Sedation Practice in Paediatric Intensive Care Evaluation

BABY SPICE
A Pilot Study Comparing Early Goal Directed Sedation to Standard Care

Debbie Long & Simon Erickson
for the ANZICS PSG
Conflicts of Interest

- Hospira Unrestricted Grant – SE
- Perth Children’s Hospital Foundation Grant-SE
- Pfizer Unrestricted Grant - DL
Background

- Critically ill children who are mechanically ventilated usually receive analgesia and sedation for comfort and safety.
- Opioids and benzodiazepines are the most frequently administered drugs
- Current approaches are often inadequate, sedation related AEs common -> oversedation
  - Deep sedation in up to 75% intubated children (Baby Spice observational data)
- Early goal directed sedation using dexmedetomidine as the primary sedative may provide more targeted sedation with less AE’s
  - Dexmedetomidine is an alpha-2 agonist with sedative, anxiolytic, sympatholytic and analgesic properties
  - Dexmedetomidine, although not TGA approved for paediatric use, is becoming widely used, both as sedative and to treat and prevent withdrawal
  - Efficacy and safety has not been evaluated in a large, rigorous RCT
Context

- 7 PICUs
- 8000 Adm/yr
- 40% Vent
- Study performed at 6/7 PICUs
- DSMB based in SA
Objective and Outcomes

- To assess the feasibility of conducting a randomised trial comparing EGDS (with dexmedetomidine as primary sedative) vs. standard sedation in critically ill children

**Primary Outcomes - Feasibility**
- Screening and recruitment
- Timely randomisation and drug administration
- Protocol adherence

**Secondary Outcomes - Clinical**
- Level of sedation
- Duration of ventilation
- PICU and Hospital Length of stay
- Adverse effects
Methods

• Design – open label, pilot RCT conducted in 6 PICUs ANZ

• Participants
  – **Mechanically ventilated** via ETT and has been intubated for **less than 12 hours**, and the treating clinician believes that:
    o 1. The patient requires **immediate AND ongoing sedative medication**
    o 2. The patient is expected to **remain intubated for at least 24 hours after enrolment**.

• Procedures
  – Block randomised, concealed envelopes
    o EGDS or Standard Therapy
  – RedCap
  – SBS q4h, ≥ -1 default (light sedation), up to 14 days

• Statistical Analysis – descriptive, univariate

• ≥16 years or older
• Acute or chronic primary brain lesion/lesion that may result in global impairment of conscious level or cognition, permanent or prolonged weakness of upper and lower limbs.
• Burn injuries
• Receiving or expected to need frequent or continuous NMBA
• Allergy to dexmedetomidine
• Cardiovascular instability
  – MAP or HR < 2 SD below normal for age despite resuscitation or vasopressors
  – AV block (2\textsuperscript{nd} or 3\textsuperscript{rd} degree) in the absence of a functioning pacemaker
• End stage liver failure or acute fulminant hepatic failure
• Patient is on ECLS
• Death is deemed imminent and inevitable
• There is an underlying disease that makes survival to 90 days unlikely
• Pregnant or lactating women
• Intravenous clonidine within the past 80 hours
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

<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>
Commence **DEXMEDETOMIDINE** infusion at 1.0 mcg/kg/hr without a loading dose. This will take about 45 minutes to produce full sedative effect.

Supplemental propofol can be used up to a maximum of 24 hours and a maximum dose of 4 mg/kg/hr.

45-60 min
Check SBS

- SBS -3 TO -2
  - Reduce Dexmedetomidine
  - Nil Change required

- SBS -1 TO +1
  - Titrate Dexmedetomidine infusion dependant on age to a maximum
    - 0-1yr 1.0 mcg/kg/hr
    - 1-5 yrs 1.4 mcg/kg/hr
    - 5-10yrs 1.3 mcg/kg/hr
    - > 10 yrs 1.0 mcg/kg/hr

- SBS +2 or +3
  - Continue Dexmedetomidine infusion and Boluses or infusion of both opioids, as chosen by the treating clinician, at a dose specified by the treating clinician to provide analgesia.

Commence MIDAZOLAM infusion (50-250 mcg/kg/hr) or other benzodiazepines (primary sedative agent)

Supplemental propofol can be used up to a maximum of 24 hours and a maximum dose of 4 mg/kg/hr.

45-60 min
Check SBS

- SBS -3 TO -2
  - Reduce Midazolam or Benzodiazepine
  - Nil Change required
  - Increase infusion rate or bolus Midazolam (50-250 mcg/kg/hr) or Benzodiazepine.
  - Optimize opioid by increasing infusion or bolus or both if required.

- SBS -1 TO +1
  - Nil Change required

- SBS +2 or +3
  - Increase primary sedative infusion rate or bolus.
  - Optimize opioid by increasing infusion or bolus or both if required.

Alternative sedative agents may be considered if a combination of primary sedative and opioid infusions do not provide sufficient sedation. E.g. include ketamine, chloral hydrate, sedating anti-histamines, phenobarbital as per physician preference.

Supplemental propofol can be used up to a maximum of 24 hours & maximum dose of 4 mg/kg/hr.

Check SBS and pain score 4/24

- SBS -3 TO -2
  - Reduce Dexmedetomidine and/or opioids
  - Nil Change required

- SBS -1 TO +1
  - Titrate Dexmedetomidine infusion dependant on age as above

- SBS +2 or +3
  - Nil Change required

Benzodiazepines (such as midazolam, diazepam and clonazepam) may be administered if sufficient level of sedation is not attained with the above measures. Please discuss with consultant.

- SBS +2 or +3 and sedation an ongoing issue

Alternative sedative agents may be considered if a combination of primary sedative and opioid infusions do not provide sufficient sedation. E.g. include ketamine, chloral hydrate, sedating anti-histamines, phenobarbital, clonidine as per physician preference.

- SBS +2 or +3 and sedation an ongoing issue
## Results - Demographics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Level</th>
<th>EGDS</th>
<th>Standard Therapy (Control)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>29</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Age in months, median (IQR)</td>
<td></td>
<td>16 (4, 30)</td>
<td>3 (1, 13)</td>
<td>0.016</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>16 (55%)</td>
<td>16 (57%)</td>
<td>0.880</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td></td>
<td>9.15 (5, 14)</td>
<td>5.65 (3.7, 9.4)</td>
<td>0.080</td>
</tr>
<tr>
<td>Cardiac Surgery</td>
<td>None</td>
<td>22 (76%)</td>
<td>23 (82%)</td>
<td>0.370</td>
</tr>
<tr>
<td></td>
<td>Immediately prior or during admission</td>
<td>7 (24%)</td>
<td>5 (18%)</td>
<td></td>
</tr>
<tr>
<td>ICU Admission Source</td>
<td>OT/Recovery</td>
<td>11 (38%)</td>
<td>8 (29%)</td>
<td>0.480</td>
</tr>
<tr>
<td></td>
<td>Emergency Department</td>
<td>2 (7%)</td>
<td>6 (21%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ward</td>
<td>4 (14%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other ICU/NICU same hosp</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Direct ICU Adm</td>
<td>11 (38%)</td>
<td>10 (36%)</td>
<td></td>
</tr>
<tr>
<td>Elective admission</td>
<td></td>
<td>8 (28%)</td>
<td>5 (18%)</td>
<td>0.380</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td>9 (31%)</td>
<td>8 (29%)</td>
<td>0.840</td>
</tr>
<tr>
<td>Diagnostic Group</td>
<td>Cardiovascular (incl post-op)</td>
<td>7 (24%)</td>
<td>6 (21%)</td>
<td>0.650</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal/Renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td></td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Post-Operative</td>
<td></td>
<td>6 (21%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td>11 (38%)</td>
<td>13 (46%)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>4 (14%)</td>
<td>5 (18%)</td>
<td></td>
</tr>
<tr>
<td>PIM3 risk of death, mean (SD)</td>
<td></td>
<td>0.032 (0.034)</td>
<td>0.035 (0.065)</td>
<td>0.830</td>
</tr>
<tr>
<td>PIM2 risk of death, mean (SD)</td>
<td></td>
<td>0.039 (0.039)</td>
<td>0.035 (0.059)</td>
<td>0.780</td>
</tr>
</tbody>
</table>
Results – Feasibility Outcomes

- Time to Randomisation – Median 6.25hrs (2.35,9)
- Ventilated > 24 hrs – 98%
- Deferred consent
  - 3 sites
  - 18 deferred, 1 revoked
- Missed – 40%
- Consent – 70%
- Protocol violations – 4
  - 2 Intervention not followed
  - 1 Standard therapy not followed
  - 1 Other
Results – Proportion of patient assessments in light sedation in first 48 hours

The difference was most marked on the day of enrolment with 66 of 103 (64%) versus 48 of 116 (41%) of SBS measurements in the light sedation range (p=0.001)
## Results – Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>EGDS</th>
<th>Standard</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation (hrs), median (IQR)</td>
<td>69.5 (31.25, 111.5)</td>
<td>57.29 (43.18, 83.08)</td>
<td>0.62</td>
</tr>
<tr>
<td>Vasopressor days, n (%)</td>
<td>29 (17.58%)</td>
<td>24 (16.67%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Accidental Line Removal days, n (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total WAT-1, median (IQR)</td>
<td>1 (0,3)</td>
<td>2 (0,3)</td>
<td></td>
</tr>
<tr>
<td>ICU length of stay, median (IQR)</td>
<td>114.75 (74.02, 215.57)</td>
<td>82.17 (68.66, 157.15)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hospital length of stay, median (IQR)</td>
<td>314.67 (214.50, 416.93)</td>
<td>286.63 (148.56, 440.70)</td>
<td>0.57</td>
</tr>
<tr>
<td>Mortality in ICU</td>
<td>0</td>
<td>1 (4%)</td>
<td>0.30</td>
</tr>
</tbody>
</table>
## Results - Efficacy

<table>
<thead>
<tr>
<th>Additional sedatives (patient days)</th>
<th>EGDS</th>
<th>Standard</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>24/165 (14%)</td>
<td>96/144 (67%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Propofol</td>
<td>48/165 (29%)</td>
<td>22/144 (15%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ketamine</td>
<td>28/165 (17%)</td>
<td>1/144 (0.7%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>165/165 (100%)</td>
<td>2/144 (1.4%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Physical restraints</td>
<td>29/165 (17%)</td>
<td>13/144 (9%)</td>
<td>0.029</td>
</tr>
</tbody>
</table>
Conclusions

- Identification, consent and randomisation in a timely manner is achievable in this target cohort
  - Median TTR 6.25 hours
  - Cohort easily identified
    - 98% ventilated > 24 hours
  - Consent rate 70%
  - Deferred consent successful
- EGDS more likely to achieve targeted light sedation in the first 48 hours
- EGDS reaches target light sedation faster
- EGDS was safe and efficacious
  - Minimal SAE’s
  - Low use of breakthrough sedatives
Discussion

• Strengths
  – Multicentre
  – Randomised
  – Short time to randomisation

• Limitations
  – Sample size, exclusions
  – Lack of blinding

• Future
  – Sedation requirements multifactorial
  – Large heterogeneity
  – Good infrastructure
  – Adaptive trial
Questions