Vitamins B_1 and C to Improve Outcomes in Patients With Severe Sepsis

NCT number NCT03592277

Document Date 08/19/2020

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Introduction and Need

Despite continued advances in medical science, the management of sepsis remains a challenge. Sepsis is the presence of a systemic infection creating a cascade of downstream effects, manifesting in a patient as acute end organ dysfunction. Estimates of upwards of 750,000 cases of

severe sepsis were identified annually in the United States and more than half of these patients required management in an intensive care unit (ICU). Severe sepsis remains highly morbid and costly with a national mortality rate of 28.6% and an estimated $16.7 billion invested in the care of these patients.[1] Internationally the disease is even more widespread with an estimated 19 million people affected annually.[2] These numbers likely underestimate the magnitude of the disease and its repercussions. Iwashyna et al. studied the long term effects of surviving sepsis and found that people who survived this acute illness exhibited more severe cognitive decline and functional dependence than their previously healthy counterparts.[3] Given the massive burden of this disease, it is prudent to seek out novel approaches to treat severe sepsis and septic shock.

Background and Rationale

Extensive research in animal models has shown a benefit to using intravenous (IV) vitamin C in sepsis.[4,5] It is a cofactor for multiple enzymatic functions.[6] In addition, one study in particular found that critically ill patients, including those with sepsis have significantly lower levels of circulating vitamin C during their acute illness than their healthy counterparts. Furthermore, the investigators found critically ill patients who were administered an infusion of vitamin C every six hours maintained normal plasma levels for the largest amount of time.[6] One study showed that critically ill patients required up to 3 grams per day of vitamin C just to return their plasma concentrations to normal baseline levels.[7] Additional research indicates that critically ill patients are often thiamine-deficient which is frequently missed and not treated by their clinicians.[8,9]

Marik et al. published a novel study implicating the use of IV vitamin C, vitamin B_1, and hydrocortisone resulted in a significantly lower mortality rate for their septic patients. His team explored the utility of these medications as compared to historical controls of their previously treated septic patients.[10] This study, while novel and inspiring, was designed with the acceptance of multiple confounders and potential for bias including the retrospective nature, the lack of randomization, and the lack of blinding. We propose investigating the use of IV vitamins B_1 and C in a randomized, prospective trial, eliminating the potential for selection bias.

Hypotheses

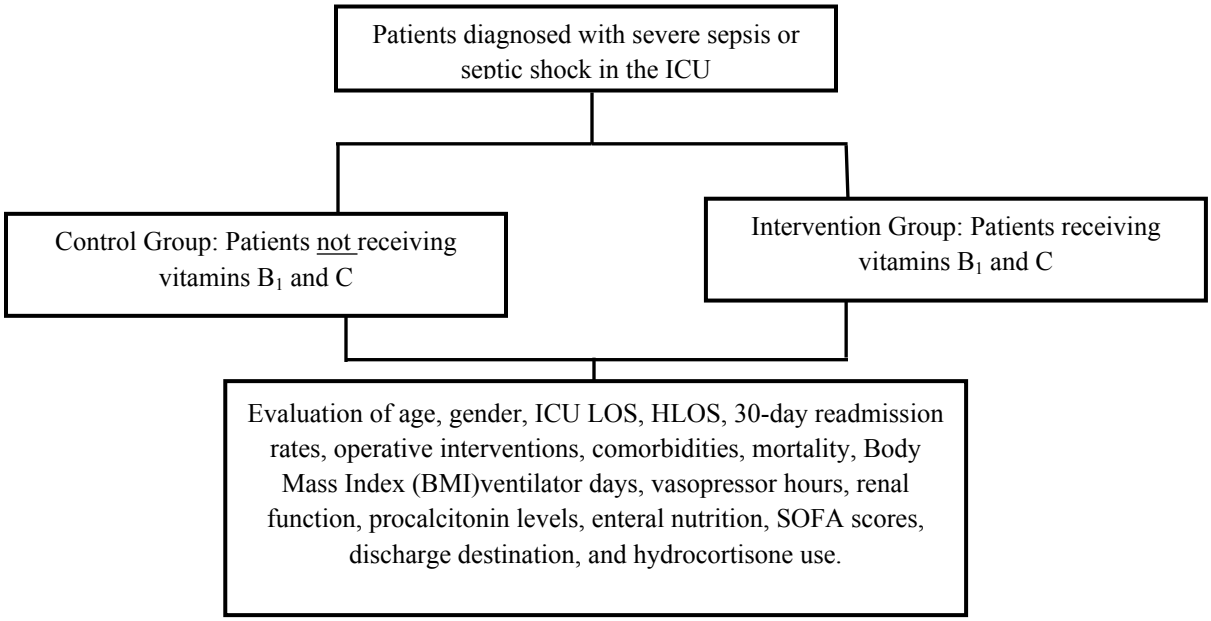
1. Primary Hypothesis: Septic patients in the ICU who receive IV vitamins B_1 and C will demonstrate a decreased mortality rate compared to septic patients who do not receive IV vitamins B_1 and C.
2. Secondary Hypotheses: Patients receiving IV vitamins B_1 and C
    a. will have shorter hospital length of stays (HLOS)
    b. will have shorter ICU length of stays (ICU LOS)
    c. will demonstrate a lower 30-day readmission rate
    d. will have fewer ventilator days
    e. will have fewer hours on vasopressors
    f. in addition to IV hydrocortisone for refractory septic shock will have a more profound reduction in mortality when as compared to those receiving IV vitamins B_1 and C alone

g. who also record to higher Sequential Organ Failure Assessment (SOFA) scores will have a more significant reduction in mortality than patients who record lower SOFA scores

Objectives

The objective of this study is to determine if the administration of IV vitamins B_1 and C are effective in decreasing the mortality rates of patients with severe sepsis or septic shock. In addition, we will investigate if there are benefits to those patients who also receive hydrocortisone in an effort to explore the synergistic relationship that vitamins B_1 and C have with hydrocortisone.

Overview of Study Design



Patient Selection Criteria

1. Inclusion Criteria: Patients admitted to the ICU at Saint Francis Hospital and Medical Center who are:
    a. Between the ages of 18 and 90 years old
    b. Have severe sepsis or septic shock
        i. Severe sepsis and septic shock will be defined by the Surviving Sepsis 2012 guidelines[11]
    c. Weight more than 30 kg
    d. Full code

2. Exclusion Criteria: Patients
    a. Not diagnosed with severe sepsis or septic shock
    b. Younger than 18 or older than 90 years old
    c. Who are pregnant
    d. Weigh less than 30 kg

e. Currently on hemodialysis
f. Not located in the ICU
g. Do not resuscitate (DNR) or do not intubate (DNI), no escalation of care, or comfort measures only (CMO)

Enrollment/Randomization

Once identified, patients who meet inclusion criteria will be approached. The majority of patients are likely to be intubated and sedated at the time of their diagnosis of severe sepsis or septic shock. In these cases, the next of kin or consenting party will be approached for each patient. The providers in the ICU, mainly physician's assistants (PAs) and residents, always contact patient's family members for consent for central lines and other invasive procedures while in the ICU. The study staff will speak to this same consenting person (in person or on the phone) and will ask them about the potential enrollment of their loved one in the study. In the absence of documentation of a healthcare proxy or conservator (as is often the case with septic patients, as it is an unexpected illness), priority will be given to the patient's spouse, followed by an adult child, followed by a parent, followed by an adult sibling. .

Due to the impact of the COVID-19 pandemic and associated restrictions and worry, it has been increasingly challenging to provide informed consent *in person* with legally authorized representatives. Hospital restrictions combined with a general reluctance of LAR's desire to come to the hospital and risk exposure makes in-person consent problematic. Consent will be obtained via one of two methods: (1) obtained in-person and documented by double signature, or (2) obtained telephonically with an additional hospital signatory witness. The research team will then memorialize written consent by post (mail) or electronic mail, when possible, but telephonic consent will be sufficient for recruitment of subjects and protocol start. If the consenting party is only available via phone, the study will be discussed with this Legally Authorized Representative, and additional family member as desired, thoroughly, and the research staff will then return a call at a reasonable interval, usually in two hours, to respond to any questions. Questions provided immediately will be answered in real time. During the two hour interval, the consent form will be faxed or emailed to the legally authorized representative for review. This telephonic consent will be witnessed by another member of the hospital team to ensure that the study is clear to the family member and all questions have been answered. We will then randomize the patient and begin treatment. If and when the subject has regained the mental capacity to participate in the informed consent process, s/he will be approached by the research staff and consented clarified. If the patient does not continue consent, they will be withdrawn from the study.

Prior to the recruitment process the pharmacy will enter numbers 1-120 in ascending order into a randomizing website. This randomly assigned each number to either placebo or intervention. Prior to recruitment, kits in blocks of 10, containing either the placebo or unmixed forms of vitamin B_1 and C are made and placed in identical packages labeled with their corresponding number. These numbers will be assigned in ascending order corresponding to the order in which they are consented. Once ordered by the providers the pharmacy with open the identical kits and, if it is the intervention, mix the vitamin B_1 and C for IV administration. This process will ensure the study coordinators, healthcare providers, and the patients remain blinded. Vitamins B_1 and C will be ordered for all patients in Epic, giving the impression that all of those

enrolled are in the intervention group. However half the kits will contain the intervention and half will contain the placebo. This is being done due to logistical issues with preparing and storing the vitamin B_1 and C. Having premade kits allows the pharmacy to more easily prepare and distribute the vitamin B_1 and C. These also need to be refrigerated and given limited space kits will be made in blocks of 10 to limit crucial storage space the pharmacy needs for other medications.

We plan to enroll 120 patients; 60 in the control arm and 60 in the intervention arm. Our current mortality rate is 35% at Saint Francis Hospital and Medical Center for patients with severe sepsis and septic shock. We expect our mortality rate to decrease to 30% with this intervention. We believe this is a reasonable expectation given that Marik et al. demonstrated that his intervention group's mortality rate dropped from 40.4% to 8.5% after a similar intervention.[10] In order to demonstrate this difference, 120 patients are needed according to our power calculation.

Informed Consent/Ethical Issues

We anticipate a full board IRB approval, as this is a prospective study involving vitamins B_1 and C as the intervention. Appropriate patients will be approached and consented (often via proxy consent) by members of the research team. Patients will then be randomized by computer to receive vitamin C and vitamin B_1, or normal saline (control). The treating physicians, the research team, and the patients will all be blinded. The pharmacist mixing the drugs will be the only non-blinded team member.

Data will be kept on an encrypted, password-protected computer behind two locked doors. Data will be managed by the investigators who will each have their own login.

Study Workflow

Patients admitted to the ICU who have severe sepsis or septic shock will be identified by the nursing staff, PAs, or physicians caring for them. These patients' consenting party will be approached within 24 hours of their presentation to the ED in an attempt to obtain informed consent. Following consent, the pharmacy will be notified of the study patient, randomization will occur, and the mixed medications (control or intervention) will be delivered to the patient's bedside in the ICU. Consented patients will receive 1.5g of vitamin C in 100mL of 0.9% sodium chloride (normal saline) every six hours for four days or until discharge from the ICU, whichever happens first (seventeen dose maximum). In addition, they will receive 200 mg IV vitamin B_1 every 12 hours in 100 mL of normal saline for four days or until ICU discharge (whichever happens first, nine dose maximum). Patients in the control arm will receive the 100 mL of 0.9% sodium chloride every six hours and 100 mL of 0.9% sodium chloride every 12 hours to act as placebos for the vitamin C and B_1 respectively. Doses up to 200 mg/kg/day were found to be safe in humans in one study.[6] Several studies have been conducted in human subjects using IV vitamin B_1 and C, often at higher doses than proposed here, and have not seen serious side effects.[10,12-14]

Some patients may receive hydrocortisone IV for refractory septic shock outside of this study protocol. This will be at the discretion of the treating physician and will not be included in the randomized and blinded intervention. Hydrocortisone has been shown in some studies to help

in patients with refractory septic shock.[15,16] However, it is not uniformly employed. Patients receiving hydrocortisone will undergo a subgroup analysis to better elucidate the synergistic effects of hydrocortisone with vitamins B_1 and C.

After discharge, patients will be followed for 30 days to track hospital readmissions.

Reporting of Adverse Events

The study personnel will report adverse events as soon as they become aware of them and within 24 hours of them being informed. All adverse events or unanticipated problems will be reported to the IRB. If the adverse event is thought to be related to the intervention, the medication will be stopped and the patient will be withdrawn from the study. They will be monitored closely for resolution of the adverse event. In order to ensure that the patient receives the ideal treatment for their adverse reaction and their newly-discovered allergy is documented appropriately, the research staff will un-blind the ICU staff and themselves. This will be accomplished by keeping duplicate sealed randomization envelopes. In the case of an adverse event, the research staff will open this additional envelope and inform the treating physicians.

Side Effects

Possible side effects for patients receiving IV vitamin C include diarrhea, nausea, vomiting, heartburn, headache, insomnia, and nephrolithiasis. Possible side effects for patients receiving IV vitamin B_1 include nausea, hives, wheezing, or angioedema. In the event of these reactions, the patients will be treated immediately for their allergic reaction by the primary team and will be withdrawn from the trial as previously mentioned.

Study Withdrawal

All patients who have a serious adverse event thought to be directly related to the intervention will be withdrawn from the study. The patient or their consenting proxy may revoke consent and withdraw from the study at any point as participation is completely voluntary.

Statistical Issues

The intervention arm (vitamin B_1 and C) and the control arm (sodium chloride 0.9%) will be compared statistically for demographics and patient characteristics; including age, gender, comorbidities, need for operative intervention, enteral nutrition, and Body Mass Index (BMI). Outcomes between these two groups will also be compared including hours of vasopressor use, ventilator days, HLOS, ICU LOS, comorbidities, renal function measured by patients' GFR and creatinine levels, procalcitonin levels, SOFA scores, discharge destination, readmission rates, and mortality rates. We will do a subgroup analysis of patients with septic shock as compared to those with severe sepsis. We will also do a subgroup analysis of the patients who receive hydrocortisone as opposed to those who do not.

Fisher's exact test will be used to compare gender, operative intervention, rate of mortality and the 30-day readmission rate. Average BMI and average age will be evaluated via student's t-

test. Median number of ventilator days, average hours of vasopressor use, median daily SOFA scores, average procalcitonin levels, average creatinine levels, median GFR, median ICU LOS and median HLOS will all be compared via Mann-Whitney U test. A contingency table will be used to analyze the different types of enteral nutrition and patients' discharge destination. A multivariate regression analysis will be conducted to analyze patients' comorbidities.

Duration of Review

We will start recruiting patients on September 10,, 2018. We expect recruitment and data collection to take 12 months. Data analysis and completion of a manuscript is expected to take another 12 months.

All data will be kept on a password-protected and encrypted computer located behind two locked doors. We will retain all data for three years after the completion of the study. Following this, all data will be deleted from the hard drive where they will be kept.

Publication Plan

We plan to write and submit a manuscript for publication in a peer-reviewed journal.

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