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Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU) - Protocol for a randomised placebo-controlled trial of haloperidol in patients with delirium in the ICU.

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Abstract

Background

Delirium among patients in the intensive care unit (ICU) is a common condition associated with increased morbidity and mortality. Haloperidol is the most frequently used pharmacologic intervention, but its use is not supported by firm evidence. Therefore, we are conducting Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU) trial to assess the benefits and harms of haloperidol for the treatment of ICU-acquired delirium.

Methods

AID-ICU is an investigator-initiated, pragmatic, international, randomised, blinded, parallel-group, trial allocating adult ICU patients with manifest delirium 1:1 to haloperidol or placebo. Trial participants will receive intravenous 2.5 mg haloperidol three times daily or matching placebo (isotonic saline 0.9%) if they are delirious. If needed, a maximum of 20mg/daily haloperidol/placebo is given. An escape protocol, not including haloperidol, is part of the trial protocol. The primary outcome is days alive out of the hospital within 90 days post-randomisation. Secondary outcomes are number of days without delirium or coma, serious adverse reactions to haloperidol, usage of escape medication, number of days alive without mechanical ventilation; mortality, health-related-quality-of-life and cognitive function at 1-year-follow-up.

A sample size of 1000 patients is required to detect a 7 day improvement or worsening of the mean days alive out of the hospital, type 1 error risk of 5% and power 90%.

Perspective

The AID-ICU trial is based on gold standard methodology applied to a large sample of clinically representative patients and will provide pivotal high-quality data on the benefits and harms of haloperidol for the treatment ICU-acquired delirium.

1. Introduction

Delirium is a clinical syndrome diagnosis covering an acute state of organic brain dysfunction. Delirium often accompanies severe somatic illness, and typical symptoms comprise acutely changing or fluctuating mental status including inattention, disorganized thinking, and an altered level of consciousness.[1] Clinically, patients may present with or without agitation, denoted hyperactive and hypoactive delirium motor subtypes.[2] Delirium is a frequent condition in the Intensive Care Unit (ICU), with reported incidences varying between 30 to 50% and even higher among mechanically ventilated patients.[3-5] Delirium is associated with various detrimental outcomes, such as increased number of days on mechanical ventilation, increased ICU and hospital lengths of stay (LOS), long-term disability and cognitive decline, higher cost of care and increased mortality.[3,6-10]

Despite of the fact that no intervention to date has proven consistently efficacious,[11-14] various pharmacological agents are used to intervene against delirium.[15,16] According to a recent international investigational cohort of patients from 99 ICUs, haloperidol is the most frequently

used agent to treat delirium.[17] This is in accordance with various international guidelines.[18-21] However, these recommendations are not supported by evidence. Consequently, the Society of Critical Care Medicine (SCCM) has changed their guidelines (PADIS Guideline 2013 and 2018)[22,23] and does not recommend haloperidol to treat delirium due to the lack of evidence of effect. Nevertheless, this recommendation is based on low quality of evidence due to the absence of adequately powered randomized clinical trials (RCTs).

Conflicting guidelines built on a low level of evidence, a recent overview of reviews finding appalling lack of evidence for the use of haloperidol[24] and the continued use of pharmacological agents, especially haloperidol, to treat delirium reveal an urgent need for an RCT with low risk of bias assessing the balance between benefits and harms of haloperidol in adult ICU-patients with delirium. Therefore, we are conducting Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU) trial.

1.2 Trial hypotheses

We hypothesise that treatment with haloperidol as compared to placebo in adult delirious ICU-patients will affect the number of days alive out of the hospital within 90 days post-randomisation and reduce the duration of delirium in these patients. Furthermore, we expect that haloperidol as compared with placebo increases the total number of serious adverse reactions (SAR) and the number of SARs per patient.

2. Methods

This trial protocol was written in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 statement.[25] The SPIRIT checklist is presented in Appendix 1.

2.1 Trial design

The AID-ICU trial is an investigator-initiated, pragmatic, international, randomised, blinded, parallel-group, trial allocating adult ICU patients with delirium to 1:1 of haloperidol versus placebo. Stratified for trial site and delirium motor subtype (hyperactive or hypoactive) at the time of inclusion.

2.2 Registration

The trial was registered at the European Union Clinical Trial Register (EudraCT no. 2017-003829-15 approved November 30, 2017) and at ClinicalTrials.gov (Identifier no.NCT03392376 January 8, 2018) before inclusion of the first patient.

2.3 Setting

European ICUs admitting adult patients. A complete list of participating trial sites is available at ClinicalTrials.gov (Identifier no. NCT03392376).

2.4 Study population

Inclusion criteria

Adult patients acutely admitted to the ICU with delirium diagnosed using a validated screening tool, i.e. the Confusion Assessment Method – Intensive Care Unit (CAM-ICU)[26] or the Intensive Care Delirium Screening Checklist (ICDSC)[27], are eligible for inclusion.

Exclusion criteria

Patients will be excluded from the trial if they meet one of the following exclusion criteria: (1) known contraindications to haloperidol, (2) habitual treatment with any antipsychotic medication or treatment with antipsychotics in the ICU prior to screening, (3) permanently incompetent (e.g. dementia, mental retardation), (4) delirium assessment non-applicable (language barriers, serious auditory or visual disabilities), (5) withdrawal from active therapy or brain death, (6) fertile women (< 50 years) with positive urine human chorionic gonadotropin (hCG) or plasma-hCG, (7) consent according to national regulations not obtainable, (8) patients under coercive measures by regulatory authorities, or (9) patients with alcohol-induced delirium (delirium tremens).

2.5 Screening

All patients admitted to a participating clinical trial site is considered for participation. Experienced ICU nurses screen patients for delirium with a validated screening tool (CAM-ICU or ICDSC) at least two times a day. When an adult patient at the ICU is diagnosed with delirium, the patient is screened for eligibility of enrolment by local investigators using a central web-based screening system (OpenClinica®). The distribution of trial participants will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) diagram.[28]

2.6 Randomisation

Eligible patients are randomised 1:1 according to a computer-generated allocation sequence list, the stratification variables, and permuted blocks of varying sizes. The allocation sequence list will exclusively be known to the data manager at Copenhagen Trial Unit (CTU) and will be unknown to the investigators to allow immediate and concealed allocation of trial participants. Each trial participant is allocated a unique patient screening number, which will link the patient to the allocated trial intervention.

2.7 Trial intervention

Enrolled patients are randomised to receive either intravenous haloperidol (Haldol®, Jannsen-Cilag, Birkeroed, Denmark) or placebo (Isotonic saline 9 mg/ml) 0.5ml (2.5mg haloperidol or matching placebo) three times daily. If needed, additional trial medication may be administered up to a maximum dose of 20 mg haloperidol/placebo daily (corresponding to 5 additional administrations of 0.5ml of trial medication). In case of incontrollable delirium, trial participants may receive escape medication (propofol, benzodiazepines or alfa2-agonists), but not haloperidol, as decided by the clinical team.

The intervention period will be from randomisation until ICU discharge for a maximum of 90 days. If a trial participant is readmitted to an ICU, participating in the trial, within the 90–day intervention period, the intervention will be resumed.

Trial medication will pause during the intervention period if the patient is delirium-free as defined by the pausing criteria: two consecutive negative CAM-ICU or ICDSC (< 4) scores on the same day (morning and evening assessment). Delirium screening, data registration and follow-up will continue. If a participant again becomes delirious, he/she will resume the allocated intervention.

2.8 Outcome measures

Primary outcome measure

Number of days alive and out of hospital within 90 days post-randomisation.

Secondary outcome measures

1. Number of days alive without delirium or coma in the ICU

2. Number of patients with one or more SARs to haloperidol and total number of SARs to haloperidol
3. Number of patients using escape medicine and number of days with escape medicine per patients
4. Number of days alive without mechanical ventilation in the 90-day period
5. 1-year mortality post-randomisation
6. Health-related quality-of-life assessed by EuroQol 5 dimensions 5 level questionnaire and EQ visual analogue scale (EQ-5D-5L)[29] 1-year post-randomisation.
7. Cognitive function at inclusion assessed by proxy using the Informant Questionnaire for Cognitive Decline in the Elderly (IQ-CODE)[30], and cognitive function measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[31] score and Trail Making Test A&B[32] 1-year post randomisation, at selected sites.
8. A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-effectiveness vs. cost-minimisation analyses). Outcomes will be 1-year mortality and Quality Adjusted Life Years (QALYs). The latter will be conducted based on EQ-5D-5L. The calculation of QALYs generates a cost-utility analysis.

2.9 Blinding

The allocated trial medication is blinded to the clinical staff, to the patient, the investigators, the outcome assessors, the statistician conducting the analyses and the steering committee when drafting the abstract for primary publication.

The Hospital Pharmacy of the Capital Region of Denmark (HP), which holds a Good Manufacturing Practice certificate, is responsible for the placebo production, import of the investigational medicinal product (IMP) from Jannsen-Cilag A/S, blinding, labelling and distribution of IMP and placebo to Danish trial sites. World Currier will handle distribution of IMP to international trial sites.

Haloperidol is contained in liquid form in an ampoule. Placebo will be contained in an identical ampoule. The solution of haloperidol is colourless and cannot be visually distinguished from isotonic saline. Each ampoule will contain the same volume (1 ml), corresponding to 5 mg haloperidol. Three ampoules of either placebo or IMP are packaged in a box with a unique trial medication ID. Labelling of ampoules, primary package end secondary package of IMP and placebo will be identical and contain the required information of trial drugs.

Trained ICU nurses will dispense trial medication through a centralised web-based medication dispensation system (Meddis®). The system will ensure allocation of the right intervention (IMP/Placebo) to the patient by linking trial participant ID to a unique trial medication number each time additional trial medication is needed.
Un-blinding of the intervention may be done if deemed necessary by the clinician or investigator for the benefit of the trial participant's treatment or safety (e.g. suspected unexpected serious adverse reaction, (SUSAR)). Furthermore, the data-monitoring and safety committee (DMSC) can request un-blinding of the trial, if the interim analysis gives strong indications of one intervention being more beneficial or harmful than the other.

2.10 Data registration and monitoring

Data will be entered into a central web-based electronic case report form (eCRF) using the clinical data management system OpenClinica® software (OpenClinica, LLC, Waltman, MA 02451, USA). The eCRF is password protected, encrypted and supported by CTU and allows for detailed centralised and decentralised surveillance of data completeness overall and at each site. Each participating trial site will only have access to their own data. Details and definitions of collected data are presented in Appendix 2.
The trial will adhere to Good Clinical Practice (GCP) principles.[33] Monitoring will follow a predefined monitoring plan developed in collaboration with the GCP Unit at University of Copenhagen, which will coordinate the monitoring done by local GCP units and/or monitors in all Danish regions and participating countries. The coordinating investigator or her delegates will do a centralised day-to-day monitoring through the eCRF.

2.11 Safety

An independent DMSC with two physicians/researchers and a statistician may recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. The DMSC charter is presented in Appendix 3.

Patients can be withdrawn from the trial at any time if:

- A SAR or SUSAR occurs.
- The responsible physician in conjunction with the sponsor decides it to be in the patient's interest.
- The patient after inclusion is subject to involuntary hospitalization (coercive measures)

- The patient after inclusion develops QTc prolongation (> 500 msec).
- The trial guardian, patient or next of kin withdraws consent.

In these cases, data collection will continue, and follow-up will be conducted. The patient will remain in the intention-to-treat population if he/she has received the trial medication.

Serious adverse reactions

Adverse reactions are specified in the summary of product characteristics of haloperidol (Appendix 4). We consider the following conditions related to the intervention to be SARs:

- Anaphylactic reaction
- Agranulocytosis
- Pancytopenia
- Ventricular arrhythmia
- Extrapyramidal symptoms
- Tardive dyskinesia
- Malignant neuroleptic syndrome
- Acute hepatic failure

SARs will be evaluated and recorded daily in the electronic case report form (eCRF) during the ICU stay. The distribution of SARs will be compared by the DMSC at interim and final analyses. SUSARs are defined as serious adverse reactions (SARs) not described in the summary of product characteristics of haloperidol. Trial investigators will report SUSARs to the sponsor within 24 hours, further reporting to national health authorities is done by the sponsor within 7 days. On a yearly basis the sponsor will conduct a safety report of all reported SARs and SUSARs to the Danish Medicines Agency and National Ethics Committee.

2.12 Approvals

The trial is approved by the Danish Medicines Agency (EudraCT no. 2017-003829-15), the Committees on Health Research Ethics in the Zealand Region of Denmark (SJ-646) and the Danish Data Protection Agency (REG-169-2017) and by all required authorities in participating countries. All patients are enrolled after achievement of consent for participation according to national regulations.

2.13 Statistics

A detailed statistical analysis plan will be published before the enrolment of the last trial participants.

The primary analyses will be based on the intention-to-treat population being all randomized patients who received trial medication.[34] To obtain maximum statistical power, the primary outcome will be compared between treatment groups using a likelihood ratio test building on a logistic model for mortality and a linear regression model for days alive out of the hospital within 90 days. Both models will be adjusted for the stratification variables: site and type of delirium at randomization (hypo or hyperactive delirium). The likelihood ratio test will produce a single p-value. The size of the treatment effect will be quantified using raw means in the two groups along with confidence intervals for each mean and for the difference derived from the likelihood function underpinning the likelihood ratio test. A secondary analysis will be adjusted for the stratification variables and other prognostic co-variates and Simplified Mortality Score (SMS-score[35]) at baseline.

Subgroup analyses of the primary outcome will be performed defined by stratification variables (site and delirium motor subtype) and other important baseline variables: surgical admittance (yes/no), age (<69 y, ≥69 y[36]), sex, one or more risk factors of delirium (+/-) and SMS score (<25, ≥25)).

Pre-planned sensitivity analyses of the primary outcome include a per-protocol analysis, excluding patients with major protocol violations (patients who did not receive the allocated intervention for at least two days despite having delirium, patients receiving the allocated intervention for two days despite fulfilling pausing criteria (not delirious), treatment with other antipsychotics during ICU stay and withdrawal from trial intervention). The sensitivity analyses will be adjusted for stratification variables and for other known prognostic co-variates.

Significance

A two-sided P-value of less than 0.05 or a 95% confidence interval not including 0 for the primary outcome will be considered statistically significant. The secondary outcomes will be given with 99% corresponding to a modified Bonferroni adjustment[37,38] and 95% confidence intervals. P-values will also be provided for the secondary outcomes, but 99% confidence intervals not including 1 (for Risk Ratio - RR) or 0 (for Mean Difference -MD) will be considered as definitely statistically significant, while 95% confidence intervals not including 1 (for RR) or 0 (for MD) will be considered only possibly statistically significant.

2.14 Sample size estimation

A Wilcoxon rank sum test was applied for power calculations as observational data[17] on the primary outcome showed a non-normal distribution. Assuming that the treatment will a) lower in-hospital mortality by 15% and b) shift the distribution of 'days alive out of the hospital at day 90' of the remaining population to the right with a combined effect on the mean of 8% improvement and that 500 patients are randomized to each arm, we will have 90% power (β=0.1) at the 5% (α=0.05 two-sided) significance level.

2.15 Interim analysis

Interim analyses will be conducted after patient no. 500 has been followed for 90 days. The independent DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs is found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function, or otherwise finds that the continued conduct of the trial clearly compromises patient safety.

2.16 Trial organisation and management

The AID-ICU trial is performed within the Centre for Research in Intensive Care (CRIC), Denmark - a national research centre including the CRIC partners: The departments of Intensive Care at Copenhagen (Rigshospitalet), Aalborg and Zealand University Hospitals, CTU, The Department of Biostatics, University of Copenhagen and VIVE, the Danish Center for Social Science Research.

The Management committee is responsible for the overall management and coordination, which will be supervised by the Steering committee. Site investigators will manage and coordinate the trial at the sites. The principal investigator is responsible for data collection and maintenance of trial documents.

Co-enrolment of participants in other interventional trials has to be approved by the AID-ICU steering committee but is generally appreciated.

2.17 Data sharing

The trial results will be submitted to a peer-reviewed international clinical journal.

De-identified data will be made publicly available 12 months after 1-year follow-up of the last randomized patient according to the recent ICMJE recommendations.[39] All trial documents,

including protocol amendments, will be available on the public AID-ICU trial website (www.cric.nu/aid-icu).

2.18 Finances

The AID-ICU trial has received financial support from Innovation Fund Denmark (4108-00011B), the Regional Medicines Fund, the Zealand Region Research Fund, Intensive Care Symposium Hindsgavl and Foghts Foundation. The funding sources have no influence on trial design and will have no influences on data collection, analysis or reporting.

3 Discussion

Intervention

Haloperidol is presently the most frequently used agent for treatment of delirium in the ICU,[17] although there is very limited evidence to support this practice.[12,14,40,41] Recent data raises concerns about the potential harmful effects of haloperidol,[42-45] which further challenges its ongoing use. Haloperidol was chosen as the interventional drug because of the need to establish firm evidence about the benefit and harms of this current, widespread intervention against manifest delirium in the ICU.

Outcome

In ICU delirium research core outcome sets (COS) have been called upon, but at the moment none exist.[46] Outcome measures in ICU delirium research are challenged by the fluctuating delirium status over time, the inability to screen comatose patients, the discontinued delirium assessment after ICU discharge and a high mortality in ICU patients. A composite outcome of death and delirium status – 'delirium-free days' has been used in previous studies, however this measure does not address the status of coma. This has led to another prevalent outcome measure 'delirium and coma free days'.[46] Other outcome measures encountered in ICU delirium research include ICU or hospital LOS, days on mechanical ventilation, delirium resolution and mortality.[12]

To address the overall benefits and harms of the intervention consistent objective outcome measures are preferable. The use of outcome LOS is biased by the competing event of death, as in-hospital mortality influences LOS, and confounded by different discharge criteria. We choose 'days alive out of the hospital within 90 days' as the primary outcome because it not only addresses mortality but also includes morbidity (causing prolonged hospitalization or

readmissions). The outcome measure is objective, informative, consistent and likely patient-centered. Furthermore, a composite outcome creates higher event rates minimizing the required sample size (n=1000) and thereby also limiting research costs, while still achieving power to determine the overall benefits and harms of haloperidol in the treatment of ICU delirium.

Strength

The AID-ICU trial is an investigator-initiated, international, randomised placebo controlled trial of haloperidol, considering rescue use of haloperidol a protocol violation. The trial design is based on a stringent methodology, which includes concealed group allocation, blinding to the patient, clinical staff, the investigators, the outcome assessors, and the trial statistician. The trial is GCP monitored and an independent DMSC will be responsible for the interim analysis. Sample size estimations and trial design are based on a recent inception cohort study, yielding data from 99 ICUs and 1260 patients worldwide,[17] making the trial relevant and representative of current practice and survival rates.

Limitations

The AID-ICU trial requires patients to be delirious to receive trial medication, which is challenging, as the delirium may have a fluctuating course. If the patient is diagnosed as delirium free (two consecutive negative delirium screenings in the same day) trial medication should be paused and resumed if the patient again becomes delirious (one positive delirium assessment). Delirium screening is hereby paramount for compliance with the protocol. Inconsistent delirium screening may lead to misleading recruitment by possibly overlooking hypoactive delirium subtypes and also insufficient pausing/activation of trial medication. Delirium screening should be implemented as standard care at the sites participating in the trial. Comatose patients, whether intended or unintended, are not assessable for delirium and their delirium status in coma is thereby unknown. Patients should generally continue to receive trial medication while in coma. However, clinicians shall on a daily basis, if appropriate, ease the level of sedation to ensure sufficient level of consciousness to perform delirium screening. In case, the coma is suspected to be caused by the trial medication, all other causes should be considered and abolished (e.g. level of sedatives, analgesics etc.) before the trial medication is paused according to the coma-criteria.

4. Perspective

Encompassing 1000 patients and estimated participation of 20 European ICUs, the AID-ICU trial in the ICU aims to give firm evidence on the efficacy and safety of haloperidol in the treatment of delirium in the ICU. The trial is conducted with a stringent methodology, which complies with international guidelines for clinical trials and good clinical practice. The results will be included in a future updated systematic review whereby we aim to achieve established knowledge about the effect of haloperidol on delirium in the ICU.

5. Trial status

The trial is currently recruiting at 13 active trial sites. The first patient was enrolled in June 2018. Trial status is displayed on the trial website www.cric.nu/aid-icu/. The current protocol is version 4.2 dated June 7 2019. Inclusion of patients is expected to end in 2020.

Conflict of interest

Dr. BE has received lecture fees and/or is part of Advisory Boards of Bristol.myers Squibb, Eli Lilly and Company, Janssen-Cilag, Otsuka Pharma Scandinavia AB, Takeda Pharmaceutical Company and Lundbeck Pharma A/S.

Authors' contributions

NAR and OM drafted the manuscript in close collaboration with LP, AP, JW, BE and TL. SE, JH, MM, GC, LZ, JC, MB, SA, SW, HS, TH, CT, TJ, LG, ad ND all made substantial contributions to the development of the protocol and this manuscript. All authors have read and approved the final manuscript. All authors are members of the AID-ICU steering committee. LP is the sponsor and NAR is coordinating investigator. JH, MM, GC, LZ and JC are national principal investigators of the AID-ICU trial. MC, MB, SA, SW, HS, TH, CT, TJ, LG, ad ND are principal investigators at trial sites.

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