Early Goal Directed Sedation in Critically Ill Patients

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Disclosure

• Unrestricted Grant-In-Aid Hospira Inc.
  – Investigator initiated trial
  – Granting body had no involvement in the study concept, design, data management, analysis or publication.

• Endorsed by ANZICS Clinical Trials Group
  – Complied with endorsement guidelines
  – Managed by the ANZIC RC Monash University
    • School of Epidemiology and Preventive Medicine

• EGDS RCT is funded by NHMRC Grant 2012-17
Incidence of mechanical ventilation 217/100,000
69% Increase in number mechanical ventilation days
30% Increase in proportion of in-patients days with mechanical ventilation / total adult inpatient days
Ventilated patients showed increased 30 day crude mortality 27% to 32% over the 8 years period
- Age, Charlson score, Year

In contrast to lower mortality trends seen in sepsis and in ICU patients over the last 20 years

Crit Care Med 2013
Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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2013 SCCM PAD

2 main Recommendations

• Analgesia First
• Light sedation

• Didn’t specify when to deliver light sedation?
How often is light sedation achieved?

2013, Coma
Median 3 days

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>In-Hospital Cohort (N=821)</th>
<th>Follow-up Cohort (N=467)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients — %</td>
<td>517 (63)</td>
<td>265 (57)</td>
</tr>
<tr>
<td>No. of days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2–6</td>
<td>1–5</td>
</tr>
</tbody>
</table>
How often is light sedation achieved?

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protocolized Sedation (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Opioid infusions</td>
<td>184 (87)</td>
</tr>
<tr>
<td>Days of infusion, median</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>Benzodiazepine infusions</td>
<td>169 (81)</td>
</tr>
<tr>
<td>Days of infusion, median (IQR)</td>
<td>1 (1-3)</td>
</tr>
</tbody>
</table>
How often and When is light sedation NOT achieved?

Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal study

Early Intensive Care Sedation Predicts Long-Term Mortality in Ventilated Critically Ill Patients

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Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the ANZICS Clinical Trials Group*

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Rationale: Choice and intensity of early (first 48 h) sedation may affect short- and long-term outcome.

Objectives: To investigate the relationships between early sedation and time to extubation, delirium, and hospital and 180-day mortality among ventilated critically ill patients in the intensive care unit (ICU).

Methods: Multicenter (25 Australia and New Zealand hospitals) prospective longitudinal (ICU admission to 28 d) cohort study of medical/surgical patients ventilated and sedated 24 hours or more. We assessed administration of sedative agents, ventilation time, sedation depth using Richmond Agitation Sedation Scale (RASS), four hourly, delirium (daily), and hospital and 180-day mortality. We used multivariable Cox regression to quantify relationships between early deep sedation (RASS, -3 to -5) and patients’ outcomes.

Measurements and Main Results: We studied 251 patients (mean age, 61.7 ± 15.9 yr; mean Acute Physiology and Chronic Health Evaluation [APACHE] II score, 20.8 ± 7.8), with 21.1% (53) hospital and 25.8% (64) 180-day mortality. Over 2,678 study days, we completed 14,736 RASS assessments. Deep sedation occurred in 191 (76.1%) patients within 4 hours of commencing ventilation and in 171 (68.9%) patients at 48 hours. Delirium occurred in 111 (50.7%) patients with median (interquartile range) duration of 2 (1-4) days. After

712 patients
8500 ICU days
4 countries
43 ICUs

AT A GLANCE COMMENTARY
Scientific Knowledge on the Subject
This is the first prospective multicentre longitudinal study of the practice of sedation in critically ill patients who were mechanically ventilated for longer than 24 hours. In addition, this manuscript contains novel data, which have primacy in identifying the quantitative relationship between early sedation depth (48 h after initiation of mechanical ventilation) and three important clinical outcomes: time to extubation, time to delirium, and hospital and 180-day mortality.

What This Study Adds to the Field
In 251 critically ill patients at multiple centers, we identified deep sedation within 4 hours of commencing ventilation as an independent negative predictor of the time to extubation, hospital death, and 180-day mortality. The early phase of ICU sedation is usually unaccounted for in randomized controlled trials due to late randomization.
Light sedation is NOT achieved for up to 72 hours after ventilation

- Common
- Unrecognized
- Unjustified?

Shehabi et al, *Int Care Med* Feb 2013

Shehabi et al, *AJRCCM* 2012
Early Deep Sedation Can be Harmful
Independently predicts time to extubation


Early Deep Sedation Can be Harmful
Independent predictor of 6 month mortality

EGDS, Rationale

• Light sedation is desirable
• Median ventilation time is usually 5-7 days
• Deep sedation is common in the early phase after initiating mechanical ventilation
  – 79% deeply sedated soon after
  – > 50% still deeply sedated at day 4
• Previous sedation trials ignored the first 48-72 hours after starting ventilation
Early Goal Directed Sedation Principles

- Delivered early within less than 6 hours of initiation of sedation and mechanical ventilation;
- Rely on an integrated process of targeting light sedation through frequent assessment of sedation levels and
- Incorporates the use of sedative agents known to promote wakefulness and arousal and/or agents with favorable pharmacokinetic profile such as short onset and offset time
Early Goal Directed Sedation

Key Elements

1. Early effective analgesia titrated to effect according to standardized pain assessment;

2. Early delivery of sedative agents including dexmedetomidine as a primary sedative

3. Tight targeting of light sedation early, from the time of initiation, with regular and frequent assessment of patient wakefulness/sedative state and titration of sedative infusions;

4. Avoidance of benzodiazepines

5. Reduced overall sedation depth with targeted light sedation.
Patient is mechanically ventilated

Sedation assessment

On-going Sedation

Pain assessment

Clinicians choice Opioid, other

Adequate analgesia

Dexmedetomidine infusion 1 mcg/kg/hr. (No Loading)

RASS \leq -3

Stop propofol first

↓ dexmedetomidine 0.2 mcg/kg/hr every 30 minutes

RASS \leq -3 \geq 2

Dexmedetomidine 0 – 1.4 mcg/kg/hr.

RASS -2 to +1

Sedation no longer needed Stop Infusion

RASS \leq -3 \geq 2

Propofol 0 – 70 mg/hr.

RASS \geq 2

Propofol 10-70 mg/hr.

RASS -2 to +1
Is EGDS Feasible?

- First, How soon can EGDS be effectively delivered?
- Second, how effective is EGDS in providing optimal sedation and preventing early deep sedation?
- Third, is EGDS only effective with a dexmedetomidine based algorithm?
- Fourth, is EGDS achievable outside high intensity bedside nursing?
- Finally, is EGDS feasible in the context of randomized clinical trials?
Is Early Goal Directed Sedation Feasible?

Is Early Deep Sedation Modifiable?
Randomized control trial
Early Goal-Directed Sedation Versus Standard Sedation in Mechanically Ventilated Critically Ill Patients: A Pilot Study*

Yahya Shehabi, FCICM, FANZCA, EMBA¹,²,³; Rinaldo Bellomo, MD, FCICM, FRACP²,³; Michael C. Reade, MBBS, MPH, DPhil, FCICM⁴; Michael Bailey, PhD³; Frances Bass, RN, BN, GDipICU⁵; Belinda Howe, RN, BN³; Colin McArthur, FANZCA, FCICM³,⁶; Lynne Murray, FAIMS³; Ian M. Seppelt, MBBS, FANZCA, FCICM⁷; Steve Webb, MPH, PhD, FCICM³,⁸; Leonie Weisbrodt, RN, BN, MN(Hons)⁹; for the Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group
Time spent in light sedation first 48 hours EGDS vs. STDS

Light sedation 203/307 (66%) vs. 74/197 (38%) (P=0.01)
Deep sedation 93/307 (30%) vs. 112/197 (57%) (P=0.02)
Patients achieving light sedation during the first 7 study days

- P=0.011
- P=0.036
- P=0.005
• Objectives:

– The feasibility of EGDS outside a high intensity ANZ ICU model of care
– The feasibility of achieving EGDS with standard sedatives
– Outcomes of combined ANZ and MY cohorts
Inclusion Criteria

Patient is **mechanically ventilated** in the previous 12 hours, **and** the treating clinician believes that:

1. The patient requires **ongoing sedative medication** for comfort, safety, and to facilitate the delivery of life support measures

2. The patient is expected to **remain intubated** the day after tomorrow. (> 24 hours).
Exclusion Criteria

- Age < 18 years.
- Pregnant and/or lactating.
- Proven or suspected acute primary brain lesion that may result in global impairment of conscious level or cognition, such as traumatic brain injury, intracranial haemorrhage, stroke, or hypoxic brain injury.
- Proven or suspected cervical spinal cord injury or pathology that may result in permanent or prolonged weakness of upper and lower limbs.
- Proven or suspected primary neurological pathology associated with prolonged weakness, such as Guillain-Barré syndrome
- Admitted as a consequence of a drug overdose
- Recent burn injuries
- Receiving or expected to need ongoing neuromuscular blockade
- Allergy to propofol or dexmedetomidine
Exclusion II

• Cardiovascular parameters
  – A mean arterial blood (MAP) pressure is less than 55 mmHg either with or without resuscitation and vasopressor therapy
  – A heart rate (HR) less than 55/min unless being treated with a β blocker
  – A high grade atrio-ventricular block in the absence of a functioning pacemaker
• Patient has end stage liver failure or acute fulminant hepatic failure
• Patient does not communicate in English
• Death is deemed imminent and inevitable
• Patient is a full time nursing home or hostel resident
• Patient has an underlying disease that makes survival to 90 days unlikely.
## Patients' Demographics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>EGDS N=52</th>
<th>STDS N=45</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysian sites (10) (% N)</td>
<td>60% (31)</td>
<td>64% (29)</td>
<td>0.63</td>
</tr>
<tr>
<td>Age mean (SD) years</td>
<td>54.6 (18.7)</td>
<td>56.5 (15.2)</td>
<td>0.60</td>
</tr>
<tr>
<td>Male % (n)</td>
<td>56% (29)</td>
<td>58% (26)</td>
<td>0.84</td>
</tr>
<tr>
<td>Weight mean (SD) kg</td>
<td>72.2 (20.9)</td>
<td>72.4 (24.5)</td>
<td>0.96</td>
</tr>
<tr>
<td>APACHE II mean (SD)</td>
<td>18.5 (7.4)</td>
<td>19 (7.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Operative elective</td>
<td>4% (2)</td>
<td>13% (6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Operative emergency</td>
<td>15% (8)</td>
<td>9% (4)</td>
<td>0.33</td>
</tr>
<tr>
<td>Admission ED % (n)</td>
<td>35% (18)</td>
<td>33% (15)</td>
<td>0.89</td>
</tr>
<tr>
<td>Admission Hosp. ward</td>
<td>38% (20)</td>
<td>42% (19)</td>
<td>0.71</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>42% (22)</td>
<td>36% (16)</td>
<td>0.50</td>
</tr>
<tr>
<td>GI disorder</td>
<td>8% (4)</td>
<td>11% (5)</td>
<td>0.56</td>
</tr>
<tr>
<td>Cardiovascular failure</td>
<td>10% (5)</td>
<td>22% (10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sepsis</td>
<td>19% (10)</td>
<td>9% (4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Vasopressor</td>
<td>67% (35)</td>
<td>67% (30)</td>
<td>0.95</td>
</tr>
<tr>
<td>Dialysis</td>
<td>21% (11)</td>
<td>22% (10)</td>
<td>0.90</td>
</tr>
<tr>
<td>Drugs given</td>
<td>EGDS N=52</td>
<td>STDS N=45</td>
<td>% Rx EGDS vs. STDS</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
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<td>-------------------</td>
</tr>
<tr>
<td><strong>Dexmedetomidine ug</strong></td>
<td>1559 (#490-3660)</td>
<td>799 (260-1338)</td>
<td>98% vs 4%</td>
</tr>
<tr>
<td><strong>Time on Dexmed D</strong></td>
<td>3 (2-5)</td>
<td>0 [0-0]</td>
<td></td>
</tr>
<tr>
<td><strong>Midazolam mg</strong></td>
<td>4.5 (#2-9)</td>
<td>56 (36.5-123)</td>
<td>19% vs 80%</td>
</tr>
<tr>
<td><strong>Time on Midazolam D</strong></td>
<td>0 [0-0]</td>
<td>2 (2-3)</td>
<td></td>
</tr>
<tr>
<td><strong>Propofol mg</strong></td>
<td>535 (#150-1200)</td>
<td>2150 (880-4630)</td>
<td>42% vs 47%</td>
</tr>
<tr>
<td><strong>Time on Propofol D</strong></td>
<td>1.23 (2.15)</td>
<td>1.42 (2.03)</td>
<td></td>
</tr>
<tr>
<td><strong>Morphine mg</strong></td>
<td>131.5 (#24-279)</td>
<td>110 (21-199)</td>
<td>27% vs 51%</td>
</tr>
<tr>
<td><strong>Fentanyl ug</strong></td>
<td>420 (#140-1000)</td>
<td>1340 (512.5-1950)</td>
<td>58% vs 62%</td>
</tr>
</tbody>
</table>
RASS achieved in First 48 hours
Relevant outcomes
% ICU days

- MY
- RASS -2 +1
- CAM ICU +ve
- CAM ICU -ve
- Ph Rest
- Dex
- MDZ
- Prop
- Mor
- Fent
- Nil Sed

EGDS
Stand

P-values:
- P=0.006
- P=0.05
- P<0.0001
- P=0.0006
- P=0.04
<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>EGDS Pilot Combined</th>
<th>STDS Pilot Combined</th>
<th>EGDS Pilot MY sites</th>
<th>STDS Pilot MY sites</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to randomization hrs. Median [IQR]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>2.1 (0.21-5.5)</td>
<td>1.1 (0.5-4.65)</td>
<td>2.17 (0.17-6)</td>
<td>1.5 (0.5-5.33)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>RASS --2 to +1 first 48 h % Light sedation range</strong></td>
<td>71% 517/732</td>
<td>51% 312/606</td>
<td>74% 314/425</td>
<td>58% 238/409</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>RASS -3 to -5 first 48 h % Deep sedation range</strong></td>
<td>26% 187/732</td>
<td>46% 278/606</td>
<td>22% 94/425</td>
<td>41% 166/409</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Physical restraints % (n)</strong></td>
<td>5% (1)</td>
<td>31% (5)</td>
<td>7 (23%)</td>
<td>14 (48%)</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Ventilation time Med (IQR) hrs</strong></td>
<td>61.8 (43.5-100.5)</td>
<td>65.0 (44-125.1)</td>
<td>53.17 (41.5-90.2)</td>
<td>71.8 (46.3-6.6)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>ICU Length of Stay Med (IQR) D</strong></td>
<td>4.3 (2.76-8.63)</td>
<td>5.04 (3.5-9.35)</td>
<td>3.55 (2.25-6.14)</td>
<td>4.84 (3.8-9.35)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Hospital Length of Stay Med (IQR) Days</strong></td>
<td>11.7 (7.3-28.85)</td>
<td>14.57 (8.5-26.8)</td>
<td>11.16 (6.9-15.89)</td>
<td>14.04 (8.94-4.83)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Hospital mortality N (%)</strong></td>
<td>7 (13%)</td>
<td>5 (11%)</td>
<td>4 (13%)</td>
<td>4 (14%)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>90 day mortality N (%)</strong></td>
<td>11 (21%)</td>
<td>7 (16%)</td>
<td>6 (19%)</td>
<td>5 (17%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>
Conclusions

- EGDS is feasible and can be delivered:
  - *Early* in the context of RCT
  - *Effectively* with
    - Reduced Early Deep Sedation
    - Light sedation targets
    - Reduced use of traditional sedative
  - *Safely* with
    - Reduced physical restraints use
    - No other safety issues
  - *External validity* of EGDS algorithm
Should EGDS be tested in a large scale RCT?

- EGDS is aligned with current actual practice and in line with international guidelines;
- EGDS mimics clinical reality and deliver an intervention that combines potentially safer drugs and beneficial light sedation targets;
- EGDS mandates frequent monitoring of patient responsiveness (“wakefulness”), sedation depth, and delirium;
- All interventions are delivered soon after initiation of mechanical ventilation maximising their potential benefits;
- Primary outcomes will be patient centered and long-term.
- Therapy is delivered by bedside nurses, EGDS will be applicable to currently practiced ICU model of care.
Early Goal Directed Sedation vs. Standard Care Sedation

Sedation Practices in Intensive Care Evaluation:

SPICE III: A Prospective Multicentre Randomised Controlled Trial of

Early Goal Directed Sedation Compared with Standard Care in Mechanically Ventilated Patients in Intensive Care