SESLHDMG/133

Medicine Guideline

Subcutaneous Ketamine for refractory Neuropathic Pain in the Palliative Care Setting - Medicine Guideline

Areas where Protocol/Guideline applicable	SESLHD Inpatient setting (including Calvary hospital)
Authorised Prescribers:	Specialist Palliative Care Service
Indication for use	Refractory neuropathic pain not responding to standard analgesic drugs, including optimal use of opioids and adjuvant therapy. Must be under the supervision of a Palliative Care and/or Renal Supportive Care Specialist.
Proposed Place in Therapy	• Ketamine is to be used third or later line, when neuropathic pain remains refractory despite standard analgesic medications including opiates and adjuvant therapy. • Ketamine is a parental dissociative general anaesthetic agent. • At sub anaesthetic doses, Ketamine may be used for the provision of analgesia in a wide range of clinical situations and also as an adjuvant medication with analgesics, particularly opioids. • Ketamine acts as an antagonist (blocker) at the N-methyl-D-aspartate (NMDA) receptor. The glutamate section of the NMDA receptor is involved in the development of central (dorsal) horn sensitisation, and “wind-up" pain (where consistent nociceptive stimulus produces a pain response out of proportion to the stimulus both in duration and intensity). NMDA receptor activation is involved in severe and prolonged pain from both nociceptive input (e.g. mucositis, incident bone pain) and neuropathic pain. Ketamine may “wind down” this pain response, by turning off the transmission at the NMDA receptor level.

Contra-indications	The use of Ketamine is contraindicated in patients in whom a significant elevation of blood pressure would be dangerous, including patients with the following conditions:
	  ○ Cerebral trauma
	  ○ Intra-cerebral mass or haemorrhage
	  ○ Increased intracranial pressure.
	
	• In addition, the use of Ketamine is contra-indicated in patients with the following conditions:
	  ○ Delirium
	  ○ History of serious psychiatric illness
	
	• Ketamine is also contra-indicated with concurrent use of aminophylline or theophylline as it may lead to a reduced seizure threshold.

Precautions and	• Other relative contraindications include:

relative Contraindications	○ Severe cardiovascular disease ○ Heart failure ○ Severe or poorly controlled hypertension ○ Arrhythmia ○ Recent myocardial infarction ○ History of cerebrovascular accident ○ Recent seizures or a history of uncontrolled epilepsy ○ Haemorrhage ○ Acute illness ○ Increased intraocular pressure (e.g. glaucoma) ○ History of acute intermittent porphyria ○ History of uncontrolled hyperthyroidism • **IF THE PATIENT HAS ANY OF THE ABOVE CONDITIONS LISTED** – Discussion with the Palliative Care Medical Consultant **MUST** occur before commencing Ketamine. • Where the use of Ketamine is contraindicated, Lidocaine or Methadone may be considered for use.
Important Drug Interactions	• Any medicine that raises blood pressure or heart rate – will increase adverse effects of ketamine. • Strong inhibitors of CYP3A4 may increase ketamine effect –e.g. clarithromycin, ketoconazole, posaconazole (considered less significant for subcutaneous ketamine but may need consideration) • Strong inducers of CYP3A4 may reduce ketamine effect -e.g. carbamazepine, phenytoin, primidone, rifampicin (considered less significant for subcutaneous ketamine but may need consideration)
Suggested Dosing	• Trial a single dose of 10 to 25mg subcut to establish absence of severe immediate side effects • Commence at a starting dose of 50 to 100mg/24hr by Continuous Subcut Infusion with sodium chloride 0.9% • If necessary, up titrate by 50 to 100mg per 24hr, until adequate pain relief is achieved. • The usual maximum dose is 500mg/24hr (maximum reported dose 3.6g/24hr)
Preparation	Ketamine (as hydrochloride) 200 mg per 2 mL vial (Ketalar®) • contains 0.1 mg/mL benzethonium chloride as preservative • pH = 3.5 to 5.5 • Schedule 8 drug
Diluents	Sodium chloride 0.9%

Drug Compatibility	Ketamine is preferably administered alone due to low pH. It ideally should not be mixed in a syringe with any other medication due to lack of robust compatibility data. **Compatible fluids:** sodium chloride 0.9% (preferred), water for injection
Duration of Therapy	• Duration of administration should be based on individual pain response, presence of adverse effects, effect on performance status and patient preference. • Ketamine should not be continued longer than 5 days if there is no improvement in the average pain score.
Prescribing Instructions	Ketamine must be prescribed on the eMR, eRIC, or in Mosaiq/ARIA. In the absence of eMM systems, the appropriate paper medication chart may be used.
Administration Instructions	The ketamine can be diluted and administered in a 10mL or 20mL syringe via Continuous Subcut Infusion over 24 hours
Known Adverse effects	The adverse effects of Ketamine are quite common when used for patients with cancer pain and vary in severity and frequency according to: route of administration, dose, infusion rate and illness of the patient, co-morbidities, type and duration of the pain, gender, age and concurrent medications. • **Cognitive/Psychological**: dissociation, hallucinations/illusions, vivid dreams, nightmares, delirium, confusion and irrational behaviour; euphoria • **Cardiovascular:** elevated blood pressure, increased heart rate, bradycardia, arrhythmias (rare) • **Gastrointestinal:** nausea and vomiting, anorexia, increased salivation. • **Respiratory:** increased secretions, laryngospasm (rare). • **Ocular:** diplopia, nystagmus, increased ocular pressure. • **Central nervous system**: sedation, drowsiness, insomnia, dizziness, disorientation, tonic/clonic movement. • **Dermatologic:** irritation at injection site (due to low pH) may require re-siting subcut cannula daily or more often

Monitoring requirements	• Pain assessment should occur prior to, during, and after administration of Ketamine; the assessment should be documented in the patients Electronic Medical Record (eMR2) and scored in pain chart of BTF observations every four hour or as advised by the Palliative Care team. • Assess patient for side effects of ketamine (see Known Adverse Effects as above), with documentation of same in eMR • Use validated assessment tools for delirium where possible i.e.NuDESC or 4AT • 4 hourly SC site checks as per Subcutaneous Syringe Driver inpatient management form SES130.021 • Any signs of Adverse effects / Toxicity stop infusion and **notify the Palliative Care Consultant**
Management of Complications	Any signs of Adverse effects / Toxicity stop infusion and **notify the Palliative Care Consultant**
Basis of Protocol/Guideline	• Analgesic Expert Group. (2009). Therapeutic guidelines: Analgesic. Version 5, 2007. Melbourne: Therapeutic Guidelines Limited • Amin P at al, Case report: Efficacy & Tolerability of ketamine in opioid-refractory cancer pain; *Journal of Pain & Palliative Care Pharmacotherapy*;28;2014;233-242. • Cochrane Collaboration 2003; Updated May 2012. Bell RF et al. 3 new studies identified-all 3 excluded from review "Current evidence is insufficient to assess the benefits & harms of Ketamine as an adjuvant to opioids for the relief of cancer pain. More RCTs are needed." • Equip National Guidelines 12.11.1 • Hardy, Janet., Quinn, Stephen., Fazekas, Belinda., Plummer, John., Eckermann, Simon., Agar, Meera., Spruyt, Odette., Rowett, Debra., and Currow, David C. 2012. Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain , *Journal of Clinical Oncology 2012*. 30(29) pp3611-3617 • Jackson K et al, Ketamine & cancer pain: the reports of my death have been greatly exaggerated, JCO 31(10), April 1 2013 • Leppert W, Ketamine in the management of cancer pain; JCO 31(10), April 1 2013 • MIMS Online – accessed via CIAP. • Palliative Care Formulary online. In Medicines Complete. Pharmaceutical Press. Available via CIAP. • Palliative Care (December 2024). In Therapeutic Guidelines Ltd. Available via CIAP. • Spruyt O et al, Integrating new evidence about an old drug: growing pains as Palliative Medicine matures; *Journal of Pain and*

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GOVERNANCE	
Enactment date *Reviewed* (Version 1.1)	1 February 2024 April 2025
Expiry date:	April 2028
Ratification date by SESLHD DTC	3 April 2025
Chairperson, DTC Committee	Stuart Binns, Acting Chair, SESLHD DTC
Version Number	1.1