Sedation in the ICU-drugs, regimens of administration and monitoring

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Senior Resident, Dept. of Pulmonary medicine
PGIMER
22 September 2006.
Sedation in the ICU-why bother?

1. To relieve Dyspnea and intractable coughing

2. For amnesia during critical illness.

3. To manage agitated (delirious) patient from harming self and care-providers

4. To facilitate invasive management like ventilation and improve synchrony

5. To decrease VO2 and VCO2 (especially with cardiopulmonary compromise)

6. Unpleasant memories & PTSS
The yin of sedation.

Sedatives are commonly over-used.

Substituted as pharmacological restraints.

In a survey, <5% were agitated when assessed objectively. Likely to represent over-sedation.

Associated with
- prolonged ventilation duration
- long ICU stays
- cognitive impairment
- complications of critical care
  - critical care neuropathy
  - critical care myopathy (NM agents with steroids)
- increased cost of care
- complications may be missed
  - Pain induced immuno-suppression

Ely et al. JAMA 2003; 289(22):2983-91
The yang of sedation.

Agitation is common in the ICU.

Pharmacological & physical measures commonly needed.

Agitation is associated with
- Serious self harm
- Injury to health care providers
- Asynchrony during ventilation
  - Barotrauma
  - Increased WOB
  - Hypoxia and decompensation
AGITATION: Agitation is characterized by extreme arousal, irritability, excess motor activity driven by internal sense of discomfort such as disease, pain, anxiety and delirium.

Anxiety: A sustained state of apprehension with accompanying autonomic arousal in response to a real or perceived threat.

DELIRIUM: An acute, potentially reversible impairment of consciousness and cognitive function that fluctuates in severity.

PAIN: is an unpleasant sensory & emotional experience associated with actual or potential tissue damage
Delirium in the ICU.

Feature 1: acute onset of mental status changes or a fluctuating course.

and

Feature 2: inattention

and

Feature 3: disorganized thinking

or

Feature 4: altered level of consciousness

= Delirium
AGITATION in the ICU

PAIN

Environment/iatrogenic

Patient

Illness

DELIRIUM

Physical problems

CNS/ CVS dis

Drugs/Withdrawal

Electrolyte abn

ANXIOUS

Infection

CNS/iatrogenic

Patient

Why agitation occurs in the ICU?

Illness

Environmental/iatrogenic

Patient
1. Unidimensional pain rating scales
   Visual analog scale (for Pain)

No pain  some pain  worst ever pain

Other methods of quantification:

1. Verbal rating scale (VRS)
2. Numeric rating scale (NRS)
3. FACES scale (non verbal, non-oriented)
Multidimensional pain rating scales

McGill pain questionnaire

Wisconsin brief pain questionnaire

Less useful in the ICU

Behavioral pain rating scales

Pain-related behaviors (movement, facial expression, and posturing) and physiological indicators (heart rate, blood pressure, and respiratory rate) and the change in these parameters following analgesic therapy can be used. (Grade of recommendation B)

SCCM, ACCM. Crit Care Med 2002;30:123
Delirium in the ICU.

Extraordinarily common in intensive care. In patients on mechanical ventilation, >80% may be delirious.

Commonly under-diagnosed by care-providers. Agitation & hallucinations NOT required for diagnosis.

Hypoactive or mixed forms more common than hyper-active forms (which is easily recognized)

Age and pre-existing impairment are the most powerful risk factors.

Incidence is hence likely to increase

Confusion assessment method is an useful tool for recognition.

Psychoactive drugs including analgesics & sedatives are major risk factors.
Delirium derived from Latin deliria (to be out of your furrow)

Traditionally, then lethargus (Greek for hypoactive) or hypoactive form has been under-recognized.

Missed in 66-84% of patients

Is an independent risk factor for increased morbidity, ICU stay and mortality.

ICU literature refers to delirium as “ICU Psychosis”

Suggests that the ICU is linked in causation! and is to be expected!

Most patients do not have psychosis but are delirious

This term should thus be abandoned.
Currently, validated techniques for delirium recognition have changed the perspective in the ICU.

These tools are as good as diagnosis by a geriatric psychiatric (in the hands of non-psychiatrists, including nurses, pharmacists)

The Society For Critical Care Medicine (SCCM), American College Of Critical Care Medicine (ACCM) recommends daily delirium monitoring in patients on Mechanical ventilation.

20,000 observations
613 patients.
Ventilated & non-ventilated patients
Hypoactive more in elderly
Associated with worse outcomes.

Delirium in the ICU

**HOST FACTORS**
- Underlying co-morbidities (liver, renal, diabetes, hypertension)
- Elderly
- Pre-existing cognitive impairment/dementia
- Hearing/vision impairment
- Neurologic disease (stroke, seizure)
- Alcoholism, smoking

**IATROGENIC/ENVIRONMENTAL**
- Sedative/analgesic use
- Immobilization (restraint, catheters)
- TPN
- Sleep deprivation
- Malnutrition
- Anemia (phlebotomy)

**ACUTE ILLNESS.**
- Severe sepsis
- ARDS
- MODS
- Drug overdose/illicit drugs
- Nosocomial infection
- Metabolic disturbance
In non-ICU patients:

Mortality (in hospital) of 25-33% (independent)
Hazard ratio of 2.11
Prolonged hospital stay
3 times increased likelihood of discharge to a nursing home


In ICU patients:

Predictor of 6 month mortality
3 fold increase in death (multi-variate analysis)
Increased risk of dementia over 2-3 years.

Rockwood K. Age ageing 1999; 28:551
Rakhonen T. J Neurol Neurosurg Psychiatry 2000; 69:519
275 patients in an ICU (81.7% of whom had delirium)

Patients who developed delirium had higher 6-month mortality rates (34% vs 15%, P=.03)

Spent 10 days longer in the hospital than those who never developed delirium

Independently associated with

1. higher 6-month (3.2; 95% CI 1.4–7.7; P=.008) mortality
2. longer hospital stay (adjusted HR, 2.0; 95% CI, 1.4–3.0; P=.001)
3. longer post-ICU stay (HR, 1.6; 95% CI, 1.2–2.3; P=.009)
4. fewer median days alive and without mechanical ventilation
5. higher incidence of cognitive impairment at hospital discharge (adjusted HR, 9.1; 95% CI, 2.3–35.3; P=.002).

Ely et al. JAMA 2004; 291:1753
Figure 3. Kaplan-Meier Analysis of Delirium in the Intensive Care Unit and 6-Month Survival

No. at Risk
No Delirium 41 34 28 25 22 21 19
Delirium 183 136 116 111 104 98 86

No. at Risk
No Delirium 17 15 11 11 10 10 10
Normal 24 19 17 15 12 11 9
Coma-Normal 60 51 42 39 34 33 29
Delirium 123 87 74 72 70 65 59

Ely et al. JAMA 2004; 291:1753
About 39% higher ICU costs & 31% higher hospital costs.

Individual increase in costs about $9000 per patient.

Causes of agitation that require specific interventions

Potentially life threatening

1. Gas exchange: Hypoxemia/ Hypercarbia
2. Metabolic: Hypoglycemia/ Acidosis
3. Ventilator related: Endotracheal tube malposition/ Tension pneumothorax
4. Infection: Central nervous system infection/ Sepsis
5. Drug and alcohol related: Intoxication/ Withdrawal
6. Ischemia: Myocardial/ Intestinal/ Cerebral

Miscellaneous

7. Patient-ventilator dyssynchrony/ Inadequate flow rates/ Excessive tidal volumes
8. Uncomfortable bed position
9. Fear/ Inability to communicate/ Sleep deprivation
10. Full bladder/ Nausea/ Need to defecate
11. Nicotine withdrawal
12. Drug side effects: Anticholinergic/ Paradoxical response to benzodiazepines
### Agitation & delirium: an aide memoire for routine use

#### I WATCH DEATH

- Infection
- Withdrawal
- Acute metabolic
- Trauma/ pain
- CNS pathology
- Hypoxia
- Deficiencies (B1, B12)
- Endocrinopathies
- Acute vascular
- Toxins/ drugs
- Heavy metals

#### DELIRIUM

- Drugs
- Electrolyte abnormalities
- Lack of drugs
- Infection
- Reduced sensory input
- Intracranial problem
- Urinary retention & fecal impaction
- Myocardial infarction
Drugs that can cause Delirium

Anti-arrhythmics
- Lidocaine
- Mexilitine
- Quinidine

Antibiotics: Penicillin

Anti-cholinergics: atropine

Anti-histaminics

Beta-blockers: propranolol

Narcotics: meperidine

Morphine

Pentazocine
### The Ramsay Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious and agitated or restless, or both</td>
</tr>
<tr>
<td>2</td>
<td>Co-operative, oriented and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Responsive to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Brisk response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Sluggish response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td>No response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>Score</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>7</td>
<td>Dangerously agitated</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
</tr>
<tr>
<td>4</td>
<td>Calm, cooperative</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable</td>
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</table>
### The Richmond Agitation Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated—pulls or removes tubes or catheters; aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated—frequent, non-purposeful movements, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless—anxious, apprehensive but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy—not full alert, but has sustained (&gt;10 second) awakening (eye contact) to voice.</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation—drowsy, briefly (&lt;10 second) awakens to voice or physical stimulation</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation—movement or eye opening (but not eye contact) to voice</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation—no response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable—no response to voice or physical stimulation.</td>
</tr>
</tbody>
</table>
HOW TO SCORE RASS?

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score 1 to 4 using the criteria listed)?

2. If patient is not alert, in a loud speaking voice state patient’s name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score 1).
   Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score 2).
   Patient has any movement in response to voice, excluding eye contact (score 3).

3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score 4).
   Patient has no response to voice or physical stimulation (score 5).
Excellent inter-rater reliability (0.956, lower 90% CI 0.948; \( \kappa = 0.73 \), 95% CI 0.71-0.75) with five investigators & 192 observations (phase 1).

Robust \((r = 0.922-0.983)\) \((\kappa = 0.64-0.82)\) was demonstrated for patients with and without mechanical ventilation, and with and without sedative medications.

Good co-relation with Ramsay & Riker’s scales. In phase 2, good reliability with investigator & 27 trainees in 101 observations.

Good predictor of changes with time & co-related with other scales (BSE).
Until recently, the recognition of delirium in the ICU was limited by the non-verbal state of most patients.

The CAM-ICU is a delirium measurement tool that has recently been developed

Administered by a nurse

Takes < 1-2 minutes

Is 98% as accurate for detecting delirium (compared to DSM-4)

# Confusion assessment method for the intensive care unit.

## 1. Acute onset or fluctuating course
- **absent**
- **present**
  - Is there an evidence of an acute change in mental status from baseline?
  - or
  - Did the abnormal behavior fluctuate over the last 24 hours, ie, increase and decrease in severity as evidenced by the sedation scale (RASS, GCS, previous delirium assessment)

## 2. Inattention
- **absent**
- **present**
  - Did the patient have difficulty focusing attention, as evidenced by a score <8 on auditory or visual component of the attention screening examination

## 3. Disorganized thinking
- **absent**
- **present**
  - Is there an evidence of disorganized or incoherent thinking, as evidenced by incorrect answers to >2/4 questions or inability to follow the below?

  **Set A**
  - Will a stone float on water?
  - Are there fish in the sea?
  - Can 1 pound weigh more than 2 pounds?
  - Can you use a hammer to pound a nail?

  **Set B**
  - Will a leaf float on water?
  - Are there elephants in the sea?
  - Do 2 pounds weigh more than 1 pound?
  - Can you use a hammer to cut wood?

  **Other**
  - Are you having any unclear thinking?
  - Hold up this many fingers (hold up 2 fingers in front of the patient)
  - Now do the same thing with the other hand (do not repeat the number of fingers)

## 4. Altered level of consciousness
- **Absent**
- **present**
  - Is the patient level of consciousness anything other alert, such as vigilant, lethargic or stuporous (RASS <0)
    - **ALERT**: spontaneously fully aware of environment and interacts appropriately
    - **VIGILANT**: hyperalert
    - **LETHARGIC**: drowsy but easily aroused; unaware of some elements in the environment or spontaneously not interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally
    - **STUPOROUS**: becomes incompletely aware when prodded; can be aroused only by strong and repeated stimuli; and as soon as the stimuli ceases, lapses back into unresponsive state

**Overall assessment: presence of features 1 & 2 and either feature 3 or 4?**
- **Yes**
- **No**
Large-scale implementation of sedation and delirium monitoring in the intensive care unit: A report from two medical centers*

Brenda Truman Pun, RN, MSN, ACNP; Sharon M. Gordon, PsyD; Josh F. Peterson, MD, MPH; Ayumi K. Shintani, PhD, MPH; James C. Jackson, PsyD; Julie Foss, RN, MSN; Sharon D. Harding, RN, MSN, CCRN; Gordon R. Bernard, MD; Robert S. Dittus, MD, MPH; E. Wesley Ely, MD, MPH

711 admitted to the medical ICUs for >24 hrs and followed over 4,163 days during a 21-month study period.

With minimal training, the compliance of bedside nurses using sedation and delirium instruments was excellent. Agreement of data from bedside nurses and a reference-standard rater was very high for both the sedation scale and the delirium assessment over the duration of this process-improvement project.

The two most-often-cited barriers to implementation were physician buy-in and time.
Limitations of behavior observation scales

1. Require clinical judgment (and hence extensive training)

2. Require institutional validation

3. Little value in those with cognitive dysfunction disorders

4. Not useful in those on neuromuscular blockers

5. Cannot measure depth of sedation in those who are unarousable
Bispectral index monitors, using EEG signals, have been shown to accurately correlate with depth of sedation with non-dissociative general anesthesia in the operating room setting among adults and children.

Theoretically appealing but is of unproven role

Does not have discriminating power to quantify sedation in intubated patients.


Co-relates with but is no better than conventional sedation scaling


The role of BERA is experimental.
SOME GENERAL MEASURES FOR AGITATION:

Reassurance (for fear, anxiety)

Writing board if unable to communicate

Re-positioning the patient

Repositioning ET > 2 cms from carina

Treatment of withdrawal state

Optimization of ventilator settings

Correcting metabolic derangements

Catheterization

Music therapy

Hypnosis
Does primary prevention with general methods prevent delirium?

Data available for non-ICU patients only.

The available evidence is contradictory.

40% reduced risk in 852 general medical patients > 70 years (15% vs 9.9%)


Only in those without dementia.


No benefit at all


Costs nothing
Widely applicable
Intuitive
Can be used widely
HOW IS THE USE OF SEDATIVES & ANALGESICS DIFFERENT IN THE ICU?

1. Advanced age
2. Malnutrition
3. Obesity
4. Altered renal & liver function
5. Effects of underlying disease
6. Polypharmacy
7. Slowed metabolism
8. High body water/ increased volume of distribution
9. Decreased protein binding
Pharmacologic therapies include opioids, NSAIDs and acetaminophen.

The selection of an agent depends on its pharmacology and potential for adverse effects.

Desirable attributes include
1. rapid onset,
2. ease of titration,
3. lack of accumulation of the parent drug or its metabolites, and
4. low cost

Side-effects are pharmacodynamic. Include
1. Respiratory depression
2. Hypotension
   - Sympatholysis (Volume depleted)
   - Vagally-mediated bradycardia
   - Histamine release (morphine)
3. Ileus
4. Depression of sensorium
Currently Fentanyl infusion is preferred over Morphine (if continuous infusion is to be used).

Use of remifentanil is associated with better hours of optimal sedation, fewer infusion changes, shorter mechanical ventilation time & extubation time

Prevention of pain more effective than treating it.

Continuous or scheduled intermittent bolus better than prn dosing

Other routes of delivery:

1. Patient controlled analgesia
   cognition
   hemodynamic reserve
   previous opioid use.
2. Transdermal patch.

Dahaba, Anesthesiology, 101:640–646, 2004
<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Fentanyl</th>
<th>Meperidine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting dose</strong></td>
<td>2-5 mg</td>
<td>25-50 μg</td>
<td>20-50 mg</td>
<td>5-10 mg</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>10 min</td>
<td>0.5-1 min</td>
<td>3-5 min</td>
<td>10-20 min</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>4 h</td>
<td>0.5-1 h</td>
<td>1-4 h</td>
<td>6-24 h</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
<td>Hepatic</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
<td></td>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiolysis</strong></td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Analgesia</strong></td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td><strong>Hypnosis</strong></td>
<td>No reliable effect</td>
<td>No reliable effect</td>
<td>No reliable effect</td>
<td>No reliable effect</td>
</tr>
<tr>
<td><strong>Amnesia</strong></td>
<td>No reliable effect</td>
<td>No reliable effect</td>
<td>No reliable effect</td>
<td>No reliable effect</td>
</tr>
<tr>
<td><strong>Sz threshold</strong></td>
<td>No effect</td>
<td>May decrease</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td><strong>CV effect</strong></td>
<td></td>
<td></td>
<td>Venodilatation</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory effect</strong></td>
<td></td>
<td></td>
<td>Hypoventilation</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>N/V, ileus, itching</td>
<td>N/V, ileus, itching, seizures</td>
<td>N/V, ileus, itching seizures</td>
<td>N/V, ileus, itching</td>
</tr>
</tbody>
</table>
Protocol For Haloperidol Use

In the ICU, large doses are required

Starting doses are 2-10 mg (5 mg) bolus over 5-10 minutes. Repeated every 20 minutes till end-point achieved.

25% of the cumulative dose is given q6 hourly.

In the non-ICU setting, the starting dose is 0.5-1 mg oral or parenterally every 20 minutes till en-point.

The basis is to block 60% of the D2 receptor while avoiding side-effects associated with complete D2 blockade.

Once calm, smaller doses can be used.
Available parenteral preparations of Haloperidol.

<table>
<thead>
<tr>
<th>Depidol</th>
<th>Torrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ml (50 mg/ml)</td>
<td>Rs. 110.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seronorm</th>
<th>Sun Pharma</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg (1 ml)</td>
<td>Rs. 4.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serenate</th>
<th>RPG Life Sciences</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/ml (5 1 ml)</td>
<td>Rs. 25.00</td>
</tr>
</tbody>
</table>

Estimated cost with the given regimen & use < 25 mg/day is Rs. 25.00
Typical adverse effects of haloperidol include:

1. Hypotension
2. Acute dystonias
3. Extra-pyramidal side-effects
4. Laryngeal spasm
5. Malignant hyperthermia
6. Glucose & lipid dysregulation
7. Anticholinergic side-effects
8. Torsade de pointes arrhythmia

Adverse effects are rare and these agents are usually well tolerated

ECG monitoring of QTc when large doses are used (in ICU)
Newer agents include atypical agents like risperidone, quetapine and olanzapine

Rationale is the possible antagonism of other neurotransmitters also.

Adequately powered RCT’s not available.

All agents are associated with significant side-effects.

At present, there is no data for routine use of these agents.
<table>
<thead>
<tr>
<th></th>
<th>Midazolam</th>
<th>Lorazepam</th>
<th>Diazepam</th>
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<tbody>
<tr>
<td><strong>Starting dose</strong></td>
<td>1-2 mg</td>
<td>.5-1 mg</td>
<td>5-10 mg</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>.5-2 min</td>
<td>3-5 min</td>
<td>1-3 min</td>
</tr>
<tr>
<td><strong>Duration action</strong></td>
<td>2 h</td>
<td>6-10 h</td>
<td>1-6 h</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic</td>
<td>Hepatic(age, liver disease less influence)</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td><strong>Anxiolysis</strong></td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Analgesia</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hypnosis</strong></td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Amnesia</strong></td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Seizure threshold</strong></td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td><strong>CV effect</strong></td>
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<td>Venodilatation</td>
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<tr>
<td><strong>Respiratory depression</strong></td>
<td></td>
<td>Hypoventilation</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td></td>
<td>Paradoxical agitation</td>
<td></td>
</tr>
</tbody>
</table>
128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs in a medical ICU.

Median duration of mechanical ventilation was 4.9 vs 7.3 days (\(P=0.004\)),

Median length of stay in ICU was 6.4 vs 9.9 days (\(P=0.02\)).

Complications (e.g., removal of the endotracheal tube by the patient) occurred in three of the in the intervention group (4 %) and four of the patients in the control group (7%, \(P=0.88\)).
## Available preparations of Midazolam

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Manufacturer</th>
<th>Volume</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midaz</td>
<td>NPIL</td>
<td>10 ml</td>
<td>Rs. 52.95</td>
</tr>
<tr>
<td>Sedoz</td>
<td>Claris life sciences</td>
<td>10 ml</td>
<td>Rs. 53.00</td>
</tr>
<tr>
<td>Fulsed</td>
<td>Ranbaxy</td>
<td>10 ml</td>
<td>Rs. 60.40</td>
</tr>
<tr>
<td>Mezolam</td>
<td>Neon Labs</td>
<td>10 ml</td>
<td>Rs. 54.00</td>
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<tr>
<td>Midapic</td>
<td>Rusan HC</td>
<td>10 ml</td>
<td>Rs. 50.00</td>
</tr>
</tbody>
</table>

**Estimated cost of therapy:** 5 mg/hr = 120 mg/day  
Rs. 600/day
Available preparations of Lorazepam

Lopez
2 ml amp (1 ml = 2 mg)

Intas
Rs.15.00

Calmese

Themis

10 2 ml

Rs 118

Estimate cost of therapy (at 4 mg/3 hrly = 30 mg/day) < Rs 100/ day
A case for Lorazepam in the ICU.

NOT metabolized by the CYP450 system—less of drug interactions.

Less subject to toxicity in hepatic dysfunction.

No active metabolites

Less expensive (10 times)

Compared with Midazolam, sedation targets met more often & earlier recovery (data conflicting)

High doses can cause high AG acidosis because of accumulation of propylene glycol.
The active ingredient in Propofol is 2,6-diisopropylphenol in 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide.

Disodium EDTA (0.05 mg/ml) or sodium metabisulfite (0.25 mg/ml) is added to inhibit bacterial growth.

Is hepatically modified & renally excreted

Key benefits include:
1. Rapid onset & offset of action.
2. Easy titration
3. Metabolism independent of hepatic & renal function
4. Sedative-hypnotic with anxiolytic & amnestic properties
5. Is also a bronchodilator, anti-epileptic, muscle relaxant and anti-oxidant.
# Available preparations of Propofol

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Manufacturer</th>
<th>Volume</th>
<th>Price (Rs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freseofol</td>
<td>Fresenius Kabi</td>
<td>50 ml</td>
<td>388</td>
</tr>
<tr>
<td>Profol 1%</td>
<td>Claris Lifesciences</td>
<td>50 ml</td>
<td>350.00</td>
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<tr>
<td></td>
<td></td>
<td>100 ml</td>
<td>600</td>
</tr>
<tr>
<td>Cleofol</td>
<td>Themis</td>
<td>20 ml</td>
<td>150.00 (500 mg=375)</td>
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<tr>
<td>Rofol</td>
<td>Neon labs</td>
<td>50 ml</td>
<td>351.00</td>
</tr>
</tbody>
</table>

**Estimated cost of therapy:**

- At 1 mg/kg/hr infusion (after 0.3 mg/kg bolus):
  - 2.5 vials (Rs. 875.00)

- At maximum doses (3 mg/kg/hr, often required):
  - Rs. 2520.00
Problems with Propofol

1. Hypotension
2. Hypertriglyceridemia
3. Sepsis due to contamination
4. Pancreatitis
5. Metabolic acidosis
6. Adrenal insufficiency
7. Immune dysfunction
8. PRIS
9. Is very expensive
10. Practically no benefit over Midazolam in terms of earlier extubation and shorter stay.

Fares poorly in cost-benefit Analysis.
Will remain 2nd line agent
Role of Dexmedetomidine

Is an α2 agonist.

Increasing role, especially in post-operative patients

Advantages include
1. Maintenance of respiratory drive
2. Rapid awakenings
3. Analgesia
4. Amnesia
5. Good hemodynamic tolerance
6. Decreased requirement for other medications

Is it the sedative of the future?

It is a capital crime to theorize before it is available, Watson.
Propofol infusion syndrome (PRIS) defined as the occurrence of acute bradycardia resistant to treatment and progressing to asystole associated with Propofol infusion.

Bradycardia has to be combined with lipaemic plasma, fatty liver enlargement, metabolic acidosis with base excess < 10 mmol/l, rhabdomyolysis or myoglobinuria.

The syndrome usually leads to fatal cardiac and renal failure (24 children & 14 adults).

Identified risk factors are
1. airway infection,
2. severe head injury,
3. high-dose long-term sedation for more than 48 h at more than 5 mg/kg per hour, increased catecholamine and
4. increased glucocorticoid serum levels and
5. low energy supply

The infusion rates described in publications reporting on Propofol have used up to 44.2 mg/kg/hr.

Management includes stopping drug, dialysis, carbohydrates & supportive care.
Sedation needed—target to Ramsay 3
Exclude reversible causes of agitation
Is pain likely?

No

Is the agitation causing acute Deterioration necessitating acute Control?

No

Diazepam/ Midazolam 2-5 mg every 5 min until desired sedation (RASS) -1 TO -2

No

Requiring diazepam/ Midazolam Bolus> every 2 hours?

Yes

Morphine 1-5 μg every 2 hours

No

Fentanyl 25-100 μg every 5 min Till analgesia

No

Targeted sedation achieved?

Yes

Decrease fentanyl by 25 μg/ hr or lorazepam 0.25 mg/hr till infusion completed

No

Lorazepam infusion 0.5-1 mg/ hr

No

Rebolus & increase fentanyl by 25 μg/ hr or lorazepam 0.25 mg/hr till sedated

Reassess sedation regimen & Ramsey Score q4 hrly

Lorazepam 1-4 mg up to every 2 hours.
Is the patient comfortable and at goal?

- Rule out/ correct reversible causes
- Non-pharmacological optimization of environment
- Pain scale quantification
- Sedation scale for agitation/anxiety
- Quantify delirium scale

Set goals for analgesia

- Reassess goal daily
- Titrate and taper therapy to maintain goal
- Consider daily wake up
- Taper if >1 week high-dose therapy and monitor for withdrawal

Hemodynamically unstable
- Fentanyl: 25-100 μg 5-15 min

Hemodynamically stable
- Morphine 2-5 mg 5-15 min
- Repeat till pain resolves, then prn

Acute agitation
- Midazolam: 2-5 mg 5-15 min till acute event controlled

Ongoing sedation
- Lorazepam: 1-4 mg 10-20 min till goal
  Then q2-5hrly+prn or
  Propofol 5 μg/kg/min titrate till goal

- Haloperidol 2-10 mg q 20-30 min, then 25% of loading dose q6h

Taper at 10-25%/d

IV doses
- Every 2h?

Infusion preferred
- Lorazepam infusion
- Set goals for analgesia

>3d of propofol
- Set goals for delirium
- Yes

Set goals for sedation

Set goals for agitation/anxiety
CONCLUSIONS

Sedatives are commonly (over)used in the ICU.

Pharmacokinetics varies widely from other arenas.

Structured approach to agitation (like hypoxemia) required.

Adequate sedation begins with adequate analgesia & appropriate general measures.

Evaluation of sedation efficacy by scales (RASS) regularly is useful & simple.
Protocol driven sedation improves outcomes.

Delirium (hypoactive) is common and missed. CAM-ICU scale useful adjunct.

Downward titration protocols after 48 hours must irrespective of bolus or continuous infusion strategies.

For the latter strategy, daily interruption & re-starting at half the dose useful.