Study Title: Double-Blinded Randomized Prospective Study On the Effects of Vitamin C, Hydrocortisone and Thiamine in Severe Sepsis and Septic Shock Patients.

October 25th 2017

AIM OF OUR STUDY:
The goal is to determine the effects on clinical course and outcome of patients with severe sepsis and septic shock treated with vitamin C, hydrocortisone and thiamine.

BACKGROUND:
This study will be conducted in the intensive care unit of Department of Gastroenterology, UMC Ljubljana. All of the patients with severe sepsis and septic shock admitted to the ICU in the past 12 hours will be screened for possible inclusion in the study. The diagnosis of severe sepsis and septic shock will be based on the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions.

PLAN OF THE STUDY:
After determining the eligibility for inclusion in our study, we will acquire the written consent from the patient or relatives. We will randomize the patient either in the treatment or placebo group. The randomization will be done before-hand with the online tool Research Randomizer (online: https://www.randomizer.org). After acquiring the randomized numbers, they will be placed in sealed envelopes. These envelopes will be available to the on-call doctor. The envelopes will then be sent to our outpatient clinic, where the studied substances will be mixed by a nurse, that will have no contact with the patients or the ICU staff. The substances will be marked with Vitamin C, Thiamine and Hydrocortisone, regardless if normal saline or the actual substances are inside the vials. Only this nurse will have the data regarding the contents of the vials.

Vitamin C: Vitamin C will be mixed as 1500 mg vitamin C in 50ml container, which will then be infused over 30 minutes to 1 hour. The bag will be labeled by the pharmacy as Vitamin C. The dosing schedule is 1500mg every 6 hours for 4 days or until discharge from the ICU.

Vitamin C placebo will consist of an identical container of 50cc normal saline (but with no vitamin C) and will be labelled vitamin C. Placebo will be infused over 30-60 minutes as per the infusion instructions of the active vitamin.

Hydrocortisone: Hydrocortisone will be mixed as 50 mg of Hydrocortisone in 50 ml of 0.9 % Nalco. Patients will be treated with hydrocortisone 50mg IV q 6 hourly for 4 days or until ICU discharge.

Hydrocortisone placebo will be provided in an identical 50 ml bag of 0.9 % NaCl. Off label treatment with hydrocortisone or another corticosteroid will not be allowed.

Thiamine: Intravenous thiamine will be given in a dose of 200mg q 12 hourly for 4 days or until ICU discharge. Placebo patients will receive a matching vial of Normal Saline.

Based on literature we expect that survival and clinical course in sepsis and septic shock is correlated with fluid resuscitation and vasopressor use. Because of this, all of the included patients will be monitored with invasive hemodynamic monitoring (in our ICU we will be using the Edwards EV 1000 monitors).

All of the patients will be treated the same as per internationally recognized guidelines for treatment of septic shock. While the use of corticosteroids in severe sepsis is off-label, the patients will be informed of possible side-effects. This fact will also be written in the consent.

Neither the patients or the relatives will receive no financial compensation for study inclusion. During the hospitalization, the patients will receive three different substances in dosages, that are non toxic. During the study we will conduct intermittent statistical analysis, and if we would discover increased mortality or severe side effects, the study will be terminated. The confidentiality of personal data will be protected accordingly with the rules and laws of patient's privacy. The identity of patients will not be disclosed. The data acquired during the study will be available to the study participant. The anticipated costs will be covered by the Department of Gastroenterology, UMC Ljubljana. No financial compensation will be given to researchers.

INCLUSION CRITERIA:

I. Diagnosis of severe sepsis or septic shock within 12 hours of admission in our ICU.
II. Informed consent.

EXCLUSION CRITERIA:

I. Age < 18 years
II. Pregnancy
III. DNR/DNI with limitations of care
IV. Patients with fatal underlying disease who are unlikely to survive to hospital discharge (e.g.: disseminated malignant disease)
V. Patients primarily admitted for acute coronary syndromes, acute cerebrovascular incidents or active GI bleeds
VI. Patients that need immediate surgical treatment
VII. Patients with HIV and a CD4 < 50 mm2,
VIII Patients with known glucose-6 phosphate dehydrogenase (G-6PD) deficiency.
IX. Patients with severe sepsis/septic shock transferred from another hospital
X. Patients with features of sepsis/septic shock > 24 hours
XI. Patients who require treatment with corticosteroids for an indication other than sepsis (chronic corticosteroid use, known Addison’s Disease, Ulcerative colitis, Crohn's disease...)

During the study we will be acquiring the following data from patients:

1. Age,
2. Sex,
3. Body weight,
4. Admitting diagnosis and source of infection,
5. Isolated pathogens,
6. Comorbidities,
7. The need for mechanical ventilation,
8. The use of vasopressors (all doses will be converted to Norepinephrine equivalents),
9. The duration of vasoactive therapy,
10. Daily urine output,
11. Fluid balance after 24 and 72 hours,
12. The presence of acute kidney failure
13. Duration of ICU stay and hospital stay,
14. Survival in ICU, hospital, after 28 and 60 days
15. Routine blood test for the first 4 days,
    a. creatinine
    b. WBC
    c. Platelets
    d. Bilirubin
    e. PaO_2/FiO_2 ration
    e. procalcitonin (PCT) and procalcitonin clearens
    f. lactate
    g. blood samples will be stored for possible additional analysis

The patients' admission APACHE II and APACHE IV scores will be recorded. The APACHE IV score allows calculation of the predicted hospital mortality and predicted ICU length of stay (LOS). The daily SOFA (Sepsis-related Organ Failure Assessment) score will be recorded for the first 4 treatment days.

STUDY END-POINTS:

PRIMARY END-POINT

i. Hospital Mortality

SECONDARY END-POINTS

i. 60-day mortality
ii. 28-day mortality
iii. Time to vasopressor independence. Defined as the time from starting the active treatment/placebo to discontinuation of all pressors
iv. PCT clearance (PCT-c) calculated using the following formula: initial PCT minus PCT at 96 hours, divided by the initial PCT multiplied by 100.
v. Delta SOFA score, defined as the initial SOFA score minus the day 4 SOFA score
vi. ICU mortality
vii. ICU length of stay (LOS) and ICU free days. ICU free days is calculated as the number of days alive and out of the ICU to day 28
viii. Hospital LOS

DATA ANALYSIS

Summary statistics will be used to describe the clinical data and presented as mean ± SD, median with interquartile range (IQR) or percentages as appropriate. Chi squared analysis with Fisher's exact test (when appropriate) and Student's t test (Mann Whiney U test for non-normal distributions) were used to compare data between the active treatment group and the placebo group with statistical significance declared for probability values of 0.05 or less.

EXPECTED RESULTS:

We expect a faster recovery, shorter hospitalization, shorter use of vasoactive drugs and better survival in treatment group vs. control group.

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