Pain, Agitation, Delirium and Sleep in the ICU

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Disclosure

• I have no actual or potential conflict of interest in relation to this program
• I did not review literature regarding this topic in the pediatric patient population

Objectives

Pharmacists

■ Define pain, agitation, delirium and sleep (PADS) in the intensive care unit (ICU)
■ Identify best practices for management of PADS
■ Review recommendations by the 2018 SCCM pain, agitation, delirium, immobility and sleep guidelines

Technicians

■ Recognize the different monitoring options for PADS in the ICU
■ Review pharmacological and non-pharmacological treatment options for PADS

Delirium
Withdrawal from chronic psychoactive medication
Sleep deprivation
Substance abuse or withdrawal
Noise
Sedatives

Pain
Anxiety
Frustration
Lack of homeostasis
Ventilator dyssynchrony
Inability to communicate
Physical restraint

Agitation

Pain, Agitation, Sedation, Delirium, Sleep

PAIN
Pain - Monitoring

- Pain patterns are highly individualized
- Self-reported pain is the gold standard
- Scales demonstrate the greatest validity and reliability

Devlin JW, Yoanna S: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018 Sep;46(9):e825-e873

Numerical Rating Scale

- Uses 0 to 10 scale to rate severity
- Has low variability between assessors
- Can be quickly used to assess pain
- Cannot be used for non-communicative patients

Opioids

- Analgesic activity through mu-opioid receptor activation
- Mainstay for pain management in the ICU
- Pharmacokinetics, metabolism and side effects vary considerably between agents
- Fentanyl, morphine and hydromorphone are the most commonly used agents
- Can cause respiratory depression and hypotension

Morphine
- Prototype opioid agent
- Onset: IV 5 to 10 min
- Half-life: 3 to 5 hours
- Active metabolites
- Available PO or IV

Fentanyl
- Highly lipophilic
- Onset: Almost immediate
- Half-Life: 2 to 3 hours
- No active metabolites
- Only IV formulation

Hydromorphone
- Semi-synthetic morphine derivative
- Onset: IV 5 min
- Half-Life: 2 to 3 hours
- Active neuroexcitatory metabolite
- Available PO or IV

Acetaminophen
NSAID
Ketamine
Neuropathic pain medication

Multimodal Analgesia


Critical Care Pain Observational Tool

- Validated in intubated and non-intubated patients
- Can be used for non-communicative and communicative patients

Acetaminophen

- Most common adjunct to opioid analgesic
- Decreases opioid requirements
- IV formulation is associated with hypotension
- Not recommended in patients with hepatic insufficiency

Nonsteroidal antiinflammatory drugs

- Cyclooxygenase inhibitor who potent anti-inflammatory properties
- Adverse effects acute kidney injury and GI bleeding
- Side-effects limit use in critically ill patients

Ketamine

- Reduces glutamate release by blocking NMDA receptors
  - Also has activity in opioid and catecholamine receptors
- Has analgesic and sedative properties
- Non-ICU literature shows reduced opioid requirements, though no reduction in pain intensity
- ICU literature primarily in post-surgical and trauma population

Small-dose ketamine in the SICU

- Inclusion criteria
  - Adult patients in the SICU post major-abdominal surgery
- Intervention
  - Randomized to receive morphine PCA with either placebo or ketamine
  - Ketamine Dose:
    - Initial bolus of 0.5 mg/kg
    - 0.2 ug/kg/min during the first 24 hours
    - 0.1 ug/kg/min for the last 24 hours

Small-dose ketamine in the SICU

- Ketamine vs Placebo Group: PCA Morphine Usage
- Ketamine vs Placebo Group: VAS scores
Small-dose ketamine in the SICU

- Similar to non-ICU observation studies
- Reduction of opioid usage but no effect on pain severity
- Safety outcomes were not reported
- Data limited to abdominal surgery patients only

Ketamine

- Potent dissociative sedative with marked analgesia
- Diverse dosing recommendation depending on indication and route of administration
- Dosing for analgesia:
  - Bolus: 0.1 to 0.5 mg/kg
  - Infusion: 0.05 to 0.4 mg/kg/hour

IV Lidocaine

- Sparse literature exists describing agent as an adjunct to opioids
- One single-center, placebo controlled, RCT in cardiac surgery population
  - Intervention: 1.5 mg/kg IV bolus over 10 mins followed by 30 ug/kg/min for 48 hours
  - No difference in reported pain score or opioid usage

Pain - Summary

- Depending on the patient, different monitoring scales should be used
- Agent should be chosen depending on assessment of pain and pharmacokinetic properties
- Safety concerns related to specific non-opioid analgesics should be taken into account

Agitation/Sedation

- Sedatives are frequently administered to relieve anxiety and reduce stress
- Multiple factors contribute to increased agitation
  - Intubation
  - IV access lines
  - Increased environmental stimulus
- Goal: prevent agitation related harm

AGITATION/SEDATION
Agitation/Sedation – Monitoring

Light vs Deep Sedation

- Light sedation has not been well defined in literature
- RASS goal of -1 to +1 has been commonly used in recent studies
- Deep sedation has been linked
  - Increased delirium
  - Reduced chance of early extubation
  - Increased sedation also has been linked with symptoms of PTSD after their ICU stay

Maintaining Light Sedation

- Daily sedative interruption
  - Sedative medication is discontinued to assess patient
  - Agents are restarted at starting doses
- Nurse protocolized targeted sedation
  - Allows bedside to assess sedation
  - Nurse titrates sedatives to established goal

Choice of Sedative

- Benzodiazepines
  - GABA agonist
  - Affinity and half-life depends on agent
  - Potent anxiolytic, with minimal analgesia
- Propofol
  - GABA agonist
  - Quick onset and short half-life
  - Can cause hypotension
- Dexmedetomidine
  - Alpha-2 agonist
  - Moderate anxiolytic and analgesia
  - Associated with fever and bradycardia

Benzodiazepine and Delirium

- Benzodiazepines is considered to be an independent risk factor for delirium
- Among 1112 patients, benzodiazepines was associated with:
  - Increased risk of delirium (OR 1.04, 95% CI 1.02-1.05)
  - Particularly with continuously infusion (OR 1.04 vs 0.97)

Propofol Vs Dexmedetomidine

- Inclusion Criteria
  - Adult mechanically ventilated patients requiring light to moderate sedation
- Exclusion Criteria
  - MAP < 50 mmHg, HR < 50 bpm, use of alpha-2 agents prior to study
- Outcomes Studied
  - Proportion of time in target sedation; duration of mechanical ventilation
  - Rates of delirium, agitation and anxiety at 48 hours


Propofol Vs Dexmedetomidine

- Time at target sedation:
  - Propofol, 64.7%, vs dexmedetomidine, 64.6% (1.07, 95% CI, 0.97-1.18; P = .15)
- Duration of mechanical ventilation:
  - 118 hours for propofol vs 97 hours for dexmedetomidine (P = 0.24)
- Rates of delirium, agitation and anxiety:
  - 18.3% for dexmedetomidine vs 28.7% for propofol (P = 0.008)

Delirium

An acute alteration in consciousness with a change in cognition or disturbance that fluctuates over time. 
Associated with worse outcomes
- Cognitive impairment at 3 and 12 months post-discharge

Regular assessment with a validated tool such as the CAM-ICU or the ICDSC is recommended for critically ill adults.

Agitation/Sedation – Summary

- Multiple factors affect agitation in the ICU
- Light sedation should be targeted if possible
- Continuous benzodiazepine infusion have been associated with increased delirium
- Propofol or dexmedetomidine is recommended over benzodiazepine for routine sedation

Delirium – Risk Factors

- Modifiable
  - Benzodiazepine use
  - Anticholinergic use
  - Opioids
  - Blood transfusion
  - Poor sleep
- Non-modifiable
  - Age
  - Dementia
  - Prior coma
  - Pre-ICU emergency surgery or trauma
  - Higher Acute Physiology and Chronic Health Evaluation (APACHE) score and American Society of Anesthesiologists (ASA) classification system
**REDUCE Trial – Pharmacological Prevention**

- Randomized, double-blind, placebo-controlled
- Adult ICU patients who were delirium free, with stay of at least 2 days
- Received either 1-2 mg of haloperidol every 8 hours or placebo
- Outcomes:
  - Delirium incidence
  - Delirium and coma-free days

**Patient Population:**
- Haloperidol group: 1087
- Placebo group: 709
- Medical: 46%
- Surgical: 48.9%
- No difference in outcomes

**Delirium - Non-pharmacological treatment**

Multi-component intervention focused on risk reduction
- Improve sleep
- Improve wakefulness
- Reduce visual/hearing impairment
- Reduce immobility

**Pharmacological Treatment**

- Haloperidol
- Atypical antipsychotics
- Limitation of sedation
  - Awake and interactive sedation goals
  - Daily awakening and breathing trials
  - Judicious use of sedatives/analgesics

**Quetiapine for ICU Delirium**

- Inclusion Criteria
  - Adult ICU patients with delirium with no neurological condition (n=36)
- Intervention:
  - Quetiapine 50 mg BID (can be increased to 200 mg BID)
- Outcomes:
  - Time to delirium resolution: (1 vs 4.5 days, p=0.001)
  - Duration of delirium: (56 vs 120 hours, p=0.02)

**MIND-USA Trial**

- Inclusion Criteria:
  - Adult ICU patients with delirium (n=566)
  - Heavy predominance of hypoactive delirium
- Intervention:
  - Received either haloperidol, ziprasidone or placebo for 14 days
- Outcome:
  - Days without delirium: No difference compared to placebo
Atypical Antipsychotics

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Treatment - Guidelines

Atypical antipsychotics, statins or haloperidol should not be routinely used to treat delirium
- Conditional recommendation with a low quality of evidence
- Haloperidol or an atypical antipsychotic may benefit patients who are experience significant distress
- Though many patients often remain on these medications unnecessarily after discharge

Delirium - Summary

- There are both modifiable and non-modifiable risk factors
- Management includes reducing exacerbating medication
- Antipsychotics should not be used routinely
- Reserved for patients who are acutely agitation refractory to non-pharmacological therapy

Sleep Disruption - Treatment

Non-pharmacological
- Noise and light reduction
- Sleep-promoting protocol such as ear plugs and eye shades

Pharmacological
- No recommendation for melatonin or dexmedetomidine to improve sleep
- Recommend against using propofol to improve sleep
Nocturnal melatonin in the ICU

- Inclusion Criteria:
  - Critically ill patients with a tracheostomy who are not receiving sedation
- Intervention:
  - Randomized to receive melatonin (3mg) or placebo at night (n=32)

Outcomes:
- Similar median observed nocturnal sleep (240 vs 243 mins)
- Same procedures done through the night
- Incidence of agitation was higher in the melatonin group (31% to 7%)

Summary

PADS and inadequate treatment is associated with worsening outcomes.

Pain should be regularly assessed managed through opioids with adjuncts. Agitation should be managed with light sedation.

Delirium should be regularly assessed but routine pharmacological therapy is not recommended.

Sleep is best achieved by non-pharmacological therapy such as noise and light reduction.