Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

A. Statement of Study Purpose and Rationale

Septic shock is a common problem in the intensive care unit and carries a high burden of morbidity and mortality. Septic shock is currently managed at CUMC according to the Surviving Sepsis Campaign Guidelines. However, other strategies for managing septic shock have been employed in other countries with encouraging results (1).

The most promising of these strategies involves the early use of Polymyxin B hemoperfusion. Polymyxin B is an antibiotic with high affinity for endotoxin, which is one of the principal components on the outer membrane of gram-negative bacteria (2). Endotoxin has been shown to be integral in the pathogenesis of septic shock and high levels of endotoxin activity are associated with worse clinical outcomes in the intensive care unit (3).

Polymyxin B has been bound and immobilized to polystyrene fibers in a medical device for hemoperfusion produced commercially in Japan under the name Toraymyxin (4). This device can effectively bind endotoxin both in vitro and in vivo and could potentially interrupt the biological cascade of sepsis (5).

A review of the literature suggests that Polymyxin B hemoperfusion has favorable effects on mean arterial blood pressure and PaO2/Fi02 ratio in patients with septic shock in randomized, non-blinded studies (6). However, the conclusions have been limited by the low methodological quality of the available studies and by the heterogeneity of the study populations.

A recent prospective study performed in ten intensive care units in Italy was stopped early after an apparent mortality benefit was shown in the Polymyxin B hemoperfusion group (7). However, the decision to stop this trial prematurely has been criticized because mortality was not a primary endpoint and because the trial was small and underpowered (8).

Septic shock of intra-abdominal origin is likely to be due to gram-negative bacteria or mixed pathogens and consequently associated with high endotoxin levels and there fore represents a condition in which endotoxin-therapy may be of particular benefit (9). We propose to evaluate the use of a Polymyxin B-immobilized fiber column in abdominal sepsis by performing a randomized, double-blind, placebo-controlled trial in a targeted population of patients with septic shock who undergo emergency surgery for intra-abdominal infection. Our hypothesis is that a mortality benefit will be seen in patients subjected to Polymyxin B hemoperfusion.

B. Description of Study Design and Statistical Analysis

Study Aims:

To assess whether the early use of Polymyxin B hemoperfusion in abdominal septic shock is associated with a mortality benefit.

Study Design:

Randomized, double-blind, placebo-controlled study of 830 patients with septic shock due to intra-abdominal cavity infection requiring emergency abdominal surgery. Assuming a mortality rate of 50% in the

placebo group, we will be powered to 80% to detect a 10% mortality benefit in the treatment group, assuming a p-value of 0.05.

Primary Endpoint:

Twenty-eight day mortality and all-cause mortality after emergent surgery for abdominal septic shock.

Variables to be collected:

1. Demographic

*Age

*Gender

*Race

2. Co-morbidites

*Apache Score

*Mean arterial blood pressure, mm Hg

*Vasopressor Dependency Index

*White Blood Cell Count

*PaO2/FiO2

*Creatinine

*Renal Replacement Therapy, No. (%)

3. Infection Profile
*Organisms cultured
*Sites of infection
*Multiple Sites/Multiple Organisms

4. Mortality
*28 Days
*In-Hospital

C. Description of Study Procedures:

Eligible patients will be randomly assigned within six hours of their surgery to treatment with either conventional medical therapy (according to the Surviving Sepsis Campaign guidelines) or conventional therapy with direct hemoperfusion of Polymyxin B. Mortality will be assessed at 28 days. Patients will be followed until the day of hospital discharge to account for all-cause in-hospital mortality.

D. Study Drugs/Medical Devices:

An adsorbent column containing 5mg of Polymyxin B per gram of polystyrene fiber (Toraymyxin, Toray Industries, Tokyo, Japan)

E. Study Questionnaires:

None

F. Description of Study Subjects:

Inclusion Criteria:

1. Adults age 18 and older
2. Septic Shock due to intra-abdominal cavity infection requiring emergent surgery
3. Septic shock as defined by the consensus definition of the American College of Chest Physicians

Exclusion Criteria:

1. Age less than 18
2. Unable to give consent as determined by treating physician
3. Pregnancy
4. Inclusion in other ICU studies in past month
5. Organ transplantation in the past year
6. Terminally ill patients classified as ?do not resuscitate.?
7. History of sensitivity to Polymyxin B or heparin
8. Uncontrolled hemorrhage within the last 24 hours
9. Severe Granulocytopenia (WBC count less than 500)
10. Severe Thrombocytopenia (Platelets less than 30,000)

G. Recruitment of Subjects

A study coordinator stationed in the emergency department will approach those patients meeting inclusion criteria and lacking exclusion criteria and informed consent for study participation will be obtained.

H. Confidentiality of Study Data:
Computerized records are kept on a secure, password-locked internet database. All patients? written records will be kept secure in a locked location on campus. I. Potential Conflict of Interest

None

J. Location of Study
Columbia University Medical Center

K. Potential Risks
Prior studies involving hemoperfusion with Polymyxin B have indentified cartridge clotting, bleeding and tachycardia as the primary risks associated with this therapy, although such occurrences are rare (6% or less of study subjects). There has been no evidence of neurotoxicity or nephrotoxicity associated with polymyxin hemoperfusion, although these are both side effects of systemic administration of polymyxin B.

L. Potential Benefits
The morbidity and mortality associated with septic shock is significant with numerous studies reporting a mortality rate exceeding fifty percent. Small studies have indicated that patients derive a mortality benefit from Polymixin B hemoperfusion, although this has not yet been studied in a large, randomized, placebo-controlled trial.

M. Alternative Therapies

None

N. Compensation to Subjects
None

O. Costs to Subjects
None
P. Minors as Research Subjects
Minors are not included in the study
Q. Radiation or Radioactive Substances

Not applicable

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