Article Title/Citation:
Daily Sedation Interruption in Mechanically Ventilated Critically Ill Patients Cared for With a Sedation Protocol - A Randomized Controlled Trial
SLEAP Study: Sedation Lightening and Evaluation of A Protocol

STUDY OBJECTIVES/PURPOSE: (and research hypothesis if applicable)
Will mechanically ventilated adults managed with protocolized sedation plus daily interruption receive less sedation and have a shorter duration of mechanical ventilation than patients managed with protocolized sedation alone?

BRIEF BACKGROUND: (why issue is important, summary of previous literature)
(Dr. Kim Weibe will give a brief overview of previous literature)
Early clinical trials with specific strategies to reduce excessive sedation led to strong recommendations for their use in practice. However, results of subsequent clinical trials varied, and use of these strategies in clinical practice has been inconsistent. Concerns about daily interruption of sedation included patient discomfort, unintentional device removal, and increased clinician workload. A systematic review of 5 trials that evaluated daily interruption highlighted the need for further research. This study was conducted to determine whether adults managed with both strategies (sedation protocol & daily interruption) would receive less sedation and a shorter duration of mechanical ventilation compared to a sedation protocol alone.

METHODS
STUDY DESIGN AND METHODOLOGY: (type of trial, Randomization, blinding, Controls, study groups, Length of study, etc.)
1) Multicenter randomized controlled trial in 16 centers from US and Canada.
2) Not blinded
3) January 2008 to July 2011
4) (Interruption group) protocolized sedation plus daily interruption
5) (Control group) protocolized sedation alone

PATIENT SELECTION AND ENROLLMENT: (inclusion/Exclusion criteria, sample Size etc.)
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<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<td>1) Patients expected by the ICU team to require mechanical ventilation for at least 48 hours after enrolment.</td>
<td>Patients admitted to the ICU: 1) after cardiac arrest 2) after TBI 3) receiving neuromuscular blocking agents 4) enrolled in another trial 5) previously enrolled in the current trial 6) for whom there was a lack of commitment to maximal treatment.</td>
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<td>2) Patients for whom the ICU team had decided to initiate continuous sedative and/or opioid infusion(s).</td>
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SAMPLE SIZE = 423
1) 2091 eligible patients,
2) 1661 were not enrolled, primarily because of lack of an authorized decision maker (24.3%), consent refusal (22.3%), or physician refusal (10.8%)
3) 430 randomized patients, 7 withdrew consent in the first 3 days of the study and were excluded from the analysis.
INTERVENTIONS: (if applicable)

Protocolized Sedation n=209 (Control Group):
Bedside nurses titrated analgesic and sedative infusions according to a protocol that prioritized pain assessment using continuous opioid and/or benzodiazepine infusions. Using validated scales, nurses titrated infusions to achieve light sedation. If the patient showed signs of agitation or distress, bolus doses were administered as needed. When patients were extremely agitated (SAS score 7; RASS score 3 or 4), nurses could deviate from this protocol. Intermittent dosing was permitted for procedures. Propofol, ketamine, and dexmedetomidine infusions were not permitted.

Protocolized Sedation PLUS Daily Sedation Interruption n=214 (Interruption Group):
Bedside nurses titrated analgesic and sedative infusions according to the protocol described above. In addition, once daily the bedside nurses interrupted benzodiazepine and opioid infusions daily and assessed hourly for wakefulness, defined as SAS score 4 to (RASS score −1 to 4) and ability to perform at least 3 of the following on request: eye opening, tracking, hand squeezing, and toe moving. If the bedside nurse and a physician agreed that infusions were no longer required (the patient was free of discomfort and agitation and the SAS score was between 2 and 5 or the RASS score was between −4 and 1), oral or bolus intravenous therapy was used at their discretion. Alternatively, if they judged that ongoing benzodiazepine or opioid infusions were required, nurses resumed infusions at half of the previous dose and titrated to achieve the target level of light sedation.

For both groups:
1) Infusions were discontinued when a patient was oversedated (SAS score 1 or 2; RASS score of −4 or −5)
2) Patients were assessed for delirium and for readiness for unassisted breathing with spontaneous breathing trial.
3) Patients were weaned from mechanical ventilation at the discretion of the ICU team.

OUTCOME MEASURES/ENDPOINTS:

<table>
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<tr>
<th>Primary Study Outcome</th>
<th>Secondary Outcomes</th>
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<tr>
<td>Time to successful extubation, defined as time from randomization to extubation (or</td>
<td>Unintentional device removal (eg, ETT)</td>
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<td>tracheostomy mask) for 48 hours.</td>
<td>Physical Restraint Use</td>
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<td>Delirium</td>
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<td>Tracheostomy</td>
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<td>Barotraumas</td>
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<td>Total doses of sedatives and analgesics</td>
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<td>Organ dysfunction</td>
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<td>ICU and hospital lengths of stay</td>
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<td>Death</td>
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<td>Additional clinical workload</td>
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STATISTICAL ANALYSIS:
The sample size estimate assumed a median time to successful extubation of 7 days among controls and a 2-day reduction with the addition of daily interruption (hazard ratio 1.4). This resulted in a sample size of 205 patients per group (total = 410), which would provide a power of 90%, with an α level of 5%.

All statistical analyses were based on an intention-to-treat approach. All participants were analyzed according to the allocated intervention, whether they received it or not. They used the Kaplan-Meier method to estimate and plot the distributions of time to successful extubation and an unadjusted Cox proportional hazards model to estimate a hazard ratio. To examine between-group differences in categorical variables, they used χ² or Fisher exact tests, as appropriate. For dichotomous outcomes, they presented relative risks or hazard ratios and their 95% CIs. If all assumptions were met for parametric analyses of the continuous variables, they used a 2-sample t test; otherwise, they used a 2-sample Wilcoxon rank sum test.
Patients were enrolled in 14 Canadian and 2 US centers. Patient characteristics were similar in the 2 groups. (84% received medical diagnoses)

**SUMMARY OF PRIMARY & SECONDARY OUTCOMES:** *(including subgroup analysis etc. include both efficacy and safety parameters)*

**Primary Outcome:**
The median time to successful extubation was 7 days in both groups (hazard ratio, 1.08; 95% CI, 0.86-1.35; P=.52). Adjustment for age, body mass index, APACHE II score, and admission type gave consistent results (adjusted hazard ratio, 1.04; 95% CI,0.83-1.31).

**Secondary Outcome:**
No between-group differences in ICU or hospital lengths of stay, hospital mortality, rates of unintentional device removal, delirium, ICU neuroimaging, barotrauma, tracheostomy, or organ dysfunction.

**Interruption group:**
-Received higher mean daily benzodiazepine doses and a greater number of boluses per day.
-Received higher daily opioid doses, both as infusion and boluses.

**Protocol Adherence and Clinician Workload:**
-Adherence with daily interruption was 72.2% of all eligible study days for an average patient and 85.6% for all eligible patient-days.
-Nurse workload was significantly higher in the interruption group.
-Respiratory therapist workload was similar in the 2 groups.
-Adherence with the performance of spontaneous breathing trials and with extubation after a successful spontaneous breathing trial was similar in the 2 groups.

**Subgroup Analysis:**
Surgical and trauma patients randomized to daily interruption had significantly shorter time to successful extubation than those randomized to protocolized sedation alone (6 vs 13 days; hazard ratio 2.55; 95% CI, 1.40 to 4.55)
There was no difference among medical patients (9 vs 8 days; hazard ratio, 0.92; 95% CI, 0.72 to 1.18)
AUTHOR'S DISCUSSION AND CONCLUSIONS

BRIEF SUMMARY OF AUTHORS' MAIN DISCUSSION POINTS:
1) Protocolized sedation and daily sedative interruption did not improve on the clinical outcomes observed when compared with protocolized sedation alone.
2) These results contrast with those of 2 earlier trials supporting daily interruption of sedative infusions in mechanically ventilated adults.
3) Research personnel were present for sedation interruption and had decisional authority regarding resumption of infusions in these 2 earlier trials. In this study, sedation was not directed by research staff but was managed by bedside ICU staff with their usual patient assignments.
4) These 2 earlier studies compared daily interruption of sedation with “usual care”. This study compared a sedation strategy adding daily interruption to a control group strategy of protocolized sedation that targeted light sedation, which is likely superior to “usual care”.
5) The multicenter design of this study reflects actual practice in ICUs with variable workloads and ICU staffing models.

AUTHOR'S CONCLUSIONS:
For critically ill patients receiving mechanical ventilation, when nurses implemented a sedation protocol that targeted light sedation, daily sedation interruption did not reduce the duration of mechanical ventilation, offered no additional benefits for patients, and may have increased both sedation and analgesic use and nurse workload.

YOUR DISCUSSION AND CONCLUSIONS

STUDY STRENGTHS:
1) Multicenter design/Randomized
2) Broad mix of patients
3) Perceived additional nursing workload associated with daily sedation interruption. (this may suggest sedation protocol may be more feasible than daily interruption)

**STUDY LIMITS, WEAKNESSES, POTENTIALS FOR BIAS:**
1) Blinding of caregivers was not feasible
2) Did not screen for drug withdrawal
3) Results may not be applicable to patients receiving shorter acting agents such as propofol or dexmedetomidine.
4) Health care teams are very uncomfortable with daily awakening routines
5) Selection Bias (Excluded a lot of patients)

**APPLICABILITY & IMPACT:**
Some form of sedation minimization in the ICU appears to benefit adult critically ill patients on mechanical ventilation.

**ADDITIONAL THOUGHTS/COMMENTs:**
- This study suggests that adding a daily sedation interruption to a sedation protocol is not helpful, but it does not prove that it is harmful.
- This study does not prove that daily awakening is inferior to a sedation protocol.
- Perhaps protocolized sedation may be better accepted, as opposed to daily sedation interruption, given the perceived increased workload for nurses and hesitancy among the health care team to do daily sedation awakenings.

**CONCLUSIONS AND RECOMMENDATIONS:**
Should our own institution adopt a protocolized sedation regime as opposed to a daily sedation awakening regime in an effort to minimize sedation in our adult critically ill patients on a mechanical ventilator?

**DISCUSSION:**
- In Winnipeg we have a daily interruption protocol that is not used routinely on all patients. We also have an SBT protocol.
- The Quality group has been working on an ABCDE’s of ICU (Sedation/Mobilization/Delirium combination approach)
  o Awake and Breathing
  o Choice of Sedative and Analgesia
  o Delirium Screening and Monitoring
  o Early Mobilization
- A point prevalence audit of our clinical practice shows:
  o 32% of vented patients on continuous sedation
  o 92% had a RASS score documented, only 42% were documented q4h
  o 35% had a CAM documented, 13% documented q12h
  o 40% of patients meet criteria for daily awakening
  o 61% vented patients meet criteria for SBT
- Nursing workload was higher in the paper, unclear if this is a function of protocol or nursing opinion
- General consensus agreed that reducing the ongoing dose is likely better than daily interruptions. Implementation of a protocol or practice guideline will need help from Medical Leadership and Nursing Leadership.