Systemic and local inflammation in burn wound patients.

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Objective: Since the inflammatory reaction plays an important role in wound healing problems and scar formation the main goal of this project is to unravel different inflammatory mechanisms involved. • Explore relationships between local and...

Ethical review	Approved WMO
Status	Completed
Health condition type	Epidermal and dermal conditions
Study type	Observational invasive

Summary

ID

NL-OMON47865

Source
ToetsingOnline

Brief title
Systemic and local inflammation in burns.
Acronym: SLIB

Condition

- Epidermal and dermal conditions

Synonym
partial and full-thickness burns

Research involving
Human

Sponsors and support

Primary sponsor: Rode Kruis Ziekenhuis
Source(s) of monetary or material Support: collectebusfond NBS

Intervention

Keyword: Burns, Immunological factors, Inflammatory reaction

Outcome measures

Primary outcome

Main objectives are to analyse components of the complement system and inflammatory cells involved in the different inflammatory mechanisms and systems described above. These include complement C3, C4, C5 and NETs levels (cell free DNA (cfDNANA)) in blood at different time points between day 0 and 30 pb and when the patient has to undergo escharectomy in eschar obtained at the day of surgical procedure. Timeframes for analyses are: day 0, 3-6, 7-14 and 21- 30. The latter time points will only apply for patients with more severe burn wounds and hospitalisation during the entire period. The analysis will be performed by ELISA.

In addition complement (e.g. C3, C4, C5) as well as neutrophils (MPO), macrophages (CD68), lymphocytes (CD45), thrombi (CD31), NETosis (H3 histon citrulline), tissue factor (TF) and dipeptidyl peptidase 4 (DPP4/CD26) will be analysed in burned tissue samples (eschar collected at the day of the planned surgical procedure) by using (immuno) histochemistry for the cells and FACS analysis.

Secondary outcome

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Study description

Background summary

Upon tissue injury an inflammatory reaction is induced which is essential to combat invading microorganisms, debride the wound from damaged tissue and orchestra the healing process.
However in patients with burn wounds a massive inflammatory response is induced that not only negatively affects the healing process of the burn wound, but additionally exerts systemic effects resulting in secondary (organ) injury. The biological factors involved in this secondary response to burn wounds are largely unknown.
The inflammatory reaction comprises a wide range of reactions in which different cell-types of the innate and adaptive immune system play an important role.
The current study will investigate various immunological factors involved in burns related effects.

Part 1. The acute phase response: Immunological factors and secondary organ injury
An important factor in the inflammatory response is the acute phase response (APR), in which complement is playing a central role. It is known that these acute phase proteins are elevated up to months after the initial burn trauma. We have shown that these proteins are also elevated locally in the wound up to at least 4 weeks post-burn (pb). Recently, we described in a rat burn wound model that application of C1-esterase inhibitor (C1-inh), a complement inhibitor, improved healing of the burn wound and additionally reduced systemic effects, more specific, inflammation of the heart. In humans the local and systemic activation of the complement system is not resolved yet. Therefore we will analyse different inflammatory factors related to complement activation and the early inflammatory reaction in the blood (systemic) and in the burn wound in patients. In addition we want to analyse the time frame of infiltration of inflammatory cells (i.e. neutrophilic granulocytes, macrophages and lymphocytes) in the burn wound.

Part 2. Inflammation and burn wound extension: Neutrophilic extracellular traps in expansion of necrosis of the burn wound
Neutrophils are the first inflammatory cells to arrive at the wound site. These cells are pivotal for debridement of the injured tissue and the clearance of microorganisms. However they can also be detrimental to the healing process. Secondary microvascular damage and thrombosis are important underlying factors in the expansion of necrosis into vital tissues neighboring the initial burn injury. Neutrophil extracellular trap formation (NETosis) has been shown to be a major initiator of microvascular damage, coagulation and inflammation in non-burn related major trauma, sepsis and autoimmune disease. However, its role in burn injury, a pathology characterized by extensive (secondary) tissue damage, prolonged inflammation and hypercoagulability is unknown. We recently found evidence for the involvement of NETosis in the instigation of

microvascular thrombosis in the burn wound. In a rat burn wound model we showed that thrombus formation in the blood vessels within the burn wound was significantly higher than in the skin tissue taken from the non-burn hind leg (internal control). Remarkable is the presence of thrombi in non-affected healthy skin samples, which supports the idea of bigger generalised systemic response. Furthermore, we found indications of causative factors resulting in pb thrombi formation, like the formation of neutrophilic extracellular traps (NETs), an increase of tissue factor (TF) (pro-coagulant) and a decrease of DPP4/CD26 (anti-coagulant) expression in blood vessels, correlated with thrombi formation within the burn wound.

Part 3. Inflammation, pain and psychological stress
Pain is a major complication following burns and it is still difficult to treat. Burn pain results from tissue inflammation in which a range of inflammatory mediators are released that in turn sensitise and stimulate pain fibres throughout the wound healing process. Stress-induced hyperalgesia may exacerbate the existing pain. We will explore associations between inflammation of the wounds, pain and the psychological stress response

Study objective

Objective:
Since the inflammatory reaction plays an important role in wound healing problems and scar formation the main goal of this project is to unravel different inflammatory mechanisms involved.
• Explore relationships between local and systemic inflammation and clinical outcome with respect to complement activation. (part 1)
• Determine the relation between NETs in the blood and NETosis in burn wounds and their prognostic potential with regards to clinical outcome. (part 2)
• Determine the timing of the different mechanisms involved in wound healing and scar formation. (part 1 and 2)
• Determine the correlation between the above mentioned parameters with total body surface area (TBSA %), co-morbidities and clinical course. (part 1 and 2)

Study design

Prospective observational cohort study in all burn patients admitted to the ICU. In addition twenty healty volunteers will be included. Duration of the study is 4 year. The study will be performed in the burn centre in Beverwijk (Rode Kruis Ziekenhuis). For reference values 20 healthy volunteers will be included.

Study burden and risks

Patients: The burden of the study is limited to blood withdrawals via venipunctures and for patients with more severe burn wounds also eschar tissue

collection during planned operations. The venipuncture procedures are embedded in the clinical routine. An extra blood tube for serum will be taken.
Venipunctures are common procedures at the burn centres and will be performed by qualified people. The collection of (secondary necrosis) debridements will take place during clinical routine.
Healthy volunteers: twice blood draw 1 tube 5 ml; minimal risks; blood draw can be painful or cause a hematoma. The amount od blood drawn will not give problems.

Contacts

Public
Rode Kruis Ziekenhuis

Vondellaan 13
Beverwijk 1942LE
NL
Scientific
Rode Kruis Ziekenhuis

Vondellaan 13
Beverwijk 1942LE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patient group
>=18 years

Competent and temporarily incompetent patients
Informed Consent by patient or the legal representative
No acute psychiatric disorders
Speak sufficient Dutch'
Healthy volunteers:
18 years or older
competent
informent consent
sufficient dutch proficiency

Exclusion criteria

patients:
See inclusion criteria
Healty volunteers:
any medication exept contraceptives
known underlying diseases as cancer, inmune deficiency, hypertension, complement disorder

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-05-2016
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	07-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2019
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
CCMO	NL56217.094.15

Study results

Date completed:	15-03-2020
Results posted:	18-02-2021
Actual enrolment:	83

Summary results
Trial ended prematurely

First publication
29-01-2021