Comparative Effectiveness Review
Number 220

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

Evidence Summary

Background

Appropriate management of acute pain is an integral part of patient management in the prehospital setting. The prevalence of pain specifically in the prehospital setting varies, with estimates ranging from 20-53 percent.[1] Adequate pain relief is known to minimize anxiety and cardiac complications associated with acute pain.[2] However, as many as 43 percent of adults[3] and 85 percent of pediatric patients[4] have insufficient prehospital pain relief.

For patients experiencing moderate to severe traumatic injury pain, current guidelines (based on moderate quality evidence) strongly recommend initial prehospital management with a weight-based opioid, either intravenous (IV) morphine or IV/intranasal (IN) fentanyl.[5] Complicating the appropriate use of prehospital opioids is the fear of their abuse and the resulting epidemic in the United States.[6, 7] When combined with concerns of adverse events, such as vomiting and subsequent airway obstruction, respiratory depression, hypotension, and sedation,[8] alternative analgesics have been sought. Nonopioid analgesics, including ketamine, acetaminophen (APAP), nitrous oxide/oxygen and nonsteroidal anti-inflammatory drugs (NSAIDs) (specifically ketorolac and ibuprofen) may

Purpose of Review

To evaluate effectiveness and harms of opioids compared to nonopioid analgesics as treatment of moderate to severe acute pain in the prehospital setting.

Key Messages

- As initial therapy in the prehospital setting:
  - Nonsteroidal anti-inflammatory drugs provide similar pain relief to opioids and may cause fewer overall side effects and less drowsiness.
  - Acetaminophen 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 acetaminophen. The intranasal route was common in studies reporting adverse events for the comparison of opioids versus ketamine.

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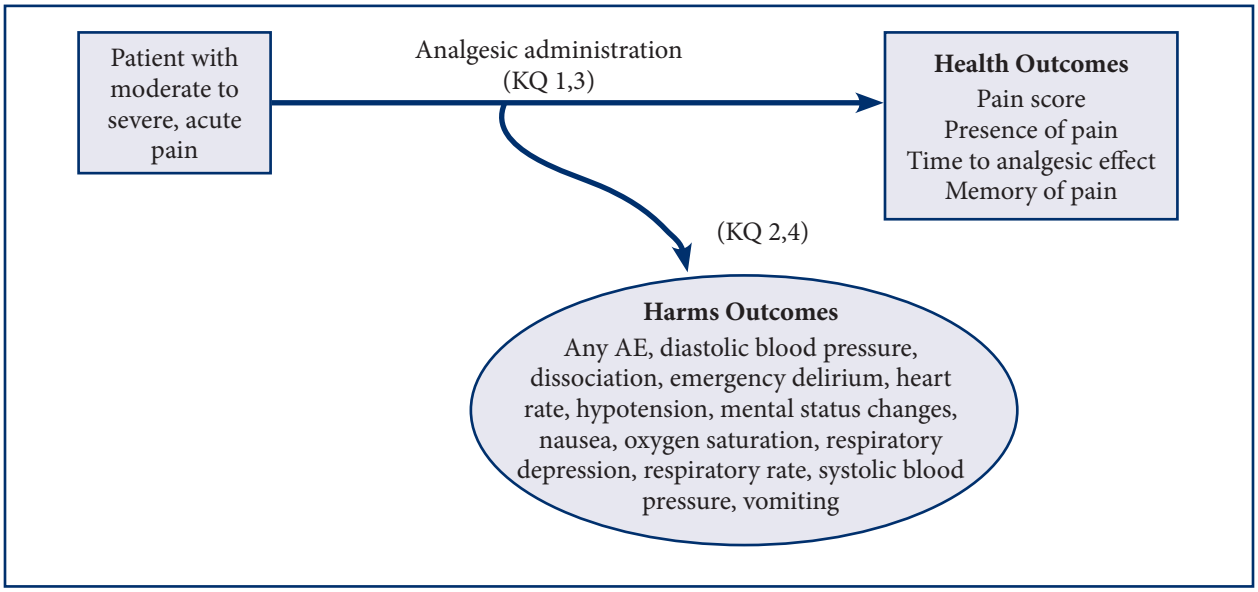
provide adequate analgesia. This systematic review assesses the comparative effectiveness and harms of opioids compared to nonopioid analgesics for the prehospital management of acute pain (Figure A).

Figure A. Analytic framework



Abbreviations: AE=adverse event; KQ=Key Question

Data Sources

We searched MEDLINE®, Embase® and Cochrane Central bibliographic databases from earliest date through May 9, 2019; hand searches of references of relevant studies; www.clinicaltrials.gov and the International Controlled Trials Registry Platform. The systematic review protocol is available in the full report.

Methods

The protocol was registered in PROSPERO (CRD42018114959) and posted on the AHRQ website. The draft report will be posted for public and peer review and we will revise the report based on these comments. After input from the Technical Expert Panel (TEP), NHTSA, AHRQ and our EPC, we chose the following analgesic comparisons and outcomes upon which to formulate conclusions with graded strength of evidence (SOE):

comparisons (opioids versus ketamine, opioids versus APAP, opioids versus nitrous oxide, opioids versus NSAIDs, combination opioid and ketamine versus opioids) and outcomes (pain severity, pain presence, time to analgesic effect, any adverse event, hypotension, mental status changes, and respiratory depression).

Conclusions are made in the context of clinically important differences that were established based on the input of NHTSA, AHRQ, the TEP, and our EPC. This includes 2 points on a 0 to 10 pain scale, 5 minutes for time to analgesia, 10 percent absolute difference for any adverse event and 5 percent absolute difference for hypotension, respiratory depression and mental status changes review. We judged the SOE for our conclusions in consideration of five domains: study limitations, consistency, directness, precision and reporting bias.[9] The four levels of SOE include high (+++), moderate (++), low (+), or insufficient.

The results for analgesics comparisons and outcomes that are not graded are reported in the full report.

Results

We included 52 randomized controlled trials (RCTs) and 13 observational studies, of which 37 RCTs and 4 observational studies provided evidence for graded comparisons and outcomes (Table A).[10-74] We aimed to base conclusions on direct evidence from the prehospital setting, but this was not always possible because of a lack of studies. In the absence of sufficient prehospital evidence, we used evidence from the emergency department but downgraded strength of evidence for indirectness.

Table A. Characteristics of included studies for graded comparisons, per comparison

Characteristic	Opioids Versus Ketamine	Opioid+Ketamine Versus Opioid	Opioids Versus APAP	Opioids Versus Nitrous Oxide	Opioids Versus NSAIDs
N of studies	17 RCT 3 OBS[a]	6 RCT 2 OBS[a]	10 RCT	1 RCT	3 RCT
Countries and N of studies	Afghanistan 2[b]; Australia 1; Israel 1; Iran 5; Sweden 1; 1 New Zealand; USA 8; Vietnam 1	Afghanistan 1[b]; France 1; Iran 3; Switzerland 1; USA 2	Iran 4; Turkey 4; Qatar 1; UK 1	Iran 1	Canada 1; Iran 1; USA 1
N of patients	2,484	1,566	2,001	100	474
Gender (Range of males, %)	23.3 to 100	40 to 100	43 to 83	72 to 84	56.4 to 70.5
Age (Range of means, y)	7 to 77.3	23 to 51.58	29.1 to 44.6	35.8 to 37	11.7 to 39.3
Pain Classification (N studies)	Traumatic: 13 Nontraumatic: 1 Mixed: 6	Traumatic: 3 Nontraumatic: 2 Mixed: 3	Traumatic: 4 Nontraumatic: 5; Mixed: 1	Traumatic: 1	Traumatic: 1 Nontraumatic: 1; Mixed: 1
Setting (N studies)	Prehospital: 4 ED: 14 Battlefield: 2	Prehospital: 2 ED: 5 Battlefield: 1	ED: 10	ED: 1	ED: 3
Administered doses (N studies)[c]	Single: 11 Multiple: 7 NR: 2	Single: 6 NR: 2	Single: 10	Single: 1	Single: 1 Multiple: 2
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 NEB vs. IV: 1 Mixed/NR: 2	IV+IV vs. IV: 6 IV+IN vs. IV: 1 NR: 1	IV vs. IV: 10	IV vs. inhaled: 1	IV vs. IV: 2 PO vs. PO: 1

Table A. Characteristics of included studies for graded comparisons, per comparison

Characteristic	Opioids Versus Ketamine	Opioid+Ketamine Versus Opioid	Opioids Versus APAP	Opioids Versus Nitrous Oxide	Opioids Versus NSAIDs
Specific drugs (N studies)	Morphine: 12 Fentanyl: 6 Mixed: 2	Morphine: 6 Mixed: 2	Morphine: 9 Fentanyl: 1	Fentanyl: 1	Morphine: 3 Ketorolac: 2 Ibuprofen: 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	Low/medium: 1	Low: 2 Medium: 1

Abbreviations: APAP=acetaminophen; ED=emergency department; IM=intramuscular; IN=intranasal; IV=intravenous; NEB=nebulized; NR=not reported; NSAIDs=nonsteroidal anti-inflammatory drugs; OBS=observational; PO=oral; RCT=randomized controlled trial; UK=United Kingdom; USA=United States of American; vs=versus

[a]Two observational studies included two comparisons: opioids vs. ketamine and morphine vs. fentanyl, one of these studies also compares opioids+ketamine vs. opioids.

[b]These studies took place in Afghanistan but were U.S. military forces.

[c]Studies were classified according to the number of doses given of the randomized analgesic. Studies either allowed one dose or multiple doses.

[d]One trial included three arms and thus has two comparisons: morphine IV vs. ketamine and morphine IM vs. ketamine.

[e]Some studies had different risk of bias based on the individual outcome, and in these cases were listed as "low/medium" risk of bias.

Initial Analgesia

Key Questions (KQ) 1 and 2 aimed to evaluate comparative effectiveness (KQ 1) and harms (KQ 2) of initial analgesics (Table B). Conclusions are based on indirect evidence from the emergency department setting. Opioids, ketamine and NSAIDs were primarily administered IV, and for APAP this was the only route studied. The IN route was also common in studies reporting adverse event outcomes for the comparison of opioids versus ketamine.

We found no evidence of clinically important differences in pain reduction between opioids and ketamine administered primarily IV, IV APAP or NSAIDs administered primarily IV. Combining opioids and ketamine may be more effective than opioids alone, administered primarily IV.

Opioids may cause fewer adverse events than ketamine, primarily administered IN. Based on subgroup analysis, this risk may be associated with age or route of administration. Opioids may cause more adverse events than NSAIDs, administered primarily IV. Opioids may cause more side effects than APAP, both administered IV.

Table B. Summary of the comparative effectiveness and harms of initial analgesics in the prehospital setting

Outcome	Opioida Versus Ketamine[a]	Opioid+ketaminea Versus Opioid[a]	Opioida Versus IV APAP	Opioida Versus Nitrous Oxide	Opioida 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

Abbreviation: IV=intravenous

Strength of evidence: white = no evidence; yellow = insufficient; orange (+) = low; blue (++) = moderate. Conclusions of no clinically important difference are based on a priori determined thresholds of 2 points on a 0 to 10 pain scale, 5 minutes for time to analgesia, 10% absolute difference for any adverse event and 5% absolute difference for hypotension, respiratory depression and mental status changes.

[a]Routes of administration were primarily intravenous, with exception of opioid versus ketamine for "any adverse event" where analgesics were primarily administered IN. (see table A, dosage form row).

[b]Change in 15 and 30 minutes; no clinically important difference at 60 min.

[c]At 30 and 60 min, inconclusive at 15 min.

[d]Insufficient for drowsiness, changes in RAAS, reduced GCS, sleepiness/tired, confusion, sedation, difficulty concentrating.

[e]For dizziness, sedation.

[f]Inconclusive for mild sedation.

[g]For dizziness.

[h]Insufficient for depression (as a mental status change), dizziness.

Analgesia When Initial Choice Is Insufficient

KQ 3 and 4 aimed to evaluate comparative effectiveness and harms of subsequent analgesia when initial analgesia is ineffective. Giving a patient ketamine IV instead of continuing to administer morphine IV when the initial morphine IV administration does not provide the patient with pain relief may reduce pain more and may reduce pain more quickly. This is based on direct evidence from the prehospital setting. Evidence of harms was either insufficient or nonexistent.

Table C. Summary of the comparative effectiveness and harms of subsequent analgesics in the prehospital setting

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

Discussion

Our review found that as an initial analgesic and primarily administered IV, opioids are no different than the nonopioid analgesics ketamine, APAP and NSAIDs in reducing pain. The combination of opioids and ketamine may be more effective in reducing pain, compared with opioids alone. When initial IV morphine is not effective, switching to IV ketamine may be better in reducing pain than continuing to administer morphine.

To put these findings in context there are key parameters concerning applicability to consider. The studies that compared the efficacy of opioids with ketamine mostly compare weight-based IV morphine 0.1mg/kg with IV ketamine (variable weight-based dosing). Some studies evaluated IN fentanyl and IN ketamine, which were prepared from the IV formulations and delivered IN via an atomizer. The IN ketamine product on the US market is not approved for pain management and is specific to management of treatment-resistant depression. The doses of ketamine varied and too few studies were available to identify associations based on dose. When ketamine was studied in combination with opioids, a single IV dose was added to the opioid regimen. How administration of more than one ketamine dose impacts outcomes is unknown. Nine of the 10 trials that compared opioids with APAP compared IV morphine 0.1 mg/kg with IV APAP 1g, thus results cannot be extrapolated to other routes or doses. There were only three studies comparing opioids with NSAIDs with a mixed representation of oral and IV dosage forms. We were unable to draw conclusions about the efficacy of opioids compared with nitrous oxide (based on a single study with limitations).

Comparative harms of specific adverse events vary among analgesics and in the absence of clinically important differences in pain reduction, can inform individualized treatment decisions. The overall frequency of total adverse events in trials that compared opioids with ketamine suggests that at least 50 percent of treated patients will experience some type of adverse event but low-strength evidence suggests that opioids may cause fewer total adverse events than ketamine. These trials studied primarily IN analgesic administration and based on our subgroup analyses, the lower overall adverse event risk with opioids may be associated with either age or route of administration. Opioids may cause more respiratory depression while ketamine causes more dizziness. In contrast to the comparison of opioids with ketamine, opioids may cause more adverse events than IV APAP or NSAIDs when used as initial analgesics. In patients who do not adequately respond to initial morphine, comparative harms of giving ketamine compared with giving additional morphine are uncertain.

The focus of this report is to synthesize existing evidence. We do not make clinical recommendations. We encourage application of this evidence toward future work generating evidence-based clinical guidelines.

The major limitation of this review is the indirectness of evidence, which may have significant implications and led to our downgrading of conclusions. We believe the single most important future research need is addressing this evidence gap with pain management studies set in the prehospital environment. In addition, research is needed to explore subgroups, including patient and drug regimen characteristics and EMS personnel training and how these characteristics may modify comparative effectiveness and harms of analgesics.

Conclusion

As initial analgesia administered primarily IV, opioids are no different than ketamine, APAP, and NSAIDs in reducing acute pain in the prehospital setting. Opioids may cause fewer total side effects than ketamine, but more than APAP or NSAIDs. Differences in specific side effects vary between analgesics and can further inform treatment decisions. Combined administration of an opioid and ketamine may reduce acute pain more than an opioid alone but comparative harms are uncertain. When initial morphine is inadequate in reducing pain, giving ketamine may provide greater and quicker acute pain relief than giving additional morphine, although comparative harms are uncertain. Due to indirectness, strength of evidence is generally low, and future research in the prehospital setting is needed.

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Full Report

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