Optimizing Clinical Trials When Conducting Delirium Research

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Outline

Study Protocol Considerations:
• Objective
• Design
• Sample
• Confounding variables
• Intervention
• Outcome(s)
• Sample size
• Data management and analysis
• DSMB

Background

• Delirium is a common sequelae of critical illness and worsens both ICU and post-ICU outcomes

Intensive Care Delirium Screening Checklist (ICDSC)

1. Altered level of consciousness
2. Inattention
3. Disorientation
4. Hallucinations
5. Psychomotor agitation or retardation
6. Inappropriate speech
7. Sleep/wake cycle disturbances
8. Symptom fluctuation

Delirium = ≥4 of 8 domains
- Inattention must be present
Subsyndromal delirium = 1-3 of 8 domains
Neither Delirium nor SSD = 0 of 8 domains

Role of Antipsychotics for Delirium Prevention in the ICU?

• Strong evidence supports the routine use of non-pharmacologic delirium prevention strategies in the ICU
  – Will a pharmacologic delirium prevention strategy provide additional benefit?
    Girard TD et al. Lancet. 2008; 371:126-134

• Peri-operative antipsychotic administration may reduce delirium burden in non-critically ill populations
  Prakash M. Intensive Care Med 2007; 33:714-19
  Prakanrattana U, Anaesth Intens Care 2007; 35:714-19

• One uncontrolled study suggests that haloperidol use over the course of the ICU stay may reduce delirium and mortality
  Larsen KA et al. Psychosomatics. 2010;51:489-10

• However, two RCTs, suggest that use of haloperidol in critically ill patients (with delirium or at high risk for delirium) does not influence patient outcome
Hypothesis

- Administration of scheduled, low-dose, IV haloperidol in mechanically ventilated, critically ill adults with subsyndromal delirium will reduce the conversion to delirium.

Defining the Study Objective(s)

- **Should include:**
  - An expression describing the overall approach
  - To assess, to compare, to determine
  - A clear description of the intervention
  - Note: If medication should include dose, route and frequency
  - The disease being evaluated
  - The patient population being evaluated
  - The general purpose of study
  - Efficacy, safety, quality of life
  - The primary study outcome

**Objective:** To compare the efficacy and safety of scheduled low-dose haloperidol versus placebo for the prevention of delirium (Intensive Care Delirium Screening Checklist ≥ 4) administered to critically ill adults with subsyndromal delirium (Intensive Care Delirium Screening Checklist ≤ 1–3).

- Limit the number of secondary objectives
  - Too many multiple comparisons will affect statistical rigor of study
  - If pilot study, additional objectives may include feasibility, evaluation of multiple methods to measure primary outcome, determination of variance around the mean (to guide future sample size calculation)

Considerations when transitioning from one mental state to another

Study Design

- **Randomized**
  - Only method to estimate causality
  - Best way to account for confounding and bias
- **Cohort**
  - Non-time dependent
  - Time dependent
  - Use of a Markov model(s) that incorporates confounding and bias
  - Both baseline and daily variables
What about bias?

Systematic deviation in the variable of interest

observer bias
selection bias
proportional bias
referral bias
Berkson’s bias
interviewer bias
Verificaton bias

Immortal time bias
- When a period of ‘immortal time’ is excluded

Death
Follow-up time

Critical illness
Delirium

Immortal time

Study Sample
- Who is your sample?
  - This is your inclusion criteria
  - A broader sample can be an advantage
  - Single center vs. Multi-center?
- Pragmatism vs. control of confounding factors
  - Exclusion criteria = external validity
  - IRB required (pregnancy, prisoner, consent not available etc)
- Factors that might confound ability to measure clinical response
  - This is most common reason external validity is low in many delirium studies
  - Consider a prior stratification at time of randomization to account for confounders
  - At the very least consider SELECTIVE post-hoc secondary analysis (that is defined a priori)
- Use your DSMB as tool to influence an IRB that may be excessively “risk averse”

<table>
<thead>
<tr>
<th>Variable</th>
<th>Logistic regression</th>
<th>Competing risks survival regression</th>
<th>Marginal structural model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted*</td>
<td>x.40 (1.79 to 3.00)</td>
<td>3.14 (2.22 to 5.04)</td>
<td>3.14 (2.22 to 5.04)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.77 (1.16 to 2.69)</td>
<td>1.86 (1.13 to 3.07)</td>
<td></td>
</tr>
</tbody>
</table>

All mechanically ventilated adults admitted to 3 different ICUs (medical n=2; surgical n=1) were evaluated q12h with SAS and the ICDSC for up to 3 days from the time of ICU admission:

- Important way to reduce inclusion bias
- Potential treatment effect of haloperidol to prevent delirium felt to decrease over time

Among the 481 patients who had SSD only 68 were randomized = 14.1%

The Tufts MC IRB started off making us exclude patients >/=80 years from trial. DSMB helped get this up to 85 years.

Important to carefully consider and define the criteria for stopping study intervention.
Intervention(s)

- Need to carefully describe and justify
  - Remember: this is the one thing you control
- Is a placebo feasible and/or available?
- Are there attributes/effects of the intervention that could allow treatment allocation to be detected?
  - Bedside clinicians love to try and guess allocation
- If bedside clinician is expected to administer intervention (e.g., medication) then cannot be time consuming and must be within scope of practice
- Make sure the study medication is incorporated in existing drug distribution/administration system.
- Use the CPOE system to control for the administration of confounding medications
  - Non-study antipsychotics; dexmedetomidine

Outcomes: Delirium as the Primary Outcome?

Prevention of Delirium

- Incidence
- ICU days without it
- Time to first delirium episode
- Duration of first delirium episode
- Severity of the delirium that occurs
- Motoric subtypes

Treatment of Delirium

- Time to first resolution
- Duration of delirium
- Days without delirium in the ICU
- Consider each ICU day as an individual measurement and report the daily OR from delirium to non-delirium

“Important to ask: But should a “characterization” of delirium be my primary outcome? Do think about the primary outcomes most important to the patient (and their families)

Rapidly Reversible vs. Persistent Delirium

If CAM-ICU + = rapidly reversible, sedation-related delirium

If CAM-ICU + = persistent delirium

Patient Outcome

102 mechanically ventilated MICU adults managed with propofol/fentanyl

Sedation Interruption

Evaluation nursing charts for anxiety, hallucinations, disorientation AND impaired/fluctuating consciousness AND/OR cessation of scheduled antipsychotic therapy

Test characteristics compared to delirium expert team: Sensitivity = 0.75 Specificity = 0.88 Inter-rater agreement = 0.94


Consider the Rigor of the Delirium Assessment

1. Is once daily delirium assessment enough?
2. Will CAM-ICU assessment by bedside clinicians alone miss delirium?
3. Will the presence of sedation influence delirium detection?

UMC-Utrecht: Assessment of delirium every 8 hours

< 24 hours maximum RASS (Shytle) ≤ -3 or -4 ≤ 24 hours positive CAM-ICU bedside nurse ≤ 24 hours start haloperidol/quetiapine RASS ≤ -3 CAM-ICU RASS ≤ -3 CAM ICU + Evaluation nursing charts for anxiety, hallucinations, disorientation AND impaired/fluctuating consciousness AND/OR cessation of scheduled antipsychotic therapy

Yes

Unable to assess

Delirious

Delirious

Delirious

Delirious

No

No-Delirium

Patel SB et al. AJRCCM 2014; 189: 658-665

Davis DHJ et al. Am J Geriatr Psych 2015
Rapidly Reversible vs. Persistent Delirium
- Rapidly reversible delirium (before sedation interruption) is 10.5 times more likely than persistent delirium (after sedation interruption)
- This relationship not affected by the specific ICU admission day or the presence of delirium risk factors (e.g., age, severity of illness, corticosteroid use)

Mortality (%) vs. Time from enrollment (days)

Patel SB et al. AJRCCM 2014; 189: 658-665

How were these issues accounted for in the haloperidol study?

- ICSDC used in study ICUs for more than 10 years
- All nurses receive formal ICDSC re-education every 6 months that includes the correct evaluation of at least two patients (vs. a clinical nurse educator)
- Well-established DA-SBT protocol
- ICDSC assessment protocolized to occur after sedation DA (i.e. when patient maximally awake)
- All positive delirium assessments (ICDSC ≥ 4) were confirmed with a study investigator (using ICDSC) and a consultant psychiatrist using DSM-IV criteria

Table 3: Clinical Outcomes During Study Drug Administration

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Haloperidol (n=34)</th>
<th>Placebo (n=34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of first episode of delirium (d)</td>
<td>(21-33)</td>
<td>(9-32)</td>
<td>0.29</td>
</tr>
<tr>
<td>Proportion of 12 h ICU nursing shifts without concomitant delirium (%)</td>
<td>96 (87-100)</td>
<td>96 (69-100)</td>
<td>0.53</td>
</tr>
<tr>
<td>Proportion of 12 h ICU nursing shifts without delirium (%)</td>
<td>100 (100-100)</td>
<td>100 (50-100)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hours per day study spent agitated (Sedation Agitation Scale 2 D)</td>
<td>2 (1-4)</td>
<td>2 (1-6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Days where confusional V sedation administered (%)</td>
<td>26 (13-100)</td>
<td>12 (50-100)</td>
<td>0.096</td>
</tr>
<tr>
<td>Days where DA criteria met and DA completed (%)</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>0.992</td>
</tr>
<tr>
<td>Days where DA criteria met and DA completed (%)</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>0.992</td>
</tr>
<tr>
<td>Patients receiving early mobilization (%)</td>
<td>11 (34)</td>
<td>10 (64)</td>
<td>0.476</td>
</tr>
<tr>
<td>Exposure to newly antipsychotic therapy (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Duration of first episode of subacute delirium (d)</td>
<td>5 (6-4)</td>
<td>5 (6-3)</td>
<td>0.993</td>
</tr>
</tbody>
</table>

Figure 2: Kaplan-Meier plot for the time to the first occurrence of delirium between haloperidol and placebo groups.

Table 4: Other Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Haloperidol (n=34)</th>
<th>Placebo (n=34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of mechanical ventilation</td>
<td>4.5 (3-7)</td>
<td>5.3 (4-8)</td>
<td>0.79</td>
</tr>
<tr>
<td>Duration of ICU stay (d)</td>
<td>6.5 (4-9)</td>
<td>7 (6-9)</td>
<td>0.66</td>
</tr>
<tr>
<td>ICU disposition (%)</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died in ICU</td>
<td>26.5</td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>Hospital ward</td>
<td>70.6</td>
<td>56.9</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>2.9</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Hospital disposition (%)</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died in hospital</td>
<td>26.5</td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>41.2</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>59.4</td>
<td>47.1</td>
<td></td>
</tr>
<tr>
<td>Long-term care facility</td>
<td>2.9</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>
Special Considerations When Evaluating Safety

- Consider protocolizing the detection and management of likely safety concerns
  - Want to shown the IRB you are serious about safety
  - Do not want to remove a patient from the study if potential safety concern could be caused by non-study factor(s) or it may resolve with intervention
- Clearly understand criteria to differentiate serious adverse events from non-serious adverse events and reporting of each
  - Is an SAE expected or not expected?
- Unblind treatment allocation in only very rare situations and only inform clinical team of allocation

### TABLE 5. Patients Where Study Medication Was Stopped Due to a Protocolized Haloperidol-Associated Event

<table>
<thead>
<tr>
<th>Event</th>
<th>Haloperidol (n = 34)</th>
<th>Placebo (n = 34)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc interval prolongation, % (n)</td>
<td>11.8 (4)</td>
<td>29 (1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Extrapyramidal symptoms, % (n)</td>
<td>29 (1)</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Excessive sedation, % (n)</td>
<td>29 (1)</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypotension, % (n)</td>
<td>29 (1)</td>
<td>29 (1)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Study Completion Considerations:

- What’s your elevator speech?
- Study implementation
- Data collection
- Clinical team engagement
- Informed consent
- Patient and family engagement
- Publication