Inhalation of Low Molecular Weight Heparins as a prophylaxis to prevent SARS-CoV-2 infection

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1. Primary objective: - SARS-CoV-2 binding (expressed as concentration of virus bound in pg/mL) to epithelial cells isolated from nasal cavity between intervention and control groups (every volunteer is his own control group, depending on nostril)....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON50776

Source
ToetsingOnline

Brief title
Nose-LMWH against COVID-19

Condition

- Viral infectious disorders

Synonym
corona virus infection, COVID-19

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: COVID-19, Enoxaparine, LMWH, Nose

Outcome measures

Primary outcome

Primary endpoint: SARS-CoV-2 binding to the isolated cells will be measured by the SARS-CoV-2 binding assay to obtain a proof of concept that in vivo application of LMWH block virus binding. The amount of total virus bound to epithelial cells will be measured in pg/ml.

Secondary outcome

Secondary endpoint: Descriptive characterisation of immune activation of epithelial cells. Isolated epithelial cells will be stained for specific activation markers and cytokine in supernatant after culture will be measured. We do not expect any changes in activation markers/cytokines between the LMWH treated and saline treated group.

Extension of the study (May 2021):
Secondary endpoint: In addition to measuring binding using a pseudotyped virus (our primary endpoint), binding using the SARS-CoV-2 wildtype (WT) will be performed. This will be done to observe a truer virusbinding and block than can be achieved using the pseudotyped virus (as it*s a modified virus).

Furthermore, given the large variability in obtained cells per volunteer, priority will be given to virusbinding using the pseudotyped virus, after which priority will fall to the wild type virus.

Remaining cells will be stained for phenotyping, presence of ACE-2 and

heparansulfates. After which activation markers will be observed.

Study description

Background summary

The ongoing Coronavirus disease 2019 (COVID-19) pandemic has placed a high burden on medical resources as well as cause a large number of deaths. Moreover, it has led to a severe social and economic disruption and there is therefore an urgent need for quick and simple prophylactic agents to stop transmission of the SARS-CoV-2. Strikingly, we have identified low molecular weight heparins (LMWH) as potent inhibitors of SARS-CoV-2 infections in vitro. Because the airways are the major route of infection for SARS-CoV-2 we will investigate whether intranasal application of LMWH will prevent SARS-CoV-2 binding to epithelial cells ex-vivo. To investigate this, we have designed a study in which healthy volunteers will be exposed to LMWH via nasal inhalation and epithelial cells will be isolated with nasal brushes. Next we investigate the binding of SARS-CoV-2 to the epithelial cells.

Study objective

1. Primary objective:
- SARS-CoV-2 binding (expressed as concentration of virus bound in pg/mL) to epithelial cells isolated from nasal cavity between intervention and control groups (every volunteer is his own control group, depending on nostril). A second control group will consist of twelve clinically admitted patients receiving therapeutic doses of LMWHs for thrombotic events.
2. Secondary objectives:
- Descriptive characterization of activation markers and cytokine production by nasal epithelial cells ex vivo after LMWH application

Study design

A single center, open label intervention study. Cohort 1 consists of healthy volunteers (n=12) that serve as their own internal control. Every volunteer will receive a saline solution (NaCl 0.9%) in the left nostril. Epithelial cells will be retrieved using a nasal brush from the left nostril. Subsequently, enoxaparin (Clexane Forte, with a concentration of 150mg/ml) will be administered in the right nostril after which cells will be isolated after 30minutes.
To ensure adequate delivery to the nasal epithelium we will use a MAD Nasal* Intranasal Mucosal Atomization Device (made by Telefex medical). This allows us

to nebulise our compounds to allow a good spread through the nasal cavity. We use a volume of 370µL per volunteer, with 70µL remaining in the MAD device due to dead space. This applies a volume of 300µL evenly to the nasal epithelium (corresponding with 45mg of enoxaparin).

We expect that the LMWH exposure will limit virus binding. Moreover, we will analyse the phenotype of isolated epithelial cells to investigate effect of LMWH on epithelial activation.

The effect of the regular subcutaneous treatment with LMWH on virus binding will be assessed in Cohort 2. ,This cohort consists of a total of 12 patients that are treated with therapeutic doses of LMWH for medical reasons. Virus-epithelial cell interaction will be analysed from nasal brushes, that are collected at 4 hours after administration of LMWH to allow for proper redistribution throughout the body (based on the TMAX of Enoxaparin). Epithelial cells that are isolated from nasal brushes will be incubated with SARS-CoV-2 virus and binding of virus to epithelial cells will be measured. Here we will investigate whether subcutaneous injection of LMWH protect epithelial cells from SARS-CoV-2 infection. Moreover, we will analyse the phenotype of isolated epithelial cells to investigate effect of LMWH on epithelial activation.

Extension of the study (May 2021):
Cohort 1 will be expanded from 12 to 24 volunteers. This choice is made as the original SOP for applying study medication and withdrawing cells for virus exposure proved ill-suited for a clinical setting. Therefore material provided by volunteer 1 to 7 gave largely inconsistent results. Furthermore, the amount of cells provided by volunteers shows large interpersonal variability, resulting in some volunteers not providing enough cells for comparative analysis.
An expansion of volunteers to 24 total will give enough power to compare results.

Volunteers in cohort 1 will serve as their own internal control. Every volunteer will receive a total of 300uL saline solution (NaCl 0,9%) in the left nostril, delivered in three deliveries of 100uL using the MAD Nasal Intranasal Mucosal Atomization Device at ten minute intervals.
After thirty minutes cells will be isolated using a nasal brush.
Subsequently, 300 uL enoxaparin (Clexane Forte, at 150mg/ml concentration) will be administered in the right nostril in three deliveries of 100uL at ten minute intervals. After thirty minutes cells will be isolated using a nasal brush.

Cohort 2 will be changed to include four volunteers instead of twelve clinical patients. The choice to volunteer is made as within three months of the study start no clinically admitted patients were eligible or willing to participate with the study.
Furthermore, those patients who were eligible but decided not to participate

were much older and had multiple co-morbidities, making comparison with cohort 1 problematic.
Therefore, to assure a more comparable study population to cohort 1, cohort 2 will be made up of volunteers, preferably volunteers from cohort 1 will be asked to participate (after the follow-up period has expired) in cohort 2.
The change in number of volunteers is made to lessen the burden on our participants. Due to the mechanism of virus-block it is not expected that subcutaneously administered heparins will have an effect on virus-block. Therefore it would place an unjust burden on volunteers to have a group size of 12. If no block is observed, participation will stop at 4, if block is observed, a new amendment will be created to increase the size of this group to the same size as cohort 2.
Volunteers participating in cohort 2 will receive subcutaneous 1 dose of therapeutic enoxaparin (100IE/kg) administered abdominally. 4 Hours (Tmax) after injection cells with be retrieved using a nasal brush comparable to cohort 1.

Intervention

370µL enoxaparin solution (Clexane Forte 150mg/ml) and saline (0.9%NaCl) applied with the MAD Nasal* Intranasal Mucosal Atomization Device will be administered in the left and right nasal cavity respectively in cohort 1.

Extension of the study (May 2021):
Cohort 2 will receive a single subcutaneous injection of enoxaparin at therapeutic levels (100IE/kg bodyweight) administered in the abdominal region in comparable to normal clinical practices.

Study burden and risks

The intranasal application of enoxaparin is considered safe as no systemic effects are expected for various reasons. Firstly the LMWH will be neutralised on the nasal epithelium. Secondly, the applied doses (45 mg) are much lower than the parenterally administered doses used anticoagulant treatment. Thirdly, bronchially administered (inhaled) LMWH in much higher doses of up to 2mg/kg was observed to leave the systemic coagulation unaffected, which was supported by the lack of detectable anti-Xa activity.1,2

Risks associated with sampling that consists of a nasal brush are also considered to be minimal.

Extension of the study (May 2021):
Cohort 2 will receive a single dose of therapeutic enoxaparin. Reported associated risks at therapeutic levels are bleeding associated as well as prolonged coagulation times. Furthermore a temporary increase of hepatic

enzymes, specifically transaminase increase, has been reported.
Most of these associated risks (such as bleeding) are time-dependent and become the more risky the longer a patient has to use enoxaparin. Enoxaparin has a half-life of 5 hours, which means within 24hrs almost all of it will be cleared from the body.
Furthermore, enoxaparin has an antidote (protamine). Within the AMC there is a lot of experience working with enoxaparin, as it*s widely used in the clinic as an anticoagulant. We consider the risks of a single dose of enoxaparin very low.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy men and women between ages 18-65 with no medical history of

immunodeficiencies or chronic illness.

Exclusion criteria

COVID-19 in the volunteers medical history.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-01-2021
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Clexane
Generic name:	Enoxaparin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-11-2020

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2021
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	EUCTR2020-003992-16-NL
CCMO	NL75272.018.20