Guidelines for the use of Low Dose Ketamine Infusion for Management of Sickle Cell Vaso-Occlusive Crisis at Dell Children's Medical Center

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Scope: To provide guidelines for the use of low dose ketamine in the management of pain for patients with Sickle Cell Disease (SCD).

Outside the scope of this guideline:

1) Palliative care patients receiving ketamine infusions for end of life pain management
2) Use of ketamine in doses greater than 8 mcg/kg/min

Definitions:

Opioid Tolerance: A reduced responsiveness to an opioid agonist and is usually manifested by the need to use increasing doses to achieve desired effects.

Hyperalgesia: An increased sensitivity to feeling pain and an extreme response to pain

Chronic Pain: (APST definition) Pain every day for greater than 15 days in a month for longer than 6 months.

Background:

Acute vaso-occlusive crisis (VOC) causes significant morbidity in the SCD population and is responsible for >90% of hospital admissions in SCD (1,2). The exact mechanism of VOC-induced pain is not fully understood, however is thought to stem from multicellular adhesion of sickle red blood cells, platelets and leukocytes within the endothelium, upregulation of adhesion molecules, and subsequent tissue damage and hypoxia (3,4). An inflammatory cascade ensues from injured tissues causing activation of peripheral afferent nerves and leads to nociceptive pain (4). Inflammatory mediators trigger further adhesive interactions that promote continued tissue injury and pain.

Despite the understanding that hemoglobin polymerization in SCD promotes VOC, there is vast phenotypic variability in the pain experience in patients with SCD. The Cooperative Study of Sickle Cell Disease (CSSCD) reported a subgroup of individuals with SCD who carried the majority burden of pain events with 30% of pain episodes experienced by only 5% of the patients (5). Mainstay treatments for VOC pain are IV hydration, non-steroidal anti inflammatory drugs and opioids. However, a select group of patients with SCD who experience repetitive, prolonged hospitalization for pain treated with opioid medications will develop abnormal activation of N-methyl D-aspartate (NMDA) receptors causing opioid tolerance, hyperalgesia and opioid-refractory pain (6).

Ketamine has both analgesic and anesthetic properties and was approved for use as an anesthetic in the 1960s. It is thought to modulate both opioid tolerance and opioid-induced hyperalgesia in chronic pain in malignancy, neuropathic pain and postoperative pain through blockage of NMDA receptors (6,7,8). There is supporting evidence that low dose Ketamine infusions may be beneficial in both reducing opioid utilization and pain scores in patients with

SCD (6, 9). In the majority of studies with SCD patients, Ketamine was used as an adjunctive analgesic in patients who failed to improve on opioid therapy. Of note, compared to opioids, there were more adverse events seen in patients who received ketamine, though these events were dose-dependent, mild and transient. The American Society of Hematology 2020 guidelines for management of acute and chronic pain in SCD advocate for the use of subanesthetic Ketamine in patients for whom first-line treatment with opioids has failed, however the recommendation is conditional due to the paucity of high quality studies available (9).

Guidelines:
What pediatric patients should be treated with low dose Ketamine infusions?

Indications for low dose Ketamine infusions in SCD include the following:

1) A known co-diagnosis of chronic pain, opioid-induced hyperalgesia or opioid refractory pain
2) Patient without a known diagnosis of chronic pain, but without improvement after $\geq$ 5 days on opioid medications or other pharmacological pain interventions
3) Patients with an identified neuropathic component to their pain

What are the goals of low dose Ketamine infusions?

The goal is to achieve a reduction in pain score and/or a reduction in opioid utilization for the treatment of a VOC. If successful, consideration should be given to create an individualized pain management plan utilizing low dose Ketamine infusion for subsequent admissions.

Initiation:

- Baseline Labs, including LFTs
- Preinitiation family and patient education-
    - here is what will happen, what we are starting with, what you will feel (expected), what we are looking for
- Discussion with nursing re IMC status for monitoring
- IV Access, PICC team, Compatibility

Which patients may not be appropriate for low dose Ketamine infusions?
Exclusion criteria

1. Known hypersensitivity to ketamine
2. Cardiovascular
    a. Unstable angina
    b. Poorly controlled hypertension
    c. High-risk coronary vascular disease
3. Neurological and ophthalmic
    a. Elevated intracranial pressure, including secondary traumatic brain injury or tumor

    b. Elevated intraocular pressure, acute globe injury, or glaucoma
    c. Recent seizures not treated with anti-epileptic
4. Endocrinological (due to possible potentiation of sympathomimetic effects)
    a. Hyperthyroidism
    b. Pheochromocytoma
5. Metabolic and gastrointestinal
    a. Severe liver disease (failure)
    b. Chronic liver disease (i.e. cirrhosis)
    c. Documented history of drug-induced liver injury (DILI) from ketamine
6. Psychiatric
    a. Active symptoms of delirium or psychosis
    b. History of distressing reaction to ketamine infusion
7. Other
    a. Age < 3 months
    b. Pregnancy

What is the Titration protocol for low dose Ketamine?

1. “Ketamine naive” patients
    a. Initiate with 1 mcg/kg/min
    b. May titrate infusion by 1 mcg/kg/min during morning rounds
    c. Continue titration until able to wean opioids (max dose 8 mcg/kg/min)
    d. Pause titration for side effects, including increased sedation, and consider step-back to prior dose
    e. For increased sedation without dissociation, may also consider a reduction of opioid dosing (25-50%) instead of reducing the ketamine infusion
2. Patients with prior ketamine benefit and known effective dosing
    a. May initiate ketamine infusion at effective dose from prior hospitalization, OR
    b. Initiate at 50% of the effective dose, then increase to prior effective dose the following day

Once pain control is achieved, what is the Ketamine and Opioids suggested wean plan?

Once a patient reaches an effective and well-tolerated ketamine dose, begin to wean opioid PCA in a stepwise fashion. The ketamine infusion is stopped once the patient's PCA is discontinued.

What should be considered the maximum amount of time on low-dose Ketamine?

No maximum time but if there is a failure to make progress on opioid reduction and transition to oral opioid therapy while on ketamine, then discontinuation of the ketamine infusion should be considered.

How do I troubleshoot side effects from Ketamine?

- If patient displays unstable vital signs, aggressive behavior, or major side effects, turn off ketamine infusion and provide any interventions needed to stabilize the patient
- If patient displays or experiences minor side effects:
    - If distressing to the patient or family, return to the previous dose and continue to monitor for need to further decrease
    - If not distressing to the patient or family, keep at current dose and continue to observe for need to decrease
- To counteract psychotomimetic effects of ketamine not responsive to dose reduction (e.g.,hallucinations), low doses of benzodiazepines may be considered
    - Lorazepam 0.05 – 0.1 mg/kg (initial max 2 mg/dose) IV every 6 hours
    - Clonazepam 0.01 mg/kg (initial max 0.25 mg/dose) PO every 12 hours
- To counteract excessive oral secretions, anticholinergic medications may be used.
    - Glycopyrrolate – Oral 40-100 mcg/kg/dose every 4-8 hours as needed; IV 4-10 mcg/kg/dose every 3-4 hours as needed

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