Effect of low-dose esketamine on postoperative delirium in patients undergoing noncardiac surgery.

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Primary Objective:In this pilot study, the authors aim is to investigate whether esketamine reduces the incidence of POD in elderly patientspresenting for noncardiac surgery.Secondary Objective(s):To examine whether esketamine has an effect on the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Deliria (incl confusion)
Study type	Interventional

Summary

ID

NL-OMON38654

Source
ToetsingOnline

Brief title
Esketamine and postoperative delirium.

Condition

- Deliria (incl confusion)
- Therapeutic procedures and supportive care NEC

Synonym
Postoperative confusion after noncardiac surgery

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Coolsingel

Intervention

Keyword: Delirium, Esketamine, Noncardiac surgery

Outcome measures

Primary outcome

The incidence of a postoperative delirium.

Secondary outcome

The effect of esketamine on the bloodlevels on some biomarkers.

Study description

Background summary

Postoperative delirium (POD) is a common and harmful complication of major surgery in older patients and because of our aging population growing to be a major problem. The incidence of POD varies widely, with reported rates of 25% in abdominal surgery and 44% to 61% in orthopedic surgery. POD is associated with longer hospitalization, functional decline and often results in readmission. Several etiologic factors are known to influence the development of POD such as older age, dementia or other cognitive disfunctionalities, systematic infection, medication, major trauma, alcohol abuse, anesthesia, prolonged lack of sleep, diabetes mellitus and anemia. The different types of anesthetics given during the course of the operation as well as the large inflammatory response induced by surgery itself are known to have impact on development of POD. Esketamine, a NMDA receptor antagonist, is known to induce dissociate anesthesia. In sub anesthetic doses it has excellent analgesic properties and favorable features like bronchodilatory effects. A recent prospective randomized study among cardiac surgical patients showed that a single dose of esketamine during anesthetic induction can reduce the incidence of POD by 90%.

Possible mechanisms of action of esketamine:
The mechanism by which esketamine reduces the incidence of POD is unknown. Esketamine may act as a neuroprotective drug by prevention of excitotoxic injury and apoptosis after cerebral ischemia, and

suppression of inflammatory central nervous system responses to injury caused by surgery. Measurement of inflammation markers is therefore warranted to examine whether a lower incidence of POD after esketamine coincides with lower levels of these markers in the blood. It has been found that serum concentrations of the acute-phase inflammatory marker C-reactive protein (CRP) was lower in esketamine treated patients compared to those who received placebo, but these authors used a rather insensitive method for the determination of CRP. We propose to use a more sensitive method for evaluation of CRP (high-sensitivity CRP) and also determine the pro-inflammatory substances interleukin-6 (IL-6) and neopterin. Surgery itself may increase blood levels of IL-6 while this cytokine is also significantly elevated in cardiac surgery patients who develop postoperative delirium. Neopterin is produced in parallel with reactive oxygen species (ROS) by activated cells of the immune system and this substance is also able to enhance various effects of ROS. In humans, neopterin is therefore considered both an indicator of the activation of the host defense system due to trauma and a marker of oxidative stress due to immune activation.

Esketamine has also been shown to affect the CNS cholinergic system and the resulting release of acetylcholine may theoretically play a role in the recovery of derangements in cerebral concentrations of other neurotransmitters. We therefore propose to also determine the dopamine metabolite homovanillic acid (HVA) in our cohort. The concentration of HVA in blood is a fairly good indicator of the changes in dopamine metabolism in the CNS. High plasma HVA levels may reflect increased oxidative metabolism of dopamine with the concomitant higher production of toxic metabolites, like the oxidant hydrogen peroxide. In an earlier study of our group, we showed that the concentration of HVA is increased in delirious Alzheimer*s disease patients compared to non-delirious patients. As systemic inflammatory conditions also result in a large increase in the production of free radicals, it is possible that both increased inflammatory processes and high dopamine turnover are important neurodegenerative factors that may play a role in the pathophysiology of delirium in older patients.

Insulin-like growth factor 1 (IGF-1) has also been considered in the pathogenesis of delirium since this neuroprotective cytokine inhibits cytotoxic cytokines. Low IGF-1 concentrations have been associated with the development of delirium in acutely ill, older patients. However, other studies were inconclusive. To investigate whether esketamine effects IGF-1 concentrations in blood and whether any changes may relate to the development of a POD, we will also determine this

cytokine in our patient cohort.

Our main hypothesis is that
1. a single dose of esketamine reduces the incidence of postoperative delirium in high risk patients presenting for noncardiac surgery.

Furthermore, we hypothesize that

2. If a single dose of esketamine attenuates the incidence of postoperative delirium, this attenuation is associated with a decrease in the blood levels of CRP, IL-6, neopterin and HVA compared to the placebo condition. Concerning IGF-1, we hypothesize that the concentration of this cytokine is increased in the intervention cohort.

Study objective

Primary Objective:
In this pilot study, the authors aim is to investigate whether esketamine reduces the incidence of POD in elderly patients presenting for noncardiac surgery.

Secondary Objective(s):
To examine whether esketamine has an effect on the blood levels of some biomarkers that reflect processes of inflammation, oxidative stress and neuroprotection, and which may be associated with a delirium.

Study design

In this double-blind, randomized, placebo controlled study we plan to study 250 patients. Patients at or above the age of 65, who will undergo elective hip/knee replacement surgery or major/peripheral vascular surgery under general anesthesia are eligible for inclusion. We have chosen these types of surgery because it is shown that these patients are at the highest risk for developing POD.
Patients will be allocated to the intervention or control group in a randomized and double blind fashion. Group 1 will function as the control group and these patients will receive one dose of 10 ml NaCl 0.9%. The intervention group will receive one dose of esketamine 0.5 mg/kg dissolved in 10 ml NaCl 0.9%.

On the first, second and third day after the operation the occurance of delirium will be assessd by means of questionnaires.

Prior to surgery and on the third day after surgery blood will be drawn for specific biomarkers which are associated with an increased risk of postoperative delirium.

Intervention

A single dosis of esketamine 0.5 mg/kg will be given to patients allocated to the intervention group after induction of
anesthesia.

Study burden and risks

If our hypothesis is true we will expect a lower incidence of postoperative delirium in the intervention group. Giving a single
shot of esketamine will not create a risk for the patient. When the patient has woken up, the blood concentration of esketamine
will be too low to induce side-effects.

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

- The patient has provided written informed consent.
- Age >= 65 years.
- The patient is planned for hip or knee replacement surgery or major/peripheral vascular surgery under general anesthesia, with a scheduled duration of more than one hour and a minimal hospitalization of three days.

Exclusion criteria

- The patient has severe systemic disease that limits activity and is a constant threat to life (ASA IV).
- The patient has a active of psychiatric disorders.
- The patient has an active infection and/or fever is present
- The patient has a history of hypersensitivity to one of the study drugs.
- The patient has a MMSE score below 24 points.
- The procedure will be performed under spinal anesthesia or any other locoregional technique.
- Prolonged sedation after surgery for more than 24 hours

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-01-2014
Enrollment:	250
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	11-07-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2013
Application type:	First submission
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
EudraCT	EUCTR2013-000956-16-NL
CCMO	NL43907.078.13

Study results

Date completed:	27-11-2014
Actual enrolment:	70