Rapid Administration of Carnitine in sEpsis (RACE)

NCT01665092

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Study Protocol

This study was a prospective, randomized, blinded, placebo-controlled, clinical trial utilizing Bayesian response-adaptive randomization, and designed to assess the efficacy of L-carnitine to decrease the sequential organ failure assessment (SOFA) score of patients with septic shock. SOFA score is an organ failure scoring system consisting of 6 physiological systems that ranges from 0-24, and a score of 2 or more is required for the diagnosis of sepsis. The trial took place from January 2013 to February 2018 in the emergency departments and intensive care units of sixteen large urban medical centers in the United States. The research protocol was approved by the local institutional review boards and performed in accordance with Good Clinical Practice guidelines.

Participants

Patients presenting to the participating centers during the study period with septic shock were assessed for inclusion. Criteria for inclusion were patients of age ≥ 18 years with confirmed or presumed infection, the presence of two or more systemic inflammatory response criteria, enrollment within 24 hours of recognition of septic shock with initiation of a standardized sepsis treatment pathway, high dose vasopressors (norepinephrine > 0.05 mcg/kg/min; dopamine > 10 mcg/kg/min; phenylephrine >0.4 mcg/kg/min; epinephrine > 0.05 mcg/kg/min; or any vasopressin dose) to treat shock for ≥ 4 hours at the time of enrollment, cumulative sequential organ failure assessment (SOFA) score of ≥ 6, and blood lactate level > 2.0 mmol/L. Patients were excluded if they were pregnant or breastfeeding, had any primary diagnosis other than sepsis, had an established do not resuscitate status or advanced directive restricting aggressive care, any history of seizures, known inborn error of metabolism, anticipated surgery that would interfere with the 12 hour infusion, active participation in another interventional trial, cardiopulmonary resuscitation prior to enrollment, known allergy to L-carnitine, severe immunocompromised state (absolute neutrophil count <500/uL), or active warfarin treatment.

Eligible patients were screened 7 days per week using electronic medical record based reports of admitted patients receiving both antibiotics and vasopressors and/or pager-based alerts informing study staff regarding the initiation of a sepsis treatment pathway (which comprised the screening log), in addition to active screening of the emergency department tracking board to facilitate earlier identification. Each enrolled patient, or the patient's legally authorized representative (LAR), provided written informed consent prior to randomization and collection of data.

Treatment Assignment

After informed consent was obtained, a centralized web-based portal was used to determine treatment allocation. Patients were randomly assigned to one of three doses of L-carnitine or saline placebo. During an initial "burn in" period of 40 patients, participants were allocated equally among the treatment arms. From that point on, interim analyses were conducted every 12 patients. At each interim analysis the relative allocation probability of the three active arms were adjusted to be proportional to the probability each arm would lead to the greatest improvement in SOFA score. A site-based blocked randomization approach ensured that approximately one-third of participants were allocated to the control arm throughout the trial to maintain a sufficient allocation to control and to avoid confounding

from local changes in usual care. Predefined stopping rules for both efficacy and futility were determined prior to trial initiation. The statistical rationale and methodology has been published previously.

Treatment Interventions

The three treatment arms consisted of low (6 grams), medium (12 grams), and high (18 grams) doses of L-carnitine administered intravenously over a 12-hour period. The control (placebo) consisted of an identical volume of 0.9% saline placebo. Following randomization, research pharmacists used a web-based portal to determine treatment allocation. Pharmacists were the only individuals not blinded to treatment, and had no study-related contact with the investigators or participants. Pharmacists and staff prepared either L-carnitine or placebo in identical polypropylene infusion bags with labels including the study ID number, patient name, medical record number, and infusion rate. For each dose of L-carnitine, 33% of the total dose was administered as a 20 mL bolus over 2-3 minutes followed by a fixed rate continuous infusion of 1 L over the next 12 hours. The study solution was administered through intravenous catheters using FDA-approved medical equipment (IV tubing, IV pumps, etc). Levocarnitine was provided by Leadiant Biosciences (Gaithersburg, MD, United States; formerly Sigma Tau Pharmaceuticals) and maintained by pharmacy staff, with tracking of lot numbers of L-carnitine administered. For safety, clinical physicians could elect to break study blinding, though in no instance did this occur.

Assessments and Outcome Measures

During the study treatment period the patient's physiologic parameters, laboratory results, and medical treatments were recorded. Sex, race, and ethnicity were self-reported. An investigator performed a bedside assessment and recorded vital signs, vasopressor requirements, ventilator settings, and Glasgow Coma Scale at enrollment, 12, 24 and 48 hours later. At enrollment and 48 hours blood samples were sent to the clinical laboratory for platelet count, creatinine, and total bilirubin to ensure capture of SOFA score parameters. Non-protocol (clinical) laboratory results obtained between 0 and 48 hours were recorded. Patients were followed until hospital discharge or death and then up to one year using the patient's electronic medical record and phone calls to the patient or LAR, crossed referenced with the social security death index. Study data were collected and managed using REDCap.

The primary endpoints were change in SOFA score from enrollment to 48 hours, with negative numbers indicating improvement, and 28-day mortality. In the event of early death prior to 48-hours, last-value carried forward was utilized. Secondary outcomes included ICU and hospital length of stay and percentage of patients undergoing withdrawal of care. Three preplanned blinded interim safety analyses were performed: after a burn-in phase of 40 patients, and then after one-third and two-thirds of participants were enrolled. The unblinded results were reviewed by an independent Data Safety Monitoring Board with the authority to terminate the study for safety concerns or if the predefined stopping rules for efficacy or futility were fulfilled. The trial was registered on clinicaltrials.gov (NCT01665092) prior to initiation and this report was designed to conform to the recommendations of the CONSORT statement.

Statistical Analysis

The trial was considered positive if 1) the posterior probability of any dose decreasing the SOFA more than placebo exceeded 90%, and 2) given (1), there was at least a 30% predictive probability that the most promising dose would be successful in reducing 28-day mortality in a subsequent two arm, 2,000 total patient phase III trial. Based on Monte-Carlo simulation of 30,000 simulated trials enrolling up to 250 patients, the probability of a positive trial assuming no treatment effect (the type I error rate α) was 4.3%. The power of the trial (β) was dependent on the true treatment effect. If the true SOFA effects for the three L-carnitine arms were 0, 1 and 2, corresponding to mortality effects of 0, 6%, and 12%, then the power of the trial was 91.1%.

Changes in SOFA scores between groups were analyzed using a Bayesian approach, assuming a normal dynamic linear model dose response, and posterior probabilities are reported. The normal dynamic linear model is a Bayesian analogue to a smoothing spline whose smoothness is determining by a tuning parameter. The tuning parameter is given a prior and thus is determined by a combination of the prior and the observed data. The prior was selected during the design process to provide a smooth fit while maintaining the main features of the observed data.

Conditional on a declaration of SOFA reduction, predictive probabilities of success in a subsequent phase III trial were calculated using non-informative priors. Except for these primary outcomes, remaining data were analyzed using frequentist statistics. Categorical data were compared using Chi-square tests, while continuous variables were compared with ANOVA or Wilcoxon rank sum based on normality. All non-Bayesian tests were 2-sided with $p<0.05$ considered significant. All trial design simulations, interim analyses, and Bayesian statistics were performed using the Fixed and Adaptive Clinical Trial Simulator Software (FACTS, Berry Consultants, LLC; Austin, TX, United States),while frequentist statistics were conducted using STATA 15.1 (StataCorp LLC, College Station, TX). AEJ and MAP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.