Statistical analysis plan - The Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID

Note: This statistical analysis plan was written prior to unblinding of randomisation / treatment allocation. Published online 21st October 2017

1. Introduction

The Oslo Study of Clonidine in Elderly Patients with Delirium (LUCID) [1] is a randomised, placebo-controlled, double-blinded, parallel group study with 4-month prospective follow-up. It was scheduled to recruit 100 elderly medical inpatients (age >65 years) with delirium or subsyndromal delirium in the acute geriatric ward, later expanded to inclusion from the entire medical ward. Participants were randomised to oral clonidine or placebo (with a loading dose the first day (75 µg every 3rd hour up to a maximum of 4 doses) and further 75 µg twice daily until delirium free for 2 days (Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria), or after a maximum of 7 days treatment. Assessment of hemodynamics (blood pressure, heart rate and electrocardiogram) and delirium were performed daily until discharge or a maximum of 7 days after end of treatment.

Inclusion and exclusion criteria

See table 1

Randomisation procedures

The randomisation was based on computer-generated random numbers, and carried out by a statistician (Eva Skovlund). The randomisation schedule was distributed to the producer of the study medication (Kragerø Tablettproduksjon AS), and capsules made accordingly.
The randomisation was originally stratified with respect to whether or not the patient was admitted from a nursing home, in order to balance the groups with respect to pre-admission cognitive decline, an important prognostic factor. In the end, only two patients living in a nursing home was included, and the stratification was abandoned.

Primary endpoint

Our primary objective is to explore the potential superiority of clonidine vs. placebo in decreasing delirium duration and severity, measured by Memorial Delirium Assessment Scale (MDAS) [2] in patients diagnosed with delirium or subsyndromal delirium (according to

Diagnostic and Statistical Manual of Mental Disorders, DSM-5 [3]. The primary endpoint, the trajectory of delirium, is the severity of delirium (measured by MDAS) over time.

Secondary endpoints

We will compare the actively treated group with the placebo group with respect to secondary endpoints shown in table 2. The main secondary endpoint is the duration of delirium, monitored daily by the DSM-5 diagnostic criteria. We will also study the feasibility of oral clonidine in a geriatric ward and effects of clonidine upon a variety of outcomes as a means to potentially design a potentially more definite study later.
Results on some of the secondary endpoints will be published in separate papers.

Blinding

This is a double-blinded study where the study physicians (BEN and KRH) who evaluated the primary endpoint (delirium), the patients and the treating physicians all are blinded to whether the patient is allocated to clonidine or placebo. To preform an evaluation of plasma concentrations and hemodynamic responses, the Data Monitoring Committee (represented by Leiv Otto Watne) was unblinded to the randomisation. He identified the samples from the 10 patients that had received clonidine and sent them to plasma analyses. These results were reported with new id- labels to make sure the study physicians and administrators (BEN and KRH) were still blinded and these results will be published in a separate paper.

Power calculation

Based on the expected number of patients fulfilling the inclusion criteria within 36 months a sample size of n=100 was chosen. It was, however, foreseen that this number of patients might be too small to achieve a sufficiently high power to detect treatment differences with the use of standard statistical analysis methods. For instance, if the proportion recovered according to DSM-5 is 40% and 65% in the two treatment groups, respectively, the power to detect this absolute treatment difference of 25% with inclusion of n=100 evaluable patients is only 71%. Correspondingly, using MDAS at one single point in time as the response measure would lead to approximately 80% power assuming a standard deviation of 9 and a difference in mean MDAS score of 5, which is potentially too optimistic. We therefore planned to perform the primary analysis by a mixed linear model taking all MDAS measurements into account in order to reduce variability and thereby increase power. The expected efficiency gain was difficult to estimate, but assuming a standard deviation of 9 on the MDAS and a

correlation between measurements of r=0.5, the power would be around 95% to detect a mean MDAS difference of 5 or a power of 80% to detect a mean difference of 3.5 between groups.

As it turned out, the inclusion rate was much lower than anticipated. This was mainly due to the frail population and the presence of exclusion criteria for patient safety (See flowchart). Inclusion started in April 2014, and by February 2017 the twentieth patient was included and the study was halted to analyse clonidine plasma concentrations and hemodynamic responses / safety of the protocol. After at thorough overall assessment, the Principal Investigator (TBW) and study physicians (BEN and KRH) decided against further inclusion to this study as the time frame to achieve 100 patients was clearly unrealistic and also with such a small percentage of eligible patients actually included is doubtful that any results would be truly generalizable.

Patient flow

Figure 1. Patient flow

2. Primary efficacy analysis

The primary endpoint is the repeated measurements of MDAS over time. Differences in the MDAS trajectories between the treatment groups will be analysed by a mixed linear model. For the comparison of the MDAS trajectories no adjustment for multiplicity will be applied. The analysis will be performed for the time frame of the treatment (i.e. 7 days). If there is no linear relationship between MDAS score and time, a log-transformation will be performed.

3. Handling of protocol violations

The study was halted after only 20 patients (not 100 as originally planned) so it is not sufficiently powered to precisely estimate effects, and we do not expect to be able to draw conclusions about any effect on our primary outcome. However, we will adhere to the original plan as described in the protocol, but regard the analyses as exploratory.

There were no patients wrongfully included or not handled according to randomisation and no patients withdrew consent.

Any patients not treated according to protocol (e.g. single dose not given by mistake) will be included in all analyses as per the intention to treat principle. No patients in the placebo group were administered clonidine.

4. Sensitivity analyses

Adjusted models

We originally planned to perform sensitivity analyses adjusting for age, gender, length of education, admission from nursing home or not, and IQCODE score. However, with the low number of patients actually included, the value of sensitivity analyses is questionable and it will in any case not be possible to include more than one or two covariates in the model.

Handling of missing data

a) Patients who died during hospital stay

Three patients died during the hospital stay or shortly after discharge. Data regarding our primary endpoint is available from all these patients and they will be included in all analyses.

b) Missing MDAS scores

The endpoint of a mixed linear model taking all MDAS measurements into account does not call for imputation of the missing values.

5. Analyses of secondary effect variables

In the protocol it was stated: *In addition we will, as a secondary endpoint, compare the time to resolution of delirium as measured by DSM-5. The Kaplan Meier method and the logrank test will be applied. In addition a Cox proportional hazards model will be applied to estimate hazard ratios. The additional different secondary endpoints will be analysed by t-tests when variables are continuous and by chi-square tests when variables are categorical. Patient survival will be compared between groups by the logrank test and Cox proportional hazards model.*

Due to the slow recruitment leading to early termination, also secondary endpoint will be considered exploratory. No formal adjustment for multiplicity as originally foreseen in the protocol will therefore be applied. The main focus will be to explore possible effects on delirium endpoints; time to resolution of delirium as measured by DSM-5, elements of delirium phenomenology using OSLA and use of rescue medications.

6. Blind analysis

The project administrators (BEN and KRH) have been active in data acquisition and the analysis of plasma concentrations and hemodynamic responses (with new patient id labels), and might theoretically understand from the clinical data from a given patient who the patient is. The statistician (ES) and the principal investigator (TBW) have, however, had no role in these analyses, and are still completely blind regarding randomisation group. To prevent bias, we will adhere to the following procedure: The Data Monitor Committee (LOW), allocates a random number to patients in the intervention group and another to the patients in the control group. The code is written and stored safely, not accessible by the statistician or the principal investigator. The statistician receives the dataset with these codes for the randomisation variable, and carries out the primary analyses. When the statistician and the principal investigator have agreed upon the final analyses, they will be unblinded.

7. Signatures

We hereby vouch for the fidelity of the study to this statistical analysis plan

21.10.17 Oslo, Norway

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8. Tables

Table 1 Selection criteria

Inclusion criteria
All of the following conditions must apply to the prospective patient at screening prior to receiving study agent: • Patient > 65 years old admitted to the acute, medical ward excluding ICU • Delirium or subsyndromal delirium within the last 48 hours • Signed informed consent from patient or relatives and expected cooperation of the patients for the treatment and follow up must be obtained and documented.
Exclusion criteria
Patients will be excluded from the study if they meet any of the following criteria: • Symptomatic bradycardia, bradycardia due to sick-sinus-syndrome, second- or third- degree AV-block (if not treated with pacemaker) or any other reason causing HR <50 bpm at time of inclusion [44]. • Symptomatic hypotension or orthostatic hypotension, or a systolic BP <120 at the time of inclusion • Ischemic stroke within the last 3 months or critical peripheral ischemia • Acute coronary syndrome, unstable or severe coronary heart disease (symptoms at minimal physical activity; NYHA 3 and 4) and moderate to severe heart failure (NYHA 3 and 4). (Acute coronary syndrome is defined according to international guidelines) • A diagnosis of polyneuropathy, phaeochromocytoma or renal insufficiency (estimated GFR<30 ml/min according to the MDRD formula) [44] • Body weight <45 kg • Considered as moribund on admission • Unable to take oral medications • Current use of tricyclic antidepressants, monoamine reuptake inhibitors or ciclosporin • Previously included in this study • Adverse reactions to clonidine or excipients (lactose, saccharose) • Not speaking or reading Norwegian • Any other condition as evaluated by the treating physician

Table 2 List of endpoints and measurements for efficacy assessment

Endpoint	**Measurements for efficacy assessment**
Primary	
Delirium trajectory	MDAS
Secondary	
Time-to-first delirium resolution	DSM-5
Incidence of "full-scale" delirium	DSM-5
Elements of delirium	OSLA
Use of "rescue medication"/ additional drugs (as other sedatives, analgetics and antipsychotics)	Registration of use of all medication
Length of hospital stay	Registrations
Pharmacokinetic response to clonidine	Serum drug concentrations
Pharmacodynamic response to clonidine	BP, HR, ECG, RASS, OSLA, symptoms of bradycardia, orthostatic hypotension or other side-effects
Survival	Registrations
Safety	
Side effects of clonidine/ in-hospital complications	BP, HR, ECG, sedation (RASS, OSLA), and any symptoms of bradycardia, orthostatic hypotension or other side-effects

9. References

1. Neerland, B.E., et al., *The protocol of the Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID: a randomised placebo-controlled trial.* BMC Geriatr, 2015. **15**: p. 7.
2. Breitbart, W., et al., *The Memorial Delirium Assessment Scale.* J Pain Symptom Manage, 1997. **13**(3): p. 128-37.
3. *Diagnostic and Statistical Manual of Mental Disorders, 5th edn. DSM-5.* 2013, Arlington, VA: American Psychiatric Association.