

REVIEW ARTICLE

SEDATION IN ICU

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ABSTRACT: The correct management of sedation is one of the most important aspects of Intensive Care management¹. Some degree of sedation (i.e. analgesia \pm hypnosis) is often required to allow patient co-operation with organ system support and the associated nursing care.² An agitated patient has a higher basal metabolic rate and may reduce the efficiency of supportive care, ventilator dysynchrony, increase in oxygen consumption, and inadvertent removal of devices and catheters. Here is an overview of sedation in ICU.

KEYWORDS: Sedation, Intensive care unit, Ventilator.

INTRODUCTION:

- Sedation comes from the Latin word sedare which means to calm or to allay fear.
- Sedation is the process of establishing a state of calm.
- Conscious sedation: A minimally depressed level of consciousness induced by the administration of pharmacologic agents in which a patient retains the ability to independently and continuously maintain an open airway and a regular breathing pattern, and to respond appropriately and rationally to physical stimulation and verbal commands.

Why is sedation necessary?²

- ▶ To improve patient comfort
- ▶ Facilitate interventions
- ▶ To allay fear, anxiety and agitation
- ▶ Adequate sleep
- ▶ Avoid pain
- ▶ Facilitation of mechanical ventilation/airway management/ weaning
- ▶ Protection against myocardial ischemia
- ▶ Amnesia during neuromuscular blockade

Goals for sedation and analgesia

- ▶ To minimize physical discomfort or pain during procedures
- ▶ To minimize psychological disturbance
- ▶ To maximize the potential for amnesia
- ▶ To guard patient safety
- ▶ To control behavior

IDEAL SEDATIVE³: The ideal sedative agent should possess the following qualities:

- Both sedative and analgesic
- Minimal cardiovascular side effects

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- Controllable respiratory side effects
- Rapid onset/ offset of action
- No accumulation in renal/hepatic dysfunction
- Inactive metabolites
- Cheap/cost-effective
- Minimal interactions with other drugs

Most sedative agents share the following problems:

- i. Accumulation with prolonged infusion, delaying weaning from supportive care.
- ii. Detrimental effects on the circulation leading to increased inotrope requirements
- iii. Detrimental effects on the pulmonary system – vasculature, increasing VQ mismatch leading to increased need for ventilator support
- iv. Suppression of cough reflex reducing clearance of pulmonary secretions.
- v. Tolerance during sedation and withdrawal when it is stopped
- vi. No sedative provides rapid eye movement (REM) sleep - i.e. useful sleep. REM sleep deprivation is thought to be one of the most important causes of ICU psychosis.

COMPLICATIONS FROM PAIN AND ANXIETY²

- ▶ Stimulation of the autonomic nervous system and release of humoral factors → increased heart rate, blood pressure, and myocardial oxygen consumption → myocardial ischemia or infarction
- ▶ Altered humoral response can lead to hypercoagulability as a result of increased level of factor VIII, fibrinogen, platelet activity, and inhibition of fibrinolysis

MONITORING SEDATION: Sedation of agitated critically ill patients should be started only after providing adequate analgesia and treating reversible physiological causes.

Over-sedation can increase time on ventilatory support and prolong ICU duration of stay.

Under-sedation can cause hyper-catabolism, immunosuppression, hypercoagulability and increased sympathetic activity.

A number of scoring systems are available for this purpose, No system is fully validated

Each system evaluates consciousness by first noting spontaneous response to observer.

Subsequently noting response to external stimuli (voice, touch)

Subjective sedation scales³

- ▶ Goal of sedation in ICU is a patient who is calm but easily arousable
- ▶ The sedation scale will allow to achieve the goal with lowest possible dose of a sedative agent and with lowest possible risk of harm to patient
- ▶ The Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients.

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Ramsay scale for scoring sedation⁴

- ▶ Ramsay score was described in 1974
- ▶ Designed to monitor level of consciousness more than the degree of agitation
- ▶ It was first scoring system described to evaluate sedation in mechanically ventilated patients
- ▶ It is chosen method of monitoring sedation in >75% ICU s

1	anxious & agitated or restless or both
2	cooperative, oriented & tranquil
3	drowsy but responds to commands
4	asleep, brisk response to light glabellar tap or loud auditory stimulus
5	asleep, sluggish response to light glabellar tap or loud auditory signals
6	asleep & unarousable

Table 1: Ramsay sedation scale

Score	Term	Description
+4	Combative	Violent; immediate danger to staff
+3	Very agitated	Pulls/ removes tubes, catheters; aggressive
+2	Agitated	Frequent non purposeful movement; patient ventilator asynchrony
+1	Restless	Anxious or apprehensive
0	Alert and calm	
-1	Drowsy	Not fully alert but awakens for >10s, with eye contact, to voice
-2	Light sedation	Briefly awakens (<10s), with eye contact, to voice
-3	Moderate sedation	Any movement to voice but no eye contact
-4	Deep sedation	No response to voice but movement to physical stimulation
-5	Un arousable	No response to voice or physical stimulation

Table 2: Richmond agitation sedation scale (RASS)⁵

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7	Dangerous Agitation Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very Agitated Requiring restraint and frequent verbal reminding of limits, biting ETT
5	Agitated Anxious or physically agitated, calms to verbal instructions
4	Calm and Cooperative Calm, easily arousable, follows commands
3	Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very Sedated Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable Minimal or no response to noxious

Table 3: Sedation agitation scale (SAS)⁶: SAS Target Sedation = 3 to 4

INSTRUMENTAL MEASURES OF SEDATION

- (i) **Electroencephalograms (EEG):** EEG monitoring be used to monitor non convulsive seizure activity in adult ICU patients with either known or suspected seizures, to titrate electro suppressive medication to achieve burst suppression in adult ICU patients with elevated intracranial pressure.
- (ii) **Bispectral index (BIS):** This technique is mostly used to monitor depth of surgical anaesthesia in the operating theatre; it provides a quantitative value between 0 and 100.
A BIS value of 0 equals EEG silence, near 100 is the expected value in a fully awake.
 - ▶ Although the BIS may be a promising tool for the objective assessment of sedation or hypnotic drug effect, it has limitations in the ICU environment.
 - ▶ Objective testing of the level of sedation may be helpful during very deep sedation or when therapeutic neuromuscular blockade is being used.

SEDATION THERAPY

1. Non pharmacological therapy:

- ▶ Good communication with regular reassurance from nursing staff.
- ▶ Environmental control such as humidity, lighting, temperature, and noise.
- ▶ Explanation prior to procedures.
- ▶ Management of thirst, hunger, constipation, and full bladder.

2. Pharmacologic therapy: The sedative agent should possess the following qualities:

1. Both sedative and analgesic properties.
2. Minimal cardiovascular side effects.

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3. Controllable respiratory side effects.
4. Rapid onset/offset of action.
5. No accumulation in renal/hepatic dysfunction.
6. Inactive metabolites.
7. Less expensive.
8. No interactions with other ICU drugs.

Choice of Sedative:

- ▶ The choice of sedation in critically ill patients in critical care is determined by several factors → the patient's diagnosis, route and method of ventilation.
- ▶ Liver and kidney function and changes in the patient's condition.
- ▶ Propofol and Midazolam are sedative agents that are widely used within critical care.
- ▶ The correct way to initiate sedation is to administer a loading dose which is titrated to effect and then to start an infusion.
- ▶ Increases in sedative infusion rate should follow the same principle, i.e. a bolus, titrated to effect, should be administered and the infusion rate increased by a small increment.

Pharmacologic therapy

1. Benzodiazepines
2. Propofol
3. Short acting opioids
4. Alpha 2 agonists
5. Haloperidol
6. Ketamine
7. Barbiturates
8. NMB

1. Benzodiazepines⁷: They are most common sedatives as they have safe profile, sedation is accompanied by Amnesia, Anxiolytic, anticonvulsant, amnesic, hypnotic and provide some muscle relaxation .Effects are mediated by depressing the excitability of the limbic system via reversible binding at GABA-benzodiazepine receptor complex. Minimal cardiorespiratory depressant effect. The common drugs in this class are diazepam, midazolam, and lorazepam

Paradoxical effects: are more common in elderly, psychiatric disease, pre-existing CNS disease, substance abuse.

Continuous infusions must be used cautiously, as accumulation of the parent drug or its active metabolites may produce inadvertent over sedation.

Propylene Glycol Toxicity: Intravenous preparations of lorazepam and diazepam contain the solvent propylene glycol to enhance drug solubility in plasma. This solvent can cause local irritation to veins, which is minimized by injecting the drug into a large vein. A bolus of propylene glycol can cause hypotension and bradycardia, and prolonged administration of propylene glycol

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can cause paradoxical agitation, metabolic acidosis, and a clinical syndrome that mimics severe sepsis. When propylene glycol toxicity is suspected, it is wise to change to midazolam or propofol for sedation because these drug preparations do not contain this solvent.

Midazolam^{8, 9}: It is a BZP of choice for short term sedation, Water-soluble, 2-3 times potent than diazepam, short elimination half-life (1-4 hrs) & no long acting metabolites. In ICU patients, midazolam's elimination half-life may be greatly prolonged and clinically important accumulation may occur.

Minimal dose: 1 to 2 mg bolus, Infusions@ 0.04-0.2mg/kg/hr.

Infusion for long time can produce prolonged sedation due to:

1. Drug accumulation in CNS
2. Accumulation of active metabolite (hydroxy midazolam) in renal toxicity
3. Inhibition of CYT-P450 by other medications
4. Hepatic insufficiency

Diazepam: Elimination half-life of 21 to 37 hours, highly lipophilic, large v_d , highly protein bound. Major active metabolite, desmethyldiazepam, has a half-life of > 100 hours, eliminated by kidney, hence sedative effects prolonged in renal patients Metabolized by CYT-P 450.

Minimal dose: 5 to 10mg bolus or 0.05-0.2mg/kg

Infusions are not recommended due to risk of prolonged sedation & accumulation of parent drug & its active metabolites. Cirrhosis of liver increases the elimination half-life by 5 times.

Lorazepam¹⁰: Slower onset (5-20mins) & longer duration of action (2-6 hrs). Suited for long term sedation (ventilator dependent patients). The slow onset makes lorazepam less useful for the treatment of acute agitation. No active metabolites, lower lipid-solubility than midazolam causes less hypotension, it is metabolized by liver to inactive metabolites.

Loading dose: 0.02-0.06 mg/kg

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	MIDAZOLAM	LORAZEPAM	DIAZEPAM
LOADING DOSE	0.02–0.1 mg/kg	0.02–0.06 mg/kg	0.05–0.2 mg/kg
MAINTENANCE DOSE	0.04–0.2 mg/kg/hr	0.01–0.1 mg/kg/hr	Rarely used
ONSET	1–5 min	5–20 min	2–5 min
DURATION	1–2 hrs	2–6 hrs	2–4 hrs
CARDIAC EFFECTS	Minimal	Minimal	Present
POTENCY	3x	6x	
ANALGESIA	None	None	None
AMNESIA	Potent	None	None
ACTIVE METABOLITES	Yes	No	Yes

Table 4: comparison of benzodiazepines

Toxic effects: Hypotension, Respiratory depression, Excessive sedation.

Withdrawal symptoms: anxiety, agitation, disorientation, hypertension, tachycardia, hallucinations, seizures, unexplained delirium

Drug interactions: fluconazole, erythromycin, diltiazem, verapamil, cimetidine & omeprazole enhance the activity of BZD by inhibiting CYT-P450.

Rifampicin: increases metabolism of diazepam & midazolam

Theophylline: antagonizes benzodiazepine action by adenosine inhibition – significant interaction – should be avoided.

2. Propofol^{11, 12}: The mode of action of propofol is via the GABA receptor, Rapid onset of action; metabolized rapidly hepatically and extrahepatically Recovery within 10 minutes of discontinuation. It can accumulate with prolonged use 10% Lipid emulsion (0.1 mg fat / ml or 1.1 kcal /ml) counted as a part of daily nutrient intake in ICU patients.

Prolonged infusions –increase triglyceride and cholesterol levels .No analgesic properties. Rapidly acting sedative agent for short term sedation < 72 hrs Causes sedation & amnesia n Single iv dose – sedation within 1 minute, effects lasts for 5-8 mins Given as continuous infusion Awakening occurs within 10-15 mins even after prolonged infusion, Useful in transition from long acting sedative during patient recovery In Neurological injury – reduces cerebral O₂ consumption & icp.

Loading dose – 0.25-1 mg /kg

Onset of action < 1 min

Time to arousal – 10-15 mins

Maintenance infusion- 25-100 mcg/kg/min

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Adverse effects:

1. Hypotension- bolus dose, reliable, dose-related, Decreased SVR and contractility (CO)
2. Respiratory depression
3. Apnea with bolus dosing
4. Synergistic CV and respiratory depression with opioids
5. Vehicle (soybean emulsion): Hypertriglyceridemia-10% of patients (after 3 days of infusion)
6. Venoirritation
7. Infection/ sepsis
8. Anaphylactic reactions

Propofol infusion syndrome¹²

- Propofol infusion syndrome is an adverse idiosyncratic reaction associated with high doses (>75mcg/kg/ minute and long-term (>24-48 hours) use of propofol.
- Clinical features: Cardiomyopathy with acute cardiac failure, bradycardia, rhabdomyolysis, hyperlipidemia, lactic acidosis.
- Mechanism: Cytopathic hypoxia of electron transport chain & impaired oxidation of long chain fatty acids.

Management:

- Supportive treatment addressing the clinical manifestations.
- The propofol infusion should be discontinued immediately.
- Alternative sedative should be started.
- Intravenous crystalloid and colloid replacement and vasopressor and/or inotropic support.
- Cardiac pacing may be used for symptomatic bradycardia.
- Hemodialysis to treat the acute renal failure.

3. Dexmedetomidine

Introduced in 1999 it is highly selective alpha 2 adrenergic iv agonist.

Produces sedation, anxiolysis, mild analgesia, sympatholysis causes no respiratory depression.

Onset of action 1-3 mins

Duration of action -6-10 mins

Given as continuous infusion

Loading dose – 1 mcg /kg slow over 10 mins

Continuous infusion – 0.2 to 0.7 mcg/kg/ hr

Metabolism: biotransformation in liver to inactive metabolites + excreted in urine, No accumulation after infusions 12-24 h Pharmacokinetics similar in young adults + elderly

Molecular targets: neural substrates, locus ceruleus, natural sleep pathways.

Dose should be reduced in patients with severe liver dysfunction.

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Adverse effects:

- ▶ Hypotension (30%)
- ▶ Bradycardia (8%)
- ▶ Sympathetic rebound – following drug withdrawal
- ▶ Hence should not be continued for > 24 hrs.

	Propofol	Dexmedetomidine
Loading dose	0.25–1 mg/kg	1 µg/kg over 10 min
Onset of action	<1 min	1–3 min
Time to arousal	10–15 min	6–10 min
Maintenance infusion	25–75 µg/kg/min	0.2–0.7 mg/kg/hr
Active metabolites	No	No
Respiratory depression	Yes	No
Side effects	Hypotension Hyperlipidemia Contamination/Sepsis Rhabdomyolysis Propofol Infusion Syndrome	Hypotension Bradycardia Sympathetic rebound after >24 hr infusion

Table 5: comparison of propofol and dexmedetomidine

4. Haloperidol.¹³ Appealing sedative in ICU with little or no cardiorespiratory depression. Useful in agitated patients with delirium.

Actions: Sedative & antipsychotic effects – blocking dopamine receptors in CNS (basal ganglia).

Onset of action: 10-20 mins.

Prolonged duration of action: half-life 18-54 hrs

Uses:

1. Targeted for patients with delirium.
2. Ventilator dependent patients (lack of respiratory depressant action)
3. To facilitate weaning from mechanical ventilation.

Dosage:

Severity of anxiety dose

Mild 0.5-2mg

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Moderate 5-10mg

Severe 10-20mg

No evidence of sedative response for 10 mins, double the dose, if partial response at 10-20 mins second dose with lorazepam 1 mg, lack of response to second dose –switch to another agent.

Adverse effects¹⁴

1. Extrapyramidal reactions – incidence is reduced by giving it with benzodiazepenes.
2. Neuroleptic malignant syndrome – idiosyncratic reaction – hyperthermia, muscle rigidity, rhabdomyolysis. Rx – diphenhydramine & benztropine
3. Torsade de points – prolonged QT interval¹⁵

5. Opioids¹⁶

Opioids are commonly used to provide analgesia, narcosis, and anxiolysis.

Side-effects include respiratory depression, bradycardia, and hypotension secondary to histamine release.

They stimulate the chemoreceptor trigger zone and may cause nausea and vomiting.

Limitations of opioids:

- ▶ Tolerance
- ▶ Physical dependence
- ▶ Psychological dependence

a) Fentanyl

Fentanyl: synthetic opioid derived from meperidine, Short-acting opioid with rapid onset of action, after prolonged infusion the duration of action approaches that of morphine. Does not accumulate in renal failure

It does not cause histamine release and is suitable for analgesia in the haemodynamically unstable patient

Bolus: 1-3mcg/kg

Infusion: 0.01-0.05mcg/kg/min

b) Alfentanil: Alfentanil is a synthetic opioid, onset of action about five times faster than fentanyl. Alfentanil has a short duration of action and a rapid, predictable recovery even following infusion. It is hepatically metabolised to inactive substances and has a small volume of distribution. It is useful in patients with renal failure, but may accumulate in patients with liver failure. It is comparatively expensive.

Bolus dose: 10-20 mcg/kg

Maintenance infusion: 0.25-0.75mcg/kg/min

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c) Remifentanyl: Remifentanyl, an ultra-short-acting opioid metabolized by nonspecific tissue esterases. It has Rapid onset of action. Does not accumulate after infusions even in organ dysfunction. Elimination is not dependent on normal hepatic or renal function. Potency is similar to fentanyl.

Terminal half-life < 10 min, rapid blood-brain equilibrium. It can cause significant bradycardia.

Bolus dose: 0.15mcg/kg

Maintenance: 0.05-0.25mcg/kg/min

6. Ketamine: Ketamine is a phencyclidine derivative that antagonizes the excitatory neurotransmitter glutamate at NMDA receptors. It produces a state of dissociative anaesthesia, profound analgesia, and amnesia. It is also a potent bronchodilator. Ketamine is not commonly used as a sedative infusion due to sympathetic nervous system stimulation resulting in increased cardiac work and a rise in cerebral metabolic oxygen consumption. Hallucinations, delirium, nausea and vomiting frequently follow its use,

But it still has a role in the management of status asthmaticus.

7. Others

Barbiturates: Barbiturates have been used in the ICU, especially in the management of patients with head injuries and seizure disorders & for control of elevated ICP. They cause significant cardiovascular & respiratory depression and accumulate during infusions, leading to prolonged recovery times.

Neuromuscular blocking agents: Neuromuscular blocking agents do not provide sedation, occasionally used in critical care as adjuvants due to chronic muscle weakness and the risk of paralysis without adequate sedation. Development of myopathy is directly related to duration of infusion.

Indications include:

- a. Invasive ventilation modes (e.g. inverse ratios, high pressures);
- b. Control of ventilation in those with a high respiratory drive;
- c. Reduction of oxygen consumption in critically hypoxaemic patients;
- d. Control of raised intracranial pressure.

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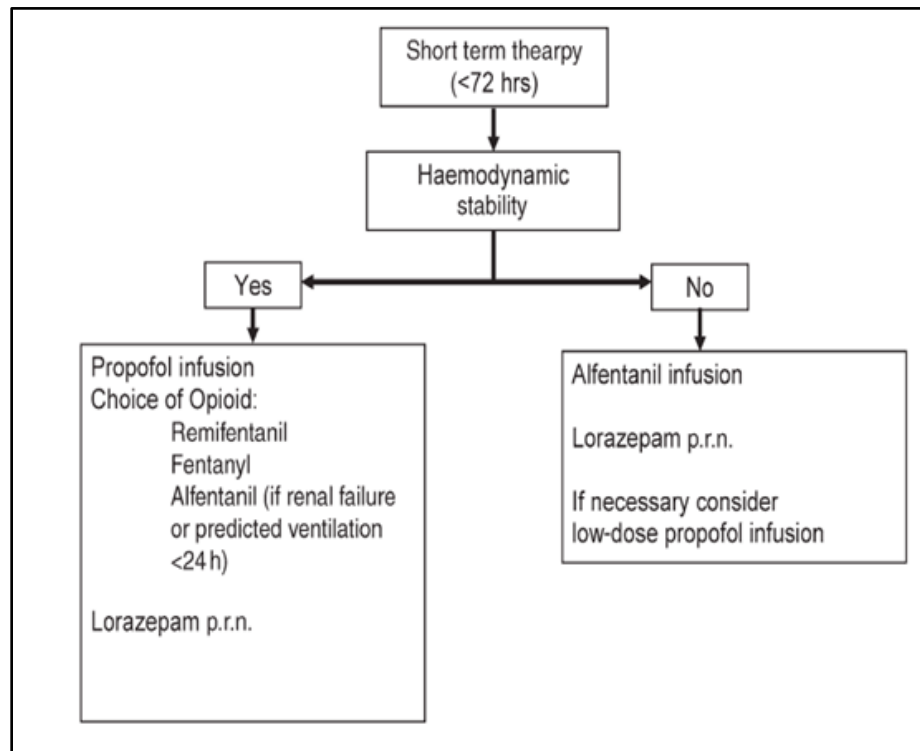
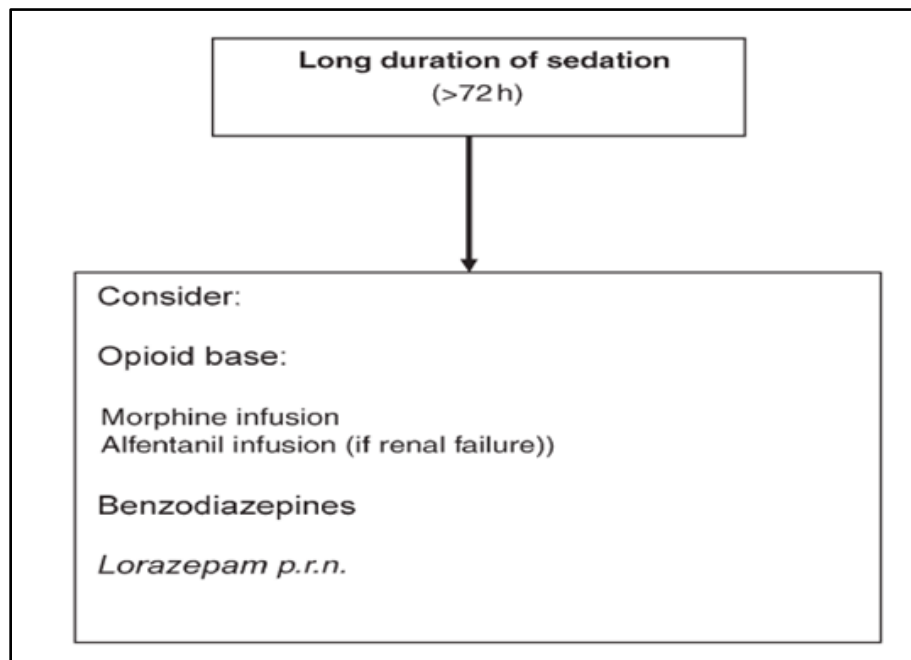


Fig. 1: Protocol for sedation¹⁷



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Bedside approach to agitated patient:

Step wise evaluation¹⁸

Recommendations:

1. Midazolam or diazepam should be used for rapid sedation of acutely agitated patients.
2. Propofol is the preferred sedative when rapid awakening (e.g., for neurologic assessment or extubation) is important.
3. Midazolam is recommended for short-term use only, as it produces unpredictable awakening and time to extubation when infusions continue longer than 48–72 hours.
4. Lorazepam is recommended for the sedation of patients via intermittent i.v. administration
5. Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. Patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol.

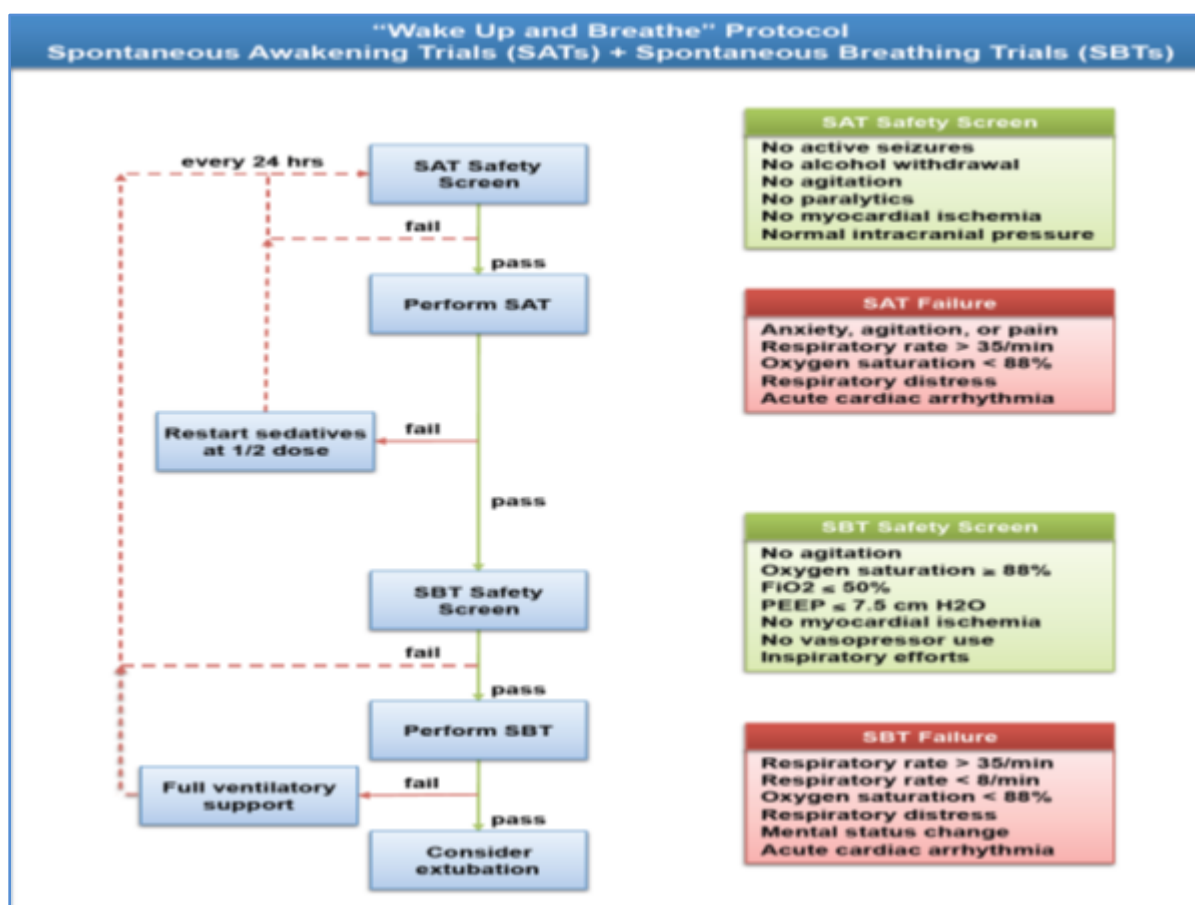


Fig. 2: Spontaneous awakening trails¹⁹

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CONCLUSION^{20, 21}:

Art of sedation

Under sedation: Fighting the ventilator, V/Q mismatch, Accidental extubation, Catheter displacement, CV stress → ischemia, Anxiety, awareness, Post-traumatic stress disorder.

Over sedation: Withdrawal syndrome, Delirium, Prolonged ventilation, CVS depression, Sleep disturbance, coma, respiratory depression, hypotension, bradycardia, gastrointestinal stasis, immunosuppression renal failure, Tolerance, tachyphylaxis.

Hence adequate sedation is essential in ICU. therapeutic dose of analgesic and sedative drugs differs for each patient, so use the recommended drug doses as a starting point, and titrate the dose as needed until the patient is comfortable.

Finally, when the patient begins to recover, start daily wake-up tests to prevent unwanted prolongation of drug effects.

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