Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU)

Intensiv symposium 2018

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Delirium in Intensive Care Unit

- Critically ill patients are at risk of developing delirium during ICU stay, incidence 32-84%\textsuperscript{1,2}

- Delirium is associated with increased morbidity and mortality\textsuperscript{3,4,5}
  - Increased days on mechanical ventilation
  - Longer hospital admittances
  - Long-term cognitive impairment
  - Long-term disability
  - Higher cost of care
  - Independent predictor of mortality

Delirium is expensive to the individual and society

Delirium and mortality

Kaplan-Meier survival curve for 1-year mortality post-intensive care unit (ICU) admission (ICU delirium days predictor).

Current evidence

Review article: Sedation and Delirium in the Intensive Care Unit. 
Reade et al. NEJM, 2014

"There is very little evidence to guide the management of established delirium, and most existing trials were categorized as pilot studies.”

Hayhurst et al. Anaesthesiology 2016

"Despite the abundance of litterature and research on delirium, there remains a paucity of large, randomized controlled trials of pharmacologic treatment of delirium.”

Pharmacological prevention and treatment of delirium in intensive care patients: A systematic review. 

"No single pharmacologic intervention was associated with reduction in mortality or hospital length of stay.”

No evidence based treatment of ICU aquired delirium is currently available
AID ICU

AID-ICU involves 3 studies

- Systematic Review
- Inception cohort study
- AID-ICU RCT Haloperidol vs. Placebo
Aim of the AID-ICU trial

To assess the benefits and harms of Haloperidol treatment in critically ill adult patients with delirium

Benefits

Harms

Mortality
Design

1000 patients

Intervention

Haloperidol 2.5mg x 3 daily

Control

Placebo: isotonic saline

Primary outcome: Days alive out of the hospital within 90 days
Inclusion criteria

- Acute (unplanned) admission to the ICU
- Aged 18 years or above
- Diagnosed delirium with validated screening tool (CAM-ICU, ICDSC)
Exclusion criteria

✖ Contraindications to haloperidol
✖ 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 (language barriers, blind, deaf)
✖ Withdrawal from active therapy
✖ Fertile women (<50 years) with positive urine hCG or plasma hCG
✖ Patients under coercive measures by regulatory authorities
✖ Patients with alcohol induced delirium (delirium tremens)
✖ Consent unobtainable according to national regulations
Intervention

Acute ICU admittance

Delirium screening x 2 daily

Screening

Positive for delirium

Randomisation

Does not meet exclusion criteria

P.n. haloperidol/placebo to a total of 20 mg daily (5 additional administrations)

Escape medicine:
- Propofol sedation
- Benzodiazepines
- Dexmedetomidine/α2-agonist

Haloperidol 2.5 mg (0.5ml) x 3

Placebo: NaCl 0.5 ml x 3
Pausing and stopping

Pausing criteria:

- 2 consecutive negative delirium scores in the same day
- OR unexplained coma (and all other relevant medication stopped)

Stopping criteria:

- Discharge from the ICU
- Transfer to another ICU (non AID-ICU trial site)
- Maximum of 90 day intervention period
- Death
AID-ICU trial organisation

Scandinavian Critical Care Trial Group (SCCTG)

Centre for Research in Intensive Care
ICU, Rigshospitalet
ICU, Aalborg University Hospital
ICU, Zealand University Hospital Koege
Copenhagen Trial Unit
Dept. of Biostatistics, UCPH
VIVE

Monitoring and Safety Committee

Good Clinical Practice (GCP) unit

Danish Medicines Agency

Regional Ethics Committee

Steering Committee

Management Committee
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www.cric.nu/aid-icu/
Inception cohort study

14 day inception cohort study in 99 ICUs worldwide
Most frequent used agents to treat delirium:
- Haloperidol
- Benzodiazepiner
- Dexmedetomidine

Power calculations for AID-ICU RCT
Conclusion: The overall quality and quantity of the present evidence underline the necessity of conducting a truly systematic review on haloperidol and the urgent need for a large pragmatic trial with overall low risk of bias for treatment of delirium with haloperidol and dexmedetomidine on patient important outcomes (days alive out of hospital, mortality, duration of delirium, etc.).
Current guidelines

- The Danish society of Anaesthesiology and Intensive Care Medicine
- The Intensive Care Society in the UK
- German guidelines

- The American College of Critical Care Medicine and the Society of Critical Care Medicine (USA)

**Haloperidol**

**Olanzapin**

**Risperidon**

No evidence of haloperidol (no evidence)

Olanzapin may reduce delirium duration (C)
Methods

- Design: Investigator-initiated, randomised multicentre placebo-controlled clinical trial with blinding
- Setting: approx. 25 ICUs in Europe
- Population: Adult ICU patients with diagnosed Delirium
- Start 2018 March, Zealand University Hospital Køge