MELBOURNE
Host of the 2019 Congress of the World Federation of the Societies of Intensive and Critical Care Medicine
PAEDIATRIC SEDATION

Protocolised/targeted/optimised/individualised?
Dr. Simon Erickson
Princess Margaret Hospital for Children
Synopsis

- Sedation issues in critically ill children
- Assessment of sedation
- Targeting sedation
- Drugs
  - Upsides
  - Downsides
- Known unknowns
- Baby SPICE
Case

- 13 year old boy
  - Relapsed ALL
  - Respiratory failure post-BMT
    - SIMV 6 mls/kg
    - PEEP 12
    - FiO₂ 0.75
  - Cardiovascular failure
    - Dobutamine 5 mcg/kg/min
    - Noradrenaline 0.2 mcg/kg/min
  - ARF-CVVHD
Sedation/analgesia/muscle relaxation
- Fentanyl 2 mcg/kg/hr
- Dexmedetomidine 1.0 mcg/kg/hr
- Midazolam 150 mcg/kg/hr
- Propofol 1 mg/kg/hr
- Pancuronium .15 mg/kg 1-3 hourly/prn

Frequent episodes of desaturation associated with movement
Episodes of hypotension with sedation boluses
Parents extremely upset that he is not adequately sedated and distressed

Ideas?

Issues
- Is sedation optimum?
- Are there better drugs?
- Adverse effects
- Metabolism
- Potential for idiosyncratic effects
- Role of delirium
Individualized sedation in children

- Protocolised sedation (Curley et al JAMA 2015)
  - Targeted sedation
  - Arousal assessments
  - Extubation readiness
  - Sedation titration

- Goal-directed/Targeted sedation
  - 70% of CCU physicians used assessment and targets (Kudchadkar et al CCM 2014)
  - Kleiber et al, PCCM 2016. Targeted sedation post-CPB provided stable conditions (CVS), less oversedation, less sedative dose

- Sedation guidelines, protocols reduced PICU LOS, sedation duration and withdrawal (Poh et al PCCM 2014)

- Safe, light sedation associated with reduced duration of ventilation (Baby SPICE)

- eCASH concept
  - Early Comfort using Analgesia, minimal Sedatives and maximal Humane care
  - Vincent JL, ICM 2016
Fig. 1 The eCASH concept: early implementation to manage and prevent pain, anxiety, agitation, delirium and immobility and facilitate patient-centred care. (#Moderate or deep sedation remains relevant for some situations, including the management of severe respiratory failure with ventilator patient dyssynchrony, prevention of awareness in patients receiving neuromuscular blocking agents, status epilepticus, surgical conditions necessitating strict immobilization and some cases of severe brain injury with intracranial hypertension)
Sedation in critically ill children

- Sedation is an important issue in children
  - Provides safety for intubated children
  - Aids ventilator synchrony
  - Provides sedation and amnesia for stressful/painful circumstances
  - Avoids consequences of wakefulness/agitation such as raised ICP, increased metabolic demands, pulmonary hypertension
  - Adequate management of pain and anxiety may reduce the incidence of post-traumatic stress disorder

- But
  - Little evidence to support guidelines/protocols (Hartman et al CCM 2009)
  - Most drugs not FDA/TGA approved
  - Organ failure in critically ill children affects clearance
  - Adverse effects prominent
    - Impaired ventilation
    - Negative CVS effects
  - Tolerance/withdrawal common
  - Long-term cognitive effects of sedatives unknown
  - Delirium
    - an unknown quantity but may be associated with psychoactive agents
    - may be associated with long-term neuro-cognitive defects
Assessment of sedation

- Scoring systems
  - State Behavioural Scale
  - Comfort B

- Pain vs. agitation
  - Thirst
  - Hunger
  - Fear
  - Delirium
  - Urinary retention

- Getting the right balance difficult (Vet et al ICM 2013)
  - Oversedation 32-68%
  - Undersedation 10%
Optimal sedation in pediatric intensive care patients: a systematic review.
Vet NJ, Ista E, de Wildt SN et al. Intens Care Med 2013
Prospective evaluation of sedation-related adverse events in pediatric patients ventilated for acute respiratory failure. Grant MJ et al. CCM 2013

<table>
<thead>
<tr>
<th>Event</th>
<th>n Events</th>
<th>n Subjects</th>
<th>Event Ratea (95% Confidence Interval)</th>
<th>Intraclass Correlation Coefficientb (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate pain management</td>
<td>173</td>
<td>83</td>
<td>27.4% (20.9%–35.1%)</td>
<td>0.080 (0.019–0.205)</td>
</tr>
<tr>
<td>Inadequate sedation management</td>
<td>242</td>
<td>93</td>
<td>30.7% (23.0%–39.6%)</td>
<td>0.130 (0.052–0.279)</td>
</tr>
<tr>
<td>Clinically significant iatrogenic withdrawal</td>
<td>54</td>
<td>24</td>
<td>8.7% (5.2%–14.3%)</td>
<td>0.088 (0.024–0.218)</td>
</tr>
<tr>
<td>Unplanned endotracheal tube extubation (per 100 ventilator days)</td>
<td>20</td>
<td>19</td>
<td>0.82 (0.55–1.23)</td>
<td>0.000 (0.000–0.038)</td>
</tr>
<tr>
<td>Postextubation stridor with chest-wall retractions at rest</td>
<td>34</td>
<td>32</td>
<td>10.3% (6.3%–16.4%)</td>
<td>0.078 (0.018–0.203)</td>
</tr>
<tr>
<td>Extubation failure/reintubation within 24 hrs</td>
<td>35</td>
<td>28</td>
<td>8.9% (5.9%–13.3%)</td>
<td>0.017 (0.000–0.102)</td>
</tr>
<tr>
<td>Unplanned removal of any invasive tube (per 100 device days)</td>
<td>24</td>
<td>20</td>
<td>0.19 (0.11–0.32)</td>
<td>0.005 (0.000–0.081)</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia (per 1000 ventilator days)</td>
<td>6</td>
<td>6</td>
<td>2.41 (1.00–5.80)</td>
<td>0.000 (0.000–0.073)</td>
</tr>
<tr>
<td>Catheter-associated bloodstream infection (per 1000 central catheter days)</td>
<td>2</td>
<td>2</td>
<td>0.77 (0.20–2.91)</td>
<td>0.064 (0.008–0.182)</td>
</tr>
<tr>
<td>Stage 2+ pressure ulcers</td>
<td>4</td>
<td>4</td>
<td>1.4% (0.5%–4.4%)</td>
<td>0.048 (0.000–0.155)</td>
</tr>
</tbody>
</table>
State Behavioral Scale: A sedation assessment instrument for infants and young children supported on mechanical ventilation

Martha A. Q. Curley, RN, PhD, FAAN; Sion Kim Harris, PhD; Karen A. Fraser, RN; Rita A. Johnson, RN, BSN; John H. Arnold, MD

Peditr Crit Care Med 2006 Vol. 7, No. 2

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>Unresponsive</td>
<td>No spontaneous respiratory effort. Minimal or no response to noxious stimulus. Does not communicate or follow commands.</td>
</tr>
<tr>
<td>-2</td>
<td>Responsive only to noxious stimuli</td>
<td>Spontaneous but ineffective respiratory effort. Opens eyes or raises eyebrows or turns head towards stimulus or moves limbs with noxious stimulus. Some spontaneous movement. Does not communicate.</td>
</tr>
<tr>
<td>-1</td>
<td>Responsive to gentle touch or name</td>
<td>Opens eyes or raises eyebrows or turns head towards stimulus or moves limbs with gentle touch or when name is spoken. Follows simple commands. Drifts off after stimulation.</td>
</tr>
<tr>
<td>0</td>
<td>Calm and cooperative</td>
<td>Spontaneous and effective tidal volumes. No external stimulus is required to elicit movement. Calm, awakens easily, and follows commands.</td>
</tr>
<tr>
<td>+1</td>
<td>Restless but cooperative</td>
<td>No external stimulus is required to elicit movement. Increased limb movement. Picking at tubes but consolable.</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Having difficulty synchronising with ventilator. No external stimulus is required to elicit movement. Attempting to sit or moves limbs to get up. Difficult to console despite frequent attempts. Requires physical restraint.</td>
</tr>
</tbody>
</table>
Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT “behavior” scale*

Erwin Ista, RN; Monique van Dijk, PhD; Dick Tibboel, MD, PhD; Matthejs de Hoog, MD, PhD.

Pediatr Crit Care Med 2005 Vol. 6, No. 1

Assess your patient following gentle stimuli.
Score your patient in the following categories a minimum of 4 hourly (more frequently if necessary).
Total score range is 6 – 30.

<table>
<thead>
<tr>
<th>Alertness</th>
<th>Choose one of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If fully ventilated</td>
</tr>
<tr>
<td>1 Deeply asleep</td>
<td>Respiratory response OR 1</td>
</tr>
<tr>
<td>2 Lightly asleep</td>
<td>No cough or spontaneous respiration 2</td>
</tr>
<tr>
<td>3 Drowsy</td>
<td>Spontaneous respiration with minimum assist from ventilator 3</td>
</tr>
<tr>
<td>4 Fully alert</td>
<td>Occasional cough, splinting or resistance to ventilator 4</td>
</tr>
<tr>
<td>5 Hyper-alert</td>
<td>Actively breathes against the ventilator 5</td>
</tr>
<tr>
<td></td>
<td>Fights ventilator, cough, gag or choking</td>
</tr>
<tr>
<td>Calmness/agitation</td>
<td>1 Quiet breathing, no crying 1</td>
</tr>
<tr>
<td></td>
<td>2 Sobbing or gasping 2</td>
</tr>
<tr>
<td></td>
<td>3 Moaning 3</td>
</tr>
<tr>
<td></td>
<td>4 Crying 4</td>
</tr>
<tr>
<td></td>
<td>5 Screaming 5</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>1 Muscles totally relaxed 1</td>
</tr>
<tr>
<td></td>
<td>2 Reduced muscle tone 2</td>
</tr>
<tr>
<td></td>
<td>3 Normal muscle tone 3</td>
</tr>
<tr>
<td></td>
<td>4 Increased muscle tone and flexion of fingers and toes 4</td>
</tr>
<tr>
<td></td>
<td>5 Extreme muscle rigidity and flexion of fingers and toes 5</td>
</tr>
<tr>
<td>Facial Tension</td>
<td>1 Facial muscles contorted and grimacing 1</td>
</tr>
</tbody>
</table>

**Aim of performing the assessment**

To identify patients who are at risk of insufficient analgesia/sedation or at risk of too much analgesia/sedation and to reduce that risk by allowing early intervention or weaning.

The scoring tool is provided as a guide. Clinical assessment of your patient is paramount.
Remember that sedation and pain are very different experiences sedation does not constitute analgesia.

This assessment should be performed on all patients following surgery and any patients receiving opioid or benzodiazepine infusions.
Factors impacting sedation

- Wide-ranging cognitive levels due to age
- Wide-ranging cognitive level due to underlying conditions
  - Some misconceptions
- Assessment difficult
- Variable psychological adjustment to stressful situations
  - Chronic illness
  - Cultural
  - Family
- Several idiosyncratic drug responses
- Issues with organ dysfunction and drug metabolism
- Tolerance/Withdrawal
- Delirium
- Safety concerns
  - Accidental extubation
  - Line removal
Age
Age

- Sedative and analgesic dose requirements dependant on clearance
  - Narcotics
    - Reduced clearance neonates
  - Benzodiazepines
    - Elimination T1/2 4-6 hours in neonates (3x adults)
    - Clearance at adult levels at 9-12 months
  - Alpha 2-agonists
    - Peak clearance 1-5 yrs

- Adverse effect profile may differ with age
  - PRIS
  - Bradycardia with dexmedetomidine
  - Loss of ETT/lines?
Underlying cognitive function

- Trisomy 21
  - Comparison of Sedative and Analgesic Requirements in Children with and without Down Syndrome following Pediatric Cardiac Surgery JJA 2016
  - Anaesthesia and postoperative analgesia in surgical neonates with or without Down's syndrome: is it really different? BJA 2012
  - The COMFORT-behaviour scale is useful to assess pain and distress in 0- to 3-year-old children with Down syndrome. Pain 2011
Diagnostic groups

- **Cardiac surgery**
  - Several case series supporting safe use of alpha-2 agonists
    - Dexmedetomidine: Chrysostomou ICM 2010, Hosokawa PCCM 2010, Bejian Cardiol Young 2009, Czaja PCCM 2009
    - Clonidine: Kleiber PCCM 2016

- **TBI**
  - Sedation depth and ICP
  - Contraindicated drugs?
    - Propofol
    - Ketamine
Chronic/previous illness

- Does neonatal surgery lead to increased pain sensitivity in later childhood? Pain 2005
  - Previous surgery associated with increased requirements and pain scores
- Intellectual disability/CP
  - Drug interactions
  - Difficulties with assessment
  - Exclusion from trials
Midazolam

- GABA agonist
- Most commonly used sedative in PICU
- Sedative and antegrade amnestic properties
- Often has a prolonged duration of action in PICU
  - Prolonged clearance in neonates
  - Accumulation of midazolam and its active metabolite, alpha-hydroxymidazolam in children with MOF
  - Reduced cytochrome P450 in SIRS/critical illness (Vet et al PCCM 2012)
  - Paradoxical effects in 3-4% (Godwalpa et al, Ped Anaesth 2004)
  - No relationship between pharmacokinetic parameters and pharmacodynamic outcome (de Wildt 2005)

- Long term cognitive effects
  - Association between midazolam use and impaired neurological function or neurodegeneration (Young et al, Br J Pharmacol 2005)
  - Delusional memories and post-traumatic stress disorder in children (Colville et al, Am J Respir Crit Care Med 2008)
Narcotics

- Analgesics but sedative effects
- Fentanyl
  - Wide volume of distribution
  - Long context-sensitive half-life
  - Hepatic metabolism
  - Clearance greatest in infants 3-12 months
- Blunting of sympathetic responses
  - useful in PHT/raised ICP
  - May predispose to CV instability
- Cognitive effects
  - associated with poor test outcome on VIQ and verbal subtests (comprehension and vocabulary) and visual attention/executive functioning (van Zellam et al, PCCM 2014)
Dexmedetomidine

- Central α-2 adrenoreceptor agonist
  - Not TGA approved in children

- Pharmacokinetics in children
  - Distribution (α) half-life-7 minutes, elimination (β) half-life 2 hours
  - Age-dependant hepatic metabolism (glucuronidation)
    - 85% by 1 year
    - Increased clearance 3-10 yrs

- Adverse effects in children
  - Bradycardia (15-30%)
    - Infants
    - Not assoc. hypotension or ECG changes
    - B-blockers, digoxin
    - Asystole described
  - Hypotension (dose-dependant)
Propofol infusion syndrome (PRIS)

- First reported 1992 (Parke et al, BMJ)
- Syndrome of metabolic acidosis, rhabdomyolysis, myocardial failure, renal failure, bradyarrhythmias and cardiac arrest
- Mitochondrial respiratory chain dysfunction
- Triggered by
  - Metabolic stress and high energy demand
  - Low carbohydrate availability
  - High fat availability (lipid emulsion)
- High mortality - 50% in children (Fong et al, CCM 2008)
- Associated with
  - Prolonged use >48 hrs
  - High dose > 5 mg/kg/hr
  - Young age
  - TBI
  - Catecholamine/steroid use
- Treatment options
  - Cessation of propofol
  - Dialysis
  - ECMO
- But
  - Several large series describing prolonged, safe use (Agudelo et al Med Intensiva 2012, Svensson et al Nurs Crit Care 2012, )
  - Do these patients have an underlying metabolic disease (Karaman et al, Paed Anaesth 2013)
  - Are there early warning signs which predict PRIS?
    - Lactic acidosis, ECG changes (Brugada-like changes, T-wave changes) (Veldhoen et al, PCCM 2009)
Known unknowns

- Delirium
- Withdrawal
- Long-term outcomes
- Effects on brain development
- Risk of apoptosis
- Tolerance/withdrawal
- Addiction?
Assessment of delirium

- Delirium in adult ICU
  - Incidence >50%
  - Assoc. with increased
    - LOS
    - mortality
    - long-term neuro-cognitive impairment

- Children
  - Incidence unclear (10-15%?)
    - Baby SPICE study: 40-50%
  - Risk of injury/extubation
  - Neuro-metabolic stress
  - Distressing for family
  - Assoc. post-traumatic stress
  - Neuro-cognitive impairment?
Pediatric Confusion Assessment Method: pCAM-ICU

Four cardinal clinical features
- Acute change or fluctuation of mental state
- Inattention
- Altered level of consciousness
- Disorganized thinking

Smith et al (Crit Care Med 2010)
- 68 children (5-17 yrs)
- Incidence of delirium
  - 11.8% (pCAM-ICU)
  - 13.2% (DSM criteria)
- pCAM-ICU
  - Sensitivity 83%
  - Specificity 99%
  - PPV 93%
  - Interrater reliability, k=0.06
Tolerance and withdrawal in children

- Tolerance and withdrawal closely associated
- **Agents**
  - Narcotics/midazolam/chloral hydrate/barbiturates/alpha-2 agonists
- **Tolerance**
  - Up to 60% critically-ill children
  - Pharmacodynamic effect but mechanism unclear
  - Risk associated with duration of receptor occupancy
  - Reduced by titration of effect/rotation of agents?/intermittent dosing
- **Features of withdrawal**
  - CNS overstimulation
  - GI symptoms
  - Autonomic dysfunction
- **Scoring**
  - WAT-1
  - Sophia Benzodiazepine and Opioid Withdrawal Assessment Tool
- **Incidence (17-35%)**
  - 10-20% CNS, GI 15-25%, 13% ANS in high risk group (Ista CCM 2008)
  - Risks
    - duration of dose (>5 days)
    - cumulative dose
    - Rapid weaning
- **Management**
  - Weaning
  - Medications
Drugs and the developing brain

- Animal studies suggest an association between midazolam and ketamine use and apoptosis (Young et al, Br J Pharmacol 2005)

- Associated with delusional memories and post-traumatic stress disorder in children (Colville et al, Am J Respir Crit Care Med 2008)

- General anaesthesia may be associated with behavioural and developmental disorders (Di Maggio et al. J Neurosurg 2009)
  - GAS study: Lancet 2016; no adverse effects at 2 yrs

- Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age? Pain 2013
  - 9 year follow-up showed no overall effects
Observational data
- 6 month prospective data collection, 8 ANZ centres
- Expected duration of ventilation > 24 hours
- Demographic data, sedative dose, sedation level, complications, 90 day outcome

231 children
- 97% ventilated for > 24 hours/80% ventilated for > 48 hours
- Hospital mortality 9.1%

Deep sedation (SBS< -1)
- Common: 75% in first 48 hours
- Correlation with
  - Midazolam dose @ 48h \( r_s = 0.18, p=0.044 \) **
  - Fentanyl dose @ 48h \( r_s = 0.29, p=0.012 \) *
  - PICU Length of Stay \( r_s = 0.16, p=0.08 \) *
  - Length of mech vent \( r_s = 0.2, p=0.002 \) *

Prevalence of Delirium
- Delirium first assessment (d1) – 37 / 84 (44%)
- Any delirium – 123 / 172 (55% of cohort)

Baby SPICE Pilot RCT just completed
Back to case

- Is sedation optimum?
  - Overall SBS or Comfort B

- Are there better drugs?
  - Propofol dose?

- Adverse effects
  - CVS

- Metabolism
  - Impaired metabolism of fentanyl, midaz, dex

- Potential for idiosyncratic effects

- Role of delirium
  - Possible, pCAM-ICU
Conclusion: Can sedation be optimised?

- Most clinicians believe that titration against sedation targets is important.
- Evidence supporting protocolised sedation conflicting.
- Limited evidence sedation requirements differ by patient group:
  - Age
  - Cognitive level
  - Diagnostic groups
  - Previous illness
- Variable efficacy/metabolism is a major concern.
- Tolerance/withdrawal/delirium are common.
- Long term effects unknown:
  - Developing brain
- Goal-directed, targeted sedation is possible, supported and likely to be beneficial.