Management of Delirium in the ICU

Yahya Shehabi
Hello! Doctor, your patient is CAM+ve

Good morning Dr,
- Am one of the RC,
- Just examined Mr XXX he is CAM +ve

Positive what? Sir replied
RC: I meant he is delirious?

He had a perfect operation? That’s what matter he is a heavy drinker, call the anaesthetist
A routine post AVR

• 83 years old male, day 3 past AVR
• 1500 - Family noticed
  – Unusually quiet and disconnected
  – Hallucinating at times
  – Reaching for things in the air
• 1730 doctors review – afebrile, normal vitals, observe
• 2330
  – Screaming loudly, help help help help
ICU Delirium is complex

• Critically ill
  – Stress / insults

• Multiple medications

• Multiple Interventions

• Strange environment
  – Noise, light, traffic, privacy

“Our relationship is like a lasagna. A layer of love, a layer of anger, a layer of joy, a layer of pain...but all together, not a bad combination!”
ICU Delirium as an Organ Dysfunction

- **Acute Kidney Injury**
  - Oliguria
  - Rising creatinine
  - NGAL

- **Acute Lung Injury**
  - Increasing FiO2
  - Low S\textsubscript{p}O2
  - X-ray

- **Acute Cardiac Injury**
  - Troponin
  - ECG

- **Acute Agitation**
  - Pulling tubes / catheters

- **Delirium**
  - Insidious, unnoticed
  - No biomarker
  - Onset is unclear
  - Offset is vague
Delirium in the ICU is not obvious

Clinicians routine exam miss 75% of delirium

Current tools lack sensitivity

Inter-rater reliability of bedside carers
ICU delirium is common

Delirium is not a benign complication

• Heralds the onset of acute brain dysfunction

• Delirium duration linked to
  – prolonged intubation and ICU stay
  – Higher hospital and 6 month mortality,

• Delirium linked to
  – Worse cognitive function at 12 month
    • Every delirium day = 35 days of cognitive decline

Shehabi et al, Delirium duration and mortality Crit Care Med 2010
Pandirabande et al, Long-term cognitive function in critical illness NEJM 2013
ICU Delirium

Drivers
Fig. 3. Severity of illness and the probability of transitioning to delirium. The probability of transitioning to delirium increased dramatically for each additional point in Acute Physiology and Chronic Health Evaluation II (APACHE II) severity of illness score until reaching a plateau APACHE score of 18.

Age and the probability of transitioning to delirium. The notable finding related to age was that probability of transitioning to delirium increased dramatically for each year after 65 yr.
Systemic Inflammation
Neurotoxins and Brain Injury

Cunnigham C, Systemic Inflammation and Delirium 2012
ICU Delirium and neurotransmitters

- Direct brain injury
  - Hypoxia
  - Hypotension
  - Acute metabolic abnormalities
  - Systemic infection

- Exaggerated Stress response
  - Extra CNS injury
  - Surgery, Pain, CPB, Infection
    - Inflammatory cytokines
    - Cortisol
Can We Prevent ICU Delirium?
Simple low risk measures improving patients and family experience

- ICU delirium friendly environment
  - Noise reduction – ear plugs
  - Sleep promotion and night time protocol
  - Communication
  - Family visit
  - Day-night orientation ambient light – the clock
  - Adequate analgesia
Neurotransmitter approach to delirium management

- Anti-dopaminergic activity
  - Haloperidol
  - Quetiapine

- Maintain central cholinergic activity
  - Dexmedetomidine
  - Physostigmine

- Reduced noradrenergic activity
  - Dexmedetomidine
  - Adequate pain control

- Melatonin agonist
Haloperidol prophylaxis in critically ill patients with a high risk for delirium

Mark van den Boogaard¹*, Lisette Schoonhoven²,³, Theo van Achterberg⁴, Johannes G van der Hoeven¹,⁴ and Peter Pickkers¹,⁴

Methods: This study was a before/after evaluation of a delirium prevention project using prophylactic treatment with haloperidol. Patients with a predicted risk for delirium of ≥ 50%, or with a history of alcohol abuse or dementia, were identified. According to the prevention protocol these patients received haloperidol 1 mg/8 h. Evaluation was primarily focused on delirium incidence, delirium free days without coma and 28-day mortality. Results of prophylactic treatment were compared with a historical control group and a contemporary group that did not receive haloperidol prophylaxis mainly due to non-compliance to the protocol mostly during the implementation phase.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Control group</th>
<th>Intervention group</th>
<th>Differences (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted delirium chance</td>
<td>73 ± 22</td>
<td>75 ± 19</td>
<td>0.50</td>
</tr>
<tr>
<td>Observed delirium incidence (n,%)</td>
<td>225 (75%)</td>
<td>115 (65%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-delirium</td>
<td>74 (25%)</td>
<td>62 (35%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Delirium subtype:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hyperactive</td>
<td>20 (7%)</td>
<td>6 (3%)</td>
<td></td>
</tr>
<tr>
<td>- Hypoactive</td>
<td>81 (27%)</td>
<td>33 (19%)</td>
<td></td>
</tr>
<tr>
<td>- Mixed</td>
<td>124 (41%)</td>
<td>76 (43%)</td>
<td></td>
</tr>
<tr>
<td>Number of delirium free days without coma in 28 days</td>
<td>13 (3 to 27)</td>
<td>20 (8 to 27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Re-intubation (%)</td>
<td>25 (8%)</td>
<td>15 (9%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Duration mechanical ventilation in hrs.</td>
<td>118 (39 to 250)</td>
<td>90 (36 to 229)</td>
<td>0.24</td>
</tr>
<tr>
<td>Unplanned removal tubes/lines (%)</td>
<td>58 (19%)</td>
<td>21 (12%)</td>
<td>0.02</td>
</tr>
<tr>
<td>- Tube</td>
<td>8 (3%)</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>- Gastric tube</td>
<td>26 (9%)</td>
<td>14 (8%)</td>
<td></td>
</tr>
<tr>
<td>- CVC/arterial line</td>
<td>24 (8%)</td>
<td>1 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Re-admission</td>
<td>55 (18%)</td>
<td>20 (11%)</td>
<td>0.03</td>
</tr>
<tr>
<td>LOS-ICU</td>
<td>7 (3 to 13)</td>
<td>6 (3 to 12)</td>
<td>0.65</td>
</tr>
<tr>
<td>LOS-in hospital</td>
<td>21 (12 to 41)</td>
<td>20 (11 to 31)</td>
<td>0.16</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>36 (12%)</td>
<td>13 (7.3%)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>
Role of Haloperidol and other antipsychotics

- 1st RCT antipsychotic RX of ICU delirium
- 73 med-surgical patients
- Oral haloperidol 2.5-5mg q 8 h
- Oral olanzapine 5mg daily with dose titration
- IV haloperidol / benzodiazepines allowed
- No differences except less EPS with olanzapine
Modifying the Incidence of Delirium MIND Trial

- DBPCRT at 6 tertiary medical centers
- Not required to have delirium at enrollment

Intervention:
- Haloperidol (5 mg) vs ziprasidone (40 mg) vs placebo
- Max 14 days
- Dose interval increased if CAM-ICU negative
- If delirium re-occurred after d/c of study drug then restarted at last effective dose (and weaned again as per above)

# MIND Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Haloperidol, n = 35</th>
<th>Ziprasidone, n = 30</th>
<th>Placebo, n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium/coma-free days</td>
<td>14.0</td>
<td>15.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Delirium days</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Delirium resolution on drug, n(%)</td>
<td>24 (69)</td>
<td>23 (77)</td>
<td>21 (58)</td>
</tr>
<tr>
<td>Coma days</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>% of days accurately sedated</td>
<td>70</td>
<td>64</td>
<td>71</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>7.8</td>
<td>12.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>11.7</td>
<td>9.6</td>
<td>7.3</td>
</tr>
<tr>
<td>Hospital</td>
<td>13.8</td>
<td>13.5</td>
<td>15.4</td>
</tr>
</tbody>
</table>
Is there a role for melatonin?

- Melatonin agonists
  - MT1 reduce electrical neuronal activity = hypnosis
  - MT2 phasic shift of circadian rhythm
- Agents with high affinity
Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial†

Tareef Al-Aama¹,², Christopher Brymer¹, Iris Gutmanis³,⁴,⁵, Sarah M. Woolmore-Goodwin⁴, Jacquelin Esbaugh⁴ and Monidipa Dasgupta¹,⁵

¹Department of Medicine-Geriiatrics, UWO, Canada
²Department of Medicine, KAU, Saudi Arabia
³Department of Epidemiology & Biostatistics, UWO, Canada
⁴Specialized Geriatric Services, SJHC, London, Canada
⁵Lawson Health Research Institute, Canada
Correspondence to: Tareef Al-Aama, E-mail: dr_tareef@yahoo.com
†ClinicalTrials.gov number, NCT00873379 [ClinicalTrials.gov].

Over 65 years, given 0.5 mg Melatonin daily.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n = 61)</th>
<th>Melatonin (n = 61)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium (assessed with CAM)⁹</td>
<td>19 (31%)</td>
<td>7 (12%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Incident delirium (excluding prevalent delirium)</td>
<td>10/52 (19.2%)</td>
<td>2/56 (3.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Initial MDAS⁶score (SD) ⁶(all participants)</td>
<td>4.4 (4.6)</td>
<td>5.2 (4.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Initial MDAS⁶d score (SD) ⁶(if developed delirium)</td>
<td>11.4 (3.0)</td>
<td>10.5 (5.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Use of paid patient attendant services</td>
<td>3/60 (1 missing) (5.0%)</td>
<td>2/57 (4 missing) (3.5%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Restraints</td>
<td>6 (10%)</td>
<td>4 (7%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Use of PRN ‡sedatives</td>
<td>38 (62%)</td>
<td>33 (54%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean LOS³h (SD)</td>
<td>14.5 (21.6)</td>
<td>18.5 (26.4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Sleep disturbance ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>37 (60.7%)</td>
<td>39 (63.9%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Mild</td>
<td>21 (34.4%)</td>
<td>18 (29.5%)</td>
<td></td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>3 (4.9%)</td>
<td>4 (6.6%)</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>8 (13%)</td>
<td>6 (10%)</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Elderly patients undergoing hip surgery were given 3 mg melatonin for 5 days. 74 were excluded after randomisation, leaving 192 vs 186 analysed.

### Table 2: Primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study group; no. (%) or median (IQR)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Melatonin (n = 186)</td>
<td>Placebo (n = 192)</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of delirium</td>
<td>55 (29.6)</td>
<td>49 (25.5)</td>
</tr>
<tr>
<td><strong>Secondary outcomes: patients with delirium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of delirium, d</td>
<td>2 (1.0–3.0)</td>
<td>2 (1.0–3.0)</td>
</tr>
<tr>
<td>Duration of delirium &gt; 2 d</td>
<td>14 (25.5)</td>
<td>23 (46.9)</td>
</tr>
<tr>
<td>Severe delirium*</td>
<td>25 (45.4)</td>
<td>26 (53.1)</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>11 (6.0–14.5)</td>
<td>11 (8.0–17.0)</td>
</tr>
<tr>
<td>Use of antipsychotics, mg</td>
<td>4.0 (1.5–7.5)</td>
<td>5.0 (3.8–8.3)</td>
</tr>
<tr>
<td>Use of benzodiazepines, mg oxazepam equivalents</td>
<td>63.4 (33.4–104.3)</td>
<td>75.0 (33.3–131.3)</td>
</tr>
</tbody>
</table>
Potential to prevent delirium in elderly medical patients.

No evidence that improving sleep-wake cycle impacts delirium

Significant heterogeneity
CAN WE PREVENT DELIRIUM BY OPTIMAL SEDATION MANAGEMENT?
Enrolled 710 participants

703 Primary population At 48 hrs

38 (5.4%) Loss of follow up 180 days survival

674 (95.9%) Analysed at 120 hrs

628 (89.3%) Analysed at 168 hrs

Excluded 7 (1%) Died / Discharged Before 48 hours

29 (4.1%) Died / Discharged Between 48 and 120 hrs

46 (6%) died or discharged Between 120 and 168 hrs
Separating RASS into 3 components

<table>
<thead>
<tr>
<th>Clinical Score</th>
<th>Term</th>
<th>Level of Sedation Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Agitated</td>
<td>Frequent nonpurposeful movement, lifts the ventilator</td>
</tr>
<tr>
<td>+3</td>
<td>Belligerent</td>
<td>Mouth opens to verbal command</td>
</tr>
<tr>
<td>+2</td>
<td>Calm</td>
<td>Lying不动responds to verbal command</td>
</tr>
<tr>
<td>+1</td>
<td>Drowsy</td>
<td>Opening of eyes to verbal command</td>
</tr>
<tr>
<td>0</td>
<td>Optimal 3Cs</td>
<td>Opening of eyes to physical contact</td>
</tr>
<tr>
<td>-1</td>
<td>Alert</td>
<td>No response to verbal command</td>
</tr>
<tr>
<td>-2</td>
<td>Sedation Index</td>
<td>No response to voice or physical stimulation</td>
</tr>
<tr>
<td>-3</td>
<td>Unarousable</td>
<td>Sum -ve RASS / No RASS</td>
</tr>
<tr>
<td>-4</td>
<td>Sum -ve RASS</td>
<td>Sum -ve RASS / No RASS</td>
</tr>
<tr>
<td>-5</td>
<td>Sum -ve RASS</td>
<td>Sum -ve RASS / No RASS</td>
</tr>
</tbody>
</table>
Sedation level and delirium % of positive CAM-ICU at each RASS

First 7 days

<table>
<thead>
<tr>
<th>CAMneg (n)</th>
<th>133</th>
<th>280</th>
<th>859</th>
<th>61</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMpos (n)</td>
<td>114</td>
<td>149</td>
<td>83</td>
<td>74</td>
</tr>
<tr>
<td>RASS</td>
<td>-2</td>
<td>-1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Percentage

- 53.8%
- 65.3%
- 91.2%
- 45.2%
EARLY (48 HOURS) SEDATION INDEX

180-day survival
Time to extubation
Delirium
MOBILISATION AS A FUNCTION OF SEDATION LEVEL
Comfort and patient-centred care without excessive sedation: the eCASH concept

Jean-Louis Vincent, Yahya Shehabi, Timothy S. Walsh, Pratik P. Pandharipande, Jonathan A. Ball, Peter Spronk, Dan Longrois, Thomas Strøm, Giorgio Conti, Georg-Christian Funk, Rafael Badenes, Jean Mantz, Claudia Spies and Jukka Takala
Comfort and patient-centred care without excessive sedation: the eCASH concept

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Fig. 1 The eCASH concept: early implementation to manage and prevent pain, anxiety, agitation, delirium and immobility and facilitate patient-centred care. (#Moderate or deep sedation remains relevant for some situations, including the management of severe respiratory failure with ventilator–patient dyssynchrony, prevention of awareness in patients receiving neuromuscular blocking agents, status epilepticus, surgical conditions necessitating strict immobilization and some cases of severe brain injury with intracranial hypertension)
ICU delirium is a serious warning
Commonest underlying cause is SEPSIS

- Medication review

- Pharmacologic options
Quetiapine and delirium

36 subjects randomized

Quetiapine 50 mg NG twice daily (N=18)

Placebo 50 mg NG twice daily (N=18)

As needed haloperidol therapy, usual sedation and analgesia therapy at the discretion of the subject’s physician

Dose Titration

Increase quetiapine or placebo dose by 50 mg every 12 hours on a daily basis if the subject received \( \geq 1 \) dose of as needed haloperidol in the previous 24 hours.

(Maximum dose=200 mg every 12 hours)

Discontinuation of study drug

1. Subject was deemed by the attending intensivist to be no longer demonstrating signs of delirium, therefore, therapy no longer required
2. 10 days of therapy had elapsed
3. ICU discharge prior to 10 days of therapy
4. Serious adverse event potentially attributable to the study drug
Table 3. Clinical outcomes during study drug administration\textsuperscript{a,b}

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine (n = 18)</th>
<th>Placebo (n = 18)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of study drug administration, hrs</td>
<td>102 (84–168)</td>
<td>186 (108–228)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Time in delirium

Figure 2. Proportion of patients with first resolution of delirium over time between quetiapine (n = 18) and placebo (n = 18) groups. Both groups of patients were treated using the same as-needed intravenous haloperidol protocol.
Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial

Michael C. Reade, DPhil, FCICM; Glenn M. Eastwood, RN, CCRN; Benjamin Cheung, MBBS, FCICM; Andrew Davies, MBBS, FICM; Frank van Haren, PhD, FCICM; Nerina Harley, MD, FCICM; John Mulder, MBChB, FCICM; Steve O’Donoghue, MBChB, for the DahLIA Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group

Approximately 21,500 admissions of intubated patients at 15 intensive care units in 2 countries

74 Patients randomized

41 Randomized to receive dexmedetomidine
40 Received dexmedetomidine as randomized
1 Study treatment discontinued (met an exclusion criterion and inappropriately randomized)

1 Withdrew consent to use data
39 Included in primary intent-to-treat analysis

33 Randomized to receive placebo
33 Received placebo as randomized

1 Withdrew consent to use data
32 Included in primary intent-to-treat analysis
Primary outcome

Figure 2. Kaplan-Meier Analysis of the Proportion of Patients Remaining Intubated During the First 7 Days of the Study

Hazard ratio, 0.58 (95% CI, 0.36-0.95); log-rank P = .03

Proportion Remaining Intubated or Sedated With Tracheostomy

No. at risk
Dexmedetomidine 39 10 4 2
Placebo 32 13 6 2

Hours After Randomization
## Delirium outcomes

<table>
<thead>
<tr>
<th>Confusion Assessment Method for the ICU</th>
<th>Time to first results indicating absence of delirium, median (IQR), h</th>
<th>Time spent with results indicating presence of delirium, median (IQR), h</th>
<th>Proportion of days postrandomization spent with results indicating presence of delirium, median (IQR), %</th>
<th>Time spent with at least 1 assessment indicating presence of delirium postrandomization, median (IQR), d</th>
<th>Required mechanical restraint on any day, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23.3 (13.0 to 54.0)</td>
<td>40.0 (25.3 to 76.0)</td>
<td>-16.0 (-28.0 to -3.0)</td>
<td>1 (1 to 3)</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td></td>
<td>36 (24 to 66)</td>
<td>62 (42.5 to 106.75)</td>
<td>-24 (-41 to -6)</td>
<td>3 (1 to 4)</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td></td>
<td>47 (30 to 75)</td>
<td>62 (46 to 86)</td>
<td>-10 (-30 to 0)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>.01</td>
<td></td>
<td>.05</td>
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<td>.009</td>
<td></td>
<td>.02</td>
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<td></td>
<td></td>
<td></td>
<td>.05</td>
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<td>.02</td>
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<tr>
<td></td>
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<td>.07</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• **Delirium in the ICU**
  – Common
  – Not a benign event
  – Pathophysiology is complex, inflammatory response

• **Prevention**
  – Significant evidence gap
  – Simple non-pharmacologic means are good processes
  – Antipsychotic agents not effective
  – Melatonin may be
  – Sedative optimization
Conclusions

- **Delirium in the ICU**
  - Common
  - Not a benign event
  - Pathophysiology is complex, inflammatory response

- **Prevention**
  - Simple non-pharmacologic means are good processes
  - Antipsychotic agents not effective
  - Melatonin may be
  - Sedative optimization
  - Significant evidence gap
Conclusions

• Treating delirium
  – Identify and Treat underlying triggers
  – Quetiapine may accelerate delirium resolution
  – Dexmedetomidine in hyperactive delirium
THANK YOU