Cognitive function after critical illness with ICU-acquired delirium at the Intensive Care Unit: A 1-year follow up at selected sites of the AID-ICU trial

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Content

Abstract

Introduction:

Intensive care unit (ICU)-acquired delirium is a common clinical condition, affecting around one-third of critically ill patients admitted to the ICU. The condition is associated with multiple short and long-term consequences. The most frequently used pharmacological intervention is haloperidol, despite limited evidence for this treatment. The randomised, blinded, placebo-controlled trial "Agents Intervening against ICU-acquired delirium in Intensive Care Unit" (AID-ICU) aims to assess the benefits and harms of haloperidol in patients with delirium in the ICU.
Long-term consequences of delirium may include significant cognitive impairments. The aim of this follow-up trial is to investigate cognitive function in patients included in the AID-ICU trial one year after randomisation.

Objectives: To assess differences in cognitive function between intervention groups (haloperidol and placebo) one year after randomisation in the AID-ICU trial. Furthermore, to explore cognitive function assessed by proxy prior to admission at the ICU.

Methods: Cognitive function will be assessed with the neuropsychological test tool the "Repeatable Battery for the Assessment of Neuropsychological Status" and the Trail Making tests A&B. The cognitive function prior to admission will be explored by a proxy-survey, using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) tool.

Abbreviations

AID-ICU	Agents Intervening against Delirium in the Intensive Care Unit
ADL	Activities of daily living
FDA	U.S Food and Drug Administration
HRQoL	Health-related Quality of life
IADL	Instrumental activities of daily living
ICU	Intensive care unit
IQCODE	Informant Questionnaire on Cognitive Decline in Elderly
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple imputation
MNAR	Missing not at random
RCT	Randomised controlled trial
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SD	Standard deviation
SMS	Simplified mortality score

Introduction

Delirium in the Intensive care unit

Delirium is a clinical condition, frequently observed in patients admitted to an Intensive care unit (ICU) and with reported incidences ranging from 20% to 84%(1–7). It is described as an acute brain dysfunction characterized by fluctuating changes in consciousness and with inattention as a clinical hallmark(2,8,9). Furthermore, ICU-acquired delirium is accompanied by short and long-term cognitive disturbances (e.g. memory deficits, disorientation and perceptual disturbances)(2,8–10).

Patients with ICU-acquired delirium may experience an array of symptoms due to the fluctuating nature of ICU-acquired delirium, ranging from apathy and lethargy to hypervigilance, agitation and combative behavior(11,12). ICU-acquired delirium is divided into three motoric subgroups; hypoactive (e.g. apathy, withdrawal), hyperactive (e.g. agitation, restlessness) and a mixed type where the patient fluctuates between hypo- and hyperactive subtype(10). The most common subtype is the mixed ICU-acquired delirium, followed by the hypoactive and the hyperactive delirium (11,12). The pathophysiology of ICU-acquired delirium seems to be multi-factorial. Numerous risk factors have been identified; predisposing factors such as age, baseline cognitive impairment, co-morbidities, and numerous precipitating factors, including use of sedatives and analgesics, severity of illness, hypoxemia and hypotension (2,5,6,13).

The short and longer term consequences of ICU-acquired delirium include unintentional removal of devices/catheters, complications to mechanical ventilation (MV) i.e. self-extubation, nosocomial pneumonia, and delirium is an independent predictor for increased duration of mechanical ventilation, prolonged length of stay in ICU and prolonged hospital stay, higher mortality, increased healthcare cost, and a strong predictor for cognitive impairment for years after the ICU stay(1,3–5,14–16). Recent cohort studies have found reduced cognitive function both 3 and 12 months after ICU-discharge and at a level corresponding to light Alzheimer's disease(1,17).

Treatment of ICU-acquired delirium is currently a mix of non-pharmacological and pharmacological approaches. Of non-pharmacological interventions, creating a circadian rhythm with mobilization, noise-reduction and sleep protocols, have demonstrated some beneficial effects (1,18). The most frequent pharmacological intervention is haloperidol despite limited evidence for efficacy of this treatment(7,18).

"Agents Intervening against delirium in the Intensive Care Unit" trial (AID-ICU-trial).

Pharmacological intervention with haloperidol, a first-generation antipsychotic drug, continues to be a first-line drug for treatment of ICU-acquired delirium independent of subtype. This was recently confirmed in a large inception cohort study that included 1260 patients from 99 mostly European ICU's, demonstrating that haloperidol was the most frequently used pharmacological treatment (7). However, the literature presents limited evidence for the efficacy of haloperidol as pharmacological treatment of ICU-acquired delirium(19). Furthermore, haloperidol may be associated with several significant adverse effects, especially neurological and cardiovascular adverse effects. Also, the U.S Food and Drug Administration (FDA) has issued a warning for the use of haloperidol in elderly patients with dementia-related psychosis because of an increased risk of death(20). Thus, as of now we do not know if haloperidol for treatment of ICU-acquired delirium is beneficial or harmful.

Therefore, the multi-centre randomised, blinded, placebo-controlled trial the "Agents Intervening against delirium in the Intensive Care Unit" trial (AID-ICU)(21) has been initiated aiming to assess the benefits and harms of haloperidol treatment of delirium in adult critically ill patients admitted to the ICU. The primary outcome of AID-ICU is the number of days alive and out of hospital within 90 days(21). Secondary outcomes include one-year mortality, health related quality of life and cognitive function one year after randomisation. AID-ICU is currently recruiting patients and is expected to complete inclusion in June 2020, results are pending.

Cognitive impairment after critical illness with ICU-acquired delirium

The term "cognitive impairment" after ICU treatment has been described by Morandi et al. as *"the neuro-psychological changes found following a critical illness that tend to persist and reflect deficits of a magnitude that are, indeed, functionally impairment"* (10).

ICU-acquired delirium is a strong predictor of cognitive impairment up to years after discharge from the ICU (1,3–5,10,14,15). Especially, the duration of ICU-acquired delirium has been found to be independently associated with long-term cognitive impairment (1,22,23).
Long-term cognitive impaired domains include memory (memory loss), executive functions (e.g. difficulties with planning, problem-solving, organizing) and attention (poor concentration) (1,22,24). Impairments like these affect the ability to perform activities of daily living (ADL) (e.g. bathing, dressing, toileting) but also instrumental activities of daily living (IADL) (e.g. adherence to medication, housekeeping, cooking) (25–28). Furthermore, it has been shown that such cognitive impairments negatively affect employment status for ICU survivors, affects quality of life, causes a tendency to social isolation and also affect caregivers and relatives (25,26,29,30).

Evaluation of cognitive function in ICU survivors

To evaluate the neuropsychological status of ICU patients, focusing on cognitive function, the neuropsychological test “Repeatable Battery for the Assessment of Neuropsychological Status” (RBANS) has been used (31,32). The RBANS was developed to identify and characterize abnormal cognitive decline in geriatric patients but has also been used to evaluate a wider age range and different neurological and psychiatric conditions (31,33). The RBANS test takes less than 30 minutes to perform, and serves as a more general screening instrument of neurocognition, which makes it suitable for a heterogenic population like ICU-patients, with variations of both age, illness type and severity (10,32,34). Furthermore the RBANS has been found to be more sensitive in detecting cognitive deficits caused by delirium in former ICU-patients as compared to another neuropsychological screening instrument; the Mini Mental State Examination (MMSE) (35).
The RBANS evaluates a broad spectrum of cognitive functions including five neurocognitive: immediate and delayed memory, visuo-spatial ability / construction, language and attention (10,31,36).

An area of cognition that has been reported to affect 20-48% of ICU survivors within the first year after critical illness, are executive functions which is not measured by RBANS(24). Executive functions are a set of neurological-based skills, associated with independency, self-management, managing time, setting personal goals, paying attention, problem-solving and reasoning. The Trail

Making test A & B (TMT-A & B) is a validated neuropsychological test of visual attention and task switching, which measures executive functions, and have previously been used to evaluate ICU populations (25,34,37).

When evaluating cognitive function after discharge from the ICU, patients' pre-admission cognitive function is unknown and is a limiting factor for the understanding of the effect of ICU admission on cognitive functions. It is however complicated to obtain this information due to the natural course of acute critical illness that makes patients incapable of supplying such information. Instead information on patient's pre-admission cognitive function can be obtained from their next of kin using validated screening tools.

The 'Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)', a questionnaire used by patient's next of kin, has previously demonstrated ability to identify pre-admission cognitive impairments in various populations, including prior to admission to the ICU and will be used in the present trial (24,38,39).

Aim

- To describe cognitive functions in patients with ICU-acquired delirium by using the RBANS and Trail Making Test-A&B (TMT-A&B), one year after inclusion to the AID-ICU trial at selected sites.
- To assess the effect of haloperidol on cognitive function in adult ICU-patients with ICU-acquired delirium one year after inclusion to the AID-ICU trial at selected sites. Patients dead at one-year follow-up will be assigned the lowest possible value (40) for the cognitive functions.
- To describe pre-existing cognitive function with IQCODE by proxy prior admission to ICU at selected sites.

Outcome

Primary outcome:

- Difference in RBANS at one-year follow-up between the randomised patients in the haloperidol and placebo groups of the AID-ICU trial at selected trial sites.

Secondary outcomes:

- The single sub-dimensions of RBANS one year after randomisation:
  - Immediate memory, delayed memory, attention, visual spatial ability/ construction, and language.
- TMT-A & B at one-year follow-up.
- Patient's cognitive function assessed by proxy with the IQCODE questionnaire prior to ICU admission.

Method

Study design

This is a predefined prospective randomised follow-up trial of patients included in the AID-ICU trial at selected sites. The trial is designed to assess one-year cognitive outcome in patients with ICU-acquired delirium allocated to either haloperidol or placebo (0.9% saline).

Study population

The follow-up study population will be patients included in the AID-ICU trial at Zealand University Hospital Køge, Rigshospitalet and Aalborg University with the following inclusion criteria:

- Acute admission to the ICU AND
- Age ≥ 18 years AND
- Diagnosed delirium with a validated screening tool as either CAM-ICU or ICDSC.

Exclusion criteria for AID-ICU:

- Contraindications to haloperidol (intolerance to haloperidol or additives, known Parkinson's disease or other extrapyramidal symptoms, known QTc prolongation, history of tardive dyskinesia or comatose (non-pharmacological) patients, previous ventricular arrhythmia or torsades de pointes, uncorrected hypokalaemia)
- Habitual treatment with any antipsychotic medication or treatment with antipsychotics in the ICU prior to inclusion
- Permanently incompetent (e.g. dementia, mental retardation)
- Delirium assessment non-applicable (coma or language barriers)
- Withdrawal from active therapy or brain death

- Fertile women (women < 50 years) with positive urine human chorionic gonadotropin (hCG) or plasma-hCG
- Consent according to national regulations not obtainable
- Patients under coercive measures by regulatory authorities
- Patients with alcohol-induced delirium (delirium tremens)

Further details can be obtained from the AID-ICU protocol (21).

Procedures

To explore cognitive function RBANS, TMT-A & B and IQCODE will be used. The RBANS will be used by personnel who has been trained and evaluated in the use of this test by either RBANS-experienced staff, or by a neuropsychologist.

Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS explore the domains: Immediate memory includes two subtests (list learning and story memory), visuospatial/constructional includes two subtests (figure copy and line orientation), language includes two subtests (picture naming and semantic fluency), attention includes two subtests (digit span and coding) and delayed memory includes four subtests (list recall, list recognition, story recall and figure recall–all from the four first tests). The RBANS generates an index score based on the subtests. The RBANS global cognitive performance index score is classified as followed: a score of 69 or below extremely low, 70 to 79 borderline, 80 to 89 low average, 90 to 109 average, 110-119 high average, 120 to 129 superior and 130 and above very superior(25). Total administration time is 20-30 minutes (31).

Definition of cognitive impairment assessed by neuropsychological test batteries will be one test of at least 2 standard deviations (SD) below the norm-referenced mean or 2 or more tests at least 1.5 SD below the norm-referenced mean (1,40).

When interpreting cognitive assessment results, it is important to have population-based normative data suitable for comparison to the population on which it is being used. For the interpretations of data from this study, a validated RBANS Scandinavian reference population will serve as a reference population to this study(31).

Trail Making Test A & B

The executive function tests TMT-A & B explore how rapid cognition can switch and divide attention [41]. Test A requires the participant to connect consecutive 25 numbers (e.g.1…25).

Whereas test B requires the participant to connect both numbers and letters (e.g.1-A-2-B…..) (41). The participant's completion time will be recorded (a maximal time 300 s)(41).

Informant Questionnaire on Cognitive Decline in the Elderly

The screening tool 'Informant Questionnaire on Cognitive Decline in the Elderly' (IQCODE) is a questionnaire designed to identify the magnitude of cognitive reduction based on a pre-morbid function level using an informant with close relationship to/knowledge of the patient (38). In the questionnaire, the informant is expected to compare the patient's current cognitive skills with 10 years earlier [38]. For the 16 questions, a score of 1 indicates a lot of improvement, a score of 3 does not indicate much change and a score of 5 indicates poor/worsening performance. The total score of the 16 questions is divided by 16 to generate a score from 1 to 5 with higher scores indicating worsening of cognitive function (38).

Ethical considerations, including consent

According to Danish law approval for the AID-ICU trial was obtained from the Danish Medicines Agency, the Regional Committee on Health Research Ethics and the Danish Data Protection Agency. These approvals also included follow-up one year after randomisation. Further details can be obtained in the AID-ICU protocol(21).

At inclusion to the AID-ICU trial, patients will be incompetent caused by ICU-acquired delirium, and the patients will therefore be enrolled after obtaining bystander consent from an independent physician (first trial guardian). Second and third bystander consent will be from the patient's next of kin and a second independent physician. A fourth consent from the individual participant will be obtained, as soon as the patient judged competent (delirium free). The consenting party will be provided with written and oral information concerning the AID-ICU trial. The information also consists of information about withdrawal of consent from the trial at any time. The consents obtained at inclusion include participation to the study, obtaining cognitive function prior to admission and a one-year follow-up where health-related quality of life and cognitive function are obtained.

Before one-year follow-up, we will secure the status of the participants' vital status (dead/alive) in order to only contact living individuals.

Protection of data

The present study is based on data from the participants of the AID-ICU trial. At enrolment to the AID-ICU trial each participant received a unique trial identification number in the eCRF ensuring anonymity.

Data will be obtained from patient files, national registers and home visits. Data obtained from patient files and national registers are managed electronically in the eCRF and will be handled by trained trial personnel. Data obtained by home visit test will be merged to the AID-ICU database. Data concerning IQCODE will also be merged to the AID-ICU database.
Data will be handled according to the National Data Protection Agency and protected by the Danish national laws 'Persondataloven' and 'Sundhedsloven'.

Statistical analyses

Descriptive statistics will be performed and include a description of the patients' characteristics at baseline with demography information as well as baseline measurement such as comorbid conditions.
We will perform the primary analyses in the intention to treat population.
Analyses:

- The primary analysis for cognitive function measured by RBANS and TMT-A & B will compare differences in means between the randomised groups using a general linear model adjusted for the stratification variables. Patients dead at one-year follow-up will be assigned a value of 40 (lowest possible value) for the RBANS. This highly non-normal outcome will then be compared between treatment groups using the novel method of Lange and Kryger Jensen (2018). In brief the probability of having 40 (lowest possible value) will be modelled using a logistic regression while the mean value among the non-forty values will be modelled using linear regression. A joint test for no treatment effect will be reported. The procedure can accommodate adjustment variables, see elsewhere, and the highly-skewed nature of the data distribution
- The secondary analyses of single sub-domains of RBANS (immediate memory, delayed memory, attention, visuo-spatial ability/construction, language) and TMT-B (executive

functions) will also be performed with the general linear model adjusted for the stratification variables.

Continuous variables are presented with mean score and with 95% confidence interval

P-value less than 0.05 will be considered statistically significant.

For both the RBANS and TMT-A & B, we will perform supplementary analyses for the following predefined baseline variables:

- Sites
- Sex
- Age (≥ 69 year- < 69 year)
- Delirium sub-type as hypo-active delirium, vs. mixed-type delirium vs. hyper-active delirium at inclusion
- Patients with malignancy vs. those without
- One or more risk factors for delirium vs. no risk factors
- Simplified mortality score in the ICU(SMS) (≥ 25- < 25)
- IQCODE

Dead patients and patients with missing values

Deceased patients and patients lost to follow up will be handled according to the following rules:

- Dead patients will be assigned the lowest possible value = 40.
- Patients lost to follow up (patients alive with no response or migrated patients) will be imputed if the fraction of these is > 5%.

Data concerning RBANS may be missing in patients who are alive one year after randomisation (non-responders). If data in the cognitive test is completed by Danish survivors are missing exclusively for the outcome of RBANS, in less than 5% of patients, or data are missing completely at random (MCAR), with Littles test negative (P>0.05), we will not impute missing data. If data are missing for outcomes and adjusting covariates in more than 5% of the patients missing, data will be imputed using multiple imputation (MI) assuming data missing at random (MAR), 50 imputed datasets will be generated. If MI is considered necessary aggregated analysis of the imputed

datasets will be calculated. However, assuming data missing not at random (MNAR) we will conduct analyses in best-worse and worse best scenarios where data from missing response from survivors will be imputed using the mean plus minus 1 SD of the RBANS in patients with complete data (42).

If the distribution of RBANS deviates substantially from the normal distribution the primary analysis will be adjusted for the stratification variable of sites using Van Elteren's test for differences of medians between groups. If the distribution of RBANS comes close to a normal distribution or if the distribution of the Log transformed data comes close to a normal distribution, we will perform multiple linear regression adjusted for both the stratification variable of sites and delirium subtype and we will supplement the primary analysis adjusted exclusively for stratification variables with an analysis adjusted for both the stratification variables and the predefined covariates of age, SMS score, malignancy, IQCODE and type of admission. We will provide 95% confidence intervals between means (if data are nearly normally distributed) or otherwise between medians (by bootstrapping) and a P-value less than 0.05 will be considered statistically significant.

Financing

Funding for this follow-up study will be provided by Department of Anaesthesiology and Intensive Care Zealand University Hospital, Køge. Furthermore, funding will be sought to cover additional costs. Costs of the AID-ICU trial are partly covered by Innovationsfonden and Regionernes Medicinpulje. Further funding will be sought.

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