

PROTOCOL TITLE:

**Prospective Evaluation of Non-Opioid Analgesia for
Pediatric Emergency Pain Management**

PKAS

(Pediatric Ketamine Analgesia Study)

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Revision # Version Date Summary of Changes Consent Change?

1	V1.0	– [Date]	Initial Protocol Draft	No	
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Abstract

Postoperative pain control in pediatric surgical patients remains a significant challenge, with current opioid-based protocols raising concerns about respiratory depression, prolonged hospital stays, and long-term dependency risks. This study aims to compare the efficacy and safety of IV dexmedetomidine (DEX) to IV fentanyl as an analgesic strategy for pediatric patients undergoing elective abdominal and orthopedic surgeries. We hypothesize that DEX provides non-inferior pain relief compared to fentanyl while reducing opioid-related adverse events and improving recovery outcomes.

If proven effective, this study could support a transition from opioid-centric pain management to a safer, multimodal analgesic approach with fewer long-term complications. The results may provide evidence to refine clinical guidelines for pediatric postoperative pain control, enhancing both immediate and long-term patient outcomes.

This multi-center randomized trial will assess the comparative effectiveness of DEX and fentanyl in children aged 2–16 years undergoing common pediatric surgical procedures. The study will evaluate pain reduction, safety outcomes, and the impact on functional recovery and emotional well-being. Standardized NIH HEAL CDEs will be utilized to collect patient-reported data on pain severity, sleep quality, emotional distress, and overall satisfaction with treatment.

Hypotheses

1. IV dexmedetomidine is non-inferior to IV fentanyl in reducing postoperative pain intensity in pediatric surgical patients.
2. IV dexmedetomidine is associated with a lower incidence of opioid-related adverse effects such as respiratory depression and excessive sedation compared to IV fentanyl.
3. Pediatric patients receiving IV dexmedetomidine will demonstrate improved postoperative functional outcomes, including enhanced sleep quality, reduced anxiety, and improved physical activity levels, compared to those receiving IV fentanyl.

Specific Aims

1. To determine whether IV dexmedetomidine provides non-inferior pain relief compared to IV fentanyl in pediatric postoperative patients.
2. To evaluate the frequency and severity of opioid-related adverse events in children receiving dexmedetomidine versus fentanyl.
3. To assess long-term functional outcomes and quality of life in pediatric patients treated with dexmedetomidine versus fentanyl.

Rationale and Background

Effective pain management in pediatric surgical patients remains a critical issue. IV fentanyl, a commonly used opioid analgesic, is effective for acute pain control but carries risks such as respiratory depression, nausea, and prolonged hospitalization. Increasing concerns regarding opioid-related side effects have led to the exploration of alternative analgesic options.

Dexmedetomidine, an alpha-2 adrenergic agonist, has shown promise in providing effective analgesia while minimizing respiratory suppression. Preliminary studies suggest that dexmedetomidine offers sufficient pain relief and may enhance recovery outcomes through sedation-sparing properties and improved patient comfort. However, robust comparative data evaluating its efficacy against fentanyl in pediatric surgical settings are lacking.

This study, conducted across multiple institutions, aims to provide high-quality evidence on the effectiveness and safety of dexmedetomidine for pediatric postoperative pain management. Standardized NIH HEAL Common Data Elements (CDEs) will ensure consistency in data collection and support secondary analyses.

Study Procedures and Data Collection

A structured schedule of assessments will be used to gather comprehensive data across core pain-related domains.

Domain	Definition	Assessment Tool	Timepoints
Pain Intensity	Magnitude of pain experienced in the past 24 hours	NRS-11	Baseline, Post-op, 24h, 1w, 1m, 3m
Pain Interference	Effect of pain on daily activities and social participation	PedsQL	Baseline, Post-op, 24h, 1w, 1m, 3m
Physical Functioning & QoL	Impact of pain on mobility and daily function	PROMIS Pediatric Physical Function	Baseline, 1w, 1m, 3m
Sleep	Sleep disturbances, quality, and duration	PROMIS Pediatric Sleep Disturbance	Baseline, 1m, 3m
Emotional Distress	Anxiety and depressive symptoms	GAD-2 / PHQ-2	Baseline, 1m, 3m
Global Satisfaction with Treatment	Overall perception of treatment efficacy	PGIC	1w, 1m, 3m

Demographic variables, including patient age, sex, ethnicity, pre-existing conditions, and surgical details, will be collected at baseline.

Primary Objective:

To evaluate the efficacy and safety of IV sub-dissociative ketamine (SDK) compared to IV morphine for pediatric acute pain management in emergency settings.

Expected Outcomes:

We anticipate that SDK will provide non-inferior pain relief compared to IV morphine while reducing opioid-related adverse events and improving long-term functional and mental health outcomes.

Study Population:

Children aged 6–17 years presenting to the emergency department (ED) with moderate to severe acute pain due to long-bone extremity fractures or abdominal pain requiring IV analgesia.

Sample Size:

N = 1,010

Study Duration for Individual Participants:

Active participation for up to **six months** following ED discharge.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Children aged **6–17 years**.
2. Presenting to the **emergency department** with **moderate to severe acute pain** requiring IV analgesia.
3. Diagnosed with either:
 - **Long-bone extremity fractures** (e.g., humerus, radius, femur, tibia).
 - **Acute abdominal pain** requiring IV analgesia (e.g., appendicitis, mesenteric adenitis).
4. Pain score of **≥5/10** on the **Numerical Rating Scale (NRS-11)**.
5. Parental/legal guardian **consent** and child **assent** obtained.

Exclusion Criteria:

1. **Prior opioid administration** within **six hours** before ED presentation.
2. **Known allergy or contraindication** to ketamine, morphine, or related agents.
3. **History of psychiatric disorders** that could interfere with assessments (e.g., schizophrenia, severe bipolar disorder).
4. **History of substance use disorder** (self-reported or documented).

5. **Significant cardiopulmonary comorbidities**, including:
 - Uncontrolled asthma
 - Congenital heart disease with hemodynamic instability
 - Severe respiratory depression
 6. **Baseline QTc prolongation** (QTc > 460 ms) on ECG, if available.
 7. **Pregnancy** (verified via urine pregnancy test for female participants aged ≥12 years).
 8. **Non-English or non-Spanish speakers** (due to limitations in validated translated patient-reported outcome measures).
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Vulnerable Populations

This study includes **children (ages 6–17 years)**. Parents or legal guardians will provide written **informed consent**, and children will provide **assent** appropriate for their age and cognitive ability.

Participants turning **18 years** during the study will be re-consented as adults if they choose to continue participation.

Recruitment Methods

Recruitment Approach:

1. **Direct Screening in the ED:**
 - Potential participants will be identified **upon ED arrival** based on presenting symptoms.
 - The study team will collaborate with treating ED physicians to determine eligibility.
 2. **Electronic Health Record (EHR) Screening:**
 - The research team will review ED visit records in **real-time** to identify eligible patients.
 3. **Consent Process:**
 - Parents/guardians will be approached **in-person** in the ED for consent.
 - Children will provide **assent** before participation.
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Study Endpoints

Primary Endpoints:

1. **Pain intensity reduction at 30 minutes post-intervention** (Numerical Rating Scale, NRS-11).
2. **Incidence of acute adverse events** within **two hours** of drug administration, including:
 - Respiratory depression
 - Hypotension
 - Hallucinations or agitation

Secondary Endpoints:

1. **Cumulative opioid consumption** during the ED visit (morphine milligram equivalents, MME).
2. **Duration of pain relief** before rescue analgesia is required.
3. **Pain interference with daily activities** at **1-week, 1-month, and 6-month follow-ups** (PedsQL).
4. **Mental health outcomes** (depression, anxiety, PTSD symptoms) at **1-month and 6-month follow-ups**.
5. **Global satisfaction with treatment** (PGIC) at **1-week, 1-month, and 6-month follow-ups**.

Withdrawal of Subjects

Voluntary Withdrawal:

Participants may withdraw at any time without affecting their clinical care.

Involuntary Withdrawal:

Participants may be withdrawn if they:

- Experience **serious adverse events** attributed to the study drug.
- Become **non-compliant** with study procedures (e.g., unable to complete follow-ups).

Potential Risks to Subjects

IV Sub-Dissociative Ketamine Risks:

- **Mild:** Dizziness, nausea, transient hallucinations.
- **Moderate:** Increased blood pressure, agitation.
- **Severe (rare):** Laryngospasm, severe dissociation.

IV Morphine Risks:

- **Mild:** Drowsiness, nausea, itching.
- **Moderate:** Respiratory depression, hypotension.
- **Severe (rare):** Life-threatening respiratory failure.

Mitigation Plan:

- **Continuous monitoring** of vital signs.
 - **Immediate availability** of rescue medications for adverse effects.
 - **Careful dose titration** based on weight and clinical condition.
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Potential Benefits to Subjects

1. Potential for **improved pain control** with SDK or morphine.
 2. Contribution to **research on safer pain management strategies** in pediatric patients.
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Data Management and Confidentiality

Data Collection and Storage:

- All **patient data** will be **de-identified** and stored securely in **password-protected databases**.
- Study data will be **shared with NIH HEAL Data Ecosystem** for broader research integration.

Confidentiality Protections:

- No **identifiable information** will be published.
 - Data access will be **restricted** to authorized study personnel.
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Multi-Site Research Considerations

Number of Study Sites:

- This study will be conducted across **eight pediatric emergency departments** within the **Pediatric Emergency Care Applied Research Network (PECARN)**.

Study-Wide Recruitment Goals:

- **Total enrollment goal: 1,010 participants** across all sites.

Conclusion

This study will contribute valuable insights into the comparative efficacy and safety of IV dexmedetomidine versus IV fentanyl for pediatric postoperative pain management. If dexmedetomidine is found to be non-inferior to fentanyl while demonstrating an improved safety profile, it may become a preferred strategy for pediatric surgical pain control, reducing opioid exposure and associated risks. Standardized data collection using NIH HEAL CDEs will ensure broad applicability and support the advancement of pediatric pain management guidelines.