Sedation, analgesia and neuromuscular blockade in the critically ill

5/9/2014

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Senior resident
Department of pulmonary medicine
- When to sedate?
- Which agent is better?
- Any head to head comparison?
- How to monitor?
- Does sedation have an advantage, if so what?
- Disadvantages
Goals of analgesia and sedation

- Comfort and safety of the patient
- Better ventilator-patient synchrony
- To reduce the stress related to the critical illness
Distress in the critically ill

- Critically ill patients, especially intubated patients often develop agitation – pain, anxiety, unable to communicate with care-givers
- First step: correct the cause of agitation (pain relief, correction of fever, hypoxemia, etc.)
- Delirium and its risk factors – fever, dyselectrolytemia, drug withdrawal, etc. to be looked for and corrected
Distress in the critically ill

- Initial management- conservatively managing the identifiable cause of distress
- *Non-pharmacologic management*: Reassurance, interaction with the patient and reorientation, family visits, cognitive behavior therapy¹
- *Sedation*: when these are not effective in controlling the distress

¹ Fontaine DK. Crit care Clin ; 10: 695
## Sedate or not to sedate?

<table>
<thead>
<tr>
<th></th>
<th>No sedation (n 55)</th>
<th>Sedation (n 58)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation free days (from intubation to day 28)</td>
<td>13.8 (11.0); 18.0 (0–24.1)</td>
<td>9.6 (10.0); 6.9 (0–20.5)</td>
<td>0.0191</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>13.1 (5.7–..)</td>
<td>22.8 (11.7–..)</td>
<td>0.0316</td>
</tr>
<tr>
<td>Hospital</td>
<td>34 (17–65)</td>
<td>58 (33–85)</td>
<td>0.0039</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>12 (22%)</td>
<td>22 (38%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospital</td>
<td>20 (36%)</td>
<td>27 (47%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>16 (29%)</td>
<td>17 (29%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>6 (11%)</td>
<td>7 (12%)</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Sedate or not to sedate?

<table>
<thead>
<tr>
<th>Other outcomes</th>
<th>No sedation arm</th>
<th>Sedation arm</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidental tube removal</td>
<td>6</td>
<td>7</td>
<td>0.69</td>
</tr>
<tr>
<td>CT/MRI brain</td>
<td>5</td>
<td>8</td>
<td>0.43</td>
</tr>
<tr>
<td>Re-intubation within 24h</td>
<td>7</td>
<td>11</td>
<td>0.37</td>
</tr>
<tr>
<td>Delirium</td>
<td>11 (20%)</td>
<td>4 (7%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Haloperidol usage</td>
<td>19</td>
<td>8</td>
<td>0.010</td>
</tr>
</tbody>
</table>

No sedation group however received analgesia with morphine 2.5 or 5 mg PRN 1:1 nurse: patient ratio and dedicated counselor to reassure patients whenever required (May not be feasible practically)

Strom T, Martinussen T, Toft P. Lancet. 2010;375(9713):475-80
Unconventional ventilation and sedation

- Low tidal volume (≤ 6 mL/kg IBW) strategy though highly effective in decreasing mortality – it’s not physiological

- A meta-analysis of the two trials (the two trials as well as the meta-analysis was still underpowered) concluded – low tidal volume strategy not necessarily required increased sedation/analgesia

Neto SA et al. Intensive care medicine
## Overview of sedatives

### Sedatives in ICU

**Agents causing sedation by their direct effect**

(a) GABA agonists (GABA is one of the most important CNS inhibitory system)

1. Benzodiazepines (diazepam, lorazepam, midazolam)
2. Propofol

(b) Alpha 2 agonist

1. Dexmedetomidine

**Agents causing sedation as an adverse effect**

(a) Antipsychotics

1. Typical – haloperidol
2. Atypical – risperidone, olanzapine

(b) Opioids

Which agent to use?

- Individualize based on patient factors
- Expected duration of ventilation
- Presence of organ failures, hypersensitivity to drugs
- Clinical pharmacology of the drug in use must be considered
  - Hypoalbuminemia
  - Drug interaction due to polypharmacy
  - Altered pharmacokinetics and dynamics – drug accumulation
- Cost and cost-effectiveness
Monitoring sedation

- **Sedation Agitation Scale (SAS)**
- **Richmond Agitation-Sedation Scale (RASS)**
- Observer’s assessment of alertness/sedation scale (OAA/S)
- Ramsay sedation scale
- New Sheffield sedation scale
- Sedation Intensive Care Score (SEDIC)
- Motor Activity Assessment Score (MAAS)
- Adaption to Intensive care environment (ATICE)
- Minnesota Sedation Assessment Tool (MSAT)
- Vancouver Interaction and Calmness Scale (VICS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent nonpurposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (&gt;10 seconds)</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Briefly awakens with eye opening to voice (&gt;10 seconds)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>Movement or eye opening to voice (but no eye contact)</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>
Objective measures of monitoring sedation

- Auditory Evoked Potentials (AEP)
- Bispectral Index (BIS)
- Narcotrend Index (NI)
- Patient State Index (PSI)
- State entropy (SE)

Objective measures of monitoring sedation

- May serve as useful adjuncts, but not to be used as routine
- Benefit of using these objective tests do not add much to the subjective sedation scales
- Patients who are paralyzed, cannot be monitored with the subjective scale, hence may have a role in these

How much sedation?

- Light sedation improves outcome (RASS -2 to +1 in many studies. Varies from trial to trial)
- Shorter ICU stay and ventilation days
- Though light sedation may increase some physiologic stress, (increased catecholamine levels and oxygen consumption) may not be associated with negative clinical outcomes
- No difference in post ICU psychological outcome based on the depth of sedation

Interruption of sedation

- Daily sedation interruption (DSI) defined as “short-term suspension, hold, discontinuation, cessation, or interruption of intravenous sedatives (continuous infusions or fixed dose bolus) and, in some cases, analgesic medications”

- To prevent drug bioaccumulation
- Awake state
- Assess whether liberation is possible or not and neurologic status

Interruption of sedation

- Interruption is done till patient becomes awake, and can obey simple commands

- Daily interruption of sedation (DSI) may reduce the total duration of ventilation

Total duration of ventilation was not significantly lower with DSI, but there was heterogeneity, hence subgroup analysis performed as above ($I^2 = 61\%$)

Here north American studies showed significantly lower days o ventilator

### Daily sedation interruption (DSI)

<table>
<thead>
<tr>
<th>Secondary outcome</th>
<th>DSI vs. continuous sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU and hospital mortality</td>
<td>No difference noted</td>
</tr>
<tr>
<td>Length of stay, hospital and ICU</td>
<td></td>
</tr>
<tr>
<td>Accidental ETT removal</td>
<td></td>
</tr>
<tr>
<td>New onset delirium</td>
<td></td>
</tr>
<tr>
<td>Catheter removal</td>
<td></td>
</tr>
<tr>
<td>Quality of life (3/9 trials)</td>
<td></td>
</tr>
<tr>
<td>Tracheostomy was performed less frequently in the DSI group (RR 0.73) reported in six trials</td>
<td></td>
</tr>
</tbody>
</table>

Propofol

- Rapid onset and offset
- As good as midazolam and better recovery times
- Beneficial immunomodulatory effect in sepsis, SIRS

- Arterial hypotension, myocardial depression
- Hypertriglyceridemia, hyperamylasemia, bacterial contamination, propofol infusion syndrome (children, > 48h high dose infusion >5 mg/kg/h) especially in sepsis and inflammatory diseases

Marik PE. Pharmacotherapy. 2005;25(5 Pt 2):28s-33s
Propofol vs. Benzodiazepines

Data from multicenter ICU database, propensity score matching was done. Continuous sedation > 48 h were included (2003 – 2009)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Propofol vs. midazolam</th>
<th>Propofol vs. lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>RR 0.76</td>
<td>RR 0.78 (favoring propofol)</td>
</tr>
<tr>
<td>Probability of discharge at 28 d</td>
<td>78% vs. 69.5%</td>
<td>79% vs. 71.9% (p &lt; 0.001)</td>
</tr>
<tr>
<td>Earlier removal from ventilator</td>
<td>84.4% vs. 78.1%</td>
<td>84.3% vs. 78.8% (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

- Initial studies showed that time to extubation was significantly lower in propofol sedation than with midazolam
- Propofol – used in anesthesia and in post op period for short duration
- Issues were raised regarding usefulness in long and medium term sedation in ICU
Propofol for medium (>24h to 7d) and long term sedation (>7d)

- A total of 16 trials studied in a meta-analysis
  - Mortality reported in 14 trials
  - Length of ICU stay in 9 trials
  - Duration of ventilation in 4 trials
- No difference in mortality
- But significantly lesser duration of ventilation and ICU stay (in both long term and medium term usage of propofol)

Delirium in propofol vs. midazolam

- Two studies (one was done in post cardiac surgery patients)
- Found no difference in delirium in both these groups

Dexmedetomidine

- Alpha 2 adrenergic agonist
- Similar to clonidine, but more specific
- Does not act on GABA receptors
- Acts on locus ceruleus
- No respiratory depression
Dexmedetomidine

- Recent meta-analysis: 28 studies (27 publications)
- Trials in general ICU setting – 13
- Loading dose 1 mcg/kg followed by infusion ranging from 0.1 to 2.5 mcg/kg have been used in majority (18 trials)
- Six different comparators: propofol in 11 study, midazolam in 10, placebo in 5, morphine in 2, haloperidol and lorazepam in one each

## Dexmedetomidine

### Outcome in ICU patients

<table>
<thead>
<tr>
<th>(a)Length of ICU stay in various categories</th>
<th>Number of trials</th>
<th>Dexmedetomidine vs. placebo/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term sedation</td>
<td>6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Short term sedation</td>
<td>11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Daily interruption</td>
<td>5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>High maintenance dose</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low maintenance dose (&lt; 0.7 µg/kg/hr)</td>
<td>10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Loading dose</td>
<td>11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Loading dose and high maintenance dose</td>
<td>2</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Adapted from: Pasin L, et al. PloS one. 2013;8(12):e82913 (table showing outcomes for only ICU related studies)
Dexmedetomidine

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Dexmed vs. control</th>
<th>P value (Relative risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>200/1499 (13%) vs. 173/1409 (12%)</td>
<td>0.9 (RR 1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>424/1389 (31%) vs. 279/1266 (22%)</td>
<td>0.052 (RR 1.27)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>220/1374 (61%) vs. 64/1246 (5%)</td>
<td>&lt; 0.001 (RR 2.43)</td>
</tr>
<tr>
<td>Rescue medications: Analgesics/</td>
<td>892/1459 (61%) vs. 977/1366 (72%)</td>
<td>&lt; 0.001 (RR 0.80)</td>
</tr>
<tr>
<td>Sedatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completely comfortable patients</td>
<td>12/253 (51%) vs. 103/254 (40.6%)</td>
<td>0.9 (RR 1.07)</td>
</tr>
</tbody>
</table>

Adapted from: Pasin L, et al. PloS one. 2013;8(12):e82913 (table showing outcomes for only ICU related studies)
Adverse effects

- Decreases sympathetic activity – may increase adverse cardiac events
- Especially in individuals with autonomic disturbance, elderly, diabetics, chronic hypertension. Valvular heart disease, heart blocks, severe CAD, hypotension/hypovolemia

Other agents for sedation

- Ketamine (adv in head injury patients)
- Has been used mainly for procedural sedation and analgesia
- Not rigorously studied as an agent for sedation in critically ill
- No cardiorespiratory depression offers an advantage
- Successfully used in five pediatric patients who had cardiorespiratory depression with opioids and conventional sedatives

Other agents for sedation

- Sevoflurane vs. propofol/midazolam
  - Study in 60 patients (RCT)
  - All patients received remifentanil for pain up to 96 h
  - Wake up time and time to extubation was significantly better with sevoflurane (18.6 mts to 33.6 mts mean)

- Midazolam vs. isoflurane studied earlier (<24 h sedation) shorter ventilation period and early extubation

Kong KL et al. BMJ 1989; 298:1277-1280
# Benzodiazepine vs. non benzodiazepine sedation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n (trials) (follow-up)</th>
<th>Benefit with non BDZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU length of stay</td>
<td>1235 (6) (45 d f/u)</td>
<td>-1.64 d</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>1101 (4) (45 d f/u)</td>
<td>-1.87 d</td>
</tr>
<tr>
<td>Mortality</td>
<td>1101 (4) (45 d f/u)</td>
<td>1.01</td>
</tr>
<tr>
<td>Delirium</td>
<td>469 (2) (during ICU stay only)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Benzodiazepine vs. non benzodiazepine sedation

- Thirteen trials analyzed and only six high quality studies included in another meta analysis
- ICU length of stay shortened approximately by 0.5 days (non BDZ arm)
- No mortality difference noted
- Overall conclusion: Non BDZ modestly effective in reducing ICU LOS than BDZ sedation

Disadvantages of sedation

- Prolonged hospital stay
- Prolonged weaning and ICU stay
- Increased risk of ICU acquired infections (immunomodulatory effects of sedatives, microaspiration etc.)
- Risk of delirium
- Cost and cost of hospitalisation
- Distorted sleep architecture. BDZ reduce slow wave sleep, dexmedetomidine causes distortion (but not noted to have clinical benefit)
  - Weinhouse LG. Anesthesiology Clin.2011; 29:675
Interpret with caution

- Almost all trials exclude <18 years of age
- Significant renal and liver failure patients were excluded in many studies
- Long term effect of these sedatives are not known
- Propofol and midazolam can have long term effect on cognitive function

Absolute cost vs. cost effectiveness

- Non benzodiazepine based regimens absolute cost is more than benzodiazepine based regimens, but overall effectiveness is better with non benzodiazepine regimens

Analgesia


• Routine pain assessment by valid scales enable reduction in analgesic dose
• Length of ICU stay and duration of ventilation are also reduced

Payen JF, al; DOLOREA study. Anesthesiology 2009; 111:1308–1316
<table>
<thead>
<tr>
<th>Agent</th>
<th>Analgesic Dose (IV)</th>
<th>Half-Life</th>
<th>Metabolic Pathway</th>
<th>Active Metabolites (Effect)</th>
<th>Adverse Effects</th>
<th>Intermittent Dose*</th>
<th>Infusion Dose Range (Usual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>200 µg</td>
<td>1.5−6 hr</td>
<td>Oxidation</td>
<td>No metabolite, parent accumulates</td>
<td>Rigidity with high doses</td>
<td>0.35−1.5 µg/kg IV q0.5−1h</td>
<td>0.7−10 µg/kg/hr</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1.5 mg</td>
<td>2−3 hr</td>
<td>Glucuronidation</td>
<td>None</td>
<td>—</td>
<td>10−30 µg/kg IV q1−2h</td>
<td>7−15 µg/kg/hr</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>3−7 hr</td>
<td>Glucuronidation</td>
<td>Yes (sedation, especially in renal insufficiency)</td>
<td>Histamine release</td>
<td>0.01−0.15 mg/kg IV q1−2h</td>
<td>0.07−0.5 mg/kg/hr</td>
</tr>
<tr>
<td>Meperidine</td>
<td>75−100 mg</td>
<td>3−4 hr</td>
<td>Demethylation and hydroxylation</td>
<td>Yes (neuroexcitation, especially in renal insufficiency or high doses)</td>
<td>Avoid with MAOIs and SSRIs</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Codeine</td>
<td>120 mg</td>
<td>3 hr</td>
<td>Demethylation and glucuronidation</td>
<td>Yes (analgnesia, sedation)</td>
<td>Lacks potency, histamine release</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>—</td>
<td>3−10 min</td>
<td>Plasma esterase</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>0.6−15 µg/kg/hr</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>—</td>
<td>2.4−8.6 hr</td>
<td>Renal</td>
<td>None</td>
<td>Risk of bleeding, GI and renal adverse effects</td>
<td>15−30 mg IV q6h, decrease if age &gt;65 yr or weight &lt;50 kg or renal impairment, avoid &gt;5 days use</td>
<td>—</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>—</td>
<td>1.8−2.5 hr</td>
<td>Oxidation</td>
<td>None</td>
<td>Risk of bleeding, GI and renal adverse effects</td>
<td>400 mg PO q4−6h</td>
<td>—</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>—</td>
<td>2 hr</td>
<td>Conjugation</td>
<td>—</td>
<td>—</td>
<td>325−650 mg PO q4−6h, avoid &gt;4 g/day</td>
<td>—</td>
</tr>
</tbody>
</table>
• Drug of choice – opioids

• Morphine avoided in renal failure as its active metabolite accumulates

• Fentanyl is hence used

• All opioids similar efficacy and outcomes when the same degree of analgesia is achieved

• Neuropathic pain – add gabapentin, carbamazepine

• Non-opioids – adjuncts, serve to reduce opioid

• No direct comparison of opioids vs. non-opioids

Hudson RJ, et al. Anesthesiology. 1989; 70:426-43
Adapted from: Ogura T, Egan TD. Opioid agonists and antagonists. Chap 15 clinical pharmacology
Analgosedation

- Manage discomfort and pain first
- Sedation to be considered subsequently
- Remifentanil has been used
- Titration is easy, metabolism is not dependent on renal/liver functions
- Nine trials (remifentanil analgosedation vs. midazolam, propofol, fentanyl, morphine)
- Shorter duration of ventilation, ICU stay and early weaning

Neuromuscular blocking agents (NMBAs)
Classification of NMBAs – depolarising agents

- Succinylcholine

Classification of NMBAs – non depolarising agents

<table>
<thead>
<tr>
<th>Class of Blocker</th>
<th>Long-Acting (&gt;50 min)</th>
<th>Intermediate-Acting (20-50 min)</th>
<th>Short-Acting (15-20 min)</th>
<th>Ultrashort-acting (&lt;10-12 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroidal compounds</td>
<td>Pancuronium</td>
<td>Vecuronium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pimecuroonium</td>
<td>Rocuronium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyllisoquinolinium compounds</td>
<td>(d)-Tubocurarine</td>
<td>Atracurium</td>
<td>Mivacurium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metocurine</td>
<td>Cisatracurium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxacurium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>Gallamine</td>
<td></td>
<td>Gantacurium</td>
</tr>
<tr>
<td>Asymmetrical mixed-onium chlorofumarates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenolic ether</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diallyl derivative of toxiferine</td>
<td></td>
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</tr>
</tbody>
</table>

A majority of nondepolarizing neuromuscular blockers are bisquaternary ammonium compounds. \(d\)-Tubocurarine, vecuronium, rocuronium, and rapacuronium are monou- quaternary compounds, and gallamine is a trisquaternary ammonium compound.

Indications for NMBAs

- Intubation
- Facilitation of mechanical ventilation
  - Non-conventional ventilatory strategies (35%)
  - Hypoxemia (25%)
  - Reduced lung compliance (25%)
  - Ventilator-patient dys-synchrony (18%)
  - Permissive hypercapnia (15%)
  - Prone position ventilation
- Less commonly: to reduce metabolic demands, agitation and in raised intracranial pressure

### Indications for NMBAs during MV

<table>
<thead>
<tr>
<th>Reason</th>
<th>Odd’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permissive hypercapnia</td>
<td>4.49</td>
</tr>
<tr>
<td>Prone position</td>
<td>4.36</td>
</tr>
<tr>
<td>Full ventilatory support</td>
<td>3.68</td>
</tr>
<tr>
<td>PEEP ≥ 10 cmH2O</td>
<td>3.06</td>
</tr>
<tr>
<td>Plateau pressure &gt; 35 cmH2O</td>
<td>2.19</td>
</tr>
</tbody>
</table>

Which agent to use?

- Succinylcholine for RSI and short term usage
- Many side effects: raised ICP, IOP, malignant hyperthermia, hyperkalemia, bradyarrhythmias
- For ARDS, trials are done with continuous cis-atracurium infusion
- None of the other agents have been systematically studied
Which agent to use?

- Normal hepatic renal function – pancuronium (>1h if required)
- Cardiovascular disease – vecuronium (least cardiovascular side effects)
- Hepatic and or renal dysfunction – atracurium/cisatracurium (hoffmann elimination)

Monitoring of NMBAs

- Monitoring is recommended for all patients
- Train of four (TOF) responses in the abductor pollicis muscle after stimulation of the ulnar nerve
- Four stimuli are applied over a 2 sec period, each lasting 0.5 s

![Graph showing non/partial depolarizing muscular blockers and depolarizing muscular blockade with succinylcholine]
Bevan DR, Bevan JC, Donati F: Muscle relaxants in clinical anesthesia, Chicago, 1988, Year Book, pp 49–70
## Beneficial effects NMBA in ARDS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>Outcome</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Gainnier M et al. Critical care</td>
<td>Multicenter, randomized</td>
<td>Gas exchange over 120 hr period</td>
<td>48, 96 and 120 h after randomization PaO2/fiO2 was better in the NMBA</td>
</tr>
<tr>
<td>medicine. 2004;32(1):113-9.</td>
<td>Four ICUs: (n -56) med/med surg mixed PaO2/fiO2 150, PEEP ≥ 5 cmH2O</td>
<td></td>
<td>group</td>
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<tr>
<td></td>
<td>ACMV Conv vs. 48h cisatracurium infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forel JM et al. Critical care</td>
<td>Multicenter, randomized (n -36) 1 med and 2 med surg ICU PaO2/fiO2 200,</td>
<td>Pulmonary and systemic inflammation – as</td>
<td>Significantly lower proinflammatory markers in NMBA group</td>
</tr>
<tr>
<td>medicine. 2006;34(11):2749-57.</td>
<td>PEEP ≥ 5 cmH2O</td>
<td>assessed by BAL and serum TNF, IL-1, IL-6, IL-8 at pre</td>
<td>Improved PaO2/fiO2 in the</td>
</tr>
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<td></td>
<td></td>
<td>randomization and</td>
<td></td>
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## Beneficial effects NMBA in ARDS

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<th><strong>Results</strong></th>
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<tbody>
<tr>
<td>Papazian L et al. The New England journal of medicine. 2010;363(12):1107-16.</td>
<td>Multicenter, double blind, randomized 20 ICUs: (n = 340) med/med surg mixed PaO2/fiO2 &gt; 150, PEEP ≥ 5 cmH2O ACMV Conv vs. conv with 48h cisatracurium infusion</td>
<td>Mortality in hospital Mortality at 90 d of enrollment into the study</td>
<td>Mortality benefit at 28 and 90 d No increase in ICU paresis Pneumothorax (11.7% vs. 4% p 0.01)</td>
</tr>
<tr>
<td>Outcome assessed</td>
<td>Included trials (4)</td>
<td>Results (p value of NMBA vs. conv)</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
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<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>(1),(2),(3)</td>
<td>RR 0.72 (p 0.005)</td>
<td></td>
</tr>
<tr>
<td>ICU mortality</td>
<td>(1),(2),(3)</td>
<td>RR 0.70 (p 0.004)</td>
<td></td>
</tr>
<tr>
<td>28 day mortality</td>
<td>(1),(2),(3)</td>
<td>RR 0.66 (p 0.003)</td>
<td></td>
</tr>
<tr>
<td>Days free of MV</td>
<td>(1),(2),(3)</td>
<td>MD 1.91 (p 0.002)</td>
<td></td>
</tr>
<tr>
<td>Total duration of MV</td>
<td>(1),(2),(3)</td>
<td>MD 1.21 (p 0.43)</td>
<td></td>
</tr>
<tr>
<td>ICU acquired weakness</td>
<td>(1),(2),(3)</td>
<td>RR 1.08 (p 0.57)</td>
<td></td>
</tr>
<tr>
<td>ICU stay</td>
<td>(1)</td>
<td>RR 1.80 (p 0.38)</td>
<td></td>
</tr>
</tbody>
</table>

MV – mechanical ventilation, MD mean difference, RR relative risk

(2) Forel JM et al. Critical care medicine. 2006;34(11):2749-57
Criticisms of ACURASYS trial

- Crude 90 d mortality 31.6% in NMBA group and 40.7% in placebo arm, p value 0.08
- After adjustment for baseline \( \text{paO}_2: \text{fiO}_2 \), plateau pressure and SAPS II score, the 90 d mortality rate was significantly better in the NMBA arm (p 0.04)
- Only in-hospital 90 d mortality rate assessed. All those who been randomized should have been followed up
- Muscle weakness assessed at 28 d (and no long term data)
Beneficial effects

- Improvement in oxygenation
- Reduction in inflammatory response
- Mortality benefit
- Reduced risk of barotrauma
ICU acquired weakness

- Critical illness polyneuropathy/myopathy (CIP/CIM)
- Incidence in ARDS is up to 34% - 60%
- Risk factors: hyperglycemia, immobilisation (as with NMBA), corticosteroid therapy, multiple organ dysfunction (>2), and prolonged mechanical ventilation
- CIP/CIM is higher with steroidal agents (vecuronium) is much higher than that with atracurium/cisatracurium

Interventions to prevent CIP/CIM

- Many have been tried
- Nutritional supplement (arginine, glutamine)
- Antioxidant therapy
- Testosterone
- Electrical muscle stimulation
- Early mobilization and rehabilitation
- Electrical muscle stimulation
- Control of hyperglycemia (intensive insulin therapy)

Interventions to prevent CIP/CIM

- Intensive insulin therapy (2 large trials) reduces ICU stay, duration of ventilation and 180 d mortality (but significantly more hypoglycemias)
- Early rehabilitation potentially beneficial (modest evidence)
- Other interventions do not have adequate data to support it

Anaphylaxis

- Known with atracurium (hypotension, flushing and bronchospasm 0.2% each)

- Reports of cisatracurium causing anaphylaxis are also available (none encountered in the large trials)

- Complete blinding is not possible in these trials
- No controlled trials on other NMBAs
- The studies (all three) on cis-atracurium have been done by the same group of investigators
- No head to head comparison among various NMBAs
- Hence data needs cautious interpretation
- As per current evidence
SUMMARY

- The cause for agitation should be sought and corrected whenever feasible
- Pain, especially with suctioning, position change and immobility contributes to agitation
- Adequate analgesia to be ensured before sedation is considered
- Effectively managing these factors along with pain relief can be as effective as continuous sedation (low quality evidence, one RCT from a single center)
SUMMARY

- The requirement for sedation should be individualized
- Short term sedation (<24 h): non benzodiazepine regimens are preferred, dexmedetomidine, propofol over benzodiazepines
- Medium and long duration (< 7 and > 7 d): Benzodiazepines are the time tested drugs, especially long acting lorazepam. Current evidence however supports non benzodiazepine regimens
SUMMARY

- Shorter days on ventilator has been consistently seen with non benzodiazepine regimen, whereas some studies suggest a shorter ICU stay as well
- No significant difference with regards to mortality and delirium with these two regimen
- Daily sedation interruption with awake trial and light sedation during the rest of the time are recommended
SUMMARY

- Benzodiazepines still play an important role in treating drug/alcohol withdrawal, seizures and anxiety.
- Monitoring of sedation with either RASS or SAS to be done 2 – 4 hrly
- Analgosedation with remifentanil based regimens may replace the sedative-hypnotic regimen in future, however currently combination of analgesic (opioid + BDZ/non BDZ sedative) is a reasonable option.
SUMMARY

• Cisatracurium effective when used in first 48h in severe ARDS patient (<150 or even <120 \( \text{paO}_2/\text{FiO}_2 \) with PEEP > 5 cmH\(_2\)O).

• Other NMBAs vecuronium may be used if intermittent paralysis is required (Cisatracurium short acting hence requires infusion).

• Judicious use of steroids, NMBA coupled with early rehabilitation and blood sugar control required.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Price</th>
<th>Usual Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>1 mg/mL</td>
<td>10 mL: Rs/55</td>
<td>0.02-0.1 mg/kg/hour</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2 mg/mL</td>
<td>2 ml X 5: Rs/75</td>
<td>0.01-0.1 mg/kg/hour</td>
</tr>
<tr>
<td>Propofol</td>
<td>1%</td>
<td>50 mL: Rs/368</td>
<td>0.3 mg/kg/h</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>200 mg</td>
<td>Rs/558</td>
<td>1 mcg loading f/b 0.2 – 0.7 mcg/kg/h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50 mcg/mL</td>
<td>10 mL: Rs/126</td>
<td>0.7-10 mcg/kg/h</td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
<td>0.1 mcg/kg/h initial</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td></td>
<td></td>
<td>0.5-10 mcg/kg/mt</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>10 mg vial</td>
<td>Rs/227</td>
<td>0.8-1.7 mcg/kg/mt</td>
</tr>
</tbody>
</table>