Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

STRUCTURED EVIDENCE-BASED MEDICINE REVIEW

The Use of Intravenous Acetaminophen for Acute Pain in the Emergency Department

Billy Sin, PharmD, BCPS, Mabel Wai, PharmD, BCPS, Tamara Tatunchak, MD, and Sergey M. Motov, MD, FAAEM

Abstract

Objectives: Acetaminophen (APAP) is a mainstay for pain management worldwide. The intravenous (IV) formulation has been widely used in Europe for more than 20 years in adults and children. In the United States, IV APAP obtained full approval from the Food and Drug Administration in 2010. There is emerging literature to suggest the use of IV APAP for pain reduction in the emergency department (ED). This evidence-based review examines the evidence pertaining to the use of IV APAP for acute pain control in the ED.

Methods: The MEDLINE and EMBASE databases were searched. Randomized controlled trials (RCTs) that described or evaluated the use of IV APAP for acute pain in the ED were included. Duplicate articles, unpublished reports, abstracts, review articles, and non-English literature were excluded. The primary outcome of interest in this review was the difference in pain score between IV APAP and active comparator or placebo from baseline to a cutoff time specified in the original trials. Secondary outcome measures were the incidence of adverse events and reduction in the amount of adjuvant analgesics consumed by patients who received IV APAP. Methodologic quality of the trials was assessed using the Grading of Recommendations Assessment, Development, and Evaluation criteria.

Results: Fourteen RCTs with various methodologic flaws, which enrolled a total of 1,472 patients, met the inclusion criteria. The level of evidence for the individual trials ranged from very low to moderate. In three of the 14 trials, a significant reduction in pain scores was observed in patients who received IV APAP. The first trial found a significant reduction in mean pain scores when IV APAP was compared to IV morphine at 30 minutes after drug administration (4.7 ± 2.3 vs. 2.9 ± 2.2). In the second trial, patients who received IV APAP reported of lower pain scores (31.7 ± 18 mm, 95% confidence interval [CI] = 8.2 to 25.2 mm) compared to those who received IV morphine (48.3 ± 14.1 mm, 95% CI = 8.2 to 25.2 mm), 15 minutes after drug administration. A third trial found a significant reduction ($p = 0.005$) in the mean pain scores when IV APAP was compared to intramuscular piroxicam at 90 minutes after drug administration. In the remaining eight trials, pain scores were not statistically different when IV APAP was compared to other pain medications. The incidence of side effects associated with IV APAP was very low.

Conclusions: Fourteen RCTs with various methodologic flaws provided limited evidence to support the use of IV APAP as the primary analgesic for acute pain control in patients who present to the ED.

ACADEMIC EMERGENCY MEDICINE 2016;23:543–553

CLINICAL SCENARIO

You are working in the emergency department (ED) and are about to see a 32-year-old male patient with severe left flank pain that started suddenly and radiated to his left groin. Patient also reports of two episodes of nonbilious vomiting and severe pain on urination. Patient has no significant past medical history or drug allergies. During the examination, patient has severe left costovertebral angle

From the Arnold & Marie Schwartz College of Pharmacy, Long Island University (BS), Brooklyn, NY; the Department of Pharmacy, Division of Pharmacotherapy Services, Emergency Department Clinical Research Program, Department of Emergency Medicine, The Brooklyn Hospital Center (BS, TT), Brooklyn, NY; Yale New Haven Hospital (MW), New Haven, CT; the Department of Emergency Medicine, Maimonides Medical Center (SMM), Brooklyn, NY; and the SUNY Downstate Medical Center (SMM), Brooklyn, NY.

Received October 17, 2015; revision received December 2, 2015; accepted December 3, 2015.
The authors have no relevant financial information or potential conflicts to disclose.
Supervising Editor: Shahriar Zehtabchi, MD.

Address for correspondence and reprints: Dr. Billy Sin, PharmD, BCPS; e-mail: billy.sin@liu.edu.

doi: 10.1111/acem.12921
ISSN 1069-6563
PII ISSN 1069-6563583

tenderness and normal genitourinary examination. You performed a bedside renal ultrasound of the left kidney and noted moderate hydronephrosis supporting your clinical suspicion for nephrolithiasis. You prescribe intravenous (IV) ketorolac 30 mg and IV morphine 5 mg. You share your case with a colleague who recalls seeing a paper on the use of IV acetaminophen (APAP) for acute pain. After this encounter, you decide to review the evidence justifying the use of IV APAP as the primary analgesic for acute pain in the ED.

BACKGROUND

Acetaminophen has been a mainstay for pain management for many years. The IV formulation has been widely used in Europe for more than 20 years in adults and children. In the United States, IV APAP obtained full approval from the Food and Drug Administration in 2010.[1] The mechanism of action of APAP induced analgesia is not well understood.[1,2] It has been postulated that the primary analgesic effect of APAP is induced by cyclooxygenase inhibition, *N*-methyl-D-aspartate receptor inhibition, and serotonergic antagonism in the central nervous system.[1–4] Traditional formulations of APAP include oral and rectal forms. Aside from the route of drug delivery, there are other marked differences in the pharmacokinetic properties of the IV formulation.[1–3] IV APAP results in a rapid elevation in plasma concentration.[2,3] Compared to the oral formulation, the time to reach maximum concentration for IV APAP (15 minutes) is more predictable than the oral immediate-release (10–60 minutes), oral extended-release (60–120 minutes), and rectal (variable) formulations.[1,5] APAP is primarily metabolized in the liver and less than 5% of free drug is excreted in the urine.[5] Since first-pass metabolism is bypassed with the IV route, initial drug exposure to the liver is reduced by nearly twofold compared with the oral formulation.[2] IV APAP's role as an adjunctive analgesic has been well documented in the postoperative setting.[5,6] In the ED, the use of IV APAP for acute pain is not a common practice. Its use is often a topic of controversy due its acquisition cost and perceived effectiveness for various types of acute pain. However, recent evidence has emerged that suggests the use of IV APAP as the primary analgesic for acute pain control in the ED. The objective of this review is to answer the following research question: "In ED patients with moderate to severe pain, is the administration of IV APAP as the primary analgesic, compared to placebo or comparator analgesics, safe and effective in pain control?"

CRITERIA FOR CONSIDERING STUDIES FOR THE REVIEW

Target Study Design

Randomized controlled trials (RCTs) that described the use of IV APAP as the primary analgesic in the ED were selected for the review.

Participants

Eligible participants included patients of any age range who presented to the ED for acute pain and received at least one dose of IV APAP in the ED. Patients who received IV APAP in a setting outside the ED or for indications other than analgesia were excluded.

Intervention

The intervention consisted of the administration of IV APAP. No restrictions were set for the route of administration for the comparator groups.

Comparison

The comparison consisted of the administration of placebo or active comparator (analgesic pain medications).

Outcomes

The primary outcome of interest in this review was the difference in pain scores from baseline to the cutoff time specified in the original trial between IV APAP and active comparator or placebo. Secondary outcomes included the incidence of adverse events and reduction in the amount of adjuvant analgesics consumed by patients who received IV APAP.

SEARCH METHODS

This evidence-based review was structured according to the PRISMA statement.[7] A methodologic protocol was established a priori by the study investigators (BS, MW) and adhered throughout. A search of the MEDLINE database from July 1970 to July 2015 and EMBASE from July 1970 to July 2015 was conducted. The search strategies are presented in Data Supplement S1 (available as supporting information in the online version of this paper). Additional references were identified from a review of literature citations. Abstracts were screened for relevance and subsequent publications relating to the use of IV APAP as an analgesic for acute pain in the ED were identified. Only English-published literature that evaluated the use of IV APAP as the primary analgesic for acute pain control in humans was included. Duplicate articles, unpublished reports, abstracts, and review articles were not considered. Two authors (BS, MW) independently screened all titles, abstracts, and full-text articles. Articles were eliminated according to the inclusion and exclusion criteria. Any disagreement was resolved by a third author (SM). The PRISMA checklist and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria were utilized to guide the structure and reporting of the identified literature.[7,8] The primary search identified a total of 1,360 publications. The number of citations was reduced, according to their relevance for this review (Figure 1). The search identified 14 RCTs, which fulfilled our criteria. We performed our review based on these 14 publications. Data extraction was performed independently by two authors (BS, MW) via a standardized electronic data extraction form.

Description of Included Trials

Of the 14 randomized controlled trials that met the inclusion criteria, 12 were double-blinded, and two were nonblinded. All 14 trials used validated pain scales to measure analgesic efficiency and incidence of adverse events as a measure of safety. In the literature identified, IV APAP was utilized as the primary analgesic for acute

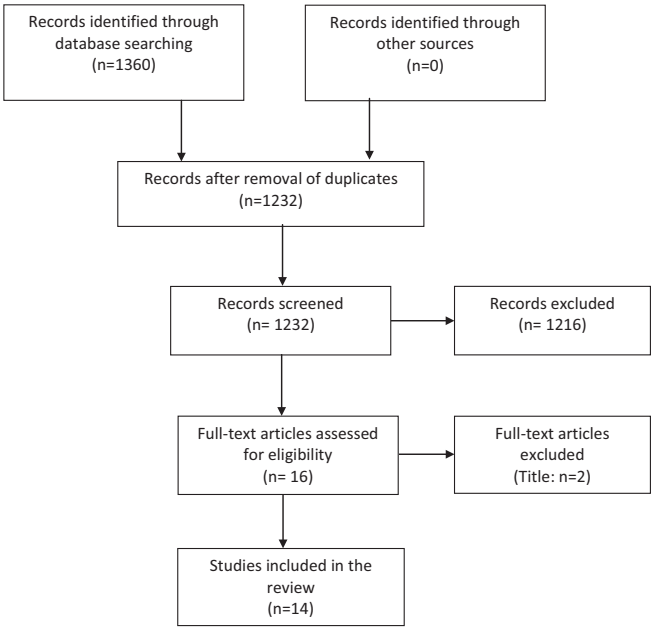

Figure 1. The process for selecting studies suitable for inclusion in the final review.

pain control due to renal colic, abdomen, lower back, headache, bone fracture, acute trauma, or scorpion sting. All patients within the randomized trials received a one-time dose of IV APAP at 1 gram per dose. Four randomized trials infused IV APAP at a rate faster than 15 minutes.[9–12] Turkcuer et al.[13] described administering IV APAP as "a rapid infusion." The characteristics of studies included in this review are summarized in Table 1.

Quality Assessment of the Included Studies

An assessment of factors (randomization concealment, patient selection, adequacy of blinding, and duration of follow-up) that may contribute to risk of bias was conducted independently by three reviewers (BS, MW, TT) based on the PRISMA statement. In the case of discrepancy, a fourth reviewer (SM) was consulted. An evaluation on the methodologic quality of the evidence based on the GRADE criteria was conducted independently by two reviewers (BS, MW).[8] In the case of disagreement, a third reviewer (SM) was consulted. An assessment of the risk of bias and level of methodologic quality for the identified literature is summarized in Table 2.

RESULTS

A summary of the primary outcome from the included literature is presented in Table 3. The data collected from a total of 1,472 patients revealed conflicting results and conclusions.

A significant reduction in pain scores with IV APAP was found in three of the 14 trials.[9,10,14] Of the three trials, two compared IV APAP to IV morphine.[9,10] In the third trial, Grissa et al.,[14] reported of a greater reduction in pain scores when IV APAP was compared with piroxicam. A total of eight randomized trials[12,13,15–20] reported no detectable differences in the observed pain scores between IV APAP and comparator groups. Oguzturk et al.,[12] Azizkhani et al.,[21] and Aksel et al.[22] reported of improved analgesia with morphine, tramadol, and topical lidocaine, respectively.

A summary of the incidence of adverse events in patients who received IV APAP is presented in Table 4. Two trials detected a significant difference in the incidence of reported adverse events.[15,21] In the first trial, Zare et al.[15] reported a higher incidence of nausea (26/79 [33%] vs. 8/74 [11%], $p = 0.001$) and itching (12/79 [15%] vs. 3/74 [4%], $p = 0.02$) in patients who received IV APAP compared to IV morphine. It should be noted that patients who received IV APAP also received oral oxycodone as part of the study intervention. In the second trial, Azizkhani et al.[21] detected a lower incidence of dizziness (0/62 [0%] vs. 15/62 [24%], $p < 0.05$) and arterial hypotension (0/62 [0%] vs. 6/62 [10%], $p = 0.014$) in patients who received IV APAP compared to IV morphine. Craig et al.[18] also reported a significant difference in the total number of patients who experienced an adverse event, favoring IV APAP versus IV morphine (7.2% vs. 29.6%, $p = 0.03$). However, description on the type of adverse events was not presented. Of interest, Masoumi et al.[9] reported three cases of "restlessness" in patients who received IV APAP. No further description of the adverse event was provided by the original reference. However, it was reported that the events resolved when the infusion rate was slowed.

A detailed summary of rescue protocols described in the identified literature is presented in Table 5. The use of rescue analgesia was described in 10 randomized trials.[9,10,13–19,22] In four trials, the number of patients who required rescue analgesia in the IV APAP group was fewer than those who received active comparators.[9,14,17,19] Of these trials, only Masoumi et al.[9] detected a significant decrease in the number of patients who required rescue opioids, favoring IV APAP. In this trial, 17/54 (31%) patients in the APAP group versus 30/54 (55%) patients in the morphine group required rescue analgesia ($p = 0.01$).

Quality of Trials

The trials identified in this review had a small sample size or various methodologic flaws.[9–11,13–17,21] Information on the procedure for blinding the data collector or data assessor were not presented.[9–11,13–17,21] Randomization concealment was not reported in five trials.[10,12,18,20,21] A detailed description of reported adverse events was not available.[16,17] Data on the power and sample size to detect significant differences for the primary outcome were not presented in three trials.[10,21,22] Protocols for the use of rescue analgesia were not mentioned in five trials.[10,12,13,20,21] In the trials which described the use of rescue analgesia, data on the agents[15,18,19] or doses[9,11,14–19,22] consumed were not presented. Two trials provided unclear descriptions of the protocols used for providing rescue analgesia.[14,18] Grissa et al.[14] and Craig et al.[18] described rescue therapy as "the need of intravenous morphine titration" and "intravenous morphine titrated to effect," respectively. Both trials did not provide data on the frequency of medication administration or the total doses that were

Table 1
Characteristics of the Studies Included in the Review

Trials	Population	Interventions [Number of Patients Assigned]	Comparison [Number of Patients Assigned]	Outcome
Masoumi et al., 2014[9]	110 patients at a tertiary ED in Iran *Age range:* 18–55 y *Inclusion:* acute renal colic *Exclusion:* allergy to morphine or APAP; hemodynamically unstable; fever > 38°C; evidence of peritoneal inflammation; pregnancy or suspected pregnancy; proven or suspected aortic aneurysm or dissection; used analgesia within 6 h of evaluation; heart, renal, liver, or respiratory failure; kidney transplant patients; opioid addiction	APAP 1 g IV over 5–10 min [*n* = 54]	Morphine 0.1 mg/kg IV over 5–10 min [*n* = 54]	*Primary:* 10-point VAS reduction at 30 min after medication administration *Secondary:* adverse events, need for rescue analgesia, discharge within 60 min
Shams Vahdati et al., 2014[10]	60 patients at a trauma center in Iran *Age range:* 18–55 y *Inclusion:* headache ≥ 40/100 mm on VAS *Exclusion:* allergy or contraindication to morphine or paracetamol; fever > 38°C; hemodynamic instability; neurologic findings; documented or suspected pregnancy; used analgesia within 6 h of evaluation; documented liver, renal, pulmonary, or cardiac disease; kidney or liver transplant	APAP 1 g IV over 10 min [*n* = 30]	Morphine 0.1 mg/kg IV over 10 min [*n* = 30]	*Primary:* 100-mm VAS at 15 and 30 min after medication administration *Secondary:* Recurrence rate of headache after 1 wk
Serinken et al., 2012[11]	73 patients at a tertiary ED in Turkey *Age range:* 18–55 y *Inclusion:* flank pain secondary to renal colic *Exclusion:* used analgesia within 6 h of ED visit, presented with fever, hemodynamically unstable, signs of peritoneal irritation or cardiac failure, history of renal or liver failure, prior allergy to APAP or morphine, were or suspected of being pregnant, had vision problems	APAP 1 g IV over 2–4 min [*n* = 38]	Morphine 0.1 mg/kg IV over 2–4 min [*n* = 35]	*Primary:* VAS reduction at 15 and 30 min after medication administration *Secondary:* VRS reduction at 15 and 30 min after medication administration, adverse events, need for rescue analgesia
Oguzturk et al., 2012[12]	210 patients at a tertiary ED in Turkey *Age range:* >17 y *Inclusion:* nontraumatic abdominal pain less than 72 h duration *Exclusion:* pregnancy, allergy to opioids or paracetamol, hypotension (<100 mm Hg), self-medication with analgesia	APAP 15 mg/kg IV over 3 min [*n* = 70]	Tramadol 1 mg/kg [*n* = 70], placebo [*n* = 70]	*Primary:* 100-mm VAS at designated intervals after medication administration *Secondary:* Adverse events, P/E findings
Turkcuer et al., 2013[13]	200 patients at a tertiary ED in Turkey *Age range:* 18–69 y *Inclusion:* headache meeting the criteria of the ICHD for migraine without aura *Exclusion:* receiving analgesic in the past 6 h of ED presentation; known or a strong possibility of pregnancy; known allergy to the study drugs; hemodynamic instability; vision problems; pain character or intensity different from former migraine attacks; illiteracy; renal transplantation; liver, kidney, cardiac, or pulmonary insufficiency	APAP 1 g IV by "rapid infusion" [*n* = 100]	Dexketoprofen 50 mg IV by "rapid infusion" [*n* = 100]	*Primary:* 100-mm VAS change at 15 and 30 min after medication administration *Secondary:* adverse reactions, rescue analgesia

(Continued)

Table 1 (continued)

Trials	Population	Interventions [Number of Patients Assigned]	Comparison [Number of Patients Assigned]	Outcome
Grissa et al., 2011[14]	100 patients at a tertiary ED in Tunisia *Age range:* >16 y *Inclusion:* acute renal colic with pain ≥ 30/100 mm on VAS *Exclusion:* history of peptic ulcer disease; asthma or bleeding disorder; use of oral anticoagulant; impaired renal or hepatic function; suspected hypersensitivity to aspirin, APAP, or NSAID; pregnant; breast-feeding; used analgesia within 6 h of evaluation	APAP 1 g IV over 15 min [*n* = 50]	Piroxicam 20 mg IM [*n* = 50]	*Primary:* number of patients with VAS reduction of 50% or more at 90 min after medication administration *Secondary:* VAS at designated intervals, adverse events, hospital admissions, new visit for renal colic within 72 h
Zare et al., 2014[15]	153 patients at a tertiary ED in Iran *Age range:* 15–60 y *Inclusion:* acute bone fracture *Exclusion:* altered consciousness; concurrent significant trauma; life-threatening condition; known opioid or APAP allergy; addition to narcotics; history of chronic respiratory, renal, hepatic, or heart failure; administration of analgesics before ED admission; pregnant; unable to understand or communicate	APAP 1 g IV over 15 min [*n* = 79]	Morphine 5 mg IV via "slow injection" [*n* = 74]	*Primary:* 10-point pain scale reduction at 30 and 60 min after medication administration *Secondary:* incidence of adverse events
Eken et al., 2014[16]	137 patients at a tertiary ED in Turkey *Age range:* 18–55 y *Inclusion:* moderate to severe acute mechanical LBP *Exclusion:* used analgesia within 6 h of evaluation; peritoneal irritation; hemodynamic instability; renal transplantation; renal, liver, cardiac, or pulmonary failure; malignancy; pain indicating sciatalgia; positive Straight Leg Raise Test; neurologic deficit; known allergy to study drugs; probable renal or biliary colic; illiteracy	APAP 1 g IV* [*n* = 46]	Dexketoprofen 50 mg IV* [*n* = 46], Morphine 0.1 mg/kg IV* [*n* = 45]	*Primary:* 100-mm VAS and VRS reduction at 15 and 30 min after medication administration *Secondary:* adverse events, need for rescue analgesia
Bektas et al., 2009[17]	146 patients at a tertiary ED in Turkey *Age range:* 18–55 y *Inclusion:* acute renal colic with mild or greater pain on a 4-point verbal rating scale or ≥20/100 mm on VAS *Exclusion:* allergy or contraindication to morphine, paracetamol, or any opioid analgesic; hemodynamic instability; fever (>38°C); evidence of peritoneal inflammation; documented or suspected pregnancy; known or suspected aortic dissection or aneurysm; used analgesia within 6 h of evaluation; previous study enrollment; known renal, pulmonary, cardiac, or hepatic failure; renal transplantation	APAP 1 g IV* [*n* = 46]	Morphine 0.1 mg/kg IV* [*n* = 55] Placebo [*n* = 51]	*Primary:* 100-mm VAS change at 15 and 30 min after medication administration *Secondary:* adverse events, need for rescue analgesia
Craig et al., 2012[18]	55 patients at a tertiary ED in United Kingdom *Age range:* 15–65 y *Inclusion:* isolated limb trauma with pain score ≥ 7/10 *Exclusion:* chest pain, GCS, allergy to morphine or paracetamol, known liver disease or patient clinically jaundiced, major trauma, known pregnancy, breast-feeding, requiring immediate limb-saving procedure, extreme stress, communication difficulties (foreign language, prior confusion)	APAP 1 g IV over 15 min [*n* = 28]	Morphine 10 mg IV over 15 min [*n* = 27]	*Primary:* 100-mm VAS at designated time intervals after medication administration *Secondary:* adverse reactions, rescue analgesia, patient satisfaction

(Continued)

Table 1 (continued)

Trials	Population	Interventions [Number of Patients Assigned]	Comparison [Number of Patients Assigned]	Outcome
Morteza-Bagi et al., 2015[19]	100 patients at a tertiary ED in Iran *Age range:* 18–50 y *Inclusion:* diagnosis of renal colic by ultrasound or abdominal radiography *Exclusion:* received any analgesic treatment before admission, allergies to medications, history of opioid dependency, high blood pressure, fever and chills, pregnancy, intolerance of pain during the first 35 min of drug administration	APAP 1 g IV* [*n* = 50]	Morphine 5 mg* IV [*n* = 50]	*Primary:* 10-point VAS at designated intervals after medication administration
Pickering et al., 2015[20]	40 patients at a trauma center in France *Age range:* 34–50 y *Inclusion:* leg or arm traumatic pain *Exclusion:* age < 18 y, known hypersensitivity to APAP or alcohol, used analgesia within 6 h of ED visit, pain > 6/10 on pain scale, suspicion of fracture	APAP 1 g IV over 15 min [*n* = 20]	Transmucous buccal 125 mg [*n* = 20]	*Primary:* 10-point NRS at 30 min after medication administration *Secondary:* NRS at designated time intervals
Azizkhani et al., 2013[21]	124 patients at a tertiary ED in Iran *Age range:* 15–80 y *Inclusion:* pain secondary to renal colic *Exclusion:* addicted or allergic to opioids or APAP; used analgesia within 6 h of evaluation; kidney transplantation; patients with known heart, liver, respiratory, or renal failure; patients with blindness or physical disabilities who were not able to communicate	APAP 15 mg/kg IV over 15 min [*n* = 62]	Morphine 0.1 mg/kg IV over 15 min [*n* = 62]	*Primary:* 10-point VAS at 30 min after medication administration
Aksel et al., 2015[22]	130 patients at a tertiary ED in Turkey *Age range:* > 18 y *Inclusion:* pain associated with scorpion sting with only localized reactions *Exclusion:* questionable stings, late presentations (>6 h); age < 18; known allergy to paracetamol, NSAID, or lidocaine; use of any IV analgesic drug within 24 h of ED presentation; hemodynamic instability; electrocardiographic abnormality; rapidly progressing local edema; abnormal neurologic examination findings; simultaneous abnormal skin conditions including local infections, ulcerations, or scars; electrocardiographic abnormality; rapidly progressing local edema; abnormal neurologic examination findings; autonomic symptoms; chest pain; pulmonary edema; altered mental status	APAP 1 g IV* [*n* = 45]	Topical 5% lidocaine [*n* = 43], ice application [*n* = 42]	*Primary:* 100-mm VAS change at designated intervals after medication administration *Secondary:* adverse events

APAP = acetaminophen; GCS = Glascow Coma Scale; ICHD = international classification of headache disorders; IM = intramuscular; IV = intravenous; LBP = lower back pain; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drugs; P/E = physical examination; VAS = visual analog scale; VRS = verbal rating scale.
*Time of infusion not provided by study investigators.

administered and consumed. Thus, we were unable to evaluate the potential impact that rescue analgesia had on the reported primary outcomes. CIs that would provide information about point estimates or the degree of uncertainty for the reported pain scores[9,10,12–15,17–20,22] or adverse events[9–11,14,18] were not consistently presented. Incomplete presentation of data was also observed. One trial reported of significant differences in the overall incidence of adverse events between the intervention and comparator group without providing descriptions of the specific adverse events that were observed.[18] Due to various methodologic flaws, the level of evidence assigned to the individual trials ranged from very low to moderate.

Table 2
Assessment of Risk of Bias and Assigned Level of Evidence in the Available Literature

Trials	Randomization Concealed	RCT Halted Early	Provider Blinded	Data Collector Blinded	Data Assessor Blinded	Duration of Follow-up (min)	Cointervention With APAP	Target Sample Size Attained	Assigned Level of Evidence*
Masoumi et al., 2014[9]	Yes	No	Yes	N/A	N/A	60	None	Yes	Very low
Shams Vahdati et al., 2014[10]	N/A	No	Yes†	N/A	N/A	30	None	N/A‡	Very low
Serinken et al., 2012[11]	Yes	No	Yes	Yes	N/A	30	None	Yes	Moderate
Oguzturk et al., 2012[12]	N/A	No	Yes	N/A	N/A	40	None	Yes	Very low
Turkcuer et al., 2014[13]	Yes	No	Yes	N/A	N/A	60	None	Yes	Low
Grissa et al., 2011[14]	Yes	No	No	No	No	90	None	Yes	Very low
Zare et al., 2014[15]	Yes	No	Yes	Yes	N/A	60	Oxycodone 10 mg tablets	Yes	Very low
Eken et al., 2014[16]	Yes	No	Yes	N/A	N/A	30	None	Yes	Moderate
Bektas et al., 2009[17]	Yes	No	Yes	N/A	N/A	30	None	Yes	Very low
Craig et al., 2012[18]	N/A	No	Yes	N/A	N/A	60	None	Yes	Very low
Morteza-Bagi et al., 2015[19]	Yes	No	Yes	N/A	N/A	35	Low-dose morphine§	Yes	Very low
Pickering et al., 2015[20]	N/A	No	Yes	N/A	N/A	120	None	Yes	Low
Azizkhani et al., 2013[21]	N/A	No	Yes	N/A	N/A	30	None	N/A‡	Very low
Aksel et al., 2015[22]	Yes	No	No	N/A	N/A	240	None	N/A‡	Very low

N/A = information not available from original study; RCT = randomized controlled trial.
*Level of evidence was determined using Grading of Recommendations Assessment, Development, and Evaluation (GRADE system).
†Two individual nurses who prepared and administered medications were blinded. It was not known if the attending physician (s) who evaluated patients for eligibility was/were blinded.
‡Minimal number of patients per group needed to detect significant difference not reported but significant differences claimed by original reference.
§The specific dose utilized was not reported by the original reference.

DISCUSSION

Returning to the clinical scenario, this review provides some guidance on the use of IV APAP in the ED. The data revealed in this review provided limited evidence to support the use of IV APAP as the primary analgesic for acute pain. Of the 14 trials included in this review, three trials reported of significant reduction in pain scores.[9,10,14] In these trials, the indications for IV APAP included acute renal colic[9,14] and headache.[10] We also noted that eight randomized trials compared IV APAP with IV morphine.[9–11,15,17–19,21] Interestingly, these trials yielded conflicting results regarding the primary outcome. Potential explanations for the observed results reported in these trials may include underdosing of morphine or a lack of repeated dosing, titrated to effect. The most frequently reported adverse events in the identified literature were nausea, vomiting, and itchiness. Of interest, no adverse events were reported for the three randomized trials, which infused IV APAP at a rate faster than 15 minutes.[9,10,12] In the identified trials that presented data on the use of rescue analgesia, four trials reported a lower number of patients requiring rescue analgesia in the IV APAP group versus active comparators.[9,11,17,19] Of interest, Masoumi et al.[9] were the only investigators to detect a significant difference in the number of patients who required rescue analgesia, favoring IV APAP. In two other trials,[16,17] patients in the IV APAP group had a higher rate of rescue analgesia requirement (not statistically significant). None of the identified randomized trials presented data on the amount of opioids consumed by patients who requested rescue analgesia.

IV APAP may be considered in scenarios where an analgesic with a fast onset of action is required. It may also be considered when the use of alternate analgesics is not indicated due to contraindications, drug–drug interactions or potential worsening of patient outcomes. There are several important factors to consider when initiating IV APAP in the ED. Prior to order entry, physicians need to determine if IV APAP is on the hospital's formulary of drugs. Policymakers need to consider the acquisition cost of the drug when considering the drug for routine use in the ED. None of the identified trials included in this review conducted cost-effective analyses. It may be necessary to retrieve IV APAP

Table 3
Summary of the Difference in Pain Scores From Baseline to the Cutoff Time as Specified in the Literature

Trials	Parameter	Result	Conclusion
Masoumi et al., 2014[9]	10-point VAS reduction at 30 min after medication administration, mean ± SD	APAP 4.7 ± 2.3* vs. morphine 2.9 ± 2.2* ($p < 0.05$)	Patients who received APAP had significant reduction in mean VAS scores
Shams Vahdati et al., 2014[10]	100-mm VAS at 15 and 30 min after medication administration, mean ± SD	*15 min:* APAP 31.7 ± 18 (95% CI = 8.2–25.2) mm vs. morphine 48.3 ± 14.1 (95% CI = 8.2–25.2) mm *30 min:* APAP 17.3 ± 15.5 mm* vs. morphine 29 ± 14.2 mm* ($p < 0.05$)	Patients who received APAP had significant reduction in mean VAS scores
Serinken et al., 2012[11]	100-mm VAS at 15 and 30 min after medication administration, mean ± SD	*15 min:* APAP 33.8 ± 22.5 (95% CI = 26–41) mm vs. morphine 39.4 ± 27.2 (95% CI = 30–49) mm *30 min:* APAP 63.7 ± 21.7 (95% CI = 57–71) mm vs. morphine 56.6 ± 24.4 (95% CI = 48–65) mm	No significant differences found
Oguzturk et al., 2012[12]	100-mm VAS at designated time intervals after medication administration, median (range)	*20 min:* APAP 45 (30–70) mm* vs. tramadol 38 (26–62) mm* vs. placebo 82.5 (70–90) mm* ($p < 0.05$) *40 min:* APAP 33 (30–37) mm* vs. tramadol 27.5 (18–30) mm* vs. placebo 85 (74–93) mm* ($p < 0.05$)	Pain severity scores were decreased most with tramadol vs. APAP or placebo
Turkcuer et al., 2014[13]	100-mm VAS change at 15 and 30 min after medication administration, mean ± SD	*15 min:* APAP 30 (15–40) vs. DK 28 (18.5–40)† *30 min:* APAP 56 (30–78.5) vs. DR 55 (34–75)†	No significant differences found
Grissa et al., 2011[14]	Number of patients with VAS reduction of 50% or more at 90 min after medication administration, *n* (%)	APAP 40 (80%)* vs. piroxicam 24 (48%)* ($p < 0.05$)	Patients who received APAP had significant reduction in mean VAS scores
Zare et al., 2014[15]	10-point pain score at 30 and 60 min after medication administration, mean ± SD	*30 min:* APAP 5.7 ± 1.3* vs. morphine 5.6 ± 1.2* ($p > 0.05$) *60 min:* APAP 4.7 ± 1.5* vs. morphine 4.5 ± 1.4* ($p > 0.05$)	No significant differences found
Eken et al., 2014[16]	100-mm VAS and VRS reduction at 15 and 30 min after medication administration, mean ± SD	*15-min VAS:* APAP 32 ± 23.7 (95% CI = 40–70) mm vs. morphine 43.4 ± 25.8 (95% CI = 34–50) mm vs. DK 28.1 ± 20.4 (95% CI = 23–33) mm *30-min VAS:* APAP 63.1 ± 24.9 (95% CI = 58–72) mm vs. morphine 67 ± 20.5 (95% CI = 60–73) mm vs. DK 55.8 ± 23.4 (95% CI = 50–64) mm *15-min VRS:* APAP 2 (2–3) vs. morphine 2 (1–3) vs. DK 3 (2–3)† *30-min VRS:* APAP 1 (1–2) vs. morphine 1 (1–2) vs. DK 1 (1–2)†	No significant differences found
Bektas et al., 2009[17]	100-mm VAS change at 15 and 30 min after medication administration, mean (95% CI)	*15 min:* results shown in graphic comparison, individual values for mean change and 95% CI was not reported *30 min:* APAP 43 (95% CI = 35–51) mm vs. morphine 40 (95% CI = 29–52) mm vs. placebo 27 (95% CI = 19–34) mm	No significant differences found
Craig et al., 2012[18]	100-mm VAS at designated time intervals after medication administration, mean ± SD	*15 min:* APAP 69.9 ± 17.8 mm* vs. morphine 61.6 ± 19.8 mm* ($p > 0.05$) *30 min:* APAP 63.5 ± 22.3 mm* vs. morphine 55 ± 29.7 mm* ($p > 0.05$)	No significant differences found
Morteza-Bagi et al., 2015[19]	10-point VAS at designated intervals, mean ± SD	*1 min:* APAP 8.0 ± 1.0* vs. HDM 8.3 ± 0.9* ($p > 0.05$) *5 min:* APAP 4.3 ± 1.1* vs. HDM 6.9 ± 0.9* ($p > 0.05$) *10 min:* APAP 4.3 ± 1.08* vs. HDM 3.9 ± 1.2* ($p > 0.05$) *15 min:* APAP 2.8 ± 1.0* vs. HDM 2.8 ± 1.3* ($p > 0.05$) *25 min:* APAP 2.2 ± 1.3* vs. HDM 1.9 ± 1.4* ($p > 0.05$) *35 min:* APAP 1.9 ± 1.3* vs. HDM 2.0 ± 1.4* ($p > 0.05$)	No significant differences found

(Continued)

Table 3 (continued)

Trials	Parameter	Result	Conclusion
Pickering et al., 2015[20]	10-point NRS at 30 min after medication administration, mean ± SD	IV APAP 3 ± 1.3 vs. B-APAP 2.7 ± 1.2* ($p > 0.05$)	No significant differences found
Azizkhani et al., 2013[21]	10-point VAS at 30 min after medication administration, mean ± SD	APAP 2.4 ± 3.3* vs. morphine 0.75 ± 1.31* ($p < 0.05$)	Patients who received morphine had significant reduction in mean VAS scores
Aksel et al., 2015[22]	100-mm VAS change at designated intervals after medication administration, median (range)	*30 min:* APAP 10 (0–40) mm vs. lidocaine 25 (0–52) mm vs. ice 14.5 (0–40) mm* *60 min:* APAP 20 (0–60) mm vs. lidocaine 40 (10–70) mm vs. ice 23 (0–50) mm* *120 min:* APAP 35 (0–90) mm vs. lidocaine 52 (10–100) mm vs. ice 30 (0–70) mm* *240 min:* APAP 45 (28–62.5) mm vs. lidocaine 60 (60–75) mm vs. ice 45 (33.8–55.3) mm*	Patients who received lidocaine had significant reduction ($p < 0.05$) in mean VAS scores at 30, 60, and 120 min; there was no significant difference ($p > 0.05$) found between ice and APAP at any designated intervals

APAP = acetaminophen; B-APAP = buccal acetaminophen; DK = dexketoprofen; HDM = high-dose morphine; IV = intravenous; NRS = numeric rating scale; VAS = visual analog scale
*95% CI not reported.
†Data reported as median (interquartile range) from original reference.

Table 4
Summary of the Incidence (%) of Adverse Events in Patients Who Received Acetaminophen

Trials	Nausea	Vomiting	Itching	Dizziness	Headache
Masoumi et al., 2014[9]	0	0	0	0	0
Shams Vahdati et al., 2015[10]	0	0	0	0	0
Serinken et al.,2012[11]	2 (5.3)*	2 (5.3)*	0	0	0
Oguzturk et al., 2012[12]	7 (10)	6 (8.6)	0	0	0
Turkcuer et al., 2013[13]	0	0	0	0	0
Grissa et al., 2011[14]	0	1 (2)	0	0	0
Zare et al., 2014[15]	26 (32.9)†	0	12 (15.1)†	0	0
Eken et al., 2014[16]	2 (4.3)*	2 (4.3)*	2 (4.3)	0	0
Bektas et al., 2009[17]	7 (15)*	7 (15)*	0	0	1 (2)
Craig et al., 2012[18]	—‡§	—‡§	—‡§	—‡§	—‡§
Morteza-Bagi et al., 2015[19]	13 (26)*	13 (26)∞	0	0	0
Pickering et al., 2015[20]	0	0	0	0	0
Azizkhani et al., 2013[21]	0	0	0	0†	0
Aksel et al., 2015[22]	0	0	0	0	0

*Nausea and vomiting were reported as one category.
†Statistical significance detected by original investigators between intervention and comparator group.
‡Data on individual adverse events not presented by original reference.
§Statistical significance detected for total aggregate of observed adverse events between intervention and comparator group.

from the central pharmacy if a pharmacist, pharmacy satellite, or automated dispensing cabinets are not readily available in the ED. This may potentially delay patient care. The infusion time for IV APAP is 15 minutes. It is imperative that providers who are responsible for drug administration avoid "bolus" or "wide-open" infusion rates. Patients should be periodically monitored for adverse events such as rash, urticarial, dizziness, headache, nausea, or vomiting.

Applying the Evidence

Emergency physicians currently have numerous options available to them for managing pain in the ED. When parenteral administration of pain medication is preferred or indicated, IV opioids (e.g., morphine) and nonsteroidal anti-inflammatory drugs (e.g., ketorolac) are widely available and safe to use in most ED patients. In the rare instances when such medications are contraindicated or not available, IV APAP should be considered. However, the existing evidence does not support or refute its use as an effective pain control remedy in the ED setting. Nonetheless, this review showed that the incidence of adverse events seems to be limited and additional medical intervention is not required. For future implications, this review highlighted the need for well-designed clinical studies to further confirm the potential applicability and benefits of IV APAP. Future research could also shed light on whether the use of IV APAP can decrease opioid consumption in the ED and whether it can affect care process outcomes such as patient satisfaction, ED length of stay, or healthcare costs.

Table 5
Summary of Rescue Protocols Utilized in Identified Literature

Trials	Rescue Protocol per Original Reference	Rescue Agent and Dose Utilized	Number of Patients (%) Requiring Rescue Analgesia	Mean Dose Utilized
Masoumi et al., 2014[9]	At 30 min after IAD, if severity of pain was equal to or more than 5 on the VAS, rescue analgesia was utilized. If any degree of pain persisted after 60 min, a second dose of rescue analgesia was administered.	IV fentanyl 1 μg/kg	IV APAP 17 (31) vs. IV morphine 30 (55)*	Not reported
Shams Vahdati et al., 2014[10]	No rescue protocol described.	N/A	N/A	N/A
Serinken et al., 2012[11]	Subjects who required rescue analgesia due to inadequate pain relief received IV fentanyl 1 μg/kg IV.	IV fentanyl 1 μg/kg	IV APAP 6 (15.8) vs. IVmorphine 7 (20)†	Not reported
Oguzturk et al., 2012[12]	No rescue protocol described.	N/A	N/A	N/A
Turkcuer et al., 2013[13]	At 30 min after IAD, if the patient required additional treatment, rescue analgesia was provided.	IV fentanyl 1 μg/kg	APAP 33 (33) vs. DK 24 (24)†	Not reported
Grissa et al., 2011[14]	At 60 min after IAD, rescue analgesia was provided if VAS was more than 50% of the initial VAS or if VAS was more than 50/100 at two successive points.	Morphine titration‡	Not reported	Not reported
Zare et al., 2014[15]	At 30 min after IAD, rescue analgesia was provided to patients who experienced insufficient pain relief and requested additional analgesia.	Not reported	Not reported	Not reported
Eken et al., 2014[16]	At 30 min after IAD, rescue analgesia was provided if patients experienced inadequate pain relief.	IV fentanyl 1 μg/kg	IV APAP 8 (17.4) vs.DK 7 (15.2) vs. IV morphine 2 (4.4)†	Not reported
Bektas et al., 2009[17]	At 30 min after IAD, subjects who were judged to have inadequate pain relief at 30 min received rescue analgesia.	IV fentanyl 0.75 μg/kg	IV APAP 21 (46) vs. IV morphine 24 (49) vs. placebo 34 (68)†	Not reported
Craig et al., 2012[18]	If after the initial infusion the patient's pain relief was judged to be inadequate, rescue analgesia was provided.	IV morphine titrated to effect‡	IV APAP 8 (28) vs. IV morphine 8 (29)†	Not reported
Morteza-Bagi et al., 2015[19]	Patients who were unable to tolerate the pain within 35 min after administration of IV drugs were excluded from the study and were treated with common narcotic drugs.	Not reported	IV APAP 18 (36) vs. IV morphine 20 (40)†	Not reported
Pickering et al., 2015[20]	No rescue protocol described.	N/A	N/A	N/A
Azizkhani et al., 2013[21]	No rescue protocol described.	N/A	N/A	N/A
Aksel et al., 2015[22]	Rescue narcotics were used if pain persisted 30 min after presentation to the ED.	Not reported	Not reported	Not reported

DK = dexketoprofen; HDM = high-dose morphine; IAD = initial drug administration; IV = intravenous; LDM = low-dose morphine; N/A = not applicable; VAS = visual analog scale.
*Significant difference detected.
†No significant difference detected.
‡Dose not defined by the original reference.

LIMITATIONS

This review lacked the qualities of a rigorous systematic review or meta-analysis. Non-English language literature was not evaluated. None of the included trials were conducted in the United States. Therefore, the findings might not be generalizable to U.S. EDs. The quality of the review's findings was affected by the quality of the original articles. Due to significant heterogeneity in methodology and outcomes assessment, pooling the data and reporting summary results was not possible.

CONCLUSIONS

This review consisted of 14 randomized clinical trials enrolling a total of 1,472 patients. The data revealed in this review provided conflicting conclusions and limited

evidence to support the use of IV acetaminophen as the primary analgesic for acute pain.

References

1. Baley K, Michalov K, Kossick MA, McDowell M. Intravenous acetaminophen and intravenous ketorolac for management of pediatric surgical pain: a literature review. AANA J 2014;82:53–64.
2. Dela Cruz Ubaldo C, Hall NS, Le B. Postmarketing review of intravenous acetaminophen dosing based on Food and Drug Administration prescribing guidelines. Pharmacotherapy 2014;34:34S–39S.
3. Nishimoto RN. OFIRMEV: an old drug becomes new again. Anesth Prog 2014;61:99–102.
4. Smith HS. Perioperative intravenous acetaminophen and NSAIDS. Pain Med 2011;12:961–81.
5. Yeh YC, Reddy P. Clinical and economic evidence for intravenous acetaminophen. Pharmacotherapy 2012;32:559–79.
6. Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. Pain Pract 2011;11:290–6.
7. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
8. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.
9. Masoumi K, Forouzan A, Asgari Darian A, Feli M, Barzegari H, Khavanin A. Comparison of clinical efficacy of intravenous acetaminophen with intravenous morphine in acute renal colic: a randomized, double-blind, controlled trial. Emerg Med Int 2014;2014:571326.
10. Shams Vahdati S, Morteza Baghi HR, Ghobadi J, Rajaei Ghafouri R, Habibollahi P. Comparison of paracetamol (Apotel®) and morphine in reducing post pure head trauma headache. Anesth Pain Med 2014;21:e14903.
11. Serinken M, Eken C, Turkcuer I, Elicabuk H, Uyanik E, Schultz CH. Intravenous paracetamol versus morphine for renal colic in the emergency department: a randomized double-blind controlled trial. Emerg Med J 2012;29:902–5.
12. Oguzturk J, Ozgur D, Turtay MG, et al. Tramadol or paracetamol do not effect the diagnostic accuracy of acute abdominal pain with significant pain relief - a prospective, randomized, placebo controlled double blind study. Eur Rev Med Pharmacol Sci 2012;16:1983–8.
13. Turkcuer I, Serinken M, Eken C, et al. Intravenous paracetamol versus dexketoprofen in acute migraine attack in the emergency department: a randomized clinical trial. Emerg Med J 2014;31:182–5.
14. Grissa MH, Claessens YE, Bouida W, et al. Paracetamol vs piroxicam to relieve pain in renal colic. Results of a randomized controlled trial. Am J Emerg Med 2011;29:203–6.
15. Zare MA, Ghalyaie AH, Fathi M, Farsi D, Abbasi S, Hafezimoghadam P. Oral oxycodone plus intravenous acetaminophen versus intravenous morphine sulfate in acute bone fracture pain control: a double-blind placebo-controlled randomized clinical trial. Eur J Orthop Surg Traumatol 2014;24:1305–9.
16. Eken C, Serinken M, Elicabuk H, Uyanik E, Erdal M. Intravenous paracetamol versus dexketoprofen versus morphine in acute mechanical low back pain in the emergency department: a randomized double-blind controlled trial. Emerg Med J 2014;31:177–81.
17. Bektas F, Eken C, Karadeniz O, Goksu E, Cubuk M, Cete Y. Intravenous paracetamol or morphine for the treatment of renal colic: a randomized, placebo-controlled trial. Ann Emerg Med 2009;54:568–74.
18. Craig M, Jeavons R, Probert J, Benger J. Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department. Emerg Med J 2012;29:37–9.
19. Morteza-Bagi HR, Amjadi M, Mirzaii-Sousefidi R. The comparison of Apotel plus low dose morphine and full dose of morphine in pain relief in patients with acute renal colic. Addict Health 2015;7:66–73.
20. Pickering G, Moustafa F, Macian N, Schmidt J, Pereira B, Dubray C. A new transmucous-buccal formulation of acetaminophen for acute traumatic pain: a non-inferiority, randomized, double-blind, clinical trial. Pain Physician 2015;18:249–57.
21. Azizkhani R, Pourafzali SM, Baloochestani E, Masoumi B. Comparing the analgesic effect of intravenous acetaminophen and morphine on patients with renal colic pain referring to the emergency department: a randomized controlled trial. J Res Med Sci 2013;18:772–6.
22. Aksel G, Güler S, Doğan NÖ, Çorbacioğlu SK. A randomized trial comparing intravenous paracetamol, topical lidocaine, and ice application for treatment of pain associated with scorpion stings. Hum Exp Toxicol 2015;34:662–7.

Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Search strategy for MEDLINE and EMBASE.