Effects of prophylactic use of haloperidol in critically ill patients with a high risk for delirium

Published: 22-02-2013
Last updated: 26-04-2024

In this study we aim to examine the effects of a low dosage of prophylactic haloperidol in patients with an expected ICU length of stay of >1 day. We use two different dosages of haloperidol in this study to compare with placebo. A dosage of 1mg...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39725

Source
ToetsingOnline

Brief title
Delirium_Haldol-prophy

Condition

- Other condition

Synonym
acute confusion, delirium

Health condition

neuropsychiatric disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw

Intervention

Keyword: delirium, high-risk, ICU, prophylaxis

Outcome measures

Primary outcome

Primary objective: To determine the effect of prophylactic haloperidol on

28-day mortality

Secondary outcome

Secondary Objective(s): There are five secondary outcome measures:

1. To determine the effect of prophylactic haloperidol on 90-day mortality

2. To determine the effect of prophylactic haloperidol on delirium incidence

3. To determine the effect of prophylactic haloperidol on number of

delirium-free and coma-free days in a period of 28 days

4. To determine the effect of prophylactic haloperidol on delirium related

outcome: duration of mechanical ventilation, incidence of re-intubation,

incidence of ICU readmission, and incidence of unplanned removal of tubes and

catheters

5. To determine the preventive efficacy of haloperidol in different patient

groups based on the a priori risk to develop delirium: patients with a

predicted risk up to 50%, 50-70%, 70-90%, above 90%

6. To evaluate side-effects of haloperidol treatment

7. Effect on quality of life

Study description

Background summary

Delirium is a neuropsychiatric disorder characterized by an acute onset of confusion and consciousness alterations that fluctuate during the day. The incidence of delirium in intensive care (ICU) patients is high, on average 30-50%, and its occurrence is associated with prolonged duration of mechanical ventilation, increased ICU- and hospital length of stay unplanned removal of tubes and catheters and an increased mortality. Therefore, preventive treatment for delirium may be beneficial.
Apart from treatment of the underlying disease, haloperidol is the most common and recommended anti-psychotic drug in delirium treatment. Recently, this drug is also used to prevent delirium. In non-ICU patients beneficial effects of prophylactic haloperidol in older and surgical patients have been reported.
For critically ill patients, data concerning preventive treatment with anti-psychotic drugs is scarce, and inconsistent.
In one retrospective cohort study ICU patients treated with haloperidol a lower mortality rate was found compared to non-treated ICU patients. Another recent study showed that haloperidol prophylaxis in non-cardiac surgical ICU patients had beneficial effects on delirium incidence and delirium free days.
Note worthily, in this study no delirium risk stratification was performed, suggesting that the beneficial effects might be diluted in the whole group of ICU patients (as also patients with a low risk to develop delirium were included) and that more pronounced preventive effects may be present in patients with a high risk to develop delirium. Recently, a delirium prediction model for ICU patients was developed and validated. With this model the extent of the preventive efficacy in different groups of delirium-risk can be determined. In view of the high incidence of delirium, the impact of delirium on outcome, and the availability of a delirium prediction model to identify high risk ICU patients a delirium prevention protocol was implemented in clinical practice using a low dosage of haloperidol. Subsequently the effect of this prophylactic treatment in patients with a high risk was evaluated on several relevant delirium outcome parameters. In this study were found: In patients with a predicted risk to develop delirium >50%, delirium incidence was (haloperidol vs control) 65 versus 75%, delirium-free and coma free days in 28 days 20 versus 13 and also complications related to delirium (e.g. unintended removal of catheters and tubes) was significantly lower in the patients that received haloperidol. Based on these results, these effects of prophylactic treatment with haloperidol need to be confirmed in a randomized controlled double-blind trial. Since no relevant side-effects were reported in prophylactic studies with a low dosage of haloperidol and the described moderate positive results (e.g. incidence from 75 to 65%) it is conceivable that a somewhat higher dose of haloperidol may exert more pronounced beneficial effects.

Study objective

In this study we aim to examine the effects of a low dosage of prophylactic haloperidol in patients with an expected ICU length of stay of >1 day. We use two different dosages of haloperidol in this study to compare with placebo. A dosage of 1mg, or 2mg three times a day in a double blinded fashion resulting in a three-armed multicentre randomized double blinded controlled trial. The PREDELIRIC-model will be used to determine the a priori chance to develop delirium, enabling us to determine the preventive efficacy of haloperidol in patient groups based on their risk to develop delirium. Patients that are included in the study, but leave the ICU within 24 hours will be discarded for further analysis. Since it is recognized that the onset of delirium is median on day 2, low dosage and a short treatment duration with haloperidol has no relevant side-effects, randomization will be started immediately prior to the informed consent procedure. This procedure will be started as soon as possible, and if no informed consent will be obtained patients are then still excluded for this study and replaced until group size is achieved.

Study design

A prospective multicentre three armed block-randomized double-blind placebo-controlled prophylactic intervention study in critically ill patients with a high risk for delirium.

Number of centers: In total 19 centers in the Netherlands with a level 2 or 3 Intensive Care Unit will participate in this study.

Estimated study duration: Follow-up of included patients is till discharge of the ICU or in case delirium occurred till the delirium has resolved (defined by three consecutive days of negative delirium screenings). Total duration for the conduct of the study: 1.5 year.

Intervention

In this study we have two prophylactic haloperidol groups and one placebo group. Patients allocated to the treatment group will receive either 3x1mg or 3x2mg prophylactic haloperidol until discharge from the ICU or when delirium occurs. In the latter case study drug will be stopped and patients are subsequently treated according to the delirium protocol with open-label haloperidol. To avoid unnecessary risk for side-effects the dose will be halved in patients:
- aged >= 80 years
- weight <= 50 kg
- liver failure (serum bilirubin level > 50 µmol/L)
Patients with an adjusted dosage of study drug remain allocated to their original group.

In case of occurrence of QTc-time prolongation of over 500msec. the study drug will be stopped immediately.

Study burden and risks

Based on historical data we know that the median predicted delirium risk is 35% in patients with an expected stay on the ICU of over one day. This is considered a high risk for delirium.
To assess patients for delirium using the CAM-ICU by ICU-nurses is part of daily practice in all participating centres. Also, patients receive three times a day a study drug of which two groups receive a low dose of haloperidol and a third arm receive placebo. Concerning haloperidol, this drug is worldwide first choice of drug in delirious patients. When delirium is diagnosed, patients are treated according to delirium protocol, using a higher dosage than in the prophylactic treatment period as described in this study protocol. It is recognized that early treatment of delirium has beneficial effects compared with delayed treatment, and also there is some evidence that delirium prevention in ICU patients has beneficial effects, but study design was not optimal.
Potential side-effects of haloperidol include, extrapyramidal symptoms, drowsiness, agitation, and ventricular arrhythmias. The latter are extremely rare (only case-reports are published and related to a higher dosage of haloperidol. With the dosage that will be used in the present study (3x1 or 3x2mg daily) no relevant side-effects are anticipated. Nevertheless, and given the preventive nature of this study, extra attention is being paid on recognition of possible side-effects of haloperidol in the protocol.
Importantly, in three recent prophylactic haloperidol studies no relevant side-effects and in particular no ventricular arrhythmias were reported using a similar low dosage of haloperidol as described in the present protocol.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
Nijmegen 6525 GA
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All consecutive ICU patients:;- age >= 18 year;- expected length of ICU stay of over one day

Exclusion criteria

- history of epilepsy, Parkinson*s disease, hypokinetic rigid syndrome, dementia or alcohol abuse
- patients admitted to the ICU for neurological reasons
- patients treated with other anti-psychotics
- prolonged QTc-time (over 500msec) or history of ventricular arrhythmia (in last 12 months)
- pregnancy
- delirious before ICU admission
- serious auditory or visual disorders
- ICU-stay <=1 day;- unable to understand Dutch
- severely mentally disabled
- serious receptive aphasia
- allergic to haloperidol
- moribund and not expected to survive 2 days

Study design

Design

Study phase: 4

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):	12-06-2013
Enrollment:	2145
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Haldol
Generic name:	Haloperidol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-02-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-06-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	06-12-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-01-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-02-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
Other	ClinicalTrials.gov nr. NCT01785290
EudraCT	EUCTR2012-004012-66-NL
CCMO	NL41979.091.12

Study results

Date completed:	01-12-2016
Actual enrolment:	1789