Protocol Title: High Dose Intravenous Ascorbic Acid in Severe Sepsis

NCT02734147

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NEW PROTOCOL DEVELOPMENT FORM

Part A

Date of Request: 12/21/15	
Name of Project/Study: The efficacy of intravenous ascorbic acid in patients with severe sepsis	
Principal Investigator: Ryan Arnold, MD	**Sub-Investigators:** Jamie M. Rosini, PharmD Matthew Barrett, MD Colleen Ellis, FNP-C,MSN Brett Schuchardt Andrea Passarelli, PharmD Debra Marco, RN
Category (*Admin/Critical Care/Resident Education, Ultrasound, Other):* Critical Care	**Lead Content Expert:** Ryan Arnold, MD
Target Start Date: 1/2016	**Target Date of Completion:** 1/2017

Part B

1. Study Question

a) Clearly define the reason(s) for the study:

A phase I safety trial of intravenous (IV) ascorbic acid in patients with severe sepsis demonstrated that ascorbic acid may positively impact the extent of multiple organ failure. Our phase 2 study will investigate those efficacy findings through evaluating the ability of ascorbic acid to decrease organ dysfunction using a modified SOFA (mSOFA) score in severe sepsis.

b) Clearly define the goal(s) for the study:

This is a randomized, double-blind, placebo-controlled study that will evaluate the efficacy of high dose IV ascorbic acid in severe sepsis (mSOFA score, , hospital length of stay, mortality)

c) Hypothesis Statement:

Severe sepsis patients administered high dose IV ascorbic acid (200 mg/kg/day) will have improvements in their mSOFA scores compared to patients who receive placebo

2. Background Information and Literature Review:

Despite an organized treatment approach outlined in expert-consensus guidelines for sepsis with fluid resuscitation to treat hypovolemia, antibiotics to target the infectious insult, and vasopressors for hypotension, mortality rates for sepsis remain high and the incidence continues to rise, making sepsis the most expensive inpatient disease.[i] Recent research has described the therapeutic benefits associated with ascorbic acid treatment for sepsis.[ii] Our **objectives** are to perform a *randomized-controlled clinical trial*

investigating the ability of ascorbic acid administration to decrease organ dysfunction in severe sepsis. The widespread occurrence of microvascular dysfunction in sepsis leading to tissue hypoxia, mitochondrial dysfunction, and ATP depletion, gives rise to organ failure.[iii] **Patients with organ failure and sepsis (severe sepsis) are at a higher risk of death** than patients with organ failure alone. Critically ill patients may have an **increased requirement for ascorbic acid** in sepsis and these patients frequently have levels below normal. Ascorbate, the redox state of ascorbic acid, has been shown to **correlate inversely with organ failure (human literature) and directly with survival (animal studies)**.[iv,v] Intravenous ascorbic acid therapy decreases organ failure by providing a **protective effect on several microvascular functions** including improving capillary blood flow, decreasing microvascular permeability, and improving arteriolar responsiveness to vasoconstrictors. Defining the utility of novel agents to augment our care for severe sepsis is an important task as we continue our institutional focus on sepsis care.

3. Study Plan/Design/Methodology

The primary goal of this interventional pilot study is to apply positive initial efficacy data with ascorbic acid in the severe sepsis patient population to calculate the effect size necessary to power a multi-center randomized controlled trial. The sample size estimate is of critical importance for the randomized controlled trial that will be powered to show the superiority of IV ascorbic acid compared to standard care in the severe sepsis population to decrease the incidence of organ failure and death.

This is a prospective, double-blind, placebo-controlled study. Patients will be randomized within 12 hours from ED arrival using block randomization per 10 patients with pre-randomization envelopes generated using an online randomizer. The study blind will be established and maintained by the pharmacy department where the study drug will be prepared and dispensed. Subjects will be assigned to one of two groups: placebo or ascorbic acid. The ascorbic acid group will receive 67 mg/kg IV ascorbic acid in approximately 115 ml normal saline over 30 minutes three times a day (TID) (200 mg/kg/day) for 72 hours. Actual body weight or patient stated weight will be used to calculate a dose with a maximum daily dose of 25 grams. The placebo group will receive approximately 115 ml 0.9% NaCl over 30 minutes TID for 72 hours. The study intends on enrolling 20 patients in each group.

4. Definition of the Study Population

a) What patients meet the criteria for inclusion into this study?

Inclusion criteria

Patients with:

1) A suspected or confirmed infection with an order for intravenous antibiotics or antivirals[vi,vii]

2)

≥ 2 Quick SOFA (qSOFA) score OR a PIRO (Predisposition, Infection, Response, and Organ Failure) score ≥ 10

Definition of qSOFA

a) altered mentation

b) respiratory rate ≥22 breaths per minute

c) systolic blood pressure ≤ 100 mmHg

Exclusion criteria

1) Age < 18 years
2) Pregnancy or breastfeeding
3) Requirement for immediate surgery within the treatment protocol timeframe
4) Inability to obtain written informed consent from subject or surrogate
5) Patient to receive comfort measures only
6) Patient diagnosed with G6PD
7) Patient diagnosed with active Hepatitis B
8) Patient with known history of Kidney Stones

b) Clearly define time period:

We intended to enroll for a one year time period or until 40 patients are enrolled.

c) Based on criteria in a) and b) – what potential information sources could the study population be derived from:

Patients will be screened in the emergency department for inclusion and exclusion criteria and if met, will be provided with informed consent.

6. Develop Data Collection Plan

a) Develop data dictionary:

Data will be collected and managed using REDCap (Research Electronic Data Capture). **Organ failure** will be assessed using a modified Sequential Organ Failure Assessment (mSOFA) score (see below). Scores will be calculated at enrollment, at 24, 48, and 72 hours. Laboratory data and physiological measures for calculating mSOFA scores will be monitored daily and recorded. **Plasma ascorbic acid levels** will be collected at enrollment and at 32 hours or prior to the 5th dose). Ascorbic acid levels will be sent out for analysis as per standard send out laboratory procedures for ascorbic acid levels. The mSOFA calculation will be performed at time 0 and daily. The investigative team will monitor for adverse events such as hypotension (defined as a systolic blood pressure < 90 mmHg), tachycardia (defined as an increase in heart rate of 20 beats per min), nausea, vomiting, or allergic reactions (rash, urticaria, hives, etc) prior to infusion (+/- 30 mins) and post infusion (+/- 30 mins). If an adverse event listed above is observed, the drug infusion will be stopped. If the patient becomes unstable, a rapid response team (RRT) alert will be called (floor patients) or a higher level of care consultation will be placed (ICU patients) as per hospital protocol. If the event resolves, the drug infusion will be restarted at 50% of the original infusion rate. If the event reoccurs, the patient will be removed from the study. A physical exam (see attached form) will be performed within the scope of practice of a practitioner caring for the patient or investigative practitioner and reviewed by one of the investigative practitioners prior to the first infusion and daily during the study period. Adverse events including hypernatremia (defined as > 146 mmol/L) will be monitored daily and documented by the investigators for 4 days after initial infusion. The investigators will assess these events to determine if clinically significant and relevant to the study drug. The patient will be followed until discharge for serious adverse events and death. Because high doses of ascorbic acid interact with point of care glucose testing (falsely elevates glucose reading), nurses will be educated that if a patient is on a

sliding scale insulin regimen, that the glucose labs should be sent to the lab and point of care measurements avoided for insulin administration.

A Data Monitoring Safety Board (DSMB) will review all outcome and safety data at 6 months or after the enrollment of 20 patients whichever comes first. The DSMB will meet again if needed based on the findings of their initial data review. **Mortality** (all-cause in-hospital mortality) will also be measured. Each patient will also be followed for the secondary outcome assessment of resource utilization 1) ICU length of stay; 2) In-hospital length of stay; and 3) In-hospital charges.

Data elements to be collected: age, gender, race, source of sepsis, systemic inflammatory response (temperature, heart rate, white blood cell count, bands), mSOFA score (see below), ascorbic acid levels at baseline and approximately 31:30 hours (30 minutes prior to 5th dose), hospital length of stay, ICU length of stay, in-hospital mortality, in-hospital charges.

PIRO:

P score		I score		R score		O score	
	Points		Points		Points		Points
Age < 65	0	Pneumonia	4	Respiratory rate > 20	3	BUN > 20	2
Age 65-80	1	Skin/soft tissue infection	0	Band > 5%	1	Respiratory failure- intubated, CPAP, BiPaP OR Hypoxemia- oxygen requirement higher than baseline	3
Age > 80	2	Any other infection	2	Heart rate > 120	2	Lactate > 4.0	3
COPD	1					SBP < 70	4
Liver disease	2					SBP 70-90	2
Nursing home resident	2					SBP > 90	0
Malignancy without metastases	1					Platetlet < 150,000	2
Malignany with metastases	2						
Total possible points	9		4		6		14

mSOFA (bilirubin removed):

	0	1	2	3	4
Respiration					
SPO_2/FiO_2	> 400	< 400	< 300	< 200	< 100
Coagulation					
Plateles x $10^3/mm^3$	> 150	< 150	< 100	< 50	< 20
Cardiovascular					
Hypotension, dose mcg/kg/min	MAP > 70	MAP < 70	Dopamine ≤ 5 ANY Dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Epinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine > 15 Norepinephrine > 0.1 Epinephrine > 0.1 Phenylephrine > 0.8 ANY Vasopressin
CNS					
Glasgow Coma Score	15	13 - 14	10 - 12	6 - 9	<6
Renal					
Creantinine (mg/dL)	<1.2	1.2 - 1.9	2.0 - 3.4	3.5 - 4.9	≥ 5.0

Protocol procedures:

			Hours										
Activity	Baseline	Enrollment (prior to study drug)	0	8	16	24	31.5	32	40	48	56	64	72
Informed Consent	X	X											
Study Drug/Placebo Infusion			X	X	X	X		X	X	X	X	X	X
mSOFA Score		X				X				X			X
Plasma ascorbic level		X					X (30 mins prior to 5th dose)						
H&P	X												
Vital Signs (0-30 minutes PRE and POST study drug infusion)			X	X	X	X		X	X	X	X	X	X
Concomitant Medications	X												
Physical exam	X					X				X			X
Adverse Events/Serious Adverse Events			X	X	X	X		X	X	X	X	X	X

d) Location of study records and database.
REDCap (a secure, web-based data collection and storage tool) and secured CCHS hard drive

a) Determine if database will be used for data collection/entry: If so, which one.
REDCap

b) Sampling considerations:
A sample size of 40 patients was determined to be adequate to determine initial efficacy data with ascorbic acid in severe sepsis patients and define a sample size needed to study this

outcome through a multicenter trial.

e) Define how and when data will be collected:
Data will be collected at CCHS using PowerChart.

7. Develop Analysis Plan (Consultations w/ Value Institute or Mia Papas)

Data analysis of all assimilated data will take place over 2 months with statistical review of the primary outcome assessment and secondary endpoints associated with the intervention by a Value Institute biostatistician. We will perform an intention to treat analysis with a planned secondary analysis of patients with low initial ascorbic acid levels.

8. Risks/Benefits

a) What are the potential risks to the study population?
Risks associated with ascorbic acid include nausea/vomiting, , false elevations in point of care blood glucose testing, and hyperoxaluria

b) What are the benefits of this study?
Expected benefits of this study are decreased rates of organ dysfunction and mortality with preliminary data to study this population in a larger multicenter study.

9. Data Communication Plan (Where will results be presented?)

We intend on submitting our results to the Society of Academic Emergency Medicine or the Society of Critical Care Medicine annual research conference and then publishing the manuscript in a relevant journal.

10. References

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637.
2. Fowler AA, Syed AA, Knowlson S, Schulthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Translat Med. 2014.12:32.
3. Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. Internat Union Biochem Molec Biol. 35(1):5-13.
4. Borrelli E, Roux-Lombard P, Graua GE, Girardin E, Ricou B, Dayer J, et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. Crit Care Med. 1996;24(3):392-7.
5. Wu F, Wilson JX, Tyml K. Ascorbate protects against impaired arteriolar constriction in sepsis by inhibiting inducible nitric oxide synthase expression. Free Rad Biol Med. 2004;37(8):1282-9.
6. Grissom CK, Brown SM, Kuttler KG, Boltax JP, et al. A modified sequential organ failure assessment (MSOFA) score for critical care triage. Disaster Med Public Health Prep. 2010;4(4): doi:10.1001/dmp.2010.40

11. Timeline and Publication Plan

Date	Task
12/2015	Present proposal to EM Faculty/Content Expert
12/2015	Present proposal to Research Governance **Research Governance meets the 1st and 3rd Thursday of each month*
12/2015	Submit proposal to IRB
01/2016	Initiate study; Enrollment/Data collection
01/2016	Complete first sections of the manuscript
06/2016	DSMB review
01/2017	Complete data collection
01/2017	Data analysis
02/2017	Abstract submission/Communication of results
04/2017	Complete draft manuscript
05/2017	Present project at regional/national forum **Note: Travel and conference expenses will be paid according to program SOPs upon receipt of draft manuscript.*
07/2017	Submit manuscript to journal and close out project with IRB

NOTABLE RESEARCH FORUMS and SUBMISSION DEADLINES

FORUM	DEADLINE	CONFERENCE
Society of Academic Emergency Medicine (SAEM)	Early December	Mid May
American College of Emergency Physicians	Early April	End October
National Association of EMS Physicians (NAEMSP)	Mid August	Mid January
American Academy of Emergency Medicine (AAEM)	Mid October	January/February
Council of Emergency Medicine Residency Directors (CORD)	December	March/April

[i] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637.
[ii] Fowler AA, Syed AA, Knowlson S, Schulthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Translat Med. 2014.12:32.
[iii] Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. Internat Union Biochem Molec Biol. 35(1):5-13.
[iv] Borrelli E, Roux-Lombard P, Graua GE, Girardin E, Ricou B, Dayer J, et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. Crit Care Med. 1996;24(3):392-7.
[v] Wu F, Wilson JX, Tyml K. Ascorbate protects against impaired arteriolar constriction in sepsis by inhibiting inducible nitric oxide synthase expression. Free Rad Biol Med. 2004;37(8):1282-9.
[vi] Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372:1629-38.
[vii] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/SCCP/ATS/SIS international sepsis definitions conference. Intens Care Med. 2003;29:530-8.