Efficacy of ketamine on acute suicidality, a multicenter double blind randomized placebo-controlled trial (Ketamine Trial Amsterdam, KETA)

Published: 23-07-2018
Last updated: 17-04-2024

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Suicidal and self-injurious behaviours NEC
Study type	Interventional

Summary

ID

NL-OMON46083

Source
ToetsingOnline

Brief title
Ketamine Trial Amsterdam (KETA)

Condition

- Suicidal and self-injurious behaviours NEC

Synonym
self-harm, suicidality

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,call suïdepreventie ZonMW

Intervention

Keyword: acute psychiatry, ketamine, mood disorders, suicidality

Outcome measures

Primary outcome

Change in suicidality scores on the BSSI between baseline and 180 minutes after 75 mg intranasal ketamine administration compared to 3.8 mg intranasal midazolam (placebo).

Secondary outcome

1. Suicidality from baseline to 60 minutes, 180 minutes, one day, three days and one week after one intranasal ketamine administration compared to placebo, as measured with:

a. Beck Scale for Suicide Ideation (BSSI)

b. Sheehan Suicidality Tracking Scale (SSTS)

c. Suicidality item on the Montgomery Asberg Depression Rating Scale. (MADRS).

2. Actual number of suicides and suicidal at 60 and 180 minutes, 1, 3 and 7 days and 6 and 12 months after ketamine/midazolam administration.

3. Depressive symptoms as measured with the MADRS from baseline to 60 minutes and 180 minutes, one, three and seven days and 6 and 12 months after one intranasal ketamine administration compared to placebo.

4. Psychotomimetic symptoms, as measured with the Brief Psychiatric Rating Scale - Positive Subscale (BPRS) from baseline to 60 minutes and 180 minutes.

5. 5. Change in BDNF concentration, genetics and other biomarkers, and the

correlation pattern between change in BDNF concentration and suicidality. Three blood samples will be taken by venepuncture at baseline: two samples into a vacuum tube containing ethylene diamine tetra-acetic acid (EDTA) that will be transferred into a heparinised tube, and onedirectly into a serum gel tube. At 180 minutes also three blood samples will be taken to measure, among others, the BDNF concentration. Two in an EDTA tube and one into a serum gel tube (57). Furthermore, at baseline one 8ml EDTA sample will be taken in order to study genetics.

6. Plasma ketamine concentration at 180 minutes after ketamine/midazolam administration

7. Structural MRI, functional MRI (fMRI), diffusion tensor imaging (DTI), H-MRS-analysis of glutamate in hippocampus and prefrontal cortex. Subjects that were administered ketamine will be compared to subjects that were administered midazolam, at one day after administration.

8. A responder/non responder analysis. (Response is defined as a 50% reduction in BSSI-score) for the total study period.

9. Correlation patterns for the total study period between changes in BSSI- and MADRS-scores

10. Correlation pattern for the total study period between change in BSSI and gender.

Study description

Background summary

Suicide is currently one of the three leading causes of death in the Netherlands in people aged 15-44 and has a substantial impact on families and society. Nevertheless, to date no evidence based pharmacological intervention for acute suicidality exists. Subanaesthetic doses of intravenous ketamine have been shown to immediately resolve depressive symptoms and suicidal ideation in depressed patients. However, this effect was never investigated for suicidality per se. Herewith, we propose a double blind randomized placebo controlled trial in 144 patients presenting with acute suicidality regardless of the underlying diagnosis, to test the hypothesis that a single dose of 75mg intranasal ketamine is able to diminish acute suicidal ideation. Additionally, we will examine ketamine*s anti-suicidal mechanism of action by measuring plasma and neuroimaging markers. This study may result into a readily available and easily applicable intervention for the treatment of acute suicidality.

Study objective

The aim of this study is to find a directly applicable intervention for acutely suicidal patients, so that the risk of these patients committing suicide is substantially lowered, leading to fewer actual suicides. To this end we propose a randomized placebo controlled trial in 144 subjects presenting with acute suicidality in two university hospitals, regardless of the underlying diagnoses. Subjects will be randomized to receive either intranasal (i.n.) racemic ketamine or midazolam as an active placebo with comparable dissociative and sedating effects.

Our primary objective is to investigate if a single administration of75 mg intranasal ketamine will diminish suicidality more than 3.8 mg intranasal midazolam, as measured on the Beck Scale for Suicide Ideation (BSSI) after 180 minutes. We hypothesize that intranasal ketamine will lower suicidality as measured on the BSSI significantly more than intranasal midazolam.
Our secondary objective is to investigate the mechanism via which ketamine may exert its anti-suicidal effects. We will determine changes in serum Brain Derived Neurotrophic Factor (BDNF) from baseline to 180 minutes after the intervention. In addition, we will explore anti-suicidal neuroimaging markers after administration of ketamine or placebo, such as hippocampal volume, hippocampal-frontolimbic connectivity and glutamate levels.
Finally, we will investigate if ketamine exerts an antidepressant effect in acutely suicidal patients and if the anti-suicidal effect is associated with the antidepressant effect. We hypothesize that ketamine will indeed exert an antidepressant effect, but that the antisuicidal effect is not entirely mediated by this. Also, we will determine the actual number of suicides in both groups until 1 year follow up.
In nearly 595 patients that were treated with i.v. ketamine doses of 0.5mg/kg for chronic pain or depression, no serious adverse events were observed. Therefore, we consider a dose of 75mg intranasal ketamine as safe, which is comparable to a dose of 0,5mg/kg intravenous ketamine.

Study design

The study will be performed in two centers: the Academic Medical Center (AMC) in Amsterdam and the University Medical Center Groningen (UMCG). The coordinating investigators (one in each center) will be supported by a research nurse (one for each center) and medical students. We choose for a double blind randomized active-placebo controlled trial because this design is the gold standard for studying the efficacy of a pharmacological intervention. In order to better understand ketamine*s mechanism of action and to determine a responder/non-responder profile, we will determine genetic polymorphisms for genes involved in the presumed mechanism of action of ketamine and we will conduct functional and structural magnetic resonance imaging (MRI)-scans one day after administration of either ketamine or midazolam.

Before the actual study, a pilot-feasibility study with 16 patients will be performed. In this study we will follow the same procedure as in the main study. Only after evaluation of both the efficacy and the safety of this pilot study, we will start the main study. Depending on the pilot study we might want to make changes to the design of the main study.

Intervention

Subjects will be randomly allocated to either 75 mg of i.n. ketamine or the active placebo midazolam (3.8mg i.n.). The patients will be treated on the emergency ward of the general hospital of the AMC or the UMCG, or if they are recruited form the psychiatric department, they will be treated at the Psychiatric Medial Unit (PMU) where sufficient somatic support is available. Vital parameters will be measured every 30 minutes until 180 minutes after administration. In case of a significant abnormality in any of the vital parameters, the subject will receive adequate medical care. Patients will remain hospitalized for 8-24 hours after ketamine/midazolam administration. They will have to be accompanied by someone when leaving the hospital. Racemic ketamine is associated with less side-effects than S-ketamine, therefore we choose to administer racemic ketamine. The intranasal ketamine and midazolam containers will be manufactured by Tiofarma. The dosage that has been used in the only previous randomized controlled trial with i.n. ketamine was 50mg. We consider this dose as conservative. A dose of 75mg intranasal ketamine is comparable to a a dose of 0,5mg of intravenous ketamine, which is a usual ketamine dose for research in psychiatry.

Study burden and risks

The side-effect profile of a single low dose of racemic ketamine seems to be relatively favourable. The most serious events that have been observed are brief periods of dissociation and an elevated blood pressure. Since in this study only a single dose will be administered, long-term side effects of

ketamine, such as cognitive or urologic problems are very unlikely to occur. Subjects are hospitalized for 8-24 hours after ketamine administration, so in case SAE or a SUSAR occurs, this can be immediately treated. Although we assess the risk of our study as low, we are aware that suicidality is a sensitive subject, and that there is a significant chance, given the characteristics of our target group, that an actual suicide might occur. For this reason, an independent Data and Safety Monitoring Board (DSMB) will be established to examine safety parameters when 50% of the subjects are included.

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

Acute suicidality: suicidal thoughts and/or behaviour have increased within the last 24 hours. A Beck Scale for Suicide Ideation (BSSI)-score of 7 or above

Subjects are in the age of 18-70

Exclusion criteria

-Earlier participation in this study
-Psychosis
-A diagnosis of schizophrenia or another psychotic disorder
-A history of PCP- or ketamine addiction
-Being under influence of GHB (Substance abuse in the (recent) history is not an exclusion criterion per se (with the exception of GHB and a high blood alcohol concentration, and intoxications leading to medical unstable conditions)
-A blood alcohol concentration (BAC)of >0.05%
-A clinically significant and unstable infectious, immunological, cardiovascular, gastro-intestinal, pulmonal, renal, hepatic, endocrine or haematological disorder, a myocardial infarction, miction problems or a complex surgical problem that needs immediate attention
-A known hypersensitivity for ketamine
-Concomitant use of a MAO-inhibitor
-Severe nose congestion or nasal polyps
-Pregnancy or giving breastfeeding
-Women using unreliable contraception
-Being unable to answer the questionnaires
-Legal incompetency
-No informed consent

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL
Recruitment status: Will not start

Enrollment:	156
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ketalar
Generic name:	ketamine

Ethics review

Approved WMO Date:	23-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2018
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	EUCTR2015-004745-70-NL
CCMO	NL55438.018.16