

PEDIATRIC PAIN MANAGEMENT TRIAL (PPMT)

Optimizing Non-Opioid Analgesia in Pediatric Emergency Care

Short Title: PPMT

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Abstract

Pain management in pediatric emergency care is a critical yet often under-addressed concern. Opioid analgesics, such as intravenous (IV) morphine, are commonly used for moderate to severe acute pain in children but are associated with adverse effects, caregiver hesitancy, and potential long-term consequences. This study aims to compare the efficacy and safety of IV sub-dissociative ketamine (SDK) to IV morphine as an alternative analgesic option for pediatric patients experiencing acute pain. We hypothesize that SDK is non-inferior to morphine in reducing pain intensity, has a lower incidence of cardiopulmonary adverse events, and may yield improved functional and mental health outcomes in the weeks and months following emergency department (ED) care.

We will conduct an eight-site, phase 3 randomized clinical trial within the Pediatric Emergency Care Applied Research Network (PECARN). The study will enroll 1,010 pediatric patients aged 6 to 17 years presenting to the ED with acute pain due to long-bone extremity fractures or abdominal pain requiring IV analgesia. Pain intensity and analgesic efficacy will be assessed at multiple time points during the ED visit and for up to six months post-discharge. Patient-reported outcomes will include measures of pain interference, quality of life, sleep disturbances, depression, anxiety, and global satisfaction with treatment. Standardized assessments using validated NIH HEAL Common Data Elements (CDEs) will ensure data harmonization and cross-study comparability.

The findings of this study have the potential to shift pediatric pain management practices by supporting the transition from opioid-based treatment to a non-opioid alternative with a favorable safety profile. If successful, this research could provide the necessary evidence for revised clinical guidelines promoting the use of SDK as a first-line analgesic in pediatric emergency care.

Study Summary

Acute pain is a leading reason for pediatric emergency department visits. Current standard care involves IV morphine, which, despite its effectiveness, poses risks such as respiratory depression and hypotension. Furthermore, hesitancy among caregivers and clinicians regarding opioid use contributes to the undertreatment of pain, potentially leading to negative long-term outcomes including chronic pain, anxiety, and opioid misuse.

Sub-dissociative ketamine (SDK) is an NMDA receptor antagonist with demonstrated analgesic properties in adult and limited pediatric studies. SDK may offer a safer alternative to opioids by providing effective pain relief with fewer cardiopulmonary adverse effects and a potential role in mitigating long-term sequelae of acute pain.

This multi-center randomized trial will compare SDK to IV morphine in children aged 6–17 years experiencing moderate to severe acute pain due to either an extremity fracture or abdominal pain. We aim to determine SDK's efficacy in pain reduction, safety profile, and impact on functional recovery and mental health outcomes. NIH HEAL CDEs will be used to collect patient-reported outcomes related to pain intensity, pain interference, sleep, depression, anxiety, and overall quality of life.

Hypotheses

1. IV sub-dissociative ketamine is non-inferior to IV morphine for decreasing pain intensity in pediatric patients with acute abdominal pain or extremity fractures.
2. IV sub-dissociative ketamine is associated with a lower proportion of cardiopulmonary adverse events compared to IV morphine.
3. Children who receive IV sub-dissociative ketamine will have better pain-related function in the first week following ED presentation and will experience more favorable long-term outcomes related to post-traumatic stress, anxiety, and depression compared to those receiving IV morphine.

Specific Aims

1. To assess whether IV sub-dissociative ketamine is non-inferior to IV morphine in reducing pain intensity in children presenting to the ED with acute pain.
2. To compare the rate of acute (<2 hours) adverse events, including cardiopulmonary complications, between IV sub-dissociative ketamine and IV morphine.
3. To evaluate the impact of ketamine on long-term functional and mental health sequelae of acute pain.

Rationale and Background

Acute pain management in pediatric emergency settings remains a challenge due to concerns about opioid use, risk of adverse effects, and long-term consequences associated with inadequate pain control. IV morphine is the most commonly used opioid analgesic for moderate to severe pain in children, but its use is limited by safety concerns and caregiver hesitancy. In contrast, ketamine has demonstrated analgesic efficacy while avoiding the respiratory depression and hypotensive risks associated with opioids.

Preliminary studies suggest that sub-dissociative doses of IV ketamine provide effective pain relief comparable to opioids while reducing the likelihood of opioid-related adverse events. Additionally, ketamine’s unique pharmacological properties suggest it may mitigate long-term sequelae such as chronic pain, opioid misuse, and post-traumatic stress. However, large-scale pediatric data comparing IV SDK directly to IV morphine are lacking.

By conducting a randomized trial within PECARN, we aim to generate robust evidence to determine whether IV SDK is a safe and effective alternative to IV morphine in pediatric pain management. Data will be collected using NIH HEAL Common Data Elements (CDEs) to ensure harmonization and facilitate future secondary analyses.

Study Procedures and Data Collection

A structured schedule of events will be followed for data collection across core pain domains defined by the NIH HEAL Initiative.

Domain	Definition	Assessment Tool	Timepoints
Pain Intensity	Magnitude of pain experienced in the past 24 hours	NRS-11	Baseline, ED, 48h, 1w, 1m, 6m
Pain Interference	Impact of pain on daily activities and social engagement	PedsQL	Baseline, ED, 48h, 1w, 1m, 6m
Physical	Difficulty with physical	PROMIS Pediatric	Baseline, 1w,

Domain	Definition	Assessment Tool	Timepoints
Functioning & QoL	activities and emotional well-being	Physical Function	1m, 6m
Sleep	Sleep quality, disturbances, and duration	PROMIS Pediatric Sleep Disturbance	Baseline, 1m, 6m
Depression	Persistent sadness, irritability, or loss of interest in activities	PHQ-2/PHQ-9	Baseline, 1m, 6m
Anxiety	Worry, nervousness, and emotional distress	GAD-2/GAD-7	Baseline, 1m, 6m
Global Satisfaction with Treatment	Patient perception of pain relief effectiveness	PGIC	1w, 1m, 6m

Demographic data, including age, sex, race, ethnicity, socioeconomic factors, and pain duration, will be collected at baseline.

Conclusion

This study will provide critical insights into the comparative efficacy and safety of IV SDK versus IV morphine in pediatric emergency pain management. If SDK is demonstrated to be non-inferior to morphine while exhibiting a superior safety profile, it could become a preferred first-line treatment for pediatric acute pain, ultimately reducing reliance on opioids and improving long-term patient outcomes. The use of NIH HEAL CDEs will ensure that findings are broadly applicable and contribute to advancing the standard of care for pediatric pain management.