REVIEW ARTICLE

A Literature Review of Randomized Clinical Trials of Intravenous Acetaminophen (Paracetamol) for Acute Postoperative Pain

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■ **Abstract**

Introduction: This study's objective was to systematically review the literature to assess analgesic outcomes of intravenous (IV) acetaminophen for acute postoperative pain in adults.

Methods: We searched Medline and the Cochrane library (January 1, 2000 to January 17, 2010, date of last search) for prospective, randomized, controlled trials (RCTs) of IV acetaminophen vs. either an active comparator or placebo.

Results: Sixteen articles from 9 countries published between 2005 and 2010 met inclusion criteria and had a total of 1,464 patients. Median sample size = 54 patients (range 25 to 165) and median follow-up = 1 day (range 1 hour to 7 days). Four of the 16 articles had 3 arms in the study. One article had 4 arms. As a result, 22 study comparisons were analyzed: IV acetaminophen to an active comparator ($n = 8$ studies) and IV acetaminophen to placebo ($n = 14$ studies). The RCTs were of high methodological quality with Jadad median score = 5. In 7 of 8 active comparator studies (IV parecoxib [$n = 3$ studies], IV metamizol [$n = 4$], oral ibuprofen [$n = 1$]), IV acetaminophen had similar analgesic outcomes as the active comparator. Twelve of the 14 placebo studies found that IV acetaminophen patients had improved analgesia. Ten of those 14 studies reported less opioid consumption, a lower percentage of patients rescuing, or a longer time to first rescue with IV acetaminophen. Formal meta-analysis pooling was not performed because the studies had different primary end points, and the IV acetaminophen dosing regimens varied in dose, and duration and timing.

Conclusion: In aggregate, these data indicate that IV acetaminophen is an effective analgesic across a variety of surgical procedures. ■

Key Words: intravenous acetaminophen, analgesics, non-narcotic, postoperative pain, systematic review

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INTRODUCTION

Further efforts to reduce postoperative pain require introduction of new analgesics into clinical practice. Oral acetaminophen, or paracetamol that is the

international nonproprietary name for acetaminophen, has been well known as a safe and effective analgesic, and antipyretic for more than a century. In some contexts, it is abbreviated as APAP, for N-acetyl-para-aminophenol. However, although intravenous (IV) acetaminophen has been approved in approximately 80 countries, it is not currently available in the U.S.A.

IV acetaminophen (OFIRMEV™, Cadence Pharmaceuticals, Inc., San Diego, CA, U.S.A.) is currently under development for the treatment of acute pain and fever in pediatric and adult populations. The objective of this study was to systematically review the literature to assess analgesic outcomes of IV acetaminophen for acute postoperative pain in adults. Studies of IV propacetamol, the pro-drug to acetaminophen, were not included in this study as it is being phased out of clinical practice in Europe and is not approved for use in the U.S.A.

METHODS

Systematic reviews apply strategies that limit bias to the assembly, appraisal, and synthesis of relevant studies on a specific topic.[1,2] We followed published guidelines[3,4] to search the National Library of Medicine's Medline and the Cochrane library databases (January 1, 2000 to January 17, 2010, date of last search) for prospective, randomized, controlled trials (RCTs) of IV acetaminophen vs. either an active comparator (except for propacetamol) or placebo on adult patients undergoing surgery and receiving general anesthesia, regional anesthesia, sedation, or local anesthesia. We limited our review to English language articles. Data from posters/abstracts, letters, retrospective trials, case reports, and unpublished data were not considered. No minimum sample sizes were required for inclusion of studies.

The following text word search terms were used:

> *Randomized AND "prospective" AND "postoperative analgesia" AND "clinical" AND "trial" AND "pain" AND "patient" AND "surgery" AND "acetaminophen" OR "paracetamol" NOT "spectrometry" NOT "cytokine" NOT "receptor" NOT "children" NOT "damage" NOT "overdose" NOT "temperature" NOT "suicide" NOT "hepatocyte" NOT "bioavailability" NOT "oral paracetamol" NOT "neonatal" NOT "osteoarthritis" NOT "oral propacetamol" NOT "propacetamol."*

After reviewing the titles and abstracts of these 1,562 unique citations, a full-text article was obtained for 74 potentially appropriate studies for further screening, of which 58 were disqualified. The most common reasons for disqualification were: suppository or oral tablets not IV acetaminophen administered ($n = 10$), foreign language (eg, Russian, Turkish) articles ($n = 8$), end point (eg, renal colic, fever, cancer pain) not postoperative pain ($n = 7$), pediatric studies ($n = 6$), study not on surgical patients ($n = 6$), reviews ($n = 5$), IV acetaminophen given in both study groups so comparison not possible ($n = 4$), propacetamol studied instead of IV acetaminophen ($n = 4$), study confounded by another analgesic in protocol ($n = 2$), letter to editor ($n = 1$), no anesthesia required for surgery ($n = 1$), acetaminophen given for IV regional technique ($n = 1$), no active comparator for IV acetaminophen ($n = 1$), comparator is propacetamol ($n = 1$), and no inferential statistics on end point ($n = 1$). The reference lists of the articles were hand searched for any additional articles (none were found).

The two authors independently abstracted data from the studies on to a standardized data extraction form, which included surgical procedure, sample sizes, IV acetaminophen dose and schedule of administration, active comparator drug if not placebo, primary end point, other end points, rescue analgesic used, whether a power analysis was done, length of follow-up, and funding. Differences between the two reviewers were resolved by reexamination of the original article until consensus was obtained. The Jadad Scale was used to assess the quality of the RCTs.[5] It includes five criteria: Is the study randomized? Is the study double blinded? Is there a description of withdrawals (patients that dropped out of study)? Is the randomization adequately described? Is the method for blindness adequately described?

These items elicit "yes" or "no" answers, such that each study was scored from 0 to 5.

RESULTS

Sixteen full-length articles from 9 countries published between 2005 and 2010 met our inclusion criteria and were fully analyzed (Table 1).

Overall, there were 1,464 patients included in the 16 RCTs including a total of 780 patients who received IV acetaminophen. The median sample size including control groups equaled 54 patients (average 68, range 25 to 165), with median follow-up of 1 day (average 1.54 days, range 1 hour to 7 days).

Four of the 16 articles had 3 arms in the study: a placebo group, an IV acetaminophen group, and an active comparator or a second IV acetaminophen group with different timing of dosing. One article had 4 arms,

Table 1. Sixteen Articles Analyzed for this Systematic Review

Article #	Study #	Surgical Procedure	Primary End Point	Comparator Group Sample Size	APAP Sample Size	IV Analgesia Comparator	1-g IV APAP Dose and Frequency	Length of Follow-Up (Days)	Funding	Result Summary
1	1	Cesarean	VAS pain	23	22	oral ibuprofen 400 mg	30 minutes before end of surgery and q 6 hours × 48 hours	2	Bristol Meyers Squibb	IV APAP equivalent to oral ibuprofen
2a	2	Total abdominal hysterectomy	VAS pain	27	28	Placebo	30 minutes prior to induction	1	Not stated	VAS at rest or movement better with IV APAP at all time points ($P < 0.05$)
2b	3	Total abdominal hysterectomy	VAS pain	27	27	Placebo	Prior to skin closure	1	Not stated	Pre induction APAP had lower morphine use (26 mg vs. 36 mg) than postoperative IV APAP with placebo = 63 mg over 24 hours ($P < 0.05$) APAP groups had reduction in nausea/vomiting/pruritus ($P < 0.05$)
3	4	Tonsillectomy	Dose needed for rescue	38	38	Placebo	End of surgical case and 6, 12, and 18 hours postoperative	1	Not stated	100% of placebo patients required rescue analgesia (mean = 82 mg) over 24 hours vs. 29% in IV APAP group (mean = 18 mg), $P < 0.001$
4	5	Lumbar discectomy	VAS pain	20	20	Placebo	At skin closure and then 6, 12, 18, and 24 hours postoperative	1	Not stated	Pain at rest and movement higher in placebo group at 12, 18, and 24 hours compared with the IV APAP group ($P < 0.001$) Morphine use not different
5	6	Major cardiac (bypass or valve replacement)	VAS pain	57	56	Placebo	Intraoperative and q 6 hours × 72 hours	3	Not stated	At 12, 18, and 24 hours after surgery, the IV APAP group had less pain at rest than placebo ($P < 0.005$) Morphine use not different
6a	7	Lumbar discectomy	VAS pain	20	20	Placebo	Once during surgery	0.1	Not stated	Metamizol superior to parecoxib, paracetamol, and placebo for pain relief in PACU with infrequent side effects ($P < 0.05$)
6b	8	Lumbar discectomy	VAS pain	20	20	Parecoxib 40 mg	Once during surgery	0.1	Not stated	
6c	9	Lumbar discectomy	VAS pain	20	20	Metamizol 1 g	Once during surgery	0.1	Not stated	IV APAP PACU pain scores comparable to placebo. No difference in opioid use
7	10	Thyroidectomy	Need for rescue	61	63	Placebo	Before anesthesia induction and q 6 hours × 24 hours	3	Not stated	Pain lower at 1, 3, 6, and 24 hours after surgery with IV APAP than placebo ($P < 0.05$). Fewer IV APAP patients received rescue analgesics compared with placebo (9.5% vs. 66%). ($P = 0.0001$). First analgesic time similar in 2 groups
8	11	3rd molar surgery	VAS pain	33	132	Placebo	Once after surgery if mod-severe pain	0.33	Bristol Meyers Squibb	IV APAP had improved pain relief vs. placebo with 2 gm better than 1 g APAP ($P < 0.001$); time to rescue 5 hours vs. 3.2 hours vs. 1.0 hour for placebo ($P < 0.0001$)
9	12	Breast cancer	Mean pain score difference	20	20	Metamizol 1 g	30 minutes before PACU and 6, 12, 18, and 24 hours postoperative	1.25	Bristol Meyers Squibb	IV APAP clinically equivalent to IV metamizol
10	13	Endoscopic sinus	Need for rescue	38	36	Placebo	End of surgery	0.17	Not stated	71% in placebo group had rescue vs. 25% with IV APAP ($P < 0.01$). Time to first rescue longer with IV APAP: 126 vs. 70 minutes ($P < 0.01$)
11a	14	Retina surgery	VAS pain	13	12	Placebo	30 minutes before surgery end	1.25	Bristol Meyers Squibb	IV APAP produced better pain relief than placebo and was comparable to IV metamizol
11b	15	Retina surgery	VAS pain	13	12	Metamizol 1 g	30 minutes before surgery end	1.25	Bristol Meyers Squibb	

12	16	3rd molar surgery	5-point pain relief scale	50	51	Placebo	Immediately after surgery	0.25	Bristol Meyers Squibb	IV APAP pain relief superior to placebo ($P \leq 0.0003$); IV APAP 7/51 vs. 2/51 did not require rescue ($P = 0.016$) Global satisfaction at 6 hours better with IV APAP ($P = 0.001$)
13a	17	Breast surgery	Opioid reduction	26	27	Placebo	20 minutes before end of surgery	1	Bristol Meyers Squibb	Total morphine use not different. APAP group 42% not requiring rescue vs. 4% for placebo ($P < 0.001$). APAP pain scores similar to placebo and metamizol till 24 hours, except at 1 hour. 1 hour earlier ambulation in APAP group vs. metamizol or placebo ($P < 0.05$)
13b	18	Breast surgery	Opioid reduction	26	27	Metamizol 1 g	20 minutes before end of surgery	1	Bristol Meyers Squibb	
14	19	Hip/knee replacement	5-point pain relief scale	52	49	Placebo	Q 6 hours × 24 hours; first dose on postoperative day 1	1	Bristol Meyers Squibb	Compared with placebo, IV APAP had better pain relief from 15 minutes to 6 hours, longer time to morphine rescue (3 hours vs. 0.8 hours) and less morphine use ($P < 0.05$)
15a	20	Lap cholecystectomy	Opioid reduction	40	40	Parecoxib 40 mg IV and valdecoxib oral 40 mg QD × 7 days	During surgery and once a day × 7 days	7	Pfizer supplied valdecoxib tabs	IV APAP followed by oral APAP was as effective as IV parecoxib/po valdecoxib, but IV APAP reduced rescue use on first day ($P < 0.001$)
15b	21	Lap cholecystectomy	Opioid reduction	40	40	Parecoxib 40 mg IV and valdecoxib oral 40 mg QD × 7 days	During surgery and once a day × 7 days	7	Pfizer supplied valdecoxib tabs	
16	22	Lap cholecystectomy	Opioid reduction	20	20	Placebo	After intubation, before incision	0.04	Not stated	IV APAP pain scores lower than control group ($P < 0.05$). First morphine use and total dose decreased with IV APAP ($P < 0.05$)

Study #

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APAP, acetaminophen; IV, intravenous; PACU, post-anesthesia care unit; QD, once a day; VAS, visual analog scale.

including an active comparator. Therefore, a study is a single comparison and one article may contain more than one study. A total of 22 study comparisons were analyzed: IV acetaminophen to an active comparator ($n = 8$ studies) and IV acetaminophen to placebo ($n = 14$ studies). Rescue analgesic was morphine ($n = 9$ studies), meperidine ($n = 5$), oxycodone ($n = 3$), ibuprofen ($n = 3$), and tilidine ($n = 2$), which is an opioid only available in Europe.

STUDY QUALITY

The RCTs were of generally high methodological quality as measured by the Jadad Scale, with median score = 5 (range 2 to 5). Fifteen of the 22 studies had the highest quality score of 5. All studies except one reported an a priori power analysis.

RCTs WITH AN ACTIVE COMPARATOR

Overall, in 7 of the 8 studies with an active comparator arm (IV parecoxib [$n = 3$ studies], IV metamizol [$n = 4$], oral ibuprofen [$n = 1$]), IV acetaminophen was found to have similar analgesic outcomes as the active comparator. Three of these 8 studies also reported that IV acetaminophen patients had a significant reduction in mean opioid consumption, a lower percentage of patients rescuing (defined as the fraction needing any rescue), or a longer time to first rescue with IV acetaminophen compared with the active comparator patients.

RCTs WITH A PLACEBO CONTROL

Twelve of the 14 placebo-controlled studies found that IV acetaminophen patients had improved analgesia. Ten of the 14 placebo-controlled studies found either a significant reduction in mean opioid consumption or a lower percentage of patients rescuing with IV acetaminophen. One study that had no observed pain difference found that IV acetaminophen patients did need less rescue compared with placebo patients.

STATISTICS

Formal meta-analysis pooling of the efficacy results was not performed because:

1. the IV acetaminophen dosing regimen varied among studies (eg, a single 1-g dose given either before surgery or during surgery, 1 g administered every 6 hours for 24 hours, or 1 g given once a day every day for 7 days).
2. the studies had different primary end points: pain score at rest or with movement (11 studies), opioid reduction (5 studies), need for rescue analgesic (3 studies), pain relief on a 5-point categorical scale (2 studies), or difference between mean pain scores (1 study). Also, duration of follow-up ranged from less than 1 hour to 3 days, with median of 1 day.

Not enough articles were available to separate surgery types into those associated with mild, moderate, and severe pain. Also, it was not possible to assess statistically whether IV acetaminophen affected the incidence of opioid side effects, because the end point was either not reported (eg, postoperative nausea and vomiting [PONV] not reported in $n = 5$ studies and pruritis not reported in $n = 13$ studies), definitions differed (eg, PONV on visual analog scale, nausea only, vomiting only, or nausea and vomiting combined), or end points occurred infrequently when measured such that the trials were not appropriately powered to assess side effect differences.

DISCUSSION

Overall, 12 of 14 placebo-controlled studies found that patients receiving IV acetaminophen had improved analgesia. When compared with IV parecoxib, IV metamizol, or oral ibuprofen, IV acetaminophen was found to have similar analgesic outcomes as the active comparator in 7 of the 8 studies. Parecoxib is a cyclo-oxygenase (COX)-2-specific anti-inflammatory agent not approved in the U.S.A. Metamizol is a nonsteroidal anti-inflammatory drug removed from the U.S. market in the 1970s because of its side effect profile, particularly agranulocytosis.

In aggregate, the data from 1,464 patients (780 received IV acetaminophen) included in the 16 RCTs indicate that IV acetaminophen is an effective analgesic in a variety of inpatient and ambulatory surgical procedures. The RCTs were of generally high methodological quality, consistent with a recent analysis showing that acute pain studies are not published unless they contain specific statements describing the primary end points, power analysis, and statistical treatment of data from withdrawals, dropouts, and protocol violations.[6] However, the heterogeneity in methods and, in particular, the definitions of the primary end points, as well as the variability in IV acetaminophen dosing regimens did not permit a formal meta-analysis with pooling of results. IV acetaminophen use was not associated with increased adverse events compared with placebo within the limited median follow-up duration for the placebo studies analyzed being no longer than 3 days and usually

just 1 day. When prescribing IV acetaminophen for surgical pain, attention must be paid to patients at risk for hepatotoxicity.[7]

The extent to which pain reduction is observed with an analgesic in a RCT may depend on the surgical procedure studied because if the procedure intrinsically is not very painful, then it will be more difficult to demonstrate a pain relief benefit. In the available published RCTS, IV acetaminophen was studied in surgeries associated with varying levels of pain, including Cesareans, total abdominal hysterectomy, tonsillectomy, coronary artery bypass grafting, thyroidectomy, hip or knee replacement, and laparoscopic cholecystectomy procedures. The average postoperative rest pain scores in the placebo arms of these studies ranged from 2.0 to 3.7 out of 10, and for dynamic pain, it ranged from 3 to 5 out of 10.

Two of the 14 placebo-controlled studies found no pain improvement or less opioid use with IV acetaminophen. One study involved patients undergoing lumbar discectomy who were administered a single 1-g dose 45 minutes before the end of surgery and with pain followed for 2 hours in the post-anesthesia care unit (PACU) (reference 6 in Table 1). This study also found no difference between IV acetaminophen and an active comparator IV parecoxib, whereas IV metamizol patients had lower pain scores on arrival to PACU with fewer patients requiring rescue.

The second study involved patients undergoing breast resection, or mastectomy with or without axillary resection, with a 1-g dose 20 minutes before the end of surgery and pain followed for 24 hours (reference 13 in Table 1). Although no difference in total morphine use was detected, 42% of IV acetaminophen patients did not receive any morphine, compared with 4% in placebo group. The authors also found that 2 of the 13 patients with more extensive surgical procedures (eg, axillary dissection) that received IV acetaminophen did not request morphine in the first 24 hours postoperatively, whereas all placebo patients did. IV acetaminophen patients did have significantly less pain only at the 1-hour measurement when compared with placebo, but from 2 to 24 hours postoperatively, average pain ratings were below 2.5 in both groups and did not differ.

Five of the studies analyzed had opioid reduction as the primary end point. However, this end point has several limitations including inter-individual variability in sensitivity to opioids and variability in the level of tolerable pain.[8] For opioid delivered by patient-controlled analgesia, other confounders include an initial learning curve for proper pump use, and patients may worry that they are pushing the button too often, creating a self-imposed maximum. In addition, when morphine consumption is used as an end point, the sample sizes required for 80% power are approximately twice that predicted unless one adjusts for age.[9]

Although the exact site and mechanism of action of acetaminophen is not clearly defined, the central nervous system is the active compartment, and it likely involves central COX inhibition and cannabinoidergic effects, along with indirect analgesic serotoninergic effects.[10] Pain research efforts over the past 5 decades have not yet yielded many other new analgesics for use in the perioperative setting. Explanations for this include: a lack of a mechanism-based classification of pain syndromes that makes it difficult to generate testable hypotheses, an inadequate predictive validity of animal models that translate into pain outcomes in humans, and the Food and Drug Administration's (FDA) requirement of safety and efficacy against placebo, rather than superiority to an active comparator, which contributes to development of "me-too" drugs.[11]

Preemptive dosing to time the peak pharmacodynamic effect of IV acetaminophen to optimize analgesic effectiveness has been studied clinically. For example, in a study of patients undergoing total abdominal hysterectomy, IV acetaminophen 1 g administered 30 minutes prior to surgical incision (prior to induction) resulted in a greater reduction in total morphine consumption compared with administering the same dose at the end of surgery just prior to skin closure (reference 2 in Table 1).

Limitations

Our systematic review had several limitations, including those that relate to the general use of a systematic review and others that pertain specifically to surgical analgesia studies. In only 5 of 16 studies did the acetaminophen group size exceed 40 patients. Small sample sizes studies are unlikely to identify rare but clinically relevant adverse effects. Because the best analgesic approach needs to be individualized to the specific surgical procedure, results from a specific study may not be applicable to other surgery types or when other analgesic interventions such as nerve blocks are added to a multimodal approach.[12] In addition, the studies used different systems for reporting the severity and duration of pruritus, nausea, and vomiting. Publication bias also cannot be excluded. Also, none of the active comparator studies included often used nonsteroidal anti-inflammatory drugs such as ketorolac, ketoprofen, or diclofenac.

An FDA advisory committee recommended in 2009 to reduce the maximum daily dose of oral acetaminophen to less than 4 g because of concerns primarily related to hepatotoxicity from acetaminophen overdose.[13] The FDA expressed concern that the relatively free over-the-counter access to acetaminophen-containing products and the lack of healthcare provider control in the outpatient setting were part of the problem. These access and control issues should not apply to IV acetaminophen in the inpatient hospital setting in which it will be administered.

The faster onset of IV acetaminophen compared with oral or rectal administration should be helpful when treating acute surgical pain particularly when oral intake is not possible. In aggregate, the 16 RCTs selected for analysis indicate that IV acetaminophen is an effective analgesic in a variety of surgical procedures.

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