ICU mortality. The NNT was not calculated for the Marik study due to this study being a before-and-after study and not a randomized controlled clinical trial. Combining the mortality data from the Zabet and Habib studies results in an NNT of 5 (Table 9). The NNT measure does require that the studies be equivalent in the duration of time for which the outcome is observed. The Habib et al study does not include enough information on the mortality outcome measure to assure equivalence in time. Therefore these studies may not be directly comparable by using the NNT measure. Nevertheless, the NNT measures from these studies individually and combined do suggest possible benefit in the treatment of septic shock, a condition which has a very poor prognosis

CONCLUSION

These studies appear to demonstrate improvements in patient outcomes when standard treatments of septic shock are supplemented with high doses of Vitamin C. Each of the studies assessed indicates a significant reduction in vasopressor requirements for septic patients when they are treated with high doses of Vitamin C as adjunct therapy to standard treatment. Two of the three studies showed a significant reduction in mortality. These studies suffer from small sample sizes, and only two of them are randomized controlled trials. Considerations for future studies include the measurement of Vitamin C levels prior to and during treatment and the comparison of SOFA scores between the treatment and control groups. If the results of these studies can be replicated in large scale randomized controlled trials, certainly there would be a case for Vitamin C to be included in the standard treatment of septic shock.

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