Long-term pain modulation by intravenous esketamine in Complex Regional Pain Syndrome: a non-inferiority study

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51901

Source
ToetsingOnline

Brief title
KetCRPS-2

Condition

- Other condition

Synonym
Complex Regional Pain Syndrome, reflex sympathetic dystrophy

Health condition

Complex Regionaal Pijn Syndroom (CRPS)

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Erasmus MC Doelmatigheid 2020 Number: 2020-20208

Intervention

Keyword: CRPS, Esketamine, Inpatient treatment, Outpatient treatment

Outcome measures

Primary outcome

Pain intensity measured by Numerical Rating Scale (NRS):

- The average NRS score of the last 24 hours

- The current NRS score reflecting the pain intensity at the moment when asked

Secondary outcome

- To assess protocol deviations due to logistical problems for each of the administration regimens: premature termination (due to i.e. bed capacity problems), waiting time for therapy (weeks) and compliance of the patients.
- Number and severity of intervention related adverse events: Psychomimetic (dysphoria, hallucinations, nightmares and vivid dreams), blurry vision or diplopia, nausea and / or vomiting, hepatic toxicity, headache and dislocation of peripheral intravenous catheter
- Objectively measured effects of each of the administration regimens on the inflammation; serum levels of sIL-2R and sCD163 will be detected with Enzyme Linked Immunosorbent Assay (ELISA) as measures for T-lymhpocyte and macrophage activation, respectively. In addition, T cell populations and monocyte populations will be identified using flow cytometry.

- To assess the sensory-discriminative dimensions of pain before and after ketamine treatment; Quantitative Sensory Testing

- Objectively measured effects of each of the administration regimens on symptoms vasomotor disturbances; Thermography

- Dose reduction of pain medication at follow after three and six months (yes/no)

- CRPS severity score (Harden et al. 2010)

- Number of administered co-interventions related to adverse events (benzodiazepines, clonidine, granisetron).

- Questionnaires COMPACT (Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies) (Grieve et al. 2017)

Study description

Background summary

Complex regional pain syndrome (CRPS) is a debilitating chronic pain condition of one or more limbs. Its diagnosis is based on (combinations of) underlying pathophysiological mechanisms. Achieving relevant pain relief fails in a significant proportion of CRPS patients. Intravenous administration of esketamine is an effective recognized therapeuticy option in refractory pain in CRPS, which sometimes in at least a part of the patients has a prolonged therapeutic effect. Unfortunately, in CRPS literature contains a wide range of ketamine dosing regimens with the result that clinical protocols on dosage and administration are very heterogeneous. In the Netherlands, both inpatient and outpatient esketamine treatments are offered. The current esketamine regimen in Erasmus MC consists of a 6-day hospital admission for continuous administration; however, logistical boundaries limit this therapy. Esketamine infusions in an outpatient setting might increase flexibility and availability of esketamine treatment. However, inpatient and outpatient ketamine treatments have never been compared in randomized controlled trials and it is therefore unknown whether these two dosing regimens are equally effective.

Study objective

This study has been transitioned to CTIS with ID 2024-511877-31-00 check the CTIS register for the current data.

The primary objective is to demonstrate non-inferiority of experimental esketamine administration of 6x 1 day per 2 weeks (in total 3 months) as compared with standard esketamine administration of 1x 6 consecutive days. The end of study is at 6 months after the start of the study/treatment.

Study design

prospective, randomized, non-inferiority study

Intervention

All patients will receive intravenous esketamine. The standard treatment group receives intravenous esketamine for 6 consecutive days (in hospital). The experimental intervention group visits the outpatient clinic to receive intravenous esketamine in day-care setting 6x 1 day per 2 weeks (in total 3 months)

Study burden and risks

This study poses a negligible risk. The added risk compared to standard treatment is the negligible risk of additional vena punctures.
All participants have baseline measurements and receive the esketamine treatment according to their study arm. At baseline and 3 months after ketamine treatment, different parameters will be recorded. Pain intensity, quantitative sensory testing and thermography will be reported and blood samples will be taken. The standard treatment group comes to the hospital for a 6-day hospital admission and 2 outpatient visits at the Center for Pain Medicine. The experimental group has 6 site visits for daycare ketamine infusion and 2 additional outpatient visits at the Center for Pain Medicine. All patients will be called at home after the esketamine infusion to assess the pain intensity and possible side effects. Each patient will be enrolled for the duration of 6 months. At the end of study, all participants will continue to receive medical care for their CRPS . If patients were a responder to esketamine treatment they can be scheduled for the standard treatment or the experimental treatment after consulting their pain physician. Patient burden can potentially be reduced by offering ketamine in a more flexible day-care treatment compared to a 6-day consecutive hospital admission.

Contacts

Public

Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
ROTTERDAM 3015GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
ROTTERDAM 3015GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Age >= 18 years.
- Meeting the new International Association for the Study of Pain (IASP) diagnostic criteria for CRPS (*the Budapest Criteria) or having met the new IASP diagnostic criteria of CRPS (*CRPS with Remission of Some features*) (Harden et al. 2010) (Goebel et al. 2021)
- Willing and capable to participate in the study.
- CRPS in one upper extremity and/or CRPS in one lower extremity
- Treatment in an elective setting.
- Adequate comprehension of the Dutch language

Exclusion criteria

Contraindications to and precautions for use of subanesthetic doses of ketamine for chronic pain are listed by Cohen et al. and the Dutch CRPS guidelines and our clinical protocol (Cohen et al. 2018; Perez et al. 2014). For each patient, the contraindications and precautions for use of esketamine infusions for CRPS

patients will be checked/assessed by their treating pain specialist. If a patient has no contraindications for esketamine treatment and the patient is eligible for esketamine treatment according to the Dutch CRPS guidelines, the patient will be placed on the waiting list. In this study we only select patients from the waiting list for esketamine treatment of the Center for Pain medicine.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-02-2022
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ketanest-S
Generic name:	Esketamine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	03-08-2021

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-11-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EU-CTR	CTIS2024-511877-31-00
EudraCT	EUCTR2021-000640-21-NL
CCMO	NL77785.078.21