TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Subanesthetic Intravenous Ketamine Infusions for Analgesia
Evidence Summary

Inclusion Criteria:
- Non-intubated
- Age >3 years
- Unresolved pain with current opioid use
- Poor side effect profile with opioids

Exclusion Criteria:
- Allergy to Ketamine
- Liver Failure
- Myocardial Ischemia
- Schizophrenia or Schizoaffective Disorders
- Bipolar Manic Patients
- Intubated
- Age ≤3 years
- Pregnancy

Background

The American Pain Society defines pain as chronic when is persists beyond the healing time without an explanation for the presence and/or extent of the pain.[1] Chronic pain can be associated with many pediatric disease process including but not limited to migraines, sickle cell disease, fibromyalgia, hypermobility and cerebral palsy. [2] Opioids have remained the first-line treatment for moderate-to-severe pain in children. However, there is a risk of side effects with long term use of this class of medications. Recently, researchers have begun to investigate the effects of low-dose ketamine in addition to opioids on pain. It is hypothesized that low-dose ketamine will provide additional pain relief without the unwanted side effects of the higher doses of this intervention.

Critically Analyze the Evidence

The **GRADE criteria** were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

PICO Question 1: In non-intubated pediatric patients with pain not resolved by opioids or other analgesic therapies, does a low-dose intravenous ketamine infusion as an adjunct to opioids significantly decrease pain scores?

Recommendation(s): Weak recommendation with **low quality evidence** to consider the use of low-dose intravenous ketamine infusions for analgesia in patients with pain not relieved by opioids [3-20]

Remarks: Although there is a paucity of evidence in the pediatric population on the efficacy of low-dose intravenous ketamine infusions for analgesia in patients with chronic pain, pediatric literature in the postoperative patient and emergency center on this topic report an opioid sparing effect with this intervention. The content expert team recommends additional research on this topic to further demonstrate efficacy in the pediatric population and determine adverse effects if any. Administration of low-dose intravenous ketamine infusions for analgesia should be utilized on a case-by-case basis as determined by the patient's clinical course.

A review of the literature found five observational studies that reported on outcomes related to the use of low-dose ketamine for the treatment of chronic pain in children. In a 2015 longitudinal cohort study, 63 children (receiving 277 infusions) with either complex regional pain syndrome or other chronic pain syndromes were treated with ketamine infusions at doses of 0.1 – 0.3 mg/kg/hr which lasted for 4-8 hours of the day for a maximum of three days. Pain scores were significantly reduced ($p<0.001$) in patients with both disease conditions. There was a greater than 20% reduction in pain score, assessed using the 0-10 numeric rating scale, in 37% of infusions (99 out of 277). However, oral morphine equivalent intake was not found to be different from baseline ($p=0.3$).[3] James (2010) retrospectively reviewed the pain scores of 16 children that received ketamine in addition to a demand-led morphine patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA) infusion. Ketamine was given at a concentration of 20 mcg/kg/ml or 40 mcg/kg/ml. Researchers found that prior to administering ketamine 48% (13 – 100%) of patients had a median pain score greater than or equal to four by self-report or the Faces, Legs, Activity, Cry, Consolability (FLACC) scale. After receiving ketamine infusions, the percentage of patients with a median pain score of greater than or equal to four was reduced to 33% (0 – 82%). Average morphine consumption in the 24 hours prior to the addition of ketamine was not statically different from the 24 hours after receiving ketamine (33.1 [±10.7] versus 35.2 [±14.3] mcg/kg/hr; $p=0.45$).[4]

In a 2011 retrospective review, the authors found that the addition of ketamine to a morphine PCA or NCA resulted in a reduction of pain from moderate to mild on a categorical pain scale (0=no pain; 1=mild pain; 2=moderate pain; 3=severe pain) in children with mucositis. The study reported that morphine consumption seemed to be reduced with the addition of ketamine.[5] Finkel (2007) retrospectively reviewed the effects of low-dose ketamine in children (n=11) with terminal cancer receiving high doses of opioids for pain control. The study found that 73% of patients had a reduction in doses of opioids and better pain control. In contrast, opioid doses increased in 20% of patients.[6] Neri (2014) did not find an improvement in mean daily pain scores with the addition of low-dose ketamine to opioid PCA. The study paired admissions for 33 children with sickle cell disease with vaso-occlusive episodes. The patient admissions with opioid PCA only had a lower mean daily pain score compared to opioid PCA/low-dose ketamine admissions (6.48 vs. 5.99, respectively; $p=0.002$).[7] Psychotomimetic side effects were infrequent in most pediatric studies investigating the use of low-dose ketamine for chronic pain.[3-9]

An expansion of the review of literature for this question found an additional five meta-analyses and four randomized controlled trials that investigated the effects of perioperative administration of low-dose ketamine on pain and morphine consumption.[10-19] Cho (2014) reviewed 24 studies with 1257 children undergoing tonsillectomy. The study found a statistically significant decrease in postoperative pain in the ketamine group compared to the control group (0 hours: standard mean difference [SMD] = -1.7085, $p=0.0221$; 1 hour: SMD = -0.8660, $p<0.0001$; and 4 hours: SMD = -0.7945, $p<0.0001$). There was no significant difference found at the 6 and 24 hour time periods between the two groups. There was no significant difference in the incidence of worse sleep change, bad dreams, and/or hallucinations.[10] A 2011 meta-analysis of 18 articles with 985 children included found that perioperative administration of ketamine was effective in decreasing pain and analgesic requirement in the immediate recovery phase but not at 6 – 24 hours after surgery. There was no association found between ketamine and psycho-mimetic adverse events (OR 1.52 [0.72-3.24], $p=0.96$).[11] Wang (2016) reviewed 36 trials (n=2,502 adults) comparing patients that received the combination of subanesthetic ketamine plus morphine or hydromorphone to patients that received morphine/hydromorphone alone. There was a small significant reduction in pain noted in the group that received the addition of low-dose ketamine to their PCA. There was a non-significant numerical decrease in the requirement of rescue analgesia (14 trials; 1,069 patients; RR 0.76; 95% CI 0.56-1.05). There were no significant differences found for hallucinations, vivid dreams, and dysphoria between groups.[12] Two randomized control trials comparing the use of low-dose ketamine to either acetaminophen or placebo reported that the ketamine groups had significantly lower pain scores; although, compared to acetaminophen ketamine had no effect on the frequency of the need for rescue narcotics to control postoperative pain.[13-14] One meta-analysis (n=6 randomized controlled trials with 438 patients) was found that evaluated the effects of low-dose ketamine compared to opioids for the treatment of adult patients in the ED. Administration of ketamine resulted in a non-significant decrease in pain when compared to morphine (SMD -0.35 [-1.13 to 0.42]) and fentanyl (SMD -0.09 [-0.59 to 0.40]).[20]

PICO Question 2: In non-intubated pediatric patients receiving low-dose intravenous ketamine infusions for analgesia, what patient monitoring regimens should be utilized?

Recommendation: Consensus recommendation that patients receiving low-dose intravenous ketamine infusions for analgesia should have continuous heart rate, respiratory rate and pulse oximetry monitoring along with every four hour blood pressure monitoring. Documentation of vital signs should be completed at a minimum of every four hours. For patients with a “Do Not Resuscitate” (DNR) order or receiving end of life care, monitoring should be individualized based upon patient/family needs and plan of care.

There were no studies found that compared monitoring regimens for patients on low-dose intravenous ketamine infusions. With reviewing existing protocols on this intervention from other pediatric institutions and considering clinical expertise from stakeholders from anesthesia, critical care and nursing, the team recommended the use of continuous monitoring for heart rate, respiratory rate and pulse oximetry in this patient type. As a result of these monitoring guidelines, low-dose ketamine infusions for analgesia may be administered on acute care floors. Patients should not be allowed to leave the acute care unit without registered nurse supervision.

Critical Points of Evidence

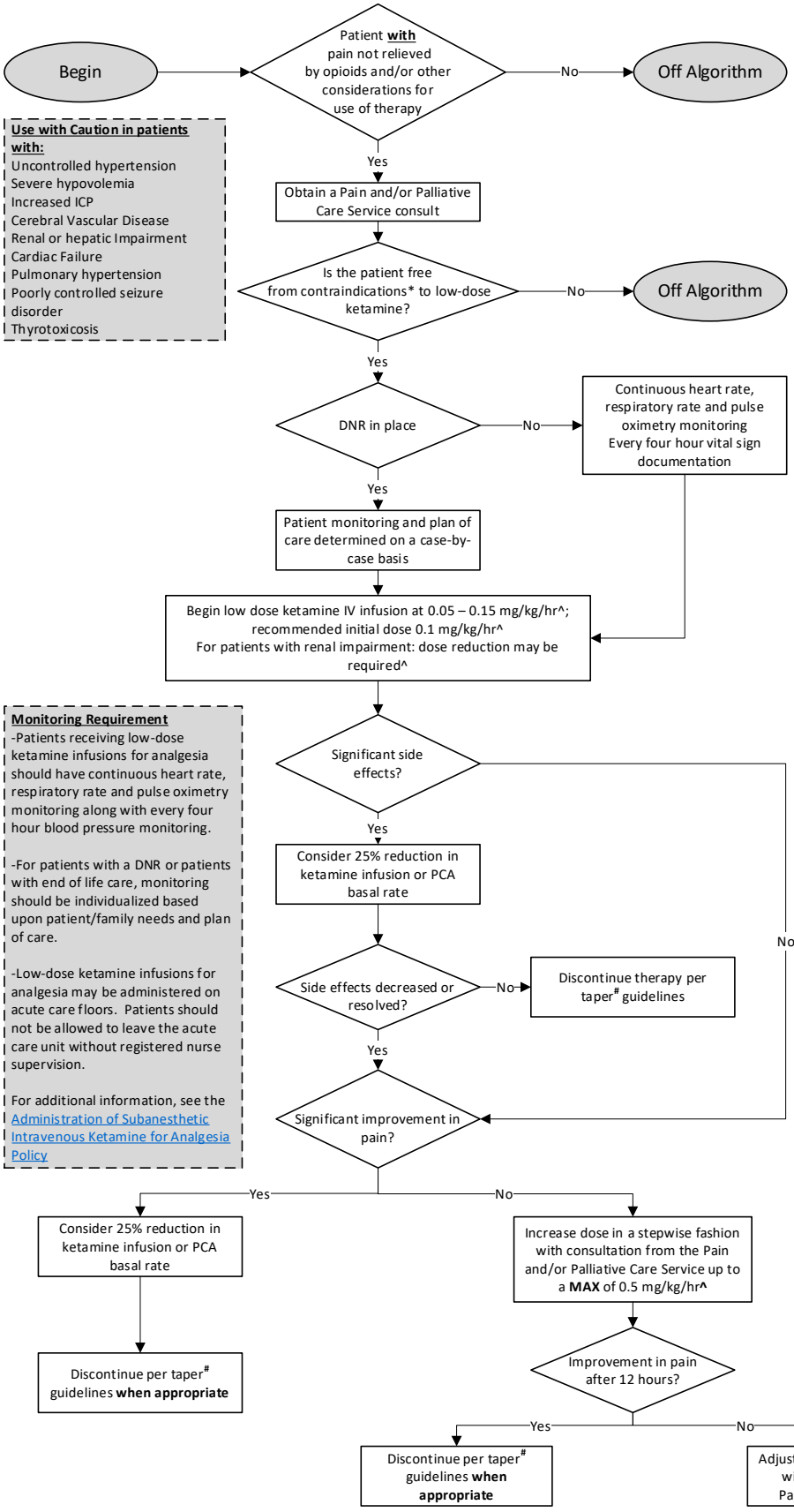
Evidence Supports

- Consider the use of low-dose intravenous ketamine for analgesia in patients with pain not relieved by opioids [3-20] – Weak recommendation, low quality evidence

Evidence Lacking/Inconclusive

- Monitor continuously heart rate, respiratory rate and pulse oximetry along with every four hour blood pressure for patients receiving low-dose intravenous ketamine infusions for analgesia. Documentation of vital signs should be completed at a minimum of every four hours. For patients with a "Do Not Resuscitate" (DNR) order or receiving end of life care, monitoring should be individualized based upon patient/family needs and plan of care. – Consensus recommendation

TCH Evidence-Based Outcomes Center
Clinical Algorithm for the Subanesthetic Intravenous Ketamine Infusions for Analgesia



Use with Caution in patients with:
Uncontrolled hypertension
Severe hypovolemia
Increased ICP
Cerebral Vascular Disease
Renal or hepatic Impairment
Cardiac Failure
Pulmonary hypertension
Poorly controlled seizure disorder
Thyrotoxicosis

Monitoring Requirement
-Patients receiving low-dose ketamine infusions for analgesia should have continuous heart rate, respiratory rate and pulse oximetry monitoring along with every four hour blood pressure monitoring.

-For patients with a DNR or patients with end of life care, monitoring should be individualized based upon patient/family needs and plan of care.

-Low-dose ketamine infusions for analgesia may be administered on acute care floors. Patients should not be allowed to leave the acute care unit without registered nurse supervision.

For additional information, see the Administration of Subanesthetic Intravenous Ketamine for Analgesia Policy

Consider low dose Ketamine in these patients:
- Patients experiencing serious opioid induced side effects (i.e., nausea, vomiting, itching, respiratory depression) not responsive to routine treatments (i.e. anti-emetics, low dose naloxone, etc.)
- Suspected or potential opioid induced hyperalgesia
- Rapid escalation of opioids resulting in untoward side effects
- Acute pain in patients on chronic high dose opioids
- Opioid intolerance or allergy
- Neuropathic pain resistant to standard treatments
- As a component of end of life care

Inclusion Criteria:
Non-intubated
Age > 3 years
Unresolved Pain with current opioid use
Poor side effect profile with opioids

Contraindications*:
Allergy to Ketamine
Liver Failure
Myocardial ischemia
Age ≤ 3 years
Pregnancy
Schizophrenia or Schizoaffective Disorders
Bipolar Manic Patients

Low-Dose Ketamine for Pain Dosing^
- 0.05 – 0.15 mg/kg/hr; recommended initial dose 0.1 mg/kg/hr;
- **MAX** dose 0.5 mg/kg/hr; higher doses may be given with approval from Pain and/or Palliative Care Service
- With approval of Pain and/or Palliative Care services, certain patients may receive doses greater than 0.5 mg/kg/hr, up to 1 mg/kg/hr.
- Palliative care patients requiring doses greater than 1 mg/kg/hr may remain on the acute care floor with nursing approval; however, they **must be transitioned off this guideline, and must utilize a ketamine continuous infusion (not a PCA pump)**.
- Doses >0.15 mg/kg/hr are more likely to produce side effects
- ^If BMI ≥30 then dose by ideal body weight.

Renal impairment:
- Dose reduction may be required
- Maximum initial dose 0.1 mg/kg/hour

Taper guidelines#
- May discontinue before or after opioids based on clinical situation
- Infusion less than 5 days: reduce rate by 50% for 6-12 hours then discontinue if tolerated
- Infusion longer than 5 days: decrease rate by 0.025 – 0.05 mg/kg/hr per day; adjust to clinical assessment and slow taper if required

Potential Side Effects of Ketamine
Confusion, delirium, dreamlike state, excitement, hallucinations, irrational behavior, vivid imagery

For additional information on potential side effects, see the TCH Formulary

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Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing Internal and External Guidelines
   - American Academy of Emergency Medicine: Is there a role for Intravenous Sub-dissociative Ketamine Administered as an Adjunct to Opioids or as a Single Agent for Acute Pain Management in the Emergency Department?, Seattle Children's Hospital Low-Dose Ketamine for Analgesia, Children's Hospital of Pittsburgh IV Ketamine Dosing Procedure for Chronic Pain Service, Lucile Packard Children's Hospital Low-Dose Ketamine Infusion and Oral Ketamine for Intractable Pain, Boston Children's Hospital Low-Dose Intravenous Ketamine Infusions for Analgesia and Opioid-Sparing Effects
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane Collaborative, Google Scholar
4. Critically Analyze the Evidence
   - 7 meta-analyses, 5 randomized **controlled** trials, and 8 nonrandomized studies, as applicable
5. Summarize the Evidence
   - Materials used in the development of the guideline, evidence summary, and order sets are maintained in Low-dose Intravenous Ketamine for Analgesia evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.

"Evidence Supports" provides clear evidence that the benefits of the intervention exceed harm.

"Evidence Against" provides clear evidence that the intervention is likely to be ineffective or that it is harmful.

"Evidence Lacking/Inconclusive" indicates there is currently insufficient data or inadequate data to support or refute a specific intervention.

The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the use of low-dose intravenous ketamine infusions for analgesia in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the guideline was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care, and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient family, to make the ultimate judgment regarding care.

Version History

Date	Comments
March 2018	First Iteration
April 2019	Revision to algorithm
Aug 2023	Reaffirmed