ASCORBIC ACID (VITAMIN C) IN SEPSIS

SUMMARY

The global burden of sepsis is substantial with an estimated 15 to 19 million cases per year. With timely diagnosis and improvements in supportive care, the 28-day mortality from sepsis has declined to about 25%; however, the mortality rate from septic shock remains as high as 50%. Free radicals have emerged as important mediators in sepsis at the cellular level. Circulating levels of vitamin C (ascorbic acid) have been found to be low in patients with sepsis. Ascorbic acid infusion appears to be a useful adjunct in minimizing the effects of free radical injury in septic patients. Parenteral administration of ascorbic acid raises plasma and tissue concentrations of the vitamin and may decrease morbidity in sepsis.

RECOMMENDATIONS

- **Level 1**
  - None
- **Level 2**
  - None
- **Level 3**
  - Ascorbic acid 1.5 gm IV q 6 hours should be administered for 4 days or until ICU discharge in patients with severe sepsis or septic shock. Each dose of ascorbic acid should be diluted in 100 ml of dextrose 5% solution or normal saline and infused over 30-60 minutes.
  - Septic patients receiving ascorbic acid should also be administered:
    - Hydrocortisone 50 mg IV q 6 hours for 7 days or until ICU discharge followed by a taper over 3 days.
    - Thiamine 200 mg IV q 12 hours for 4 days or until ICU discharge.

INTRODUCTION

Subnormal Vitamin C (ascorbic acid) concentrations in plasma and leukocytes are common in critically ill septic patients. Plasma ascorbic acid levels correlate inversely with multiple organ failure and directly with survival. Intravenous ascorbic acid injection may protect several microvascular functions including capillary blood flow, microvascular permeability, and arteriolar responsiveness to vasoconstrictors and vasodilators. Intravenous injection of ascorbic acid reverses the maldistribution of capillary blood flow in septic models (1).

The role of free radicals and endothelial damage is well documented in the literature. Up-regulation of xanthine oxidase, triggered by histamine, leads to formation of oxygen free-radicals resulting in significant cellular injury. This is enhanced by impairment in native antioxidant mechanisms and additional free-radical production by neutrophils (2,3). This increase in xanthine oxidase has been shown to correlate with mortality (4). Ischemia/reperfusion-induced and sepsis-induced endothelial dysfunction is initiated by increased amounts of reactive oxygen species (ROS) produced by the induction of enzymes such as nicotinamide adenine dinucleotide phosphate-oxidase (NOX) and uncoupling of mitochondrial oxidative phosphorylation

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

and endothelial nitric oxide synthase (eNOS). Preclinical studies show that high-dose ascorbic acid can prevent or restore ROS-induced microcirculatory flow impairment, prevent or restore vascular responsiveness to vasoconstrictors, preserve endothelial barrier function, and augment antibacterial defense. These protective effects against oxidative stress appear to mitigate organ injury and dysfunction (5).

LITERATURE REVIEW

Ascorbic Acid - Animal Studies

In animal models of sepsis, intravenous ascorbic acid injection increases survival and protects microvascular function including capillary blood flow, microvascular permeability, and arteriolar responsiveness to vasoconstrictors and vasodilators (1). Among the clinically relevant models of polymicrobial sepsis are cecal ligation and puncture (CLP) and feces injection into the peritoneum (FIP). CLP in animals increases oxidative stress markers and decreases ascorbic acid concentrations in plasma and tissue. Injection of ascorbic acid (200 mg/kg IV) increases survival in CLP mice. Survival rates at 24 hours post-CLP are 9% in saline-injected and 65% in ascorbic acid-injected mice. In FIP mice, 24-hour survival is 19% after saline injection and 50% after intravenous (10 mg/kg IV) ascorbic acid injection (1).

Ascorbic Acid Infusion – Human Studies

Marik and colleagues conducted a retrospective study looking at the effects of ascorbic acid in septic ICU patients (6). The study compared the outcome and clinical course of consecutive septic patients treated with intravenous ascorbic acid, hydrocortisone and thiamine during a 7-month period (treatment group) compared to a control group treated during the preceding 7 months. The diagnosis of severe sepsis and septic shock were based on the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions. The primary outcome was hospital survival. There were 47 patients in both treatment and control groups with no significant differences in baseline characteristics between the two groups. The treatment group was treated with intravenous hydrocortisone, ascorbic acid and thiamine within 24 hours of ICU admission. During the treatment period, patients with severe sepsis or septic shock were treated with intravenous ascorbic acid (1.5 gm IV q 6 hours for 4 days or until ICU discharge), hydrocortisone (50 mg IV q 6 hours for 7 days or until ICU discharge followed by a taper over 3 days) as well as intravenous thiamine (200 mg IV q 12 hours for 4 days or until ICU discharge). The hospital mortality was 8.5% in the treatment group compared to 40.4% in the control group ($p<0.001$). This data suggests that the early use of intravenous ascorbic acid, together with corticosteroids and thiamine may prove to be effective in reducing the mortality of patients with severe sepsis and septic shock.

Zabet et al. conducted a double‐blinded randomized clinical trial to study the effect of high-dose ascorbic acid on vasopressor drug requirement in critically ill surgical patients with septic shock (7). During the study period, 28 adult patients with septic shock requiring a vasopressor drug to maintain mean arterial pressure (MAP) >65 mmHg despite adequate fluid resuscitation were recruited. Septic shock was defined based on the Surviving Sepsis Campaign. Patients were randomized to ascorbic acid or placebo. Patients in the ascorbic acid group received 25 mg/kg IV ascorbic acid every 6 hours for 72 hours. Each dose of ascorbic acid was diluted in 50 ml of dextrose 5% solution and was administered as IV infusion over 30 minutes. Patients in the placebo group received 50 ml of dextrose 5% solution as an IV infusion over 30 minutes. Severity of illness based on the SOFA and APACHE II scores was comparable between the groups at the time of enrollment. Mean dose of vasopressor (norepinephrine) during the study period (7.44 ± 3.65 vs. 13.79 ± 6.48 mcg/min, p=0.004), mean dose of norepinephrine in the first 24 hours of enrollment (6.51 ± 3.53 vs. 12.58 ± 5.99 mcg/min, p=0.003), total dose of norepinephrine in the first 24 hours (156.42 ± 84.81 vs. 302.14 ± 143.85mcg, p=0.003), and duration of receiving norepinephrine (49.64 ± 25.67 vs. 71.57 ± 1.60 hours, p= 0.007) were significantly lower in the ascorbic acid group. Additionally, 28-day mortality was significantly lower in the ascorbic acid than the placebo group (14.28% vs. 64.28%; p=0.009). No ascorbic acid related adverse events were identified. This study concluded that high‐dose ascorbic acid may be considered as an effective and safe adjuvant therapy in critically ill surgical patients with septic shock.

Guidelines for Infusion

Additional studies must still be conducted to delineate the optimal infusion rate of ascorbic acid in patients with sepsis. The available Class III data indicates ascorbic acid should be infused at a concentration of 25 mg/kg IV every 6 hours for 72 hours. Each dose of ascorbic acid should be diluted in 50 ml of dextrose 5% solution and infused over 30 minutes (6).

REFERENCES

1. Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. Biofactors 2009; 35(1):5-13.
2. Till GO, Guilds Ls, et al. Role of xanthine oxidase in thermal injury of skin. Am J Pathol 1989; 135:195-202.
3. Horton JW. Free radicals and lipid peroxidation mediated injury in burn trauma: The role of antioxidant therapy. Toxicology 2003; 189:75-88.
4. Ritter C, Andrades M, et al. Plasma Oxidative parameters and mortality in patients with severe burn injury. Intensive Care Medicine 2003; 29:1380–1383
5. Oudemans-van straaten HM, Spoelstra-de man AM, De waard MC. Vitamin C revisited. Crit Care 2014; 18(4):460.
6. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest 2017; 151(6):1229-1238.
7. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose ascorbic acid on vasopressor requirement in septic shock. J Res Pharm Pract 2016; 5(2):94-100.

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