Continuous low dose subcutaneous lidocaine for treatment of pneumonia in COVID*19 patients.
A randomised controlled (RCT) open*label phase III study.

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The disappearance of the main symptoms of the COVID*19*induced pneumonia within 5 days after the initiation of the
continuous low dose subcutaneous infusion of lidocaine in 50% of the patients. The relief of these symptoms must be maintained for ...

Ethical review	Not approved
Status	Will not start
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON49706

Source
ToetsingOnline

Brief title
Not applicable

Condition

- Respiratory tract infections

Synonym
corona virus, COVID-19

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Dutch Covid□19 Lidocaine ARDS
Source(s) of monetary or material Support: Stichting Dutch Covid□19 Lidocaine ARDS

Intervention

Keyword: COVID-19, Lidocaine, Pneumonia

Outcome measures

Primary outcome

The disappearance of the main symptoms of the COVID*19*

induced pneumonia within 5 days after the initiation of the

continuous low dose subcutaneous infusion of lidocaine in 50% of the patients. T

he relief of these symptoms must be maintained for at least 48 hours.

Secondary outcome

1.

Reduction in time to clinical recovery (TTCR) defined as disappearance of dyspno

ea, return of fever to normal

body temperature and relief of cough in the treatment group compared to control

group.

2.

Reduction of progression to ARDS after admission to the hospital in patients wit

h confirmed COVID*19 ARDS

by 50% in the treatment group compared to the control group.

3.

Reduction of hospital stay in the treatment group compared to the control group.

In addition, reduction of

the duration of mechanical ventilation and reduction of the length of ICU stay i

n patients who deteriorate

and require mechanical ventilation after the inclusion in the study, in the trea

tment group compared to the control group.

4.

Improvement of the illness severity (delta qSOFA of minus 2 points or from *2 po

ints to <2 points) or the quality of life (delta EQ*5D*

3L of minus 3 points) within 72 hours after the initiation of the

treatment with lidocaine in the treatment group compared to the control group.

5. Improvement of the case fatality rate at 3 months after the admission.

Study description

Background summary

The COVID19 pandemic has become a major challenge for countries and global insti
tutions to control. Patients are admitted to the general ward and
ICU with respiratory symptoms, surpassing the maximum capacity of hospitals
within weeks. The major complication of a COVID-19 infection is respiratory fail
ure and acute respiratory distress syndrome (ARDS).
Invading viral pathogens in the respiratory tract provoke cellular stress. This
causes massive exocytosis of ATP
resulting in high extracellular ATP concentrations. Initially, this stimulates t
he purinergic P2Y2 and P2X4 receptors
resulting in a brief period of surfactant exocytosis, however as ATP levels cont
inue to rise, the P2X4 and P2Y2
receptors become desensitized preventing normal surfactant release. At a certain
 point in time, the extracellular
levels of ATP exceed the lower threshold for the activation of the P2X7 extracel
lular ATP receptors (P2X7Rs) located
on the cell surface of the innate immune cells. This triggers a pro*
inflammatory response of the innate immunity
followed by a massive release of inflammatory mediators and cytokine storm. The

resulting vascular leakage and
pulmonary oedema induce the disaggregation and inactivation of pulmonary surfact
ant, a key element in the
pathogenesis of ARDS, ending in alveolar collapse and impaired gas exchange. The
conversion of extracellular ATP by
ectonucleotidases into adenosine activates the different adenosine receptors (i.
e. adenosine receptor A1 * AdoRA1,
AdoRA2A, AdoRA2b and AdoR3). This leads to secondary immune suppression, the bas
is of the compensatory antiinflammatory response syndrome (CARS) sometimes follo
wed by pulmonary fibrosis.
Here we propose targeting the P2X7R in COVID*
19 ARDS patients with lidocaine. Lidocaine is widely known and used
as a safe analgesic drug. It inactivates fast voltage*gated Na
+ channels and restricts neuron transmission.
However, it is has also been described as a potent and selective P2X7R inhibitor
. Both after pharmacological inhibition and in P2X7R knock*
out mice survival in ARDS is increased in preclinical models. We hypothesize tha
t lidocaine has an anti*
inflammatory effect which can be used to prevent progression into ARDS and to tr
eat ARDS in COVID*19 patients. Last but not least the anti*
nociceptive agent lidocaine has a clear advantage over other immunosuppressive d
rugs
since it mainly targets hyperactivity of the innate immune system by inhibition
of the P2X7 receptor. For example,
corticosteroids result in broad immunosuppression diminishing the ability to fig
ht the viral infection, whilst
humanized monoclonal antibodies (i.e. tocilizumab and anakinra) are feared for t
heir severe side effects.

Study objective

The disappearance of the main symptoms of the COVID*19*
induced pneumonia within 5 days after the initiation of the
continuous low dose subcutaneous infusion of lidocaine in 50% of the patients. T
he relief of these symptoms must be maintained for at least 48 hours.

Study design

Phase III open*
label randomised controlled trial (RCT) to demonstrate the clinical efficacy of
continuous low dose
subcutaneous lidocaine to relieve the main symptoms in patients with COVID*19*
induced pneumonia requiring
hospital admission who do not require mechanical ventilation at the time of stud
y inclusion.

Intervention

Under normal conditions, a stable lidocaine plasma levels of 0.5 to 2 mcg/ml (well under the toxic levels of at plasma concentrations of 5 mcg/ml or above) can be achieved with a continuous subcutaneous infusion of 1.5 mg/kg/hr.
1. Subcutaneous loading dose of 1 mg/kg (lidocaine concentration 10 mg/ml).
2. Followed by a continuous subcutaneous lidocaine infusion of 1.5 mg/kg/hr (lidocaine concentration 10 mg/ml).
3.
The lidocaine infusion will be discontinued upon discharge from the hospital or after maximal 30 days during hospital admission.
4.
The patient in the control arm does not receive additional treatment and must be actively prevented from
receiving continuous subcutaneous or continuous intravenous infusion of lidocaine during admission. There
are no objections for an occasional bolus administration of lidocaine as anaesthetics or anti*nociceptive agent in case of surgical procedures.

Study burden and risks

The burden for the patient will be minimal.
Risks:
Very common (may affect more than 1 in 10 people)
* Low bloodpressure
* Nausea
Common (may affect up to 1 in 10 people)
* Sensation of pins and needle sticks
* Dizziness
* Slow heartbeat
* High bloodpressure
* Vomit

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age *18 years.
2. Acute disease with radiographic*
confirmed pneumonia with a positive test for COVID*19.
3.Patients admitted to the hospital ward with spontaneous breathing are eligible
for inclusion in the study.

Exclusion criteria

1.
Patients known with allergy or hypersensitivity to lidocaine, xylocaine or ligno
caine.
2. Treatment with Ivermectin. Reportedly, Ivermectin inhibits the in*
vitro replication of SARS*1 CoV*2.
3. Treatment with methylprednisolone as sepsis therapy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	100
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Xylocaine
Generic name:	Lidocaine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	22-04-2020
Application type:	First submission
Review commission:	METC NedMec

Not approved

Date:	28-04-2020
Application type:	First submission
Review commission:	METC NedMec

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	EUCTR2020-001895-13-NL
CCMO	NL73809.041.20