Comparative Effectiveness of Analgesics To Reduce Acute Pain in the Prehospital Setting

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AHRQ CER Process

Topic Refinement

- Draft KQs, PICOTS, AF
- Protocol development
- Identify Technical Expert Panel and solicit input
- Revise protocol with input from sponsor, TEP
- **Final protocol posted to PROSPERO**

Systematic Review

- Literature search
- Citation screening
- Data abstraction
- Data analysis
- Risk of bias assessment
- Strength of evidence grading
- Generate evidence tables
- **Draft report**

- AHRQ AE, peer and public review
- Disposition of comments
- Update search and revise report
- **Final report**

Objective of the Systematic Review

- To assess comparative effectiveness and harms of opioid and nonopioid analgesics administered by emergency medical services for treatment of moderate to severe acute pain in the prehospital setting.

Sobieraj DM, Baker WL, Martinez BK, Miao B, Hernandez AV, Coleman CI, Cicero MX, Kamin RA. Comparative Effectiveness of Analgesics To Reduce Acute Pain in the Prehospital Setting. Comparative Effectiveness Review No. 220. (Prepared by the University of Connecticut Evidence-based Practice Center under Contract No. 290-2015-00012-I.) AHRQ Publication No. 19-EHC021-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2019. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCCER220.

Key Questions – Initial Analgesia

KQ1. What is the comparative effectiveness of the initial analgesic agent treatment for achieving reduction in moderate-to-severe acute-onset pain level when administered by EMS personnel in the prehospital setting?

- KQ1a. How does effectiveness vary by patient characteristics?
- KQ1b. How does effectiveness vary by routes of administration, dosing, and timing?

KQ2. What are the comparative harms of analgesic agents when administered by EMS personnel to control moderate-to-severe pain in the prehospital setting?

- KQ2a. How do harms vary by patient characteristics?
- KQ2b. How do harms vary by routes of administration, dosing, and timing?
- KQ2c. What are the comparative harms to EMS personnel who administer analgesics to patients for the control moderate-to-severe pain in the prehospital setting?

Key Questions – Subsequent Analgesia

KQ3. In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what is the comparative effectiveness of switching the analgesic regimen compared to repeating the initial treatment?

- KQ3a. How does effectiveness vary by patient characteristics?
- KQ3b. How does effectiveness vary by timing of the second treatment administration?

KQ4. In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what are the comparative harms of switching to another analgesic agent?

- KQ4a. How do harms vary by patient characteristics?
- KQ4b. How do harms vary by routes of administration, dosing, and timing?

Key PICOTS

- **Population**
  - Any age
  - Moderate to severe, acute pain
- **Intervention / Comparator**

Class	Analgesics
Opioid	Fentanyl, morphine
Nonopioid	Acetaminophen, ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac or ibuprofen)
Combina-tions	Opioid (fentanyl or morphine) + ketamine

  - **Opioid vs Nonopioid**
  - **Combination opioid and ketamine vs. opioid**
  - Opioid vs. Opioid
  - Nonopioid vs nonopioid

Conclusions, graded

- **Outcomes**
  - **Pain severity scores (continuous) and presence of pain (dichotomous)**
  - **Time to analgesic effect**
  - **Any adverse event, hypotension, mental status changes, respiratory depression**
  - Self-reported recall of pain episode
  - BP, dissociative experiences, emergence delirium, HR, RR, nausea, oxygen saturation, vomiting
- **Setting, Timing, Study Design**
  - Prehospital, ED, battlefield included
  - RCT, cohort, case-control

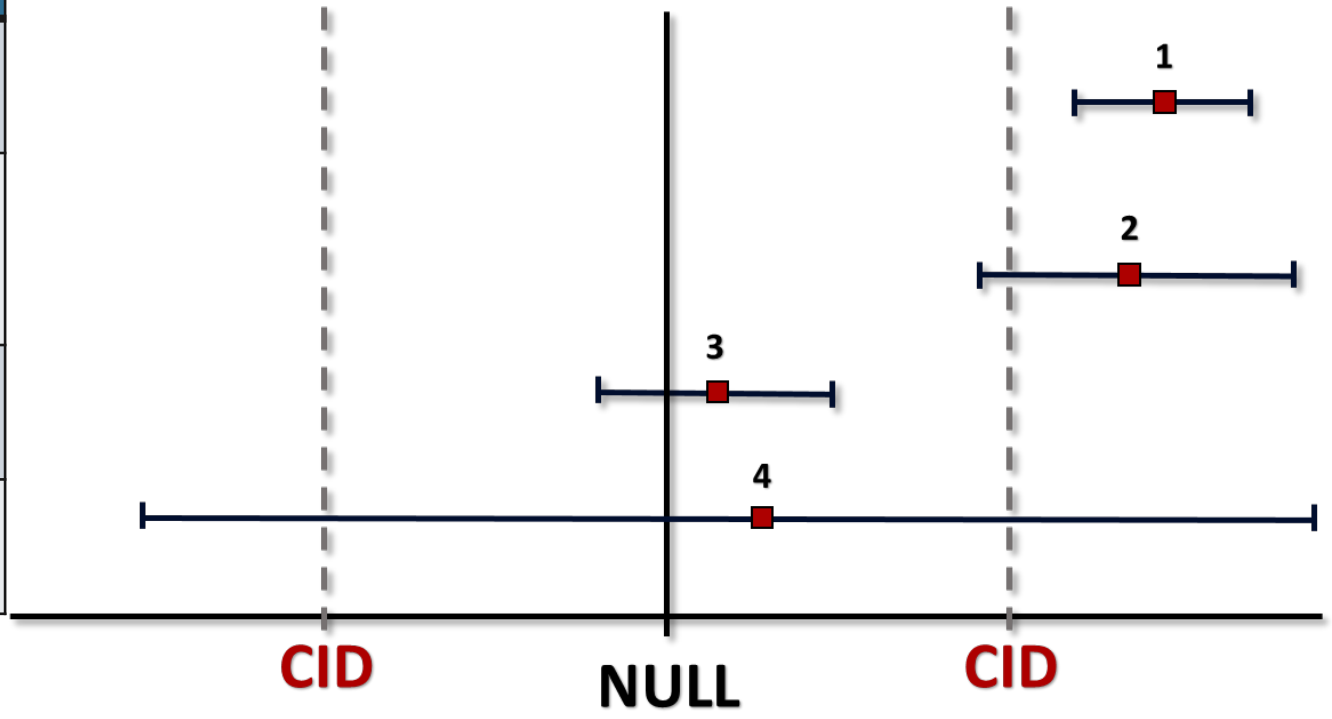
Key Methods

- Synthesis based on analgesic comparisons
  - Opioid vs Nonopioid
  - Combination vs. single opioid or ketamine
- Three time points (when applicable) – 15, 30 and 60 minutes
- Continuous pain score measurements were converted to a 0 to 10 scale
- If prehospital evidence was insufficient, we used ED evidence
  - Meta-analyses were separate per setting and noted throughout the report
- Clinically important differences

Outcome	Clinically Important Difference
Pain score	2 points on a continuous scale from 0 to 10
Presence of pain, hypotension, respiratory depression, mental status changes	Absolute risk difference of 5%
Time to analgesic effect	5 minutes on a continuous scale
Any adverse events	Absolute risk difference of 10%

Conclusions Based on Clinically Important Differences

Scenario	Conclusion
1. Point estimate and CI entirely to one side of the CID	Difference exists
2. Point estimate beyond CID, CI overlaps CID but shifted towards CID	Difference **may** exist
3. Point estimate and CI entirely within CID on both sides	No evidence of a CID
4. CI spans appreciable differences in either direction	Insufficient



CID=clinically important difference; CI=confidence interval

Strength of Evidence (SOE)

- Study Limitations
  - Collective risk of bias for the evidence base answering the given question
- Consistency
  - I^2 value from pooled analyses
  - If applicable - agreement between trial and observational study evidence
- Directness
  - Prehospital = direct
  - ED = indirect
- Precision
  - Confidence interval relative to the CID
- Publication Bias
  - Egger’s p-value, when possible

SOE Definitions

SOE	Explanation
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Distribution of Included Studies

Comparison	Overall N Studies	KQ 1	KQ 2	KQ 3	KQ 4
Opioids vs. Ketamine	17 RCT 3 OBS[a]	14 RCT 2 OBS	14 RCT 3 OBS	2 RCT	2 RCT
Opioid + Ketamine vs. Opioid	6 RCT 2 OBS[a]	6 RCT 1 OBS	6 RCT 1 OBS	None	None
Opioid vs. APAP	10 RCT	9 RCT	10 RCT	None	None
Opioid vs. Nitrous Oxide	1 RCT	1 RCT	1 RCT	None	None
Opioid vs. NSAID	3 RCT	3 RCT	3 RCT	None	None

Characteristics of Included Studies

Characteristic	Opioids Versus Ketamine	Opioid+Ketamine Versus Opioi	Opioids Versus APAP
N of studies	17 RCT 3 OBS[a]	6 RCT 2 OBS[a]	10 RCT
Countries (N studies)	Afghanistan 2[b]; Australia 1; Israel 1; Iran 5; Sweden 1; New Zealand 1; USA 8; Vietnam 1	Afghanistan 1[b]; France 1; Iran 3; Switzerland 1; USA 2	Iran 4; Turkey 4; Qatar 1; UK 1
N of patients	2,484	1,566	2,001
Gender (Range of males, %)	23.3 to 100	40 to 100	43 to 83
Age (Range of means, y)	7 to 77.3	23 to 51.58	29.1 to 44.6
Pain Classification (N studies)	Traumatic: 13 Nontraumatic: 1 Mixed: 6	Traumatic: 3 Nontraumatic: 2 Mixed: 3	Traumatic: 4 Nontraumatic: 5; Mixed: 1
Setting (N studies)	Prehospital: 4 ED: 14 Battlefield: 2	Prehospital: 2 ED: 5 Battlefield: 1	ED: 10
Administered doses (N studies)[c]	Single: 11 Multiple: 7 NR: 2	Single: 6 NR: 2	Single: 10
Dosage forms (N of studies each)	IV vs. IV: 10 IN vs. IN: 4 IV vs. IN: 2[d] IM vs. IN: 1[d] IM vs. IV: 1 Mixed/NR: 2 NEB vs. IV: 1	IV+IV vs. IV: 6 IV+IN vs. IV: 1 NR: 1	IV vs. IV: 10
Specific drugs (N studies)	Morphine: 12 Fentanyl: 6 Mixed: 2	Morphine: 6 Mixed: 2	Morphine: 9 Fentanyl: 1
Risk of bias (N studies)[e]	Low: 12 Medium: 2 High: 2 Unclear: 2 Low/medium: 2	Low: 7 Medium: 1	Low: 9 Unclear: 1

Characteristics of Included Studies

Characteristic	Opioids Versus Nitrous Oxide	Opioids Versus NSAIDs
N of studies	1 RCT	3 RCT
Countries and N of studies	Iran 1	Canada 1; Iran 1; USA 1
N of patients	100	474
Gender (Range of males, %)	72 to 84	56.4 to 70.5
Age (Range of means, y)	35.8 to 37	11.7 to 39.3
Pain Classification (N studies)	Traumatic: 1	Traumatic: 1 Nontraumatic: 1 Mixed: 1
Setting (N studies)	ED: 1	ED: 3
Administered doses (N studies)[c]	Single: 1	Single: 1 Multiple: 2
Dosage forms (N of studies each)	IV vs. inhaled: 1	IV vs. IV: 2 PO vs. PO: 1
Specific drugs (N studies)	Fentanyl: 1	Morphine: 3 Ketorolac: 2 Ibuprofen: 1
Risk of bias (N studies)[e]	Low/medium: 1	Low: 2 Medium: 1

Key Questions 1 and 2 – Initial Analgesia

Outcome	Opioid[a] Versus Ketamine[a]	Opioid+ketamine[a] Versus Opioid[a]	Opioid[a] Versus IV APAP	Opioid[a] Versus Nitrous Oxide	Opioid[a] Versus NSAIDs[a]
Pain severity (continuous)	No clinically important difference (+)	Combination may be more effective[b] (+)	No clinically important difference (+)	Insufficient	No clinically important difference[c] (++)
Pain presence (dichotomous)	Insufficient	Insufficient	Insufficient	No data	Insufficient
Time to analgesic effect	Insufficient	No data	No clinically important difference (+)	No data	Insufficient
Any adverse event	Fewer with opioids (+)	Insufficient	More with opioids (+)	Insufficient	More with opioids (+)
Hypotension	Insufficient	Insufficient	No clinically important difference (+)	No data	Insufficient
Mental status changes	Less dizziness with opioids[d] (+)	Insufficient[e]	More dizziness with opioids[f] (++)	Insufficient[g]	More drowsiness with opioids[h] (+)
Respiratory depression	More with opioids (+)	Insufficient	Insufficient	No data	No data

Strength of evidence: white = no evidence; yellow = insufficient; orange (+) = low; blue (++) = moderate

Key Questions 1 and 2 – Initial Analgesia

Outcome	Opioid[a] Versus Ketamine[a]	Opioid+ketamine[a] Versus Opioid[a]	Opioid[a] Versus IV APAP	Opioid[a] Versus Nitrous Oxide	Opioid[a] Versus NSAIDs[a]
Pain severity (continuous)	No clinically important difference (+)	Combination may be more effective[b] (+)	No clinically important difference (+)	Insufficient	No clinically important difference[c] (++)
Pain presence (dichotomous)	Insufficient	Insufficient	Insufficient	No data	Insufficient
Time to analgesic effect	Insufficient	No data	No clinically important difference (+)	No data	Insufficient
Any adverse event	Fewer with opioids (+)	Insufficient	More with opioids (+)	Insufficient	More with opioids (+)
Hypotension	Insufficient	Insufficient	No clinically important difference (+)	No data	Insufficient
Mental status changes	Less dizziness with opioids[d] (+)	Insufficient[e]	More dizziness with opioids[f] (++)	Insufficient[g]	More drowsiness with opioids[h] (+)
Respiratory depression	More with opioids (+)	Insufficient	Insufficient	No data	No data

Strength of evidence: white = no evidence; yellow = insufficient; orange (+) = low; blue (++) = moderate

Key Questions 3 and 4 – Subsequent Analgesia

Outcome	Additional Opioid Versus Switching to Ketamine
Pain severity (continuous)	Ketamine may be more effective (+)
Pain presence (dichotomous)	Insufficient
Time to analgesic effect	Ketamine may be quicker (+)
Any adverse event	Insufficient
Hypotension	Insufficient
Mental status changes	Insufficient
Respiratory depression	No data

Strength of evidence: white = no evidence; yellow = insufficient; orange (+) = low; blue (++) = moderate

Limitations

- Indirect evidence from the ED
- Subgroup analyses were not always possible for many reasons
  - Mean baseline characteristics were aggregated to one extreme (ex. baseline pain scores were always ≥7)
  - Particular route, dose or type of pain dominated the evidence base
  - No evidence, as in EMS personnel harms or EMS training
- ED data and multiple time points
- Outcomes mental status changes and emergence delirium
  - Lack of standardized definitions
  - Kept various mental status change symptoms separate
  - Did not make assumptions for emergence delirium

Key Messages

- As initial therapy in the prehospital setting
  - NSAIDS provide similar pain relief to opioids and may cause fewer overall side effects and less drowsiness.
  - APAP may provide similar pain relief to opioids and may cause fewer side effects overall and less dizziness.
  - Ketamine may provide similar pain relief to opioids. Ketamine may cause more dizziness or overall side effects, while opioids may cause more respiratory depression.
    - Combining an opioid with ketamine may be more effective in reducing pain compared with opioids alone.
    - If morphine does not adequately relieve pain, changing to ketamine may be more effective and more quickly reduce pain than giving additional morphine.
- Caveats
  - Few studies have been conducted in the prehospital setting; we relied on evidence from the emergency department.
  - Analgesics were primarily administered intravenously; this was the only route studied for APAP. The intranasal route was common in studies reporting adverse events for the comparison of opioids versus ketamine.