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Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 23: SEDATION
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 - 2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the chapter for sedation.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
23.1.1 Procedural sedation and analgesia		
- Minimal sedation and anxiolysis (no analgesic effect required)	Diazapem, IV	Amended to first line option
	Midazolam, IM	Amended to second line option
- Moderate sedation and analgesia	Fentanyl, IV	Directions for use amended
	Propofol, IV	Prescriber rights amended (i.e. in consultation with a specialist)
	Ketamine, IV	Directions for use not amended
- Reversal Agents	Naloxone, IV	Added for opioid toxicity
	Flumanzenil, IV	Not added for benzodiazepine toxicity
23.1.2 Sedation in intensive care	Ketamine, IV	Not added
- Short term sedation (less than 24 hours)	Dexmedetomidine, IV	Not added
	Propofol, IV	Amended
23.1.3 Sedation in palliative care	Lorazepam, oral	Deleted (Moved to Chapter 24: Medicines used in palliative care)
	Haloperidol, oral	Deleted (Moved to Chapter 24: Medicines used in palliative care)

General
Definitions and clinical management was aligned with the South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015, wherever possible to ensure standardisation of practice. Terminology was likewise updated for correctness, throughout the chapter.

23.1.1 PROCEDURAL SEDATION AND ANALGESIA

Minimal sedation and anxiolysis (no analgesic effect required)
Diazapem, IV: *amended to first line option*
Midazolam, IM: *amended to second line option*
Diazepam, IV recommended as 1st line option rather than midazolam, IM – as diazepam, IV has a shorter duration of action (suggested by the evidence cited in the STG[1]).

Moderate sedation and analgesia
Fentanyl, IV: *directions for use amended*
Aligned with the South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015[2], as follows:

- Fentanyl, IV, 0.25 mcg/kg.

[1] Evidence circulated to the NEMLC after the NEMLC meeting: Mitchell AR, Chalil S, Boodhoo L, Bordoli G, Patel N, Sulke N. Diazepam or midazolam for external DC cardioversion (the DORM Study). Europace. 2003 Oct;5(4):391-5. http://www.ncbi.nlm.nih.gov/pubmed/14753637
[2] The South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015. South Afr J Anaesth Analg 2015;21(2)S1-S36.

o Titrate to effect and repeat dose every five minutes until desired level of analgesia has been achieved.

Level of Evidence: III Guidelines

Propofol, IV: *prescriber rights amended*

The Adult Hospital Level Committee was of the opinion that administration of propofol should be in consultation with a specialist, due to safety concerns.

Level of Evidence: III Expert opinion

Ketamine, IV: *directions for use not amended*

Previously, the NEMLC recommended that the Adult Hospital Level ERC the evidence for the use of benzodiazepine with ketamine for inducing moderate sedation and analgesia[3].

Evidence review:

Strayer et al, 2008[4]: Systematic review of studies (few RCTs, mostly small and observational) shows that the rate of emergence reactions (e.g. disorientation, dream-like experiences, hallucinations) associated with ketamine used for procedural sedation and analgesia is 10% to 20%. Pooling of data to perform a statistical analysis was not possible as studies reviewed were heterogeneous in design and quality with most intervention RCTs done in the 1970's where concomitant medicines were used (most not currently used in clinical practice).

This qualitative analysis shows that sedating agents may prevent and terminate ketamine emergence reactions (most studies were with benzodiazepines) whilst interventions such as music and pre-induction counselling may minimise emergence reactions. Midazolam was mostly administered as premedication dosed at 0.05-0.07 mg/kg, but co-administration with ketamine and post-procedure as required for management of emergence delirium was also reported.

Akghlagi et al, 2019[5]: Small RCT (n=185), using convenience sampling in primarily young male patients undergoing orthopaedic procedures due to traumatic injuries and Richmond Agitation-Sedation Scale scores to measure agitation, showed that premedication with midazolam (0.05 mg/kg) or haloperidol (5 mg) prior to procedural sedation with ketamine likely reduces the incidence of recovery agitation, but increased recovery times and did not alter overall clinician satisfaction. Study results may not be generalisable to other patient cohorts, but is aligned with previous studies that shows the benefit of benzodiazepines in reducing ketamine-induced phenomena. Further research is required to confirm the benefit of midazolam and haloperidol for all patients and to assess the differences in adverse events.

Recommendation: The text be retained in the STG as follows:

Ketamine, IV, 0.5 mg/kg (the addition of a benzodiazepine is often recommended to reduce the incidence/severity of emergence phenomena such as hallucinations and dreaming, but the benefit of this is unclear).

Rationale: Limited RCT evidence of benefit of benzodiazepines to prevent ketamine-induced agitation in adults. Systematic review of studies of low methodological quality (old RCTs and observational studies) and a recent small RCT suggests that benzodiazepines may be safe and effective. However, further research is required.

Level of Evidence: III Systematic review (studies of low methodological quality), Disease-oriented RCT

[3] Minutes of the NEMLC meeting of 27 September 2018

[4] Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med. 2008 Nov;26(9):985-1028. https://www.ncbi.nlm.nih.gov/pubmed/19091264

[5] Akhlaghi N, Payandemehr P, Yaseri M, Akhlaghi AA, Abdolrazaghnejad A. Premedication With Midazolam or Haloperidol to Prevent Recovery Agitation in Adults Undergoing Procedural Sedation With Ketamine: A Randomized Double-Blind Clinical Trial. Ann Emerg Med. 2019 May;73(5):462-469. https://www.ncbi.nlm.nih.gov/pubmed/30611640

It is acknowledged that time constraints prevents an in depth review of relevant agents for the prevention of ketamine-induced agitation and it is recommended that this is taken forward in the next review cycle, in collaboration with the South African Society of Anaesthesiologists.

Reversal Agents

Naloxone, IV: *added for opioid toxicity*

Flumazenil, IV: *not added for benzodiazepine toxicity*

Aligned with the South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015[6] - following was added to the text of the STG:

Reversal Agents must be available as medicine doses for sedation/analgesia are highly variable as are patients age, concurrent medication and medical conditions.

For opioid toxicity:

- Naloxone, IV, 0.08 mg–0.2 mg immediately.
  - Repeat doses as required at 2 minute intervals.
  - Maximum total dose is 10 mg.

Level of Evidence: III Guidelines

Supportive measures for management of benzodiazepine toxicity has been noted in the narrative of the STG for opioid and benzodiazepine toxicity.

23.1.2 SEDATION IN INTENSIVE CARE

Ketamine, IV: *not added*

External stakeholder motivated for consideration of ketamine infusion to be used as the primary agent for sedation in the ICU setting. Systematic reviews (small RCTs, observational studies, case series, case reports)[7] [8]and a case report were submitted as supporting evidence[9].

It is acknowledged that ketamine is a valuable alternate for analgesia/sedation. However, use is cautionary as ketamine is contra-indicated in patients with hypertension and/or tachycardia, decompensated heart failure, pulmonary hypertension, raised intraocular pressure or at risk for delirium/psychiatric illness and may exacerbate or cause delirium seizure disorders, hallucination, dysphoria and new onset dysrhythmia (atrial fibrillation in particular)[10] [11]. Delirium in ICU sedation, is a concern due to associated morbidity[12].

Ketamine is used, as an adjuvant, at low dose in conjunction with other sedation agents to reduce delirium or for analgesia. Available studies did not use ketamine as the sole agent, mostly for short term use, and the deliriogenic effects of ketamine have not been evaluated long-term[13].

Recommendation: Ketamine should be reserved, at low dose, as adjuvant therapy for tertiary institutions and within specialised units, for the indication of sedation and analgesia and not be

[6] The South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015. South Afr J Anaesth Analg 2015;21(2)S1-S36.

[7] Patanwala AE, Martin JR, Erstad BL. Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. J Intensive Care Med. 2017 Jul;32(6):387-395. https://www.ncbi.nlm.nih.gov/pubmed/26647407

[8] Miller AC, Jamin CT, Elamin EM. Continuous intravenous infusion of ketamine for maintenance sedation. Minerva Anestesiol. 2011 Aug;77(8):812-20. https://www.ncbi.nlm.nih.gov/pubmed/21730929

[9] Frank D Brodkey. "The Use of Ketamine in the Intensive Care Unit". EC Pulmonology and Respiratory Medicine 2.1 (2016):44-46

[10] Patanwala AE, Martin JR, Erstad BL. Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. J Intensive Care Med. 2017 Jul;32(6):387-395. https://www.ncbi.nlm.nih.gov/pubmed/26647407

[11] SAMF, 2016

[12] Brummel NE, Jackson JC, Pandharipande PP, Thompson JL, Shintani AK, Dittus RS, Gill TM, Bernard GR, Ely EW, Girard TD. Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. Crit Care Med. 2014 Feb;42(2):369-77. https://www.ncbi.nlm.nih.gov/pubmed/24158172

[13] Patanwala AE, Martin JR, Erstad BL. Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. J Intensive Care Med. 2017 Jul;32(6):387-395. https://www.ncbi.nlm.nih.gov/pubmed/26647407

recommended as the primary agent for sedation.
Level of Evidence: III Expert opinion

Short term sedation (less than 24 hours)
Dexmedetomidine, IV: *not added*
Propofol, IV: *amended*

Dexmedetomidine, IV: Not considered as used mostly at tertiary and quaternary facilities – Tertiary and Quaternary Expert Review Committee is currently reviewing this agent.

Propofol, IV: Agent has cardiovascular effects and benzodiazepines is preferred as an effective sedative agent.
Text of STG was updated as follows:

Short term sedation (less than 24 hours)
• Midazolam, IV infusion,0.05–0.2 mg/kg/hour.
OR
Propofol, IV infusion, 0.5 mg/kg/hour.
Note: Propofol does have cardiovascular effects; benzodiazepines are preferred.

Level of Evidence: III Guidelines[14] [15]

23.1.3 SEDATION IN PALLIATIVE CARE

Lorazepam, oral: *deleted (moved to chapter 24: Medicines used in palliative care)*
Haloperidol, oral: *deleted (moved to chapter 24: Medicines used in palliative care)*

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note:** Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[14] The South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015. South Afr J Anaesth Analg 2015;21(2)S1-S36.
[15] South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.