

# Effect of C1-esterase inhibitor on systemic inflammation in trauma patients with a femur or pelvic fracture.

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<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Immune disorders NEC
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON39485

### Source

ToetsingOnline

### Brief title

CAESAR Study

### Condition

- Immune disorders NEC
- Ancillary infectious topics

### Synonym

activated immuun system, Systemic inflammation

### Research involving

Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Utrecht

**Source(s) of monetary or material Support:** Sanquin, divisie plasmaproducten. Postbus

9190, 1006 AD, Amsterdam, The Netherlands, Sanquin; divisie plasmaproducten. Postbus 9190; 1006 AD; Amsterdam; The Netherlands

## Intervention

**Keyword:** C1-esterase inhibitor, Cytokines, Systemic inflammation, Trauma

## Outcome measures

### Primary outcome

Delta interleukine-6 after surgical repair of a femur or pelvic fracture in trauma patients in the absence of presence of C1-esterase inhibitor.

### Secondary outcome

- Cytokines, cellulaire markers, complement
- Leukocyt count, CRP, base deficit/excess and lactate
- Development of inflammatory complications (Acute Respiratory Distress Syndrome, MODS, sepsis, septic shock)
- Severity of illness

## Study description

### Background summary

Systemic inflammation in response to femur or pelvic fracture and fixation is associated with complications, such as acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). The injury itself, but also the additional fixation procedure give a release of pro-inflammatory cytokines, in particular interleukin (IL)-6. This results in an aggravation of the initial systemic inflammatory response, and will cause in some patients an increased risk on the development of inflammatory complications, like ARDS and MODS. Which can lead to higher morbidity, mortality and prolonged hospital stay.

Various strategies, such as damage control orthopedics, have been proposed to prevent these complications. Another strategy is to decrease the inflammatory reaction caused by the surgical procedure, and by interventions focused on inhibition of the innate inflammatory response. This will lower the risk of

complications.

A promising candidate is the endogenously produced serum protein C1-esterase inhibitor (C1-INH). This protein is an acute phase protein, produced by the liver in response to inflammatory conditions. C1-INH is a major inactivator of the complement system, but important additional anti-inflammatory properties have been demonstrated. A previous study of from our laboratory showed that administration of the drug C1-INH significantly reduced the concentration of circulating pro-inflammatory cytokines such as IL-6, during human experimental endotoxemia. Treatment with C1-INH has been proven to be safe in treatment with humans, even in high dosages and in pregnant patients with C1-INH deficiency.

## **Study objective**

A previous study of from our laboratory showed that administration of the drug C1-INH (100E/kg) significantly reduced the concentration of circulating pro-inflammatory cytokines, such as IL-6, in healthy male volunteers during human experimental endotoxemia.

The aim of this study is to demonstrate that administration of C1-INH, in trauma patients with a femur fracture, reduces the release of early pro-inflammatory cytokines and, therefore, will attenuate the humane inflammatory response. Consequently, administration of C1-INH may attenuate the onset of SIRS and the occurrence of organ failure and can, therefore, be a potential drug for the prevention of late inflammatory complications in injured patients.

## **Study design**

A prospective double-blind randomized placebo-controlled trial in trauma-patients, between 18 and 80 years old, admitted to the shock room of our trauma centre with a femur or pelvic fracture and an injury severity score of  $\geq 18$ .

A first blood sample will be taken within 12 hours after trauma, this blood sample serves as a reference for the degree of inflammation. A second blood sample will be drawn pre-procedural just before the femoral fixation, when the patient is anaesthetized. Then the patient is randomized and C1-INH or placebo is administrated intravenously. The third blood sample is taken 2 hours after the first (femoral or pelvic fixation-procedure) skin incision and the fourth withdrawal will take place 6 hours after the procedure. Teh remaining samples will be taken 24, 48 hours, 7 and 12 days after surgery.

As long as the patient is admitted on the Intensive Care Unit, blood samples can be taken from the arterial catheter. When the patients leave the ICU, they will be asked if he/she will provide us an additional sample.

## **Intervention**

Subjects will receive once a single dose of 200E/kg C1-INH intravenously or placebo (saline 0.9%).

### **Study burden and risks**

C1-INH is a normal component of the human blood. No side effects are described by administration of C1-INH.

Patients could, theoretically, develop an allergic reaction after administration of C1-INH, manifesting as urticaria or anaphylactic shock, this has never been described.

The blood is drawn from the arterial line, if possible. The patient does not experience any discomfort of this procedure. The placement of an arterial line is standard care in this group of trauma patients. If the arterial line is removed, the blood will be drawn through venous puncture. This will be combined with clinical blood withdrawal.

## **Contacts**

### **Public**

Universitair Medisch Centrum Utrecht

Heidelberglaan 100

Utrecht 3508GA

NL

### **Scientific**

Universitair Medisch Centrum Utrecht

Heidelberglaan 100

Utrecht 3508GA

NL

## **Trial sites**

### **Listed location countries**

Netherlands

## **Eligibility criteria**

## Age

Adults (18-64 years)

Elderly (65 years and older)

## Inclusion criteria

Multi trauma patients

Femur fracture and/or pelvic fracture

Injury Severity Score (ISS)  $\geq 18$

Age 18-80 yrs

## Exclusion criteria

Congenital C1-inhibitor deficiency

Use of immune suppressants

Pregnancy

Known hypersensitivity for blood products

Fixation of femur fracture with external fixation or osteosynthesis

Fixation of the pelvic fracture with external fixation

## Study design

### Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

### Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	26-04-2012
Enrollment:	70

Type: Actual

## Medical products/devices used

Product type: Medicine  
Brand name: Cetor  
Generic name: C1-esterase inhibitor  
Registration: Yes - NL outside intended use

## Ethics review

Approved WMO  
Date: 27-01-2011  
Application type: First submission  
Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO  
Date: 12-07-2011  
Application type: First submission  
Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO  
Date: 20-04-2012  
Application type: Amendment  
Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO  
Date: 15-03-2013  
Application type: Amendment  
Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO  
Date: 28-03-2013  
Application type: Amendment  
Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

## 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	EUCTR2010-024327-24-NL
ClinicalTrials.gov	NCT01275976
CCMO	NL34932.041.11