Safety and Outcomes of Patients Receiving Intravenous Vitamin C in Severe Sepsis

Clinical Bottom Line

IV Ascorbic Acid appears to be well-tolerated with few adverse reactions and while these trials are very small, they show ascorbic acid could reduce end organ failure and improve mortality in patients with severe sepsis with little risk. Currently the data does not support routine administration of vitamin C in sepsis but is probably a reasonable adjunct to consider until larger studies are published.

PICO

P – Adult patients in septic shock
I – Administration of ascorbic acid
C – Standard sepsis treatment
O – Safety of vitamin C and end-organ failure

Background

The CDC reports that one in three patients who die in a hospital have sepsis and according to JAMA\textsuperscript{1}, mortality has remained stable in recent years. There has been recent research looking at adjuncts to our standard treatment that may affect outcomes. For example, vitamin C (ascorbic acid) has been researched for its antioxidant, anti-inflammatory properties. In 2017, Marik et al demonstrated the benefit of intravenous hydrocortisone, thiamine, and vitamin C (in addition to standard care) on patients with septic shock. This study has changed the practice of some of our critical care colleagues and there is now a “Marik protocol” order set available at our institution. Our aim is to determine if the administration of vitamin C is a safe adjunct and if it can influence outcomes in our patients who present in septic shock.

Trial 1


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4843590

Validity Rating: low risk of bias

The Basics

This was a single center, double-blinded, randomized control trial conducted in Tehran. Over a two year period this institution recruited 28 surgical critically ill patients with septic shock and a vasopressor...
requirement. They were randomized to receive standard care for septic shock (as outlined by Surviving Sepsis Campaign) and placebo or standard care with IV ascorbic acid administration over a three day period. Vasopressor requirement, duration of ICU stay, 28 day mortality, and adverse reactions secondary to ascorbic acid were monitored.

**Exclusion Criteria**

- Concomitant use of other antioxidants (vitamin E, selenium, and N-acetylcysteine)
- Corticosteroids administration
- Contraindication for high dose ascorbic acid administration (bilateral ureteric obstruction, chronic hemodialysis, iron overload, oxalate stone formers, hemochromatosis, and G6PD deficiency)

**Inclusion Criteria**

- Adults 18-65 years old
- Surgical critically ill patients (all were gastrointestinal surgeries)
- Diagnosis of septic shock with vasopressor requirement to maintain MAP >65 despite adequate fluid resuscitation

**Primary Outcome**

- Vasopressor dose and duration

**Secondary Outcomes**

- Duration of ICU stay
- 28 day mortality
- Ascorbic acid adverse reactions

**Follow-up**

The vasopressor dose and duration were monitored for the three days of treatment with ascorbic acid or placebo. All patients were followed for 28 days after treatment. No patients were lost to follow-up.

**Results**

Mean dose of vasopressor (norepinephrine) during the study period, mean dose of norepinephrine in the first 24 hours of enrollment, total dose of norepinephrine in the first 24 hours, and duration of receiving norepinephrine were significantly lower in the ascorbic acid than the placebo group. There was no significant difference in the duration of ICU stay. The 28 day mortality was significantly lower in the ascorbic acid group. There were no adverse events of the use of ascorbic acid in the treatment group.

**Limitations/Bias**
Limitations include small sample size, short period of intervention, and no assessment of the patients’ serum ascorbate baseline level. This is also a very specific population and the findings may not be reproduced in our patients.

**Trial 2**


[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937164](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937164)

**Validity Rating**: low risk of bias

**The Basics**

This was a single center, double-blinded, phase one safety trial conducted in Virginia. Over a one year period, 24 patients were admitted to their Medical Respiratory ICU and randomized to receive placebo, low-dose ascorbic acid, or high-dose ascorbic acid over four days. Patients were monitored for adverse effects of ascorbic acid. SOFA scores, plasma ascorbic acid levels, and markers of inflammation were also monitored.

**Exclusion Criteria**

The authors do not mention specific exclusion criteria. However, 35 patients were recruited over a one year period and nine were not included in the study. Three of those nine had terminal cancer and were not expected to survive for 24 hours. Consent was either refused or unable to be obtained in the six other patients.

**Inclusion Criteria**

- Patients met criteria for severe sepsis (presence of SIRS, suspected infection, and presence of sepsis-induced organ dysfunction) within 48 hours of ICU admission

**Primary Outcome**

- Vitamin C safety and tolerability measured as adverse event frequency and severity

**Secondary Outcome**

- Change in SOFA scores (marker for end-organ dysfunction)
- Plasma ascorbic acid levels
- Trend in markers of inflammation

**Follow-up**

Patients were followed for 28 days following the four-day treatment period.
Results

24 patients were randomized 1:1:1 to the treatment groups. Two patients that were enrolled and randomized to the high dose ascorbic acid group were removed from the study. One patient was withdrawn by family and transferred to another institution and the other was found to have hemophagocytic syndrome and sepsis – both were excluded from the analysis. During the four day infusion period, no patients were withdrawn due to study-related adverse events (i.e., hypotension, tachycardia, hypernatremia, or nausea/vomiting).

Plasma levels of ascorbic acid were all sub-normal in the patients at the time of enrollment. These levels fell in the placebo group and rose significantly in both the low- and high-dose ascorbic acid groups over the four day period.

SOFA scores were equal at baseline, rose in the placebo group, and dropped in the treatment group (faster rate of decline in the high dose group). Those receiving ascorbic acid also had a much faster rate of decline of inflammatory markers.

Limitations/Bias

This study has a very small sample size. In addition, the secondary outcomes do not include outcomes like mortality. They use SOFA scores and lab values as markers for improvement, but it is unclear if these surrogate endpoints translate to clinical improvement.

Resources: