SEDATION AND ANALGESIA IN ICU

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SBAH
Critically ill patients are exposed to:
- Pain
- Anxiety
- “Reluctance” to undergo mechanical ventilation

Because continuous sedation has been associated with prolonged mechanical ventilation and ICU stay, there is a shift towards:
- light sedation in stead of deep sedation
- analgesia based sedation

To meet the abovementioned goals, we need to change both the protocols and the drugs that are used.
ANALGESIA

- Titrate to the needs of the individual patient
- Administered enteral, transcutaneous or parenteral
- Parenteral route is the preferred due to:
  - delayed gastric emptying
  - ileus
  - general oedema
  - uncertain bioavailability of oral preparations (liver)
  - use of vasopressors
- Parenteral can be given as:
  - bolus
  - continuous infusion
  - PCA technique
- Combined technique with epidural infusion (e.g. fractured ribs, thoraco-abdominal surgery)
Epidural Analgesia

- Meta-analysis 5000 patients
  - Reduced time to extubation
  - Shorter ICU stay
  - Reduced incidence of renal failure
  - Reduced morphine use over 1st 24h period post-op
  - Improved forced vital capacity

- Contra-indicated in patients with sepsis?
- Effect and level depends on volume and rate of injection
Table 16–1. Contraindications to neuraxial blockade.

<table>
<thead>
<tr>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection at the site of injection</td>
</tr>
<tr>
<td>Patient refusal</td>
</tr>
<tr>
<td>Coagulopathy or other bleeding diathesis</td>
</tr>
<tr>
<td>Severe hypovolemia</td>
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<tr>
<td>Increased intracranial pressure</td>
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<tr>
<td>Severe aortic stenosis</td>
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<tr>
<td>Severe mitral stenosis</td>
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<table>
<thead>
<tr>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Uncooperative patient¹</td>
</tr>
<tr>
<td>Preexisting neurological deficits</td>
</tr>
<tr>
<td>Demyelinating lesions</td>
</tr>
<tr>
<td>Stenotic valvular heart lesions</td>
</tr>
<tr>
<td>Severe spinal deformity</td>
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<table>
<thead>
<tr>
<th>Controversial</th>
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<tbody>
<tr>
<td>Prior back surgery at the site of injection</td>
</tr>
<tr>
<td>Inability to communicate with patient¹</td>
</tr>
<tr>
<td>Complicated surgery¹</td>
</tr>
<tr>
<td>Prolonged operation</td>
</tr>
<tr>
<td>Major blood loss</td>
</tr>
<tr>
<td>Maneuvers that compromise respiration</td>
</tr>
</tbody>
</table>

¹ may be performed in conjunction with general anesthesia.
Opioids

- Remains mainstay of analgesic therapy in ICU
- Acts selectively on neurons that control nociception
- Receptors: Brain
  - Spinal cord
  - Peripheral tissues
- Dose dependant: depression of respiratory drive.
- Increased effect if combined with benzodiazepines.
- Minimal hemodynamic effect in normovolemic patients
- Prolonged/continuous infusion: dependence and withdrawal effect.
Morphine

- Most hydrophilic of all the opioids
- Dose required to produce analgesia varies acc. to factors such as:
  - Tolerance
  - Metabolic and excretory ability

- Hepatic metabolism:
  - 80% morphine-6-glucuronide (no analgesic action or neurotoxicity)
  - 20% morphine-3-glucuronide (potent analgesic = 20-40 that of morphine)

- Both metabolites are excreted via kidneys – be careful when renal dysfunction is present.
  
  Renal dysfunction – Fentanyl is the preferred drug for analgesia

- Morphine induced histamine release = rare.
Fentanyl/Sufentanil/Remifentanil (opioids)

- **Fentanyl + Sufentanil**
  - Fat soluble
  - Rapid onset of action
  - Increased volume of distribution
  - Accumulation and delayed recovery after prolonged administration
  - Hepatic biotransformation and renal excretion

- **Remifentanil**
  - Short acting: $t_{1/2} = 4\text{min}$ regardless of duration of infusion.
  - Elimination by esterases that are widespread in plasma, RBC, interstitial tissue
    → Therefore clearance is uniform and highly predictable

- **Possible concerns:**
  - Study done by Mullejans and coworkers\(^8\)
    # Respiratory depression was seen with Fentanyl, but not with Remifentanil
    # Remifentanil – Thoracic and muscle rigidity and shivering when bolusses or high infusion rates where used. Treatment = muscle relaxant
Dehaba and coworkers\(^2\) found that intubation time was significantly shorter when **Remifentanil-based** regimen was used versus when a **Morphine-based** regimen was used in ICU.

Breen and colleagues\(^3\) compared **Remifentanil and Midazolam** as sedative drugs in ICU. Their conclusion was that Remifentanil-based sedation was associated with a shorter duration of mechanical ventilation by more than 2 days.

Remifentanil exert **no prolonged effects** when administered to **renal failure** patients in ICU.

Based on studies: Remifentanil is effective for providing **analgesia and sedation** in critically ill patients, even if they have multi-organ failure.

Safe to use in neurotrauma and brain tumor patients

**Remifentanil in clinical practice:**
- Infusion = 5mg in 50ml 0,9% saline → 100ug/ml
- Infusion rate = 0.1 - 0.15ug/kg/min
- 6ml/h of abovementioned solution for 70kg person = 0.15ug/kg/min
- If sedation effect is suboptimal (Ramsay score) at 2ug/kg/min infusion rate – start Propofol at 2mg/kg/h → 0.1mg/kg/h
SEDATION

- Hypnotic drugs interact with different components of the GABA receptor complex (brain and retina).
  (Fig.1)
- Inhibitory GABA (gamma-amino-butyric acid) neurotransmitter system counterbalances the excitatory adrenergic neurotransmitter system.
Benzodiazepines

- Has a “ceiling effect” on CNS depression (specific binding site – limited modulation)
- 20% receptor occupancy = anxiolysis
- 30 -50% occupancy = sedation
- 60% receptor occupancy = hypnosis
- Dose dependent respiratory depression (worse in pt with chronic resp disease)
- Benzo + opioid: synergistic effect on resp. depression
- Midazolam: -short acting
  -water-soluble
  -oxidation liver (via cytochrome P_{450} enzyme) → water soluble metabolites → urine
  -Primary metabolite has mild CNS depression activity → accumulation in ARF
  -Drugs that use the P_{450} enzyme: Erythromycin, Itraconazole, Ca^{++} channel blocker.
Benzodiazepines

- Lorazepam: 
  - long acting
  - Metabolized by hepatic glucuronidation → cleared by kidneys
  - Continuous infusion or high dose → accumulation of solute propylene glycol (hypotension, bradicardia, agitation, metabolic acidosis and syndrome that mimics severe sepsis).
  - Other side-effects: delirium

- Hepatic dysfunction has a greater impact on oxidation (midazolam) than on glucuronidation (lorazepam).
- Barr and colleagues⁴ compared midazolam and lorazepam in ICU
  - Lorazepam: - more often deeply sedated
    - emerged from sedation more slowly → delayed extubation
**Propofol**

- Sedative /hypnotic drug
- Acts on GABA receptor
- Lipophilic properties; oil-in-water emulsion; pain at injection site
- Metabolized in liver (conjugation) → inactive metabolite → eliminated by kidneys
- High propofol infusion rates (> 5mg/kg/h and longer than 48h) → hypertriglyceridemia → Propofol infusion syndrome
  - dysrhythmias
  - heart failure
  - metabolic acidosis
  - rhabdomyolysis
  - hyperkalemia
  - mortality rate 85%
  - Glucocorticoids and catecholamines act as trigger.
Propofol

- Don’t give >4mg/kg/h for >7 days

- Time to emerge from **light** sedation administered for 3 days: 35 min
- Time to emerge from **heavy** sedation propofol infusion for 7-14 days: 3 days

- Canadian study\(^5\): **Propofol** was compared to **Midazolam** as a sedative → Propofol allowed more rapid extubation on similar Ramsay scores. Disadvantage of Propofol → more hypotension than with Midazolam. → higher cost

- Liver and kidney diseases have little impact on pharmacokinetics
- Adverse effect = systemic vasodilatation → hypotension (especially in hypovolemic patients)
Dexmedetomidine

- Centrally acting $\alpha_2$-agonist
- CNS binding site = locus ceruleus
- Sedative and analgesic properties
- $T_{1/2} = 2\text{hours.}$ Biotransformation in liver, excreted in urine. Reduce dose in patients with liver failure.
- No significant effect on respiratory drive, even if combined with opioids
- Cardiovascular system: biphasic effect.
  - 1\textsuperscript{st} vasoconstriction which results in bradicardia and hypertension
  - 2\textsuperscript{nd} hypotension due to vasodilatation due to central sympatholysis
Dexmedetomidine

**Advantages:**
- Reduced noxious sympatho-adrenal responses during intubation.
- Increased hemodynamic stability.
- Reduced need for “rescue” Midazolam sedation/no add-on Morphine
- Not necessary to reduce infusion rate during extubation
- No respiratory depression

**Disadvantages:**
- Safety not yet proven for use in patients with intracranial pathologies
- Lack of amnestic properties
- Can give nausea, fever, anemia, hypo/hypertension, tachi/bradicardia

Labelled for <24 hours analgesia sparing sedation. No studies available for long-term mechanically ventilated patients in ICU.

Iirola and coworkers⁹: Marked inhibition of gastric emptying and prolonged gastrointestinal transit
Volatile sedation

- AnaConDa filter connected between patient and ventilator maintains 90% of volatile anaesthetic inside the patient.

- Isoflurane inhalation sedation in ICU was shown to be safe and effective\(^6\)

- Significant shorter awakening time (<25 min) when compared to midazolam (57 – 837 min) in critically ill patients

- Promising alternative to IV sedatives in ICU

- Not yet licensed to be used as a sedative in ICU
Types of Sedation

- **Analgesia based sedation**: Remifentanil plus Propofol
- **Hypnotic based sedation**: Midazolam plus Propofol

Park and coworkers\(^6\) compared above two methods of sedation:
- 30% of remifentanil pt. did not require additional sedation
- Remaining 60% on remifentanil received very little Propofol as added sedation if compared to add-on Propofol doses for Midazolam
- Level of sedation achieved with Remifentanil combination was much more satisfactory

Same study was done by Breen and colleagues\(^3\) for patients up to 10 days on mechanical ventilation:
- Time from weaning to extubation was much shorter for the analgesia based sedation → 0.9 hours versus 27.5 hours
- Remifentanil was used for 10 days and no signs of development of drug tolerance was seen in any of the patients on Remifentanil
**ASSESSMENT OF SEDATION AND ANALGESIA**

- Patient’s needs differ.

- Need **subjective and objective** evaluation of level of pain control and sedation in each patient.

- Pain:
  
  Because patient is intubated and/or sedated – **Behavioral pain scale**

- Sedation:

  Ramsay sedation scale/Richmond agitation sedation scale(RASS)
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Facial expression</td>
<td>Relaxed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially tightened (for example, brow lowering)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully tightened (for example, eyelid closing)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Grimacing</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>Compliance with ventilation</td>
<td>Tolerating movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Coughing but tolerating ventilation for 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>

Scores from each of the three domains are summed, with a total score of 3 to 12 [15].

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Anxious and agitated or restless or both</td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, oriented, and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Responds to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Brisk response to a light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Sluggish response to a light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td>No response to a light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>Score</td>
<td>Term</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
</tr>
<tr>
<td>+4</td>
<td>Combative</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
</tr>
</tbody>
</table>

Performed using a series of steps: observation of behaviors (score +4 to 0), followed (if necessary) by assessment of response to voice (score -1 to -3), followed (if necessary) by assessment of response to physical stimulation such as shaking shoulder and then rubbing sternum if no response to shaking shoulder (score -4 to -5) [39].
Other methods of pain control

- Neuroaxial Anaesthesia:  
  - Epidural block  
  - Spinal block  
  - Caudal block

- Peripheral nerve blocks:  
  - Brachial plexus block (supraclavicular/intraclavicular)  
  - Musculocutaneous/radial nerve/ulnar nerve block  
  - Digital nerve block  
  - Femoral nerve/Sciatic nerve block  
  - Intercostal nerve block/Paravertebral nerve block

- Medication:  
  - Paracetamol (po/IV)  
  - NSAIDS (po/pr/IMI. IV = Rayson,Xefo)
B. Technique

(Figure 17–33) With the patient in the lateral decubitus or supine position, the level of each rib is palpated across the midline ventrally.
Anterior superior iliac spine
Lateral femoral cutaneous nerve
Femoral vein
Femoral artery
Femoral nerve
Genitofemoral nerve
Inguinal ligament
Pubic symphysis

The femoral nerve is encased in a sheath of fascia over the femur below the inguinal ligament. It supplies motor branches to the thigh muscles, including the quadriceps femoris and the adductor muscles. Sensory branches to the skin of the lateral thigh, anterior thigh, and posterior thigh are also supplied by the femoral nerve. It is frequently blocked for procedures such as skin grafting, knee arthroscopy, and patellar surgery, or as an adjunct to procedures distal to the knee that require anesthesia to the medial aspect of the leg.
This con-
superficial
marked. A 4-in, 21-gauge insulated stimulating needle
is inserted at the mark and advanced surgically.
The relationship between the axillary artery and nerves that are to be blocked. With the described position, as the axillary artery is median nerve lies superior to the pulse.

Anesthetic, many will pursue multiple injections (ie, two or three nerves) and delivery of local anesthetic to increase the likely success block.

Figure 17-9. Musculocutaneous block, showing injection into the coracobrachialis.
REFERENCES


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