Resuscitation for repair of endothelial permeability in endotoxemia

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The main objective of the proposed study is to investigate the effect of plasma products and albumin on markers of endothelial function in a human endotoxemia model.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ancillary infectious topics
Study type	Interventional

Summary

ID

NL-OMON52233

Source
ToetsingOnline

Brief title
REP in endotoxemia

Condition

- Ancillary infectious topics

Synonym
blood poisoning, Sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Endothelium, Endotoxemia, Plasma

Outcome measures

Primary outcome

Levels of soluble syndecan-1

Secondary outcome

- Levels of endothelial permeability, such as sTM, vWF, A13 antigen and

activity.

- Blood count and coagulation tests (Hb, WBC, platelet count, PT, fibrinogen,

Ddimer, AT)

- Markers of tissue oxygenation such as lactate, NIRS, mitoPo2

- Markers of tissue perfusion such as SDF, cardiac output

- Physiologic measurements (MAP, heart rate, temperature)

- Arterial pulse wave morphology and non invasive cardiac output

Study description

Background summary

Acute critical illness can impair endothelial barrier function. In acute critical illness, such as sepsis, activation of the endothelium occurs, resulting in shedding of constituents of the glycocalyx (a layer of proteins lining the luminal vessel wall), resulting in endothelial permeability, which clinically manifests as accumulation of protein-rich fluid in the extravascular space, leading to edema. Together with inflammatory and coagulation responses, these changes impair microcirculatory perfusion and tissue oxygenation, resulting in multiple organ dysfunction. Also, non-infectious causes of acute critical illness can result in strong pro-inflammatory host-responses with ensuing endothelial hyperpermeability, such as pancreatitis or major surgery.

Acute critical illness often requires volume resuscitation with fluids. However, the downside of resuscitation is the occurrence of edema. Compared to a liberal fluid balance, a restrictive fluid balance reduces the occurrence of organ failure. Most likely, fluid resuscitation results in an increased gradient of leakage over the hyper-permeable endothelium. This poses a dilemma

to the treatment of sepsis, as fluid therapy is both a cornerstone of therapy as well as a foe in the occurrence of organ failure, calling for strategies which improve endothelial barrier function.

Different fluid strategies may have differential effects on endothelial permeability. Fluids with a low protein-content, such as crystalloids, seem to have negative effects on the endothelial glycocalyx, aggravating endothelial permeability. In sepsis patients, the amount of crystalloid fluid is associated with increased glycocalyx breakdown, which may be driven by inflammatory mediators, as shown in vitro. These effects may be related to the low protein content. Albumin, but not crystalloids, was found to protect against endothelial dysfunction and improved survival by inhibiting inflammatory and oxidative stress in a rodent endotoxemia model as well as in a hemorrhagic shock model. In clinical practice, albumin iscurrently used as an additive solution to supplement crystalloid fluid therapy.

The effect of albumin on the glycocalix appears less than with the use of plasma. Indeed, plasma was found to restore glycocalyx thickness and endothelial barrier integrity, resulting in less organ failure in models of hemorrhagic shock and sepsis. In critically ill patients, we have shown that plasma resulted in a reduction in markers of endothelial activation and a reduction in pro-inflammatory cytokines. Other clinical data on the effect of plasma in sepsis are limited. In retrospective studies, plasma exchange was performed as a rescue therapy with the aim to remove toxic compounds. An improved survival was found compared to historical survival data.

Solvent-detergent (SD) plasma is a pooled and washed multiple donor (varying from 10 - 1000 male and female donors) product. In a prospective cohort in critically ill children, SD plasma, but not fresh frozen plasma, was independently associated with reduced mortality. In a randomized pilot trial in patients undergoing surgery for aortic dissection, SD plasma reduced glycocalyx shedding and reduced endothelial tight junction injury compared to FFP. This difference is possibly due to the washing process in the manufacturing of SD plasma, which might dilute harmful substances in plasma products such as anti-human leukocyte antigens. Alternatively, the centrifugation steps may remove cellular debris such as extracellular vesicles, as these substances are linked to complications such as transfusion-related acute lung injury (TRALI). In line with this, no TRALI has been reported with the use of SD plasma, and the rate of allergic or anaphylactic reactions with SD plasma is between 76% and 94% lower than that of FFP.

Specific mechanisms mediating protective effects of plasma may be related to a release of sphingosine-1-phosphate (S1P), limiting metalloproteases from cleaving the endothelial glycocalyx. Alternatively, plasma may be protective by replenishing ADAMTS13, as we have shown in observational studies, thereby balancing the excess release of von Willebrand Factor, limiting von Willebrand Factor multimerization, microthrombi formation and subsequent edema and organ

failure. It will be important to determine which proteins contribute to protective effects, in order to enable the manufacturing of these specific proteins for targeted therapy.

In this study in a human endotoxemia model, we hypothesize that fluid therapy with protein rich fluids is superior to crystalloids, which is the standard used resuscitation fluid in acute critical illness, in terms of preservation of the endothelial barrier integrity.

Study objective

The main objective of the proposed study is to investigate the effect of plasma products and albumin on markers of endothelial function in a human endotoxemia model.

Study design

Open label, randomised interventional trial in healthy male volunteers

Intervention

Group 1 (n=6): 2 ng/mL LPS + 10 ml/kg crystalloids (Plasma-Lyte, control group)
Group 2 (n=6): 2 ng/mL LPS + 10 ml/kg SD plasma (Omniplasma®)

Study burden and risks

Benefits: none

Investigational products:
1. All volunteers will receive LPS injection. Discomfort from LPS can consist of nausea, chills, fever, and hypotension, which will subside in 3-4 hours. Subject monitoring will take place at our ICU until after symptoms have subsided. A dose of 2 ng/kg LPS in healthy volunteers has proven to be safe in previous studies at this and other institutions. The LPS is distributed by the National Institute of Health (NIH), USA. The analysis and concentration of the endotoxin is determined by a gel-clot method and its standard of reference in the USA.
2. Omniplasma: Due to the manufacturing process which also dilutes allergens, allergic reactions are seldom, and usually mild (skin erythema, urticaria) (< 1:100 recipients, BIJSLUITER). More severe reactions are hypotension, bronchial hyperreactivity, tachycardia and dyspnea (< 1:10.000 recipients). These side effects are caused by the citrate in Omniplasma causing hypocalcemia. This is a particular problem in recipients with liver dysfunction. This will not be present in the healthy volunteers. High dose or high speed of infusion rate can cause circulatory overload. This is not expected in the volunteers who will

have received LPS and hence are volume depleted. Circulatory overload is a particular risk in recipients with heart failure (23). This will not be present in the healthy volunteers. The infusion speed will be set at a rate that is generally well tolerated in recipients without heart failure.
3. Plasma-Lyte: This is a so-called *balanced* crystalloid solution, as it has an electrolyte composition that resembles that of plasma. However, this solution is protein-free. Crystalloids are the current standard resuscitation fluid. There are no known allergies to crystalloids.

The experiment:
1. During the experiment an artery line will be inserted in one of the arteries of the arms of the test person. The placing of the artery line is performed by an experienced doctor. There is a small chance this procedure results in bruises or blood cloth formation in the blood vessel. During the last years no major complications occurred with this procedure in our center.

Risks assessment:
1. Infusion of E. coli LPS with a dose of 2 ng/kg has previously been proven to be safe in healthy adult volunteers in our institution.
2. Omniplasma is considered to have low risk of allergic reactions. Transfusions will be prepared and transfused using the standard clinical protocols by Sanquin and our hospital.
3. The combination of LPS with infusion is expected only to cause mild temporary side effects because subjects tolerate this LPS dose well in previous experiments, and the risk of an adverse events with the intervention fluids is very low.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Healthy male volunteer
- Between 18-35 years old
- BMI between 20-25

Exclusion criteria

- No informed consent
- Use of medication on prescription - Blood donation < 3 months
- Previous blood transfusion
- Participation in other medical study < 3months
- Participation in previous volunteer studies using LPS in the past year
- Fever at the intake or on research day (T > 38.5)
- Known allergic reaction to albumin

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-05-2023
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Omniplasma
Generic name:	Plasma
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Plasma-Lyte 148
Generic name:	Crystalloid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-12-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660

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Approved WMO Date:	06-09-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-005045-17-NL
CCMO	NL74983.018.21