Sedation Strategies: Current Best Evidence
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Objectives
• List the proposed benefits of light sedation versus deep sedation based on current literature
• Describe the rationale for using non-benzodiazepine based sedation regimens

Detriments of Agitation
• Increase oxygen consumption
• Tachycardia
• Hypertension
• Anxiety
• Sleep disturbances
• Ventilator dysynchrony
• Self-inflicted harm
• Post-traumatic stress disorder

Sedation in the ICU

Light sedation
• Patient is arousable and able to purposefully follow simple commands

Deep sedation
• Patient is unresponsive to painful stimuli
• Indications
  • Intracranial hypertension
  • Severe respiratory failure
  • Refractory status epilepticus
  • Use of neuromuscular blocking agents
  • Other
Balancing Act

Agitation
- Tachycardia
- Hypertension
- Arrhythmia/MI
- Vent Dysynchrony
- ET Tube/Line Removal

Sedation
- Respiratory Depression
- Bradycardia/Hypotension
- Ventilator Dependency
- Immobility/Pressure Ucer
- Muscle Atrophy

Sedation Goal
- Pain free
- Titrated to allow patient responsiveness and awareness
- Avoid short and long-term complications associated with either excessive or inadequate treatment

Clinical Outcomes
- Any harm from light levels of sedation?
  - Increased catecholamine concentrations
  - Increased oxygen consumption
  - Increased recall of ICU memories
  - Post ICU psychological stress
- Light levels of sedation associated with?
  - Shorter duration of mechanical ventilation
  - Shorter ICU length of stay
- Light sedation vs. Daily SAT?

Options for sedation and their affect on clinical outcomes

Pharmacologic Options
- Analgesia
- Sedation
- Suggest nonbenzodiazepine sedatives may be preferred over benzodiazepines to improve outcomes

Analgesedation
- Analgesia first sedation
- Persistent pain and discomfort
- No consistent advantage found in literature
  - Unblinded studies
  - Moderate quality studies
- What are the outcomes?
  - Ventilator days
  - ICU LOS
  - Delirium
  - Mortality
Dexmedetomidine vs. Benzodiazepine

- Ideal agent?
- Analgesic sparing effect
- Less respiratory depression
- Light level of sedation allowing patients to communicate
- Multiple studies comparing outcomes produced variable results
- Compared to lorazepam and midazolam, dexmedetomidine results shorter duration of mechanical ventilation
- Patients spend less time in delirium and have reduced prevalence

SEDCOM Trial

- Prospective, double-blind, randomized, and multi-center
- Patient population
  - Adults, mechanically ventilated for <96 hours
  - Anticipated duration of at least 3 days
- Randomized to dexamethasone or midazolam (n = 376)
  - RASS goal -2 to +1
  - Open label fentanyl and midazolam boluses permitted
  - Haloperidol permitted for agitation or delirium

<table>
<thead>
<tr>
<th>SEDCOM Trial</th>
<th>Dexametomidine</th>
<th>Midazolam</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% time within target sedation</td>
<td>77.3%</td>
<td>76.1%</td>
<td>0.18</td>
</tr>
<tr>
<td>Open label midazolam (1st day of randomization)</td>
<td>43%</td>
<td>30%</td>
<td>0.02</td>
</tr>
<tr>
<td>Open label midazolam (entire treatment period)</td>
<td>63%</td>
<td>49%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Delirium
  - 24.9% (95% CI, 16 to 31%; p=0.001) reduction of delirium in patients treated with dexametomidine
  - Prevalence: 54% vs. 76.6% (22.6% 95% CI, 14 to 33%; p<0.001)

Propofol vs. Benzodiazepines

- Outcomes should be assessed individually for each patient population
- Medical/surgical
- Cardiovascular
- Neurologic
- Overall, shorter duration of mechanical ventilation without a decrease in ICU LOS
- Weak data and evidence to conclude on difference in delirium

Dexmedetomidine vs. Propofol or Midazolam

- 2 parallel, multicenter, randomized, double-blinded non-inferiority trials
- MIDEX (n = 501) and PRODEX (n = 500) trials
- Patient population
  - Adults requiring invasive mechanical ventilation with need for light to moderate sedation
  - Sedation required for at least 24 hours
  - Randomized within 72 hours of ICU admission
- Bedside nurses titrated medications to achieve goal RASS and fentanyl boluses were permitted

- Delirium free days
  - 2.5 days vs. 1.7 days; p = 0.002
- Time to extubation & ICU LOS

- Bradycardia. 42.2% vs. 18.6%; p = 0.001
Dexmedetomidine vs. Propofol or Midazolam
- Time in target sedation goal without rescue bolus
  - MIDEK: midazolam 56.4% vs. dexmedetomidine 60.7%, 1.07 (95% CI, 0.97 - 1.18; p = 0.15)
  - PRODEX: propofol 64.7% vs. dexmedetomidine 64.6%, 1.00 (95% CI, 0.92 - 1.10; p = 0.97)
- Dexmedetomidine patients had higher actual RASS scores (p< 0.001)
- Drug discontinuation rates
  - MIDEK: 4% vs. 9%; p = 0.02
  - PRODEX: 5% vs. 14%; p = 0.001
- Discontinuation secondary to lack of efficacy within 24 hours more common in dexmedetomidine group

Dexmedetomidine vs. Propofol or Midazolam
- Hospital LOS
  - No difference
- Delirium
  - Not solely assessed, included in “neurocognitive disorders”
- Adverse Events
  - Hypotension
    - MIDEK: 11.6% vs. 20.6%; p = 0.007
    - PRODEX: NS
  - Bradycardia
    - MIDEK: 6.2% vs. 14.2%; p<0.001
    - PRODEX: NS

Benzodiazepine vs. Nonbenzodiazepine
- 13 studies including over 1500 patients
- No consistent difference in ICU LOS
- Meta-analysis performed including 6 trials
  - Sedation with benzodiazepines increased ICU LOS by 0.5 days; p = 0.04
  - Duration of mechanical ventilation
    - Limited data suggest prolonged use with benzodiazepines
  - No apparent difference in mortality

Benzodiazepine vs. Nonbenzodiazepine
- Meta analysis of 6 trials including over 1200 patients
  - Midazolam vs. dexmedetomidine
  - lorazepam vs. dexmedetomidine
  - Midazolam vs. propofol
  - Lorazepam vs. propofol
- Eligibility criteria
  - Randomized, controlled, parallel trial
  - Adult medical or surgical ICU patients
  - Predetermined outcomes
- Excluded studies evaluating cardiac surgery and critically ill obstetrical patients
Benzodiazepine vs. Nonbenzodiazepine

- Patient characteristics
  - Mean age: 59
  - Medical ICU patients majority
  - APACHE II score: 21

- Clinical Outcomes
  - ICU LOS: mean 1.65 d; χ² = 0.0005
  - Mechanical ventilation duration: mean 1.9 d; p < 0.00001
  - Delirium: variation within each study
  - All cause short term morality: RR 0.98; (95% CI, 0.76 - 1.27; p = 0.94)

Summary

- Agitation is a common occurrence in the ICU that requires prompt identification and treatment
- Light sedation is preferred over deep sedation
- Nonbenzodiazepine sedation has positive effects on multiple clinical outcomes
  - Duration of mechanical ventilation
  - ICU LOS
  - Delirium
- There is still a role for benzodiazepine based sedation in the ICU
- How do you extrapolate the data?

Learning Assessment Question

1. Non-benzodiazepine based sedation regimens have been suggested to:
   A. Decrease the incidence of delirium
   B. Increase ICU length of stay
   C. Prolong the length of mechanical ventilation
   D. Increase use of ICU resources

References


http://bit.ly/1E9HqYn
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