Buffalo theory of sedation

“It’s a well known fact that a herd of buffalo can only move as fast as the slowest buffalo. And when the herd is hunted, it’s the slowest and weakest ones at the back that are killed first. This natural selection is good for the herd as a whole because the general speed and health of the whole group improves by the regular killing of the weakest members.

“In much the same way, the human brain can only operate as fast as the slowest brain cells. Now, as we know, excessive intake of alcohol kills brain cells. But naturally, it attacks the slowest and weakest brain cells first. In this way, regular consumption of beer eliminates the weaker brain cells, making the brain a faster and more efficient machine.

“And that is why you always feel smarter after a few beers.”

Overall objectives

- Recognize informed indications for sedation
- Discuss importance of monitoring delirium
- Review best practice for sedation and delirium in the ICU

What I consider “sedation?”

- Analgesics (e.g., fentanyl, morphine)
- Sedatives (e.g., propofol, lorazepam)
- Antipsychotics (e.g., quetiapine)
- Neuromuscular blocking agents/paralytics (e.g., vecuronium)

Outline

1. Review indications for sedation
2. Review monitoring and assessment of sedation, analgesia, and delirium
3. Review evidence base for sedation in the ICU and associated management

Why do (or should) we use sedation?
Historic indications for sedation supported by literature (or not refuted)

• Effect or potentiate analgesia
• Adjunct to paralysis
• Procedures
• Alcohol/drug withdrawal states
• Reduce metabolic demand during shock
• Facilitate terminal care

Historic indications for sedation challenged (or contradicted) by existing literature

• Attenuate fear and/or anxiety
• Induce “unnecessary” recall
• Facilitate sleep
• Chemical restraint
• Enable treatment of critical illness
• Patient-ventilator dyssynchrony

Monitoring analgesia and sedation

SCCM guidelines (2002): Analgesia first with monitoring using validated tools

• Communicative patients
  – Numeric Rating Scale
• Non-communicative patients
  – Behavioral Pain Scale
  – Critical-Care Pain Observational Tool
• Frequent assessment

Behavioral Pain Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>Relaxed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially tightened (e.g., brow lowering)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully lightened (e.g., eyelids closed)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Crimacing</td>
<td>4</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>No movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially bent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully bent with finger flexion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Permanently retracted</td>
<td>4</td>
</tr>
<tr>
<td>Tolerance for</td>
<td>Tolerating movement</td>
<td>1</td>
</tr>
<tr>
<td>movement</td>
<td>Coughing but tolerating most of the time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fighting ventilator</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unable to control ventilation</td>
<td>4</td>
</tr>
</tbody>
</table>

SCCM guidelines (2002): Sedation monitoring

• Selection of a sedation scale (e.g., Richmond Agitation-Sedation Scale)
• Establishment of sedation target (e.g., RASS of -1 to 0)
• Frequent reassessment, discussion on rounds and as target of sedation protocol
Richmond Agitation-Sedation Scale (RASS)

-4: Comatose: Overtly violent, dangerous
-3: Very agitated: Pulses tubes, calisthenics, aggressive
-2: Agitated: Fights ventilator, non-purposeful
-1: Restless: Argues, not aggressive
0: Alert / calm
-1: Drowsy: Eye contact >10 sec
-2: Light sedation: Eye contact <10 sec
-3: Moderate: Eye opening, no eye contact
-4: Deep: Moves with physical touch only
-5: Un arousable: No response to voice or touch

SCCM guidelines (2002): Monitoring delirium in all ICU patients

- Delirium: acutely altered consciousness that fluctuates and is associated with inattention and occasionally perceptual disturbances (e.g., hallucinations) or impaired cognition
- Dementia: chronic, predictably progressive, and not associated with impaired attention or perceptual disturbances.

Diagnosis of delirium in the ICU

Consciousness in the ICU...

What do we measure? What do we routinely miss?

Arousal, wakefulness, level of consciousness
content of consciousness; the sum of mental function

Instruments include CAM-ICU, ICDSC

What do we measure? What do we routinely miss?

Diagnosis of delirium in the ICU

Instruments include GCS, sedation scales

Consciousness in the ICU...

Instruments include CAM-ICU, ICDSC
### Risk factors for ICU delirium*

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Disease</th>
<th>Iatrogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment</td>
<td>Sepsis/ARDS</td>
<td>Sedatives, analgesics</td>
</tr>
<tr>
<td>Age</td>
<td>Hypoxemia</td>
<td>Bladder catheter</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Metabolic derangement</td>
<td>Anticholinergic meds</td>
</tr>
<tr>
<td>APO E4</td>
<td>Illicit drug use</td>
<td>Sleep quality/quantity</td>
</tr>
</tbody>
</table>

*Note that most ICU patients have >3 risk factors

Adapted from Miller & Ely, SRCCM 2006;27:210-20

### Increasing dose of lorazepam predicts probability of delirium

Increasing dose of lorazepam predicts 20% ↑ odds per milligram of lorazepam

Pandharipande et al., Anesthesiol 2006;104:21-6

Evidence in sedation

- Sedation protocols (18+ published):
  - ↓ duration of coma
  - ↓ length of mechanical ventilation
  - ↓ complications of mechanical ventilation
  - ↓ length of ICU stay
  - ↓ sedation drug costs
  - ↓ mortality

Protocols for sedation improve outcomes

Evidence in sedation: awakening and breathing

ABCDE: Evidence-based care for the ICU patient

Evidence in sedation:

- Awareness and breathing/trial ventilation
- Early weaning from ventilator
- Early ICU and hospital discharge
- Independent functional status
- Early mobility
- Early mobility: Exercise
Daily interruption of sedation, spontaneous awakening, or sedation vacation

- Daily interruption of sedation has resulted in median 2.4 days (Kress 2000) and mean of 3.1 (Girard 2008) fewer days of ventilation

Sedation vacation yields significantly decreased duration of ventilation and length of ICU stay

Paired sedation vacation, spontaneous breathing trials yield lower mortality and more ventilator-free days than spontaneous breathing trials alone

Long-term cognitive impairment: ABC study follow-up

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th></th>
<th>12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>70%</td>
<td>Control</td>
<td>72%</td>
<td>Control</td>
</tr>
<tr>
<td>p value</td>
<td>0.03</td>
<td></td>
<td>0.89</td>
<td></td>
</tr>
</tbody>
</table>

- Less cognitive impairment over time BUT >2/3rds of patients had some impairment
- 10% had pre-existing cognitive impairment
- Similar data for psychological and functional outcomes
- Mortality benefit of interrupting / reducing sedation is not offset by adverse outcomes

Evidence in sedation: choice of sedative (lots of data to follow)
Sedative selection: MENDS / SEDCOM

- Two double-blind, placebo-controlled, randomized, multicenter trials of dexmedetomidine vs. lorazepam / midazolam
  - Treating team stayed closer to targeted level of sedation with dexmedetomidine
  - Dexmedetomidine had more days alive without delirium or coma (7 vs. 3, p=0.01) than lorazepam
  - Dexmedetomidine had lower prevalence of delirium (54% vs 77%, p<0.001), quicker extubation, etc. than midazolam
  - Lower mortality in dexmedetomidine was not statistically significant

Riker et al., JAMA 2009;301:489-99
Pandharipande et al., JAMA 2007;298:2644-53

Sedative selection: MIDEX / PRODEX

- Similar time at target RASS (57% at RASS -1 to 0 plus 40% at RASS -3 to -2)
- Similar length of stay, mortality
- More adverse cardiovascular events in dexmedetomidine group than midazolam group (all p<0.01)
- No difference in cardiovascular events (and less polyneuropathy, neurocognitive adverse events) in dexmedetomidine group versus propofol group

Jakob et al., JAMA 2012;307:1151-60

Sedative selection: MIDEX / PRODEX

- Two double-blind, placebo-controlled, randomized, multicenter European trials of dexmedetomidine vs. propofol / midazolam
  - Non-inferiority design
  - Both trials with n=~250 in each group
  - Sedation vacation in ~90% of all patients
  - No loading doses (up to 1.4mcg/kg/h dexmedetomidine)

Jakob et al., JAMA 2012;307:1151-60

Sedative selection: MIDEX / PRODEX

- Lighter sedation generally achieved in dexmedetomidine groups (both p<0.001)
- Spontaneous breathing trials more common in dexmedetomidine groups (both p ≤0.02)
- Patient interaction higher in dexmedetomidine groups (both p<0.001)
- Time to extubation shorter in dexmedetomidine groups (both p≤0.04)

Jakob et al., JAMA 2012;307:1151-60

Dexmedetomidine thoughts

- Bradycardia/heart block is idiosyncratic
- No bolus (I might use one time benzo or narcotic to bridge to effect in 10-30min)
- Start high (0.5 or so) and go higher (up to 2 mcg/kg/hr or so)
- Okay for drug withdrawal states, too
- If you're targeting coma, not your drug
Sedative regimen

• If both sedation vacation and alternative sedative regimens decrease adverse outcomes, is one strategy better than the other?

<table>
<thead>
<tr>
<th>Sedative regimen</th>
<th>Alternative sedative regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protocolized strategy of no sedatives versus sedation vacation</td>
<td></td>
</tr>
<tr>
<td>– Sedation group received propofol for 48h then midazolam</td>
<td></td>
</tr>
<tr>
<td>– Extra person used more often in no sedation group than sedation group, p=0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Sedation</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>13.8</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>22%</td>
</tr>
<tr>
<td>Propofol, mg/kg/h</td>
<td>~0</td>
</tr>
<tr>
<td>Morphine, mg/kg/h</td>
<td>0.0048</td>
</tr>
<tr>
<td>Haloperidol, mg/kg/h</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Neuromuscular blockade:
Forgotten therapy (?)

• Prospective French RCT of cisatracurium vs placebo in patients with <48h of:
  – Mechanical ventilation
  – ARDS criteria
  – P/F ratio <150 with PEEP ≥5 cm water and tidal volume of 6-8 cc/kg PBW

<table>
<thead>
<tr>
<th>Neuromuscular blockade: Forgotten therapy (?)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Crossover allowed</td>
<td></td>
</tr>
<tr>
<td>• 32% decreased odds of 90 day mortality (p=0.04) favoring cisatracurium</td>
<td></td>
</tr>
<tr>
<td>• More ventilator-free days in treatment group (p=0.04) favoring cisatracurium</td>
<td></td>
</tr>
<tr>
<td>• No difference in muscle weakness</td>
<td></td>
</tr>
</tbody>
</table>
  – Cisatracurium is non-steroidal compound (vecuronium is steroidal—? differential risk) | |
  – Rigor of muscle strength testing unknown | |

Volatile agents (?) : Sevoflurane

• Sevoflurane vs propofol vs midazolam (all received remifentanil for pain), n=47
• Sevoflurane group extubated faster (p<0.001), had fewer hallucinations (p=0.04), received less morphine for analgesia (p<0.001), and had less pain at the end of sedation (p<0.001)
• Inexpensive, easy to titrate, no adjustment for organ impairment; beware malignant hyperthermia

Evidence in sedation: delirium consequences
Delirium is associated with 3-fold higher 6-month mortality

![Graph showing survival rates for persistent coma, never delirium, and ever delirium over time.]

Adverse outcomes of ICU delirium

- 10-fold higher rate of cognitive impairment at hospital discharge after adjustment for age, sex, race, pre-existing comorbidity and cognitive impairment, and severity of illness
- Duration of delirium predicts cognitive impairment at 3-6 months among patients with severe sepsis

![Graph showing mean delirium days and cognitive impairment at 3 months.]

Duration of delirium may predict cognitive impairment at 3 months

Evidence in sedation: early mobility

- Among 1449 activity events:
  - 53% were ambulation, including 249 events in ventilated patients
  - 75% on FiO$_2 \leq 0.4$, 8% on FiO$_2 \geq 0.7$
  - 14 adverse events (1%), including falls to knees (5), SBP <90 (4), SpO$_2 <80\%$ (3), feeding tube removal (1), & SBP >200 (1)
  - No unplanned extubations

Debility

- Cohort of 109 ventilated ICU patients
  - Lost 18% of baseline body weight at discharge from the ICU
  - 49% unable to return to work at 1 year
  - Muscle wasting and fatigue major factors in functional limitations (recent data suggest need for increased protein in this group and safety of hypocaloric feeding)
- Also affects discharge disposition (cost?)

Early activity is feasible and safe in respiratory failure patients: retrospective cohort

- Among 1449 activity events:
  - 53% were ambulation, including 249 events in ventilated patients
  - 75% on FiO$_2 \leq 0.4$, 8% on FiO$_2 \geq 0.7$
  - 14 adverse events (1%), including falls to knees (5), SBP <90 (4), SpO$_2 <80\%$ (3), feeding tube removal (1), & SBP >200 (1)
  - No unplanned extubations
Early activity is beneficial and safe in respiratory failure patients: prospective, randomized trial

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=165)</th>
<th>Usual Care (n=165)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to first out of bed</td>
<td>5</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>9</td>
<td>10</td>
<td>0.16</td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td>5.5</td>
<td>7</td>
<td>0.025</td>
</tr>
<tr>
<td>Hospital length of stay, d</td>
<td>11</td>
<td>14.5</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* No adverse events

Morris et al. CCM 2008;36:2238-43

Early activity is beneficial and safe in respiratory failure patients: prospective, randomized trial

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=49)</th>
<th>Usual Care (n=55)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independence, hospital d/c</td>
<td>59%</td>
<td>35%</td>
<td>0.02</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>23.5</td>
<td>21.1</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU delirium, d</td>
<td>2</td>
<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>18</td>
<td>25</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Protocol of progressive activity by PT, OT
* One adverse event (SpO2 <80%)

Schweickert et al. Lancet 2009;373:1874-82

Practical lessons

Costs

* Relatively understudied in general
* Where studied, sedatives associated with the move toward extubation (and thus ICU and hospital discharge) faster are cheaper from hospital perspective
  - Propofol cheaper than lorazepam
  - Dexmedetomidine cheaper than midazolam

Cox et al., Crit Care Med 2008;36:706-14
Dasta et al., Crit Care Med 2010;38:497-503

Costs: I-Save study (Canada)

* Large, single-center study in Montreal
* Before and after study design
* Used RASS for sedation, numeric rating scale or BPS for pain, and ICDSC for delirium
* Numerous limitations
* ~$950 difference in cost of ICU stay per patient

Awissi et al., Ann Pharmacother 2012;46:21-8

Potential ICU outcomes

* Death
* Delirium (attendant death, etc.)
* Increased length and costs of stay
* Failure to wean ventilated patients
* Post-traumatic stress disorder
* Immobility, neuromuscular weakness
* Inability to return to work (socioeconomic impact)
* Long-term cognitive impairment

Cox et al., Crit Care Med 2008;36:706-14
Dasta et al., Crit Care Med 2010;38:497-503
Improving care of ICU patients

• Where is the patient going? (i.e., sedation and activity targets/goals)
• Where is the patient now? (i.e., current RASS/CAM-ICU, amount of sleep, activity level)
• How did they get there? (i.e., drug exposures)
• State the following (only takes seconds!):
  – Target RASS
  – Actual RASS
  – CAM-ICU
  – Drugs

Sedation pearls

• Limit/don’t use continuous infusions of benzodiazepines in 2012
• Consider avoiding routine benzodiazepines
• Prove sedation is needed rather than prove it is NOT needed

Conclusions

• Indications for sedation and perception of its safety and consequences is evolving
• Routine monitoring of sedation and pain necessary
• Attention to spontaneous awakening and breathing, careful selection of sedative, delirium monitoring, and early mobility are evidence-based in 2012
• ICU outcomes beyond mortality are the new standard in research and practically relevant

Thank you!

Questions?