Continuous low dose subcutaneous lidocaine for treatment of the symptoms of COVID*19.
A randomised controlled open*label phas e III study.

Published: 14-05-2020
Last updated: 09-04-2024

To determine the effect of lidocaine on the main symptoms of COVID-19.

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

Summary

ID

NL-OMON49145

Source
ToetsingOnline

Brief title
Not applicable

Condition

- Respiratory tract infections

Synonym
ARDS, corona virus, COVID-19

Research involving
Human

Sponsors and support

Primary sponsor: Julius Clinical

Source(s) of monetary or material Support: Dutch Covid-19 Lungdisease Action foundation (DCLA foundation)

Intervention

Keyword: ARDS, COVID-19, Lidocaine

Outcome measures

Primary outcome

To determine the clinical improvement of the patients within 5 days after the randomisation in the treatment group compared to the control group.

Secondary outcome

• Reduction of the median time to clinical improvement.

• Reduction of the proportion of patients with progression to ARDS in the treatment group compared to the control group.

• If applicable, reduction of the length of hospital stay in the treatment group compared to the control group.

• If applicable, reduction of the duration of mechanical ventilation and reduction of the length of ICU stay in the treatment group compared to the control group. Case fatality rate at 28 days and 3 months after the admission.

Study description

Background summary

The COVID-19 pandemic has become a major challenge for countries and global institutions to control. Patients are admitted to the general ward and ICU with respiratory symptoms, exceeding the maximum hospital capacity within a few weeks. The major complication of a COVID-19 infection is respiratory failure and acute respiratory distresssyndrome (ARDS). Invading viral pathogens in the airways cause cellular stress. This causes a massive exocytosis of ATP, resulting in high extracellular ATP concentrations. Initially, this stimulates

purinergic P2Y2 and P2X4 receptors, resulting in a short period of surfactant exocytosis, but as ATP levels continue to rise,the P2X4 and P2Y2 receptors are insensitive to preventing normal release of surfactants. At some point, the extracellular levels of ATP exceed the lower threshold for the activation of the P2X7 extracellular ATP receptors (P2X7Rs) located on the cell surface of the innate immune cells. This causes a pro-inflammatory response ofinnate immunity, followed by a massive release of inflammatory mediators and cytokine storm. The resulting vascular leakage and pulmonary edema cause the disaggregation and inactivation of lung surfactant, a key element in the pathogenesis of ARDS, ending in alveolar collapse and decreased gas exchange. The conversion of extracellular ATP by ectonucleotidases to adenosine activates the different adenosine receptors (i.e. adenosine receptor A1 - AdoRA1, AdoRA2A, AdoRA2b and AdoR3). This leads to secondary immune suppression, which is the basis of the compensatory anti-inflammatory response syndrome (CARS), sometimes followed by pulmonary fibrosis.Here we propose to target the P2X7R in COVID-19 ARDS patients with lidocaine. Lidocaine is widely known and is used as a safe analgesic. It deactivates fast voltage-dependent Na + channels and limits the transmission of neurons. However, it has also been described as a powerful and selective P2X7R inhibitor. Both after pharmacological inhibition and in P2X7R knockout mice, survival in ARDS is increased in preclinical models. We hypothesize that lidocaine has an anti-inflammatory effect that can be used to prevent progression to ARDS and to treat ARDS in COVID-19 patients. Finally, the anti-nociceptive agent lidocaine has a clear advantage over other immunosuppressants, as it primarily targets hyperactivity of the innate immune system through inhibition of the P2X7 receptor. Corticosteroids, for example, result in a broad immunosuppression that decreases the ability to fight the viral infection, while humanized monoclonal antibodies (i.e., tocilizumab and anakinra) are feared for their serious side effects.

Study objective

To determine the effect of lidocaine on the main symptoms of COVID-19.

Study design

Phase III open-label randomized controlled trial to demonstrate the clinical efficacy of continuous low dose subcutaneous lidocaine to alleviate key symptoms in patients with COVID-19 requiring hospitalization.

Intervention

The IMP used in this study is lidocaine. Lidocaine will be administered as a subcutaneous loading dose of 1 mg/kg, followed by a continuous subcutaneous lidocaine infusion of 1 mg/kg/hr. Treatment duration will be 21 days or (if applicable) until discharge, whichever comes first.

Patients randomized to the control arm will receive standard of care.

Study burden and risks

The subject will receive a drug that is not yet known to be effective in combating symptoms of COVID-19. However, there are currently few alternatives. There are risks that can potentially occur:reportedly, a metallic taste in the mouth may occur after a local injection of lidocaine. Type I (anaphylactic reaction) and type IV hypersensitivity to lidocaine are very rare. Other adverse effects of lidocaine (central nervous system, cardiac, respiratory and allergic effects) are caused only by plasma concentrations above 5 µg / ml (0.021 mmol / L). Examples of deaths involving lidocaine overdose and an anaphylactic reaction are shown in Table 5 (Section 6.3.2 in the protocol). It should be borne in mind that even after administration of the recommended doses by the appropriate route, the plasma concentrations of lidocaine can be unpredictable when the elimination of lidocaine by the liver and kidneys, as mentioned above, is impaired. Because side effects only occur with high blood concentrations, we do not expect to experience a serious side effect of lidocaine in this study. Minor side effects (metallic taste in the mouth, dizziness, etc.) can be reversed by discontinuing treatment with lidocaine or by administering a lower dose.Furthermore, the daily tax is low. The subject must complete a questionnaire daily for a maximum of 21 days or discharge (whichever comes sooner).

Contacts

Public
Julius Clinical

Broederplein 41-43
Zeist 3703CD
NL
Scientific
Julius Clinical

Broederplein 41-43
Zeist 3703CD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Each patient (or the patient*s legally authorized representatives) must sign an informed consent form (ICF) indicating that they understand the purpose of and procedures required for this study, are willing to participate in the study and attend all scheduled visits, and are willing and able to comply with all study-related procedures, and adhere to the prohibitions and restrictions as specified in the protocol.
2. Age >=18 years.
3. Acute disease with a positive test for COVID-19.
4. Patients with symptoms of COVID-19 admitted to the ICU, the hospital ward or residing in a nursing home are eligible for inclusion in the study. Should a patient with spontaneous breathing deteriorate requiring mechanical ventilation after the inclusion the patient will remain in the study.

Exclusion criteria

1. Patients known with allergy or hypersensitivity to lidocaine, xylocaine or lignocaine.
2. Patients with severe hypoalbuminaemia (decreased drug-protein binding),
3. Patients with potentially reduced elimination speed of lidocaine:
a. Severe liver and kidney dysfunction
b. Use of certain medications: erythromycin, beta-blockers, ciprofloxacin, cimetidine, clonidine, amiodarone or phenytoin.

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:	Lidocaine HCL CF 100 mg/ml, concentraat voor oplossing voor intraveneuze infusie
Generic name:	LIDOCAINEHYDROCHLORIDE 0-WATER
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	14-05-2020
Application type:	First submission
Review commission:	METC NedMec

Not approved

Date:	14-05-2020
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	NL74026.041.20