Pain and sedation in the ICU

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Introduction

Most ICU patients experience some pain, anxiety and insomnia . The aims of adequate sedation and analgesia are to:

- reduce fear, anxiety and pain
- provide amnesia
- facilitate patient care
- improve ventilator synchrony
- decrease metabolic demands and oxygen consumption

Sedative and analgesic agents have significant side effects and complications. Regular assessment and adjustments of sedation and pain should be performed on all ICU patients.

Pain

Do not assume that children cannot feel pain because of age or the inability to express themselves coherently. All critically ill patients should have their pain assessed regularly and treated appropriately. Effective analgesia and sedation involves both pharmacological agents and environmental and psychological factors (e.g. distraction therapy, encouraging a regular sleep/wake cycle, decreasing ambient noise/ light, music therapy). There should be a plan in place for monitoring, prevention and management of withdrawal syndrome.

Pain Classification

- Procedural pain: Transient and does not outlast duration of procedure.
- Inflammatory pain: Occurs in the setting of local tissue injury. E.g. post-operative, trauma-related pain. Usually of recent onset and limited duration.
- Neuropathic pain: Associated with nerve damage. E.g. deep tissue injury, spinal cord damage, limb amputation.
- Chronic pain: Pain greater than 6 weeks in duration. May be associated with significant inflammatory response or nerve damage.

Assessment of pain

Pain assessment should be performed regularly using a scale appropriate for the age of the patient.
When ordering pain management for a patient, consider type and duration of pain, route of administration (enteral, intravenous, epidural, patient-controlled analgesia), dosage, the use of multi-modal strategies and consideration of potential side-effects.

Pain scales:

Infants: Behavioural assessment scales incorporating facial expression, motor responses and physiological indices.
Older children: Wong-Baker faces scale, visual analogue scale and numeric rating rate

Analgesics

Paracetamol:

- Pharmacology: Anti-pyretic and analgesic properties. Bioavailability dependent on route of administration. Metabolized in liver and metabolites are renally excreted.

- Notes/precautions: Useful for mild to moderate pain. Opioid-sparing effect when used in combination with opioid agents, synergistic with NSAIDs for severe pain. Hepatotoxicity can occur after chronic dosing. Review regular dosing after 48 hours.
- Administration: Oral, IV, rectal
- Dose:
  - **Age > 3 months**: *Oral/PR*: 10-15mg/kg/dose Q4-6H (max: 90mg/kg/day, < 4g/day total), *IV*: 10-15mg/kg/dose Q6H (max: 60mg/kg/day) (note IV bioavailability is 100%).
  - **Term neonates ≥10 days**: *Oral*: 10-15 mg/kg/dose Q4-6H (max: 90 mg/kg/day); *IV* 10mg/kg/dose Q6H (max: 40mg/kg/day); *Rectal*: Loading dose: 30 mg/kg then 20 mg/kg/dose Q 6-8H (max: 90 mg/kg/day)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Pharmacology: non-selective competitive inhibition of cyclooxygenase. Anti-pyretic, analgesic and anti-inflammatory properties.
- Useful for acute and chronic pain, mild to moderate. Effective in reducing acute surgical pain.
- Precautions: asthma, history of previous allergic reaction, abnormal LFTs, gastric irritation, renal impairment, coagulopathy/ thrombocytopenia. Avoid in renal failure, active bleeding or known hypersensitivity to NSAIDs (cross-sensitivity differs depending on the type of allergy- consult an allergist).
- Administration: Oral, rectal, IV

Analgesia doses (note higher doses may be used for anti-inflammatory indications)

Ibuprofen (Brufen)

Dose (> 6 mths age): *Oral*: 5-10mg/kg/dose Q6-8H (max 40mg/kg/day or 3.2g/day)

Diclofenac (Voltaren)

Dose (> 6 months age): *Oral/ PR*: 0.3-1mg/kg/dose 8-12H (max 3mg/kg/day or 200mg/day whichever is less)

Naproxen

Dose (> 2 years): *Oral*: 5-10 mg/kg/dose every 8-12 hours (max adult 1.1g/day)

Ketorolac (Toradol)

Dose (2-16 years old): *IV/IM*: 0.5mg/kg/dose up to Q6H (max 15mg/dose)
Dose (>16 years old): *IV/IM*: 30mg/dose (NOT/kg) up to Q6H (max 120mg/day)

Mefenamic acid (Ponstan)

Dose (> 12 years): *Oral:* 10mg/kg/dose Q8H (max 500mg/dose, 1.5g/day)

Opioids

Produces analgesia through a variety of central and peripheral opioid receptors. Morphine and fentanyl are the 2 most commonly used opioids in PICUs. Side effects common to most opioids include respiratory depression, sedation, nausea, vomiting, urinary retention, ileus or constipation, and pruritus or urticaria with histamine release. Less common effects include hallucinations, seizures, dysphoria and myoclonus.

Opioid withdrawal syndrome

- Withdrawal effects may occur in children who have received opioids for as few as 3-5 consecutive days

- Withdrawal symptoms may take up to 48-72 hours to manifest
- Consider gradual withdrawal if there has been opioid use greater than 4-5 days or if high doses have been administered. Wean infusion rates by 5-10% per day
- Risk of withdrawal nears 100% if the infusion duration was greater than 9 days
- Clonidine is useful as a morphine sparing agent and in controlling withdrawal symptoms

Symptoms of acute withdrawal include: agitation, sweating, nausea, vomiting, diarrhoea, hypertension, salivation, extreme discomfort, and pyrexia.

Opiate	Oral dose	IV dose	Pharmacology	Precautions/ Notes
Morphine	0.2-0.5mg/kg/dose Q3-6H (up to 30mg/dose)	**IV/IM/SC:** **Stat dose:** 0.05-0.2mg/kg/dose Q3- 4H Max dose: Neonate:0.1mg/kg/dose, Children: 10mg/dose, Adult: 20mg/dose **Continuous Infusion:** Usual:10- 80mcg/kg/hr Max dose: Neonate: 30mcg/kg/hr; Adults: 80mcg/kg/hr	~20-40% bioavailability. Half-life and clearance age-dependent, caution with use in neonates. **Onset:** IV: 5-10 min Oral (IR): ~30mins **Duration of action:** IV: 2-4hour Oral (IR): 4 hours Active metabolites are renally excreted	Poor and variable absorption from GIT. Histamine release may potentiate vasodilation and hypotension. Caution in renal failure.
Fentanyl	Not Available	IV/IM: **Stat dose:** 0.5-2mcg/kg/ dose Q30- 60min Max dose: 50mcg/ dose **Continuous Infusion:** Usual: 0.5- 10mcg/kg/hr	Rapid onset of action, useful for procedures/ intubation. **Onset:** IV: Almost immediate IM: 7-8 mins **Duration of action:** IV: 0.5-1 hr IM: 1 – 2 hrs More rapid development of tolerance. Metabolized in liver and renally excreted.	Synthetic opioid, 100 times more potent than morphine. Causes less histamine release than morphine, less haemodynamic instability. May cause vagal bradycardia, chest wall rigidity in rapid bolus doses. Highest emetogenicity among opioids and highly apnoeagenic, Caution in renal and liver failure.
Pethidine	Not Available	IV/IM/SC: **Stat dose:** 0.5-1.5mg/kg/ dose Q3-4H Adult: 25-50mg Q3-4H Max dose: 100mg/dose **Continuous Infusion:** 0.1-0.4mg/kg/hr.	**Onset:** IV: 5 mins **Duration of action:** IV: 2-4 hr	Effects similar to morphine, but 1/10 as potent as morphine. American Pain Society and ISMP do NOT recommend its use as an analgesic for chronic pain due to significant potential for dependence development and accumulation of active metabolite norpethidine (particularly in renal failure). This may lead to potentially serious adverse effects including tremor, twitching, agitation, confusion and seizures (rare)
Codeine	Oral: Children: 0.5-1mg/kg/dose Q4-6H Max: 60mg/dose Adult: 30mg q4-6H Max:120mg/dose	IM: Children: 0.5-1mg/kg/dose Q4-6H (Max: 60mg/dose) Adult: 30mg q4-6H (Max:120mg/dose)	40-70% bioavailability. **Onset:** Oral: 0.5-1 hr IM: 10-30 mins **Duration of action:** IV: 4-6 hr Converted to metabolite (morphine) in liver.	About 1/10 as potent as morphine. Poor activity in children < 5 years old, therapeutic failure is common Dose adjustment needed in renal and liver failure.

			Efficacy dependent on liver metabolism for conversion.	
Oxycodone	0.1- 0.2mg/kg/dose Q3-4H (immediate release preparation) 0.6-0.9mg/kg Q12H (controlled release) Max=10mg/dose	Not Available	60-80% bioavailability. **Onset:** Oral (IR): 10-15 mins Oral (CR): 30-60 mins **Duration of action:** Oral (IR): 3-6 hours Oral (CR): ~ 12 hours Both oxycodone & its active metabolite oxymorphone accumulates in renal failure. Clearance reduced in renal and liver failure.	Semi-synthetic mu- and kappa-opioid receptor agonist. Releases less histamine than morphine. About 10 times as potent as codeine. Multiple oral forms available. (Oxynorm- Oxycodone Immediate Release (IR); Oxycontin- Oxycodone Controlled Release (CR)
Methadone	**Stat dose:** 0.1-0.2mg/kg/dose Q4-12H Max=10mg/dose **Narcotic dependency**: 0.05-1mg/kg/dose Q6H, increase by 0.05mg/kg/dose until withdrawal symptoms are controlled. Dosing interval can be lengthened to Q12-24H after 24-48hrs. If withdrawal symptoms occur, taper at a slower rate	Not Available	36-80% bioavailability. **Onset:** Oral : 0.5-1 hour **Duration of action:** Oral: 4-8 hours, increase to 22-48 hours with repeated doses Has NMDA receptor antagonistic activity as well as opioid agonist activity. Metabolized to morphine. Rapid acting with long and variable duration of action and half-life (36-48 hrs).	Traditionally used for patients with opioid dependence. Can also be used as long term narcotic for chronic pain. Associated with prolonged QT interval and torsade de pointes in susceptible patients.
Remifentanil	Not Available	IV: **Stat dose:** 1mcg/kg/dose **Continuous Infusion:** 0.05-0.2mcg/kg/min **Ventilated**: 0.5-4mcg/kg/min, up to 8mcg/kg/min	**Onset:** IV :1-3 mins **Duration of action:** IV: 3-10mins	Synthetic opioid, equipotent to fentanyl. Short half life (3 min). Metabolized by plasma and tissue esterases. Remifentanil's extremely rapid clearance with a small volume of distribution results in it having less tissue accumulation than other opioids. Good for inducing a transient but profound opioid effect. High cost. Prolonged use associated with rapid development of tolerance. Cardiorespiratory effects similar to other opioids.

Opioid conversion table

(Consideration should also be given to the duration of action)

Drug	Potency		Onset (mins)	Duration (hours)
	Parenteral (IV or SC) (mg)	Oral (mg)		
Codeine	130	300	PO: 30-60 IM: 10-30	4-6
Morphine IV/PO	10	30	IV:<5 mins PO: 15-60	3 - 4
Morphine SR (sustained release)	Not applicable		PO: 20-40	8 -12
Fentanyl IV	0.1	Not available	IV: 1-2	0.5-1
Fentanyl patch			8-12	72
Oxycodone	Unavailable	20	10-15	3- 4
Oxycodone CR (Oxycontin)			60	12
Pethidine	100	Not available	IV:5-10	3-4
Methadone	Not available	20	PO: 30-60	12-24
Remifentanil	0.1	Not available		0.1

Other analgesics

Ketamine

- Potent analgesic in subanaesthetic doses (1- 5 mcg/kg/min)
- Produces 'dissociative anaesthesia' characterised by catalepsy, catatonia and amnesia in anaesthetic doses
- Can be administered intravenously or intramuscularly
- Commonly administered with a benzodiazepine and atropine to counter side-effects of dysphoria and increased secretions
- Some preservation of airway reflexes with less respiratory depression when compared to other anaesthetic agents
- Preferred anaesthetic agent for patients in shock or asthma due to its indirect sympathomimetic and bronchodilatory effects
- *(See section below for doses and pharmacology)*

Clonidine

- Alpha 2 adrenergic agonist with analgesic, sedative and anxiolytic properties.
- Can be administered orally, intravenously and via an epidural.
- *(See section below for doses and pharmacology)*

Dexmedetomidine

- Centrally acting alpha $_2$ adrenergic agonist, more selective than clonidine.

- Has analgesic and sedative effects, associated with minimal respiratory depression. Inhibits sympathetic activity, and may cause hypotension and bradycardia. Metabolized in the liver.
- Dose: loading 1mcg/kg/dose over 15mins, infusion: 0.2-0.7mcg/kg/hr
- Not recommended to run more than 24 hrs duration

Sedation

Sedative infusions have been associated with increased periods of mechanical ventilation in adults, and there has been some evidence that daily sedation holidays are associated with decreased length of mechanical ventilation and ICU length of stay in adults. However, this must be weighed against the safety of the patient and potential adverse effects such as patient-ventilator asynchrony, self-extubation, agitation and tachycardia. Doses of sedative agents should be titrated to produce the degree of sedation required.

Benzodiazepines have been traditionally used to provide sedation in the PICU. Withdrawal symptoms may occur with cessation of sedative agents, especially benzodiazepines (17-30% incidence of withdrawal syndrome with the use of midazolam).

Withdrawal symptoms may occur within hours of stopping the sedative agents. Symptoms and signs include CNS (agitation, seizures, hallucinations, psychosis) and autonomic (tachycardia, sweating, fever, vomiting) features.

Strategies to decrease or prevent occurrence of withdrawal syndrome include tapering the total daily dose of benzodiazepines by 5-10% per day, daily drug holidays, planned substitution of one class of sedation with another, and use of longer acting agents or adjuncts (E.g. clonidine, lorazepam, diazepam). This should be considered after 5-7 days of continuous sedative infusion.

Sedative	Oral Dose	IV dose	Pharmacology	Notes/ precautions
Chloral hydrate	Procedural sedation: 30-50mg/kg/dose Max: 1g/dose or 2g/24hrs Sedation: 10-20 mg/kg/dose Q6-8H Max: 500mg/dose or Total: 60mg/kg/day or or 2g/24hrs	Not Applicable	Rapidly absorbed from GI tract. Elimination half-life prolonged in infants (up to 36 hrs), half-life 4-9 hr in adults. Metabolized in the liver and renally eliminated.	May be a myocardial depressant. In toxic doses can cause respiratory depression and hypotension. Caution in renal or hepatic failure. In chronic administration, do not stop the drug abruptly as it may result in delirium
Promethazine	Anti-histamine/ anti-emetic: 0.2-0.5mg/kg/dose Q6-8H; Max: 25mg/ dose Adult: 12.5mg TDS Sedative/ hypnotic: 0.5-1.5mg/kg/dose Q6-8H; Max: 50mg/ dose Adult: 50mg per dose	Anti-histamine/ anti-emetic: 0.2-0.5mg/kg/dose Q6-8H; Max: 25mg/dose Adult: 12.5mg TDS Sedative/ hypnotic: 0.5-1.5mg/kg/dose Q6-8H; Max: 50mg/ dose Adult: 50mg per dose	**Onset:** Oral : 0.5-1 hour IV: 3-5mins **Duration of action:** Oral: 2-6 hours, Half-life 7-14 hours. Metabolized in the liver.	Not recommended in patients < 24 months old. Can cause respiratory depression/ apnoea, caution in susceptible patients (bronchiolitis/ history of apnoea).
Diazepam	**Stat dose:** 0.2-0.8mg/kg/day Q6-8H Max: 10mg/dose	**Stat dose:** 0.1-0.4mg/kg/dose Q2-4H Max: 20mg/dose	Good oral bioavailability (85-100%) **Onset:** Oral : 0.5-1 hour	Less potent than midazolam when given intravenously. May cause myocardial depression with decreased cardiac output

		or 0.6mg/kg within an 8hr period	IV: Almost immediate **Duration of action:** IV: 20-30 mins Elimination half-life about 40 hours in adults. Active metabolite with long half-life (50-100hrs). Longer duration of action and offset than midazolam	and hypotension.
Lorazepam	Sedative/ anxiolytic: 0.02-0.06mg/kg/dose Q6-8hr;Max: 3mg/dose Adult: 1-3mg/dose Q8-24H;Max: 10mg/day	Procedural sedation: **Stat dose:** 0.05-0.2mg/kg/dose Max: 2mg/dose Sedation/ anxilytic: 0.05-0.1 mg/kg/dose Q4-8H Max: 4mg/dose	(90%) Good oral bioavailability Elimination half-life about 10 hours. **Onset:** Oral : 0.5-1 hour IV: 5-20mins **Duration of action:** 6-8 hours	Less lipophilic with a smaller volume of distribution and a longer intracerebral half-life (12 hours) as compared with dazepam (15–30 minutes) and, therefore, a potentially longer anticonvulsive effect
Midazolam	**Stat dose:** : 0.25- 0.5mg/kg Max: 20mg/dose Intra-nasal: 0.2-0.4mg/kg Max: 15mg/dose	**Stat dose:**: 0.1-0.2mg/kg/dose (up to 0.5 mg/kg/dose) Max: 10mg/dose Conscious sedation during mechanical ventilation **Continuous Infusion:** 1-4mcg/kg/min (up to 32mcg/kg/min for status epilepticus)	(45%) Poor bioavailability. Shortest elimination half-life of all benzodiazepines. **Onset:** Oral : 0.5-1 hour IV: 1-5 mins, peak at 5-10 mins **Duration of action:** 1-2 hours Duration of action significantly longer when given via continuous infusion. Metabolized in the liver and renally excreted.	Induces antegrade amnesia. Adverse effects include tolerance, dependence and withdrawal syndrome. Hypotension with bolus administration. Active metabolites can accumulate in renal failure.
Clonidine	Hypertension: **PO dose:** 0.5-6mcg/kg/dose Q8-12H Max: 2.4mg/day Adult: 50-300mcg/ dose Sedation/ analgesia: **PO premed:** 2.5 mcg/kg/dose Narcotic dependency: Start with Clonidine 0.5–1.0 mcg/kg/dose test dose, followed by 0.5–1.25 mcg/kg/dose Q4H x 4 days, then 0.5–1.0 mcg/kg/dose Q6H x 2-4 days, followed by 0.25–0.5 mcg/kg/dose Q6H x 2-4 days, 0.25– 0.5 mcg/kg/dose Q8-12H x 2 days then stop	Hypertension: **Stat dose:** 1-5 mcg/kg/dose slow IV Sedation/ analgesia: **Continuous Infusion:** 0.3-2mcg/kg/hr **Epidural**: 0.5 mcg/kg/hr	Alpha$_2$ agonist. Acts centrally to reduce sympathetic drive when given systemically. 75-95% bioavailability. Elimination half-life 6-24 hours. **Onset:** PO: 0.5-1hour **Duration of action:** PO: 6-10 hours Has analgesic properties; can be added to epidurals to prolong and increase potency of analgesia.	Produces sedation without respiratory depression. Has anxiolytic effects comparable to benzodiazepines. Reduces requirement for other sedative agents. Lowers blood pressure in hypertensive patients. Central effects useful in managing central dysautonomia. Sudden cessation may cause withdrawal symptoms or rebound hypertension. Adverse effects include drowsiness, bradycardia, hypotension, dry mouth. Caution with use in patients with existing bradyarrhythmias, myocardial dysfunction and chronic renal insufficiency
Ketamine	Not Available	IV/IM: **Sedation/**	Has sympathomimetic effects and direct smooth	Induction agent for general anaesthesia, also has

		<u>analgesia</u>: **Stat dose:** 0.5-2mg/kg/dose **Continuous Infusion:** 1-20 mcg/kg/min **<u>Anaesthesia</u>:** **Stat dose:** 1-2mg/kg/dose IV, 5-10mg/kg IM **Continuous Infusion:** 10-40mcg/kg/min	muscle relaxation. Direct stimulation of cardiostimulatory centres in the brain. **Onset:** IV :30 secs **Duration of action:** IV: 5-10mins IM: 15-30 mins Incompatible with aminophylline, magnesium, salbutamol	analgesic and amnesic properties. Produces a "dissociative" anaesthesia. Reduces bronchospasm. Watch for emergence phenomenon such as vivid dreams, hallucinations, nightmares and agitation. Incidence of emergence can be reduced by concomitant use of benzodiazepines. May increase upper airway secretions. Causes tachycardia and hypertension. Caution in raised intracranial pressure, heart failure/ myocardial dysfunction, open ocular injury or raised intraocular pressure, psychiatric states.
Propofol	Not Applicable	**<u>Sedation</u>:** **Stat dose:** 2-3mg/kg/dose Anaesthesia: **Continuous Infusion:** Children : 7.5-15mg/kg/hr, Adult : 3-12mg/kg/hr <u>Sedation</u>: **Continuous Infusion:** 1-3mg/kg/hr Max= 5mg/kg/hr or 80mcg/kg/min <u>Refractory status epilepticus</u>: **Continuous Infusion:** 1.5-10mg/kg/hour	Non-barbiturate hypnotic sedative. Formulated in an oil-in water emulsion made of egg lecithin & soybean oil. Avoid in patient with hypersensitivity to egg products, soybeans or soy products. **Onset (dose dependent):** 9-51 secs **Duration (dose & rate dependent):** 3-10mins. Brief duration of action (about 5 min) with rapid offset. Rapid offset due to redistribution and rapid metabolism.	Intravenous anaesthetic agent. Will produce loss of consciousness, apnoea, loss of airway reflexes and hypotension in therapeutic anaesthetic doses. NO analgesic properties. May be painful on injection. Used for induction of anaesthesia, short procedural sedation. Continuous infusion associated with ***propofol infusion syndrome****(PrIS)*- acidosis, bradyarrhythmia, rhabdomyolysis and death. Caution with continuous infusion use in children < 16 years of age. Avoid high doses more than 5mg/kg/hr over prolonged periods (> 48hrs) in children in view of PrIS. May precipitate malignant hyperthermia in susceptible population.

Recommendations for sedation and analgesia in the ICU

Procedural pain and sedation

- Local or regional anaesthetic techniques should be used where available (eg. EMLA cream, local infiltration of lignocaine prior to procedure)
- Paracetamol is useful (IV, suppository or PO) for mild to moderate procedural pain
- NSAIDs (eg. Supp diclofenac) may be considered as an adjunct in post-operative surgical management if there are no contra-indications (eg. Gastritis, renal impairment, asthma history)
- If pain is severe then consider intravenous opioids such as morphine or fentanyl, or ketamine (IV or intra-muscular)

- Propofol may be considered for procedural sedation (where the airway is already secured or where there is immediate access to advanced airway support). Note that propofol has NO analgesic properties and should be used in conjunction with an analgesic for procedures.

Post-operative pain and sedation

- Continuous morphine infusion for analgesia is our unit's preferred analgesic agent for patients after major surgical procedures. The usual starting infusion dose is 20 mcg/kg/hour.
- PCA may be considered in the older child. This is usually managed by the anaesthetic pain team.
- For post-operative cardiac patients after cardiopulmonary bypass, our unit uses a combination of morphine and midazolam infusions to provide analgesia and sedation.

Non-surgical intubated patients

- IV midazolam infusion is our unit's preferred sedative agent for the majority of intubated patients.
- The level of sedation should be titrated to patient comfort and safety, and should regularly assessed.
- Over-sedation can lead to decreased cough reflex, dependent edema and secretion accumulation.
- Consider enteral sedation once feeds are tolerated (eg. chloral hydrate, PO lorazepam, antihistamines)
- IV ketamine infusion may be useful as a sedative/analgesic agent for intubated asthmatic patients in view of its bronchodilator effects.

Neonates

- Providing adequate analgesia is challenging for a neonate in view of the difficulties with an appropriate pain assessment scale. Many agents have decreased clearance rates in the younger age group, making the risk of side-effects higher.
- Paracetamol (suppository, per oral or per rectal) can be given to the neonate for procedural pain relief provided there is no evidence of liver impairment
- Neonates who have undergone major surgical procedures can be started on an intravenous morphine infusion. In view of the delayed clearance in neonates, morphine should be started at a lower dose range (10 mcg/kg/hour) and the patient observed for side-effects such as sedation and respiratory depression
- NSAIDs are contra-indicated in this age group
- IV midazolam can be used for an intubated neonatal patient requiring sedation

Neuromuscular Blockade (NMB)

Neuromuscular blockade (NMB) in the PICU is used:

- as part of rapid sequence induction
- to prevent patient-ventilator asynchrony
- to prevent shivering when inducing hypothermia
- as part of the management of specific medical conditions (e.g. pulmonary hypertension, raised intracranial pressure)
- for certain surgical procedures to protect the surgical repair (e.g. tracheostomy, tracheo-eosphageal fistula repair, slide tracheoplasty, cardiac surgery with open sternotomy)

Neuromuscular blockade should not be provided without sedation. The degree of neuromuscular blockade can be assessed using peripheral nerve stimulation with a "train of four (TOF)" pattern. One to two contractions following TOF stimulation suggests adequate neuromuscular blockade. The most common peripheral nerves used for testing include the ulnar nerve and facial nerve.

The use of NMB agents are not without complications. Prolonged immobilisation from paralysis can lead to muscle atrophy, pressure sores, exposure keratitis, pulmonary atelectasis and joint contractures. Continuous administration of NMB agents (especially in conjunction with steroids or aminoglycoside use, sepsis or multi-organ dysfunction) has been shown to increase the risk of critical illness polyneuropathy and myopathy (CIPNM) which may cause prolonged ventilator days and increased morbidity.

Ways to minimise development of CIPNM include:

- Reviewing the need for NMB on a daily basis
- If safe to do so, consider a daily NMB cessation until spontaneous respiration and movement returns, so levels of analgesia and sedation can be assessed
- Daily assessment of the degree of NMB with peripheral nerve stimulation- adjust infusion rates accordingly
- Correct electrolyte and acid-base derangements
- Be mindful of potential drug interactions resulting in prolonged action of NMB agents
    - Drugs that potentiate blockade include steroids, anti-arrhythmic agents, midazolam, beta blockers, calcium channel blockers, cyclosporine, antibiotics (aminoglycosides, clindamycin)

NMB AGENTS (NMBA):

NMB drug	IV dose	Pharmacology	Notes/ precautions
Succinylcholine	**RSI dose:** (Neonates/ children) 1-2mg/kg/dose, (children > 12yrs) 0.6-1 mg/kg/dose Neonates/Infants: Initial: 2 -3mg/kg; Maintenance: 0.3-0.6 mg/kg every 5-10 minutes as needed Children and Adolescents: Initial: 1 mg/kg; maintenance: 0.3-0.6 mg/kg every 5-10 minutes as needed	Ultra-short acting depolarizing NMBA. **Onset :** 60–90 seconds **Duration:** Less than 8 mins. Rapidly metabolized by plasma cholinesterase. Fasciculations occur with depolarization of the neuromuscular junction.	Used mainly for purposes of RSI in view of multiple adverse effects. May cause transient increases in ICP, intra-ocular pressure, gastric pressure, masseter muscle spasm. Side effects: bradyarrythmia, hypotension and muscle fasciculations. Risk of ***hyperkalaemia*** (increases plasma levels by 0.5-1mEq/L). **Contraindicated** in: Renal failure, pre-existing hyperkalaemia (serum K>5.5 mEq/L), history of burns/ crush injury/ trauma (between 48H to 120 days post injury), neuromuscular diseases/ myopathy, family history of malignant hyperthermia, glaucoma/ open globe injury.
Atracurium	**Stat dose:** 0.3-0.6mg/kg/dose followed by maintenance doses of 0.3-0.4 mg/kg as needed to maintain neuromuscular blockade **Continuous Infusion:** 5-10mcg/kg/min Max: 20mcg/kg/min	Intermediate-acting non depolarizing NMBA. **Onset :** 2–3 mins **Duration:** 45–60 mins Broken down via Hoffman degradation and plasma cholinesterase.	The main limitation of this agent is histamine release which appears to be dose-dependent, accounting for haemodynamic instability (hypotension) and bronchospasm

		Minimal renal excretion, safe in both renal and liver failure.	
Cis-atracurium	**Stat dose:** 0.1mg/kg/ dose followed by 0.1-0.15 mg/kg over 5-10 seconds **Continuous Infusion:** 1-4 mcg/kg/minute **Max:** 10mcg/kg/min	Intermediate-acting non-depolarizing NMBA. **Onset :** 2–3 mins **Duration:** 45–60 mins Similar degradation & excretion to atracurium, hence safe in both renal and liver failure.	Cisatracurium has 2 advantages over atracurium: 1) it releases less histamine and 2) produces less laudanosine which is known to cause convulsions at high concentrations
Rocuronium	**RSI**: 0.6-1.2 mg/kg/dose stat **Stat dose:** 0.6-1.2 mg/kg stat, then 0.1-0.2 mg/kg boluses; repeat as needed **Continuous Infusion:** 5 -15 mcg/kg/minute	Intermediate-acting non-depolarizing NMBA. **Onset :** 60-90 secs **Duration:** 30–60 mins Hepatic and renal dysfunction may prolong the effect of the block	Fastest onset of action among the current non-depolarising NMBAs, may be used for RSI. Major advantage: Few cardiovascular effects, has a very stable cardiovascular profile with no histamine release even at very high doses
Pancuronium	**Stat dose:** 0.1- 0.15mg/kg/dose every 30-60 minutes **Continuous Infusion:** 0.25-0.75mcg/kg/min **Max:** 1.7 mcg/kg/min	Long-acting non-depolarizing NMBA. (85%) Primarily renal excreted. **Onset :** 3 -6 mins **Duration:** 60 - 100 mins	May cause tachycardia and hypertension as result of vagolytic and adrenergic side effects. Reduce dose in neonates. Slow onset and long duration of action. Pancuronium should only be used where prolonged relaxation is required, as the incidence of residual muscle paralysis in recovery is much higher with long-acting agents. Undergoes significant renal elimination, caution in renal failure.
Vecuronium	**Stat dose:** 0.1 mg/kg/dose; repeat every hour as needed **Continuous Infusion:** 0.5-2mcg/kg/min **Max:** 10mcg/kg/min	Intermediate-acting non-depolarizing NMBA. **Onset :** 2–3 mins **Duration:** 60 -75 mins Derivative of pancuronium. Metabolised in the liver, biliary excreted. Active metabolites renally excreted	Caution in renal/ liver failure as accumulated active metabolites may cause prolonged neuromuscular blockade in the presence of hepatorenal dysfunction

Recommendations for paralysis in the ICU

- Paralysis should NOT be started without adequate sedation and analgesia
- Succinylcholine is the recommended NMB agent for induction during intubation in view of its rapid onset of action and short half life. Be mindful of contraindications for the use of this drug (see table above). To minimise fasciculations associated with succinylcholine, a sub-paralytic dose of non-depolarising NMB (eg. rocuronium, atracurium, cis-atracurium) can be administered prior to dose of succinylcholine
- Where continuous infusions are required (eg. pulmonary hypertensive crisis, open sternotomy wound in a post-op cardiac patient), our unit prefers an IV rocuronium infusion
- Daily peripheral nerve stimulation should be performed on patients on continuous infusions, aiming for 1-2 contractions after a Train-of-Four stimulation.
- When stable, daily NMB 'holidays' should be performed, ensuring adequate sedation/ analgesia.

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