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Opioid-Sparing Effects of IV Acetaminophen for Patients Undergoing Surgery

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Rapid Review

Key Messages

What Is the Issue?

- Opioids are often used to help manage postoperative pain. However, their consumption can cause side effects, in addition to the risk of developing dependence with long-term use.
- Acetaminophen is an alternative analgesic that may provide opioid-sparing benefits for patients undergoing surgery (e.g., the need for patients to use opioids later), but there is a lack of synthesized evidence to confirm. Acetaminophen is available in different formulations, such as IV, oral, and rectal. However, there is uncertainty around the benefits of using 1 formulation over another perioperatively.

What Did We Do?

- To inform decisions about IV acetaminophen, we sought to identify and summarize literature comparing the effectiveness of IV acetaminophen to alternative analgesics (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs]), alternative formulations (i.e., oral or rectal acetaminophen), or placebo for reducing opioid consumption in patients undergoing surgery.
- A research information specialist conducted a literature search of peer-reviewed and grey literature sources published between January 1, 2019, and January 9, 2024. The search was limited to English-language documents. One reviewer screened articles for inclusion based on predefined criteria. To investigate the true effect of IV acetaminophen, we excluded studies with any intraoperative opioid use.

What Did We Find?

- For adult patients undergoing elective hip surgery, there may be no significant differences in cumulative opioid use between postoperative IV and oral acetaminophen (1 randomized controlled trial).
- For patients undergoing elective cesarian delivery, postoperative IV acetaminophen may result in a decrease in total morphine consumption after surgery compared to placebo (1 randomized controlled trial).
- For adult patients undergoing lumbar disc surgery, there may be no significant differences in total morphine consumption for patients receiving intraoperative IV acetaminophen compared to placebo (1 systematic review with 1 relevant RCT).
- We did not find any studies comparing the opioid-sparing effects of IV acetaminophen to NSAIDs that met our criteria for this review.

Key Messages

What Does It Mean?

- Limited evidence from this review suggests that the opioid-sparing effect of IV acetaminophen may vary across types of surgery when compared to placebo. Additionally, IV acetaminophen may not offer additional opioid-sparing benefits compared to oral administration. However, we require more comprehensive research with rigorous methodological approaches to understand this topic better.
- Relative to opioids, IV acetaminophen has a preferable side effect profile, including a low risk of dependence; therefore, decision-makers may wish to consider using this formulation in the surgical or postsurgical setting.

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Abbreviations

AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
MeSH	Medical Subject Headings
NSAID	nonsteroidal anti-inflammatory drug
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	randomized controlled trial

Research Question

What is the clinical effectiveness of IV acetaminophen for opioid sparing (or reducing opioid consumption) in patients undergoing surgery?

Context and Policy Issues

Postoperative Pain Management

Postoperative pain is 1 of the most common complaints after surgery.[1] Patients can feel postoperative pain immediately after surgery.[1] Mechanical trauma during surgery activates the body's nociceptive pathway responsible for the feeling of pain.[1] A meta-analysis estimated the prevalence of moderate-to-severe postoperative pain 1 to 2 weeks after discharge to be up to 58%.[2] Individuals with poorly managed postoperative pain can experience reduced quality of life, impaired physical function, and reduced sleep.[1] Acute postoperative pain may also transition to chronic pain.[1]

Many clinicians rely on a multimodal peri-operative approach to manage acute pain from surgery.[1,3] It involves non-pharmacological techniques, regional anesthesia, and pharmacotherapy, such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen.[1,3] A multimodal approach aims to minimize opioid use and its potential side effects.[1,3] The short-term side effects of opioids include respiratory depression, excessive sedation, nausea, vomiting, urinary retention, and constipation, in addition to putting individuals at risk for opioid dependence and toxicity.[3,4]

Acetaminophen in Surgical Pain Management

Acetaminophen is 1 of the first-line agents used in multimodal pain management for its analgesic properties and its potential opioid-sparing effect or potential to reduce opioid consumption.[1] Acetaminophen is available in different formulations, such as IV, oral, and rectal.[1] Pharmacokinetic studies suggest that IV administration has improved analgesic effects compared to other formulations due to greater and faster blood-brain penetration and cerebrospinal bioavailability.[5] Users may prefer the oral or rectal formulations because administering IV can cause some pain.[1] However, there is limited evidence regarding the superiority of 1 formulation over another.[1]

Why Is This Issue Important?

The opioid crisis is an ongoing and growing concern globally and across Canada.[6,7] The government of Canada reported over 40,000 apparent opioid-related deaths between January 2016 and June 2023.[8] British Columbia, Alberta, and Ontario had the highest number of opioid-related deaths across jurisdictions in 2023.[8]

Surgery is a common indication for individuals to initiate opioid use.[4] For example, 1 nonrandomized, retrospective study analyzed administrative health claims and found that up to 6.5% of adults living in the US develop new and persistent opioid use after surgery.[9] In Canada, 3% of opioid-naive older adults reported

prolonged opioid use, defined as an ongoing outpatient prescription for more than 90 days after a major elective surgery.[10]

Objective

The purpose of this report is to summarize and critically appraise the evidence regarding the clinical effectiveness of IV acetaminophen for opioid-sparing or reducing opioid consumption in patients undergoing surgery.

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were IV acetaminophen and opioid-sparing or reducing opioid consumption. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons, and any types of clinical trials or observational studies. Conference abstracts were excluded. The search was completed on January 9, 2024 and limited to English-language documents published since January 1, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, 1 reviewer screened titles and abstracts and then retrieved potentially relevant articles to assess for inclusion. Table 1 presents the final selection of full-text articles based on the inclusion criteria.

Table 1: Selection Criteria

Criteria	Description
Population	Patients (all ages) undergoing any type of surgery
Intervention	IV acetaminophen (alone or in combination with other non-opioid analgesics) provided during or postsurgery
Comparators	• Nonsteroidal anti-inflammatory drugs (e.g., celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, naproxen; any dose and any route) • Acetaminophen (any dose; oral or rectal) • Placebo
Outcome	Postoperative opioid consumption
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies

Exclusion Criteria

We excluded articles if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2019. We excluded studies with confirmed intraoperative use of opioids, except when use was limited to surgical induction. We also excluded publications if we were unable to verify the absence of intraoperative opioid use.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included publications using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[11] for the systematic review and the Downs and Black checklist[12] for the randomized studies. We did not calculate summary scores for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

Appendix 1 presents study selection details. We identified 1 systematic review[13] and 2 randomized controlled trials (RCTs)[14,15] that addressed the clinical effectiveness of IV acetaminophen for opioid-sparing (or reducing opioid consumption) in patients undergoing surgery. Appendix 5 provides additional references of potential interest that did not meet the inclusion criteria.

Summary of Study Characteristics

Appendix 2 provides detailed characteristics of the included publications.

We identified 1 systematic review[13] and 2 RCTs[14,15] regarding the clinical effectiveness, specifically the opioid-sparing effects, of IV Acetaminophen compared to relevant comparators.

Systematic Review

The systematic review compared the impact of peri-operative IV acetaminophen to placebo on total morphine consumption within 24 hours after lumbar disc surgery.[13] The systematic review authors searched 5 databases, as well as grey literature, for studies published up to October 2021. They also updated their search before submitting their review for publication. Ultimately, they included 5 RCTS.[13] Of the 5, 1 RCT published in 2014 by Shimia and colleagues,[16] met the inclusion criteria of this report. The 4 ineligible RCTs reported intraoperative use of opioids.[13] As reported by the systematic review, the RCT by Shimia and colleagues[16] compared the opioid-sparing effects of 1g of acetaminophen in 100 mL (i.e., paracetamol) to placebo (i.e., 100 mL of 0.9% sodium chloride). Both study arms received their assigned treatment within the last 20 minutes of surgery.[13,16]

Primary Studies

We identified 2 primary studies relevant to this report.[14,15] Both studies used a single-centre, double-blinded, RCT design.[14,15] The RCTs differed in their study populations, specifically by type of surgery. Namely, 1 RCT

included women undergoing elective Caesarean delivery in Turkey,[15] whereas the other included adults undergoing hip surgery in the US.[14] It is important to note that Aksoy and colleagues[15] referred their study population as women. We acknowledge that gender is a spectrum, and such language is not inclusive to trans and nonbinary persons. When study investigators used the term women in the study, we retained these terms in our reporting.

Both RCTs administered 1 g of IV acetaminophen in 100 mL solution to their acetaminophen treatment arms.[14,15]

The study by Aksoy et al.[15] focused on patients undergoing elective Caesarean delivery compared IV paracetamol to placebo (i.e., subcutaneous 20 mL and IV saline) delivered after surgery. They evaluated total morphine consumption through patient-controlled analgesia after Caesarean delivery without a clear description of the length of follow-up.[15]

The RCT by Westrich et al.[14] focused on adults undergoing hip surgery compared the opioid-sparing effects between IV and oral formulations of acetaminophen. To ensure adequate blinding, study investigators provided oral placebo to participants in the IV treatment arm, whereas they provided an IV placebo to individuals in the oral treatment arm.[14] The study investigators quantified cumulative opioid use measured as opioid consumption in milligrams of oral morphine equivalent during the first 3 days (or 72 hours) after hip surgery.[14]

We did not identify studies comparing the opioid-sparing effects of acetaminophen to NSAIDs.

Summary of Critical Appraisal

Appendix 3 presents additional details regarding the strengths and limitations of included publications.

Systematic Review

The systematic review by Yin et al. (2022)[13] clearly described its objectives and eligibility criteria. The study authors registered the review protocol in PROSPERO and used a comprehensive search strategy without language or publication date restrictions. However, they limited their inclusion criteria to RCTs without justification and did not provide a list of excluded studies, indicating potential selection bias. They used 2 independent reviewers to screen publications for inclusion, extract data, and assess risk of bias (using tools by the Cochrane Collaboration).

The authors deviated from the protocol without justification: the protocol specified that the interventions of interest included both oral and IV acetaminophen, but IV paracetamol was the intervention of interest reported in the published systematic review (i.e., oral paracetamol was not listed in their research question or eligibility criteria). Similarly, the authors did not conduct the planned subset analysis based on age or share the results as outlined in the protocol. These examples may suggest potential reporting bias.

The authors included studies with low and unclear risk of bias, and it appears the authors performed analyses to investigate the impact of risk of bias. They likely used appropriate methods to combine data for meta-analysis. For example, the authors used a random-effects model to analyze data for the relevant

outcome and account for the considerable heterogeneity between included studies. The Begg's test and Egger's test found no risk of publication bias.

The external validity of the review is unclear. The study authors conducted the systematic review in China, and the investigators of 1 relevant RCT conducted their study in Iran. The authors reported no commercial or financial conflicts of interest but did not disclose whether they received any funding to conduct the systematic review.[13]

Primary Studies

The study investigators of the 2 included RCTs detailed their objectives or hypotheses, intervention of interest, and eligibility criteria.[14,15] The study investigators of both RCTs recruited their participants from the same centre over the same period. Study authors of both RCTs sufficiently powered their study based on sample size calculations. The study investigators randomly allocated participants to treatment arms, while ensuring adequate blinding of participants as well as the clinical and research personnel involved in the study. Both RCTs reliably demonstrated compliance across study arms. We did not identify any unplanned or ad-hoc analysis from either RCTs.[14,15]

The RCT by Aksoy et al.[15] clearly reported baseline patient characteristics and did not have any participants lost to follow up. Study investigators did not clearly describe the length of follow up time for total morphine consumption outcome. Hence, it is unclear if investigators followed participants for the same amount of time across and within treatment arms, indicating potential measurement bias. We also found limitations to suggest reporting bias in the results. The study investigators indicated when P values were < 0.05 in comparing 2 treatment arms, but they did not report actual P values. Additionally, the study investigators did not consider the impact of potential confounders on opioid consumption, such as baseline pain before postoperative pain management or previous Caesarean deliveries that can influence pain perception. We are unclear if these confounding factors impacted the study results since investigators did not report their distribution across study participants. The study investigators did not report any details about adverse events. Aksoy et al.[15] declared no conflicts of interest, nor did the authors receive funding.

The RCT by Westrich et al.[14] clearly described the baseline characteristics of participants, including potential confounding factors, such as baseline pain at rest and ambulation, race and ethnicity, and surgical time. However, the study investigators did not define the range of the numerical rating scale used (i.e., the upper limit of the scale) to measure participants' baseline pain scores at rest and with ambulation. They included all the necessary details in the results section (e.g., all P values, simple outcome data, effect estimates). Study investigators did not describe the characteristics of participants lost to follow-up; however, it appears they handled losses to follow-up appropriately by performing a multiple imputation sensitivity analysis, which they described as producing a similar result. They also found that race and surgical time differed between treatment arms, but they did not address its potential impact to the findings. The PRISMA flow diagram reported that study investigators excluded individuals based on physician judgement, but the report did not provide any details about this criterion for exclusion. Hence, selection bias may be of concern in the recruitment of this study. Their hospital's Special Surgery Research and Education Fund and Mallinckrodt Pharmaceutical, which also produced the intervention drug used, funded the study.[14]

Both studies took place in a single centre outside of Canada.[14,15] We could not determine if individuals asked to participate in both RCTs were representative of the population from which they were recruited. Hence, results may not be valid or generalizable to centres or hospitals outside where studies were conducted.

Summary of Findings

Appendix 4 presents the main study findings from the 3 relevant publications.

IV Acetaminophen Versus Oral Acetaminophen

One RCT compared the opioid-sparing effects of postoperative IV acetaminophen to oral acetaminophen in adults who underwent elective hip surgery.[14] The primary and sensitivity analyses found no statistically significant differences between the IV and oral formulations of postoperative acetaminophen on cumulative opioid use between day 0 and 3 after surgery.[14]

IV Acetaminophen Versus Placebo

The relevant RCT[16] from the included systematic review by Yin et al.[13] found intraoperative acetaminophen (paracetamol) resulted in less total morphine consumption 24 hours after surgery compared to placebo. However, this numerical difference was not statistically significant.[13] The RCT conducted by Aksoy and colleagues[15] found a statistically significant decrease in total morphine consumption for the postoperative IV acetaminophen group compared to the placebo. However, the length of follow up is unclear.[15]

Limitations

Quantity and Quality of Evidence

We found limited evidence (1 systematic review and 2 RCTs) about the opioid-sparing effects of IV acetaminophen. We identified studies specific to adults undergoing lumbar disc surgery,[13] elective Caesarean delivery,[15] and elective hip surgery.[14] Hence, the results of these studies may not translate to other types of surgery or pediatric patients undergoing surgery. The quantity of evidence is further limited when considering the evidence by specific comparator. We did not identify studies comparing the opioid-sparing effects of acetaminophen to NSAIDs; therefore, we cannot form conclusions for this comparison. We identified 1 study that compared IV acetaminophen to the oral formulation[14] and 2 studies that compared IV acetaminophen to placebo.[13,15] Hence, we could not draw substantive conclusions about IV acetaminophen's clinical effectiveness, specifically its potential to reduce opioid consumption. The lack of evidence may be linked to the common practice of multimodal analgesia perioperatively, such as opioids plus non-opioid analgesia, including IV acetaminophen.[1,3] However, this report aimed to identify the true effect of IV acetaminophen on postoperative opioid consumption; therefore, we excluded studies that used opioids during surgery for either study arm.

The systematic review comparing IV acetaminophen and placebo identified 5 RCTs of low-to-moderate quality. Of the 5, 1 RCT was eligible for inclusion in this report. The systematic review authors determined that the risk of bias in this relevant RCT was unclear.

External Validity

The systematic review (SR) was conducted by authors from China, and the 1 relevant study within the SR[16] was conducted in a surgical centre in Iran.[13] Similarly, both RCTs were conducted in surgical centres outside of Canada (i.e., Turkey, US).[14,15] Peri-operative pain management and surgical approach may differ from those provided for individuals in Canada for the same indications. Hence, it is unclear whether these findings are applicable to surgical centres operating in Canada.

These limitations warrant taking caution when interpreting the findings of this review.

Conclusions and Implications for Decision- or Policy-Making

This review identified and summarized the evidence available (1 systematic review with 1 relevant RCT,[13] 2 RCTs[14,15]) on the clinical effectiveness of IV acetaminophen for reducing opioid consumption in patients undergoing surgery.

We did not identify any relevant studies addressing the clinical effectiveness of IV acetaminophen compared with NSAIDs for patients undergoing any type of surgery. The limited evidence identified suggests that IV acetaminophen may not offer decreased opioid consumption postoperatively when compared to:

- oral acetaminophen for adult patients undergoing elective hip surgery[14] or
- placebo for adult patients undergoing lumbar disc surgery.[13]

For patients undergoing elective cesarian delivery,[15] postoperative IV acetaminophen may result in a decrease in total morphine consumption after surgery compared to placebo. Though, the study authors did not provide context about the length of follow-up time for this outcome.[15]

Decision-makers may use this report to understand the evidence to inform the use in the surgical or postsurgical setting with the important caveat that these results are from the limited amount of literature identified. The included studies focused on 3 different surgical populations, and we did not find published evidence regarding other surgical populations that met the eligibility criteria for this review. All evidence identified focused on adult populations living outside of Canada, which does not tell us how IV acetaminophen might work for pediatric populations or within Canada's health care system.

To examine the true effect of acetaminophen, we excluded any study with intraoperative opioids. Future researchers may consider expanding the eligibility criteria to include studies with intraoperative or postoperative acetaminophen as an adjunct to intraoperative opioids, which may better reflect real-world application.[17-19] In addition, decision-makers may consider whether IV acetaminophen has an effect on other outcomes relevant to surgical pain management, such as subjective pain scores or opioid-related side effects, which also affects patient experience and quality of life after surgery.

A 2023 CADTH Health Technology Review explored the use of IV acetaminophen in the Emergency Department. This report stated IV acetaminophen may offer similar levels of pain relief and a similar risk of adverse events as oral acetaminophen or IV NSAIDs for adults with moderate-to-severe pain (evidence from

1 SR and 2 RCTs).[20] We identified additional studies that compared IV acetaminophen to alternate analgesics for patients in the intensive care unit, listed in Appendix 5: we excluded these studies because they were not specific to patients undergoing surgery. Together, these studies may provide a broader understanding of the clinical effectiveness of IV acetaminophen for patient populations outside the scope of this report.

In conclusion, limited evidence suggests that the opioid-sparing effect of IV acetaminophen varies depending on the surgery type compared with placebo and IV acetaminophen may not offer additional opioid-sparing benefits compared to oral acetaminophen. We require more comprehensive research with rigorous methodological approaches to understand this topic better.

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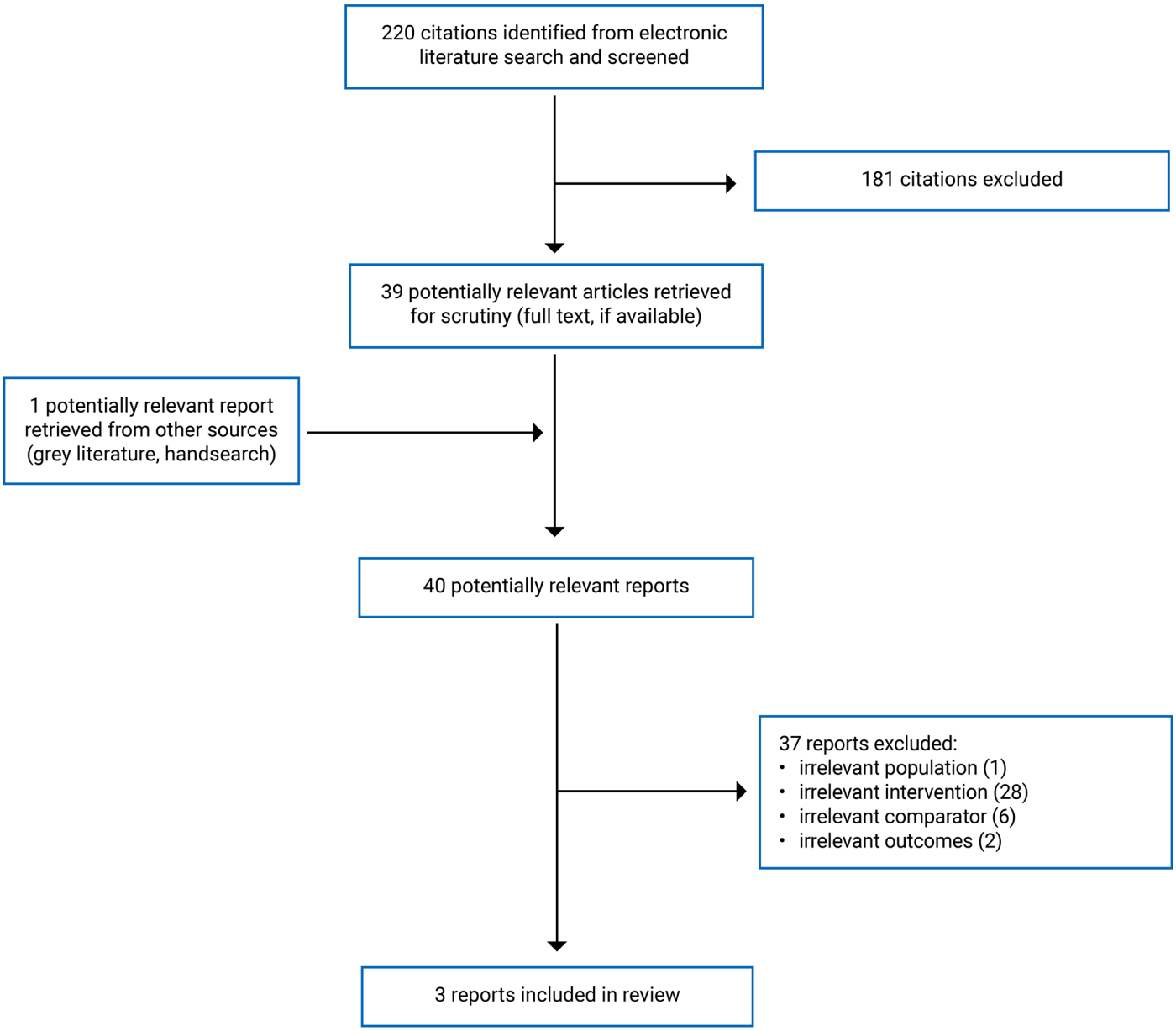
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of the Included Systematic Review

Study citation, country, funding	Study designs and numbers of primary studies included	Population characteristics	Relevant intervention and comparator(s)	Relevant outcome measure, length of follow up
Yin et al. (2022)[13] China **Funding:** NR.	**Systematic review and meta-analysis of RCTs reporting the effectiveness and safety of IV paracetamol for reducing opioid consumption in lumbar disc surgery.** Literature searched until October 2021, with an update before submission for publication. 5 RCTs included in the SR with 1 relevant RCT[a]	Individuals undergoing lumbar disc surgery. N = 271 (n = 52 for relevant RCT).	**Intervention:** Peri-operative administration of IV paracetamol **Comparator**: Placebo	**Outcome:** Total morphine consumption in mg (primary outcome) **Length of follow up:** 24-hours postsurgery

NR = not reported; RCT = randomized controlled trial.

[a]Study by Shimia and colleagues (2014).[16]

Table 3: Characteristics of Included Randomized Controlled Trials

Study citation, country, funding	Study design	Population characteristics	Intervention and comparators	Relevant outcomes, length of follow up, opioids provided
Aksoy et al. (2023)[15] Turkey **Funding:** Study authors did not receive financial support or funding.	Double-blind, 3-arm RCT with 2 arms relevant for this report. Single centre. Participants randomized in a 1:1:1 ratio via a computer-aided random number chart.	Singleton pregnant women[a] who had been scheduled for elective Caesarean delivery. N, randomized = 105 IV paracetamol, n = 35 Placebo, n = 35 Age (years), mean(SD) IV paracetamol = 26.69(6.45) Placebo = 29.51(5.38)	**Intervention:** IV paracetamol 1 g in 100 mL for infusion **Comparator**: Placebo (subcutaneous 20 mL and IV saline) All participants received their intervention after Caesarean delivery and after every 6 hours for 24 hours.	**Outcome:** Total morphine consumption **Length of follow up:** NR **Opioids**: Morphine through PCA
Westrich et al. (2019)[14] US **Funding source:** Mallinckrodt Pharmaceuticals and the Hospital for Special Surgery,	Double-blind, 2-arm RCT, Single centre. Participants randomized in a 1:1 ratio block of size 6 and 8 via a computer generated	Individuals aged 18 to 90 years old scheduled for an elective primary unilateral total hip arthroplasty using a posterior approach. N, randomized = 154 IV acetaminophen, n = 77 Oral acetaminophen, n = 77 Age (years), median (SD)	**Intervention:** 15 minute infusion of 1g of IV acetaminophen (Ofirmev) in a 100 mL solution with oral placebo (2 capsules) **Comparator**: Oral acetaminophen (1 g in 2 capsules) with IV	**Outcome and length of follow up:** Cumulative opioid usage between postoperative day 0 and day 3 (measured as opioid consumption in mg of oral morphine equivalent) **Opioids**: 50 mg of tramadol for mild pan,

Study citation, country, funding	Study design	Population characteristics	Intervention and comparators	Relevant outcomes, length of follow up, opioids provided
Research and Education Fund.	randomization schedule.	IV acetaminophen = 63(10) Oral acetaminophen = 65(10) Sex (male %) IV acetaminophen = 36.4% Oral acetaminophen = 45.5% Pain at rest, numerical rating scale, mean (SD) IV acetaminophen = 3.9(2.6) Oral acetaminophen = 4.2(2.6) Pain at ambulation, numerical rating scale, mean (SD) IV acetaminophen = 6.5(2.5) Oral acetaminophen = 6.7(2.4)	placebo (100 mL saline) All study arms received their assignment 30 minutes after admission to postanesthesia care unit.	100 mg of tramadol for moderate pain, 5 mg of oxycodone for severe pain, 10/15 mg of oxycodone as needed.

NR = not reported; PCA = patient-controlled analgesia; RCT = randomized controlled trial; SD = standard deviation.

[a]The study described their study population as women and did not differentiate between sex and gender. We acknowledge that gender is a spectrum, and such language is not inclusive of trans and nonbinary persons. When the term "women" was used in the study we retained the term in our reporting on these studies.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitations of Systematic Review Using AMSTAR 2[11]

Strengths	Limitations
Yin et al. (2022)[13]	
The population, intervention, comparators, and outcomes of interest clearly stated. The authors registered the review protocol in PROSPERO. The authors searched in 5 databases and conducted an updated search before submission for publication. The authors searched the grey literature (i.e., reports, conferences, workshop proceedings, ongoing trials, clinical trial registries, Google Scholar), and through reference lists of all included studies. The authors did not apply a language or publication date restrictions on their search. Two independent reviewers conducted study selection, data extraction, and quality assessments. The authors described the interventions, comparators, outcomes, and time frame for follow up in detail for all included studies. The reviewers used appropriate tools to assess the risk of bias of included studies. The reviewers reported how they explored whether there were conflicts of interest in included studies. They identified none. The authors appear to have conducted the meta-analysis using appropriate methods to combine data, and perform subset analysis (i.e., timing of administration and dose) to investigate heterogeneity. The authors included studies with low and unclear risk of bias, and it appears the authors performed analyses to investigate the impact of risk of bias. The authors reported considerable heterogeneity between included studies for the relevant outcome; thus, the authors used a random-effects model to analyze the data. The reviewers conducted the Begg's test and Egger's test to investigate publication bias. The authors reported no commercial or financial conflicts of interest for conducting the systematic review.	The authors deviated from the methods published protocol in PROSPERO without justification. In the protocol, the intervention of interest included oral paracetamol. Additionally, the protocol described subset analysis of results based on age, which the study authors did not report in the review. The authors limited their review to include RCTs (i.e., all other study designs excluded), but did not provide an explanation for this decision. The authors did not provide a list of excluded studies. The authors reported the quality of evidence for the outcomes, but they did not discuss in detail the potential impact of the quality of the evidence on the results. The authors did not disclose whether they received any funding to conduct the systematic review.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; PROSPERO = International Prospective Register of Systematic Review; RCT = randomized controlled trial.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[12]

Strengths	Limitations
Aksoy et al. (2023)[15]	
Reporting Study investigators clearly reported study objectives, eligibility criteria, and interventions of interest. Participant characteristics clearly reported (e.g., study authors	**Reporting** The report does not clearly describe the outcome relevant to this report, total morphine consumption, specifically the length of follow-up time.

Strengths	Limitations
described the participants by age, BMI, gravidity, parity, and gestational age). Study investigators reported no patients were lost to follow up. **External Validity** Not applicable. **Internal Validity** Study investigators reported that patients, anesthetist, surgeon, and other staff blinded to the contents of the medications. The compliance with interventions is reliable across treatment arms. The study investigators recruited participants from the same centre and over the same period. The study investigators randomized participants to ensure random allocation. **Power** The study investigators recruited the required number of participants for each treatment arm based on the sample size calculations. **Conflict of Interest and Funding** The authors declared no conflicts of interests. The authors did not receive financial support or funding.	Adverse events not reported. For results relevant to our report, study investigators reported the P values < 0.05 when there was a statistically significant difference between the 2 arms of interest; thus, actual P values not reported. Potential confounders not reported. For example, study investigators did not compare the distribution of other potential confounding factors, such as previous Caesarean deliveries and baseline pain. **External Validity** Unable to determine if the individuals asked to participate in the study were representative of the entire population from which they are recruited. The study investigators conducted the trial from a single centre in Turkey. It is unclear if the setting is representative of that in the population. **Internal Validity** Unable to determine whether patients had different lengths of follow up for the outcome cumulative opioid use; therefore, it is unclear if analyses were needed to adjust for different lengths of follow up. Unclear if the main outcome measures were accurate. **Power** Not applicable **Conflict of Interest and Funding** Not applicable
Westrich et al. (2019)[14]	
Reporting The study investigators clearly described their study hypotheses, main outcomes, eligibility criteria, and intervention of interest. Potential confounders reported (i.e., study investigators described treatment groups by age, sex, BMI, race, ethnicity, baseline pain at rest and ambulation, and surgical time). Study investigators clearly reported results (i.e., included simple outcome data, effect estimates, estimates of random variability, confidence intervals, and P values for the main outcomes). Adverse events disclosed: study investigators reported no adverse events related to treatment. **External Validity** Not applicable **Internal Validity** No data dredging (i.e., unreported/posthoc analyses) apparent. All participants recruited from the same population and over the same period. Study investigators used appropriate statistical tests to analyze	**Reporting** The study investigators did not describe the characteristics of participants lost to follow up. The study investigators did not adequately describe their numerical rating scale to measure baseline pain at rest and ambulation. **External Validity** The study was conducted at a high-volume orthopedic hospital with specialized surgeons and anesthesiologists and an experienced acute pain service. It is unclear if the setting or the treatment is representative of that in the population. Unable to determine if the individuals asked to participate in the study were representative of the entire population from which they are recruited. The PRISMA flow diagram shows that a proportion of individuals screened were excluded based on a physician's judgement (i.e., "Not appropriate as per MD"). **Internal Validity** The study investigators noted differences in race and surgical time between treatment groups but did not address its impact. **Power**

Strengths	Limitations
results. The compliance with interventions is reliable across treatment arms. The study investigators followed all participants for the same amount of time across main outcomes. The study investigators randomized participants to ensure random allocation. The study investigators reported that patients, pharmacists, physicians, and research staff blinded adequately throughout the study. The results of the Bang's blinding index indicated that intervention assignment was adequately concealed from participants. **Power** The study investigators recruited the required number of participants per treatment arm based on sample size calculations. **Conflict of Interest and Funding** Not applicable	Not applicable **Conflict of Interest and Funding** One or more study investigators declared a conflict of interest, such as financial payment, indirect or direct institutional support, or association with a biomedical entity. A private pharmaceutical company funded the study, which was the same company as the intervention drug used.

BMI = body mass index; MD = Doctor of Medicine; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 6: Summary of Findings by Comparison — IV Acetaminophen Versus Oral Acetaminophen

Citation	Study design	Outcome	Outcome result		Effect estimate (98.3% CI)	P value
			IV acetaminophen	Oral acetaminophen		
Westrich et al. (2019)[14]	RCT	Cumulative opioid use measured as opioid consumption in mg of oral morphine equivalent (available case analysis, i.e., primary analysis), mean (SD)	121(71)	108(63)	MD = 13 (−16 to 42)	0.831
		Cumulative opioid use measured as opioid consumption in mg of oral morphine equivalent (multiple imputation analysis, i.e., sensitivity analysis), mean (SD)	—	—	MD = 12 (−20 to 44)	0.982

CI = confidence intervals; MD = mean difference; NA = not applicable; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug.

Table 7: Summary of Findings by Comparison — IV Acetaminophen Versus Placebo

Citation	Study design	Outcome	Outcome results		Effect estimate (95% CI)	P value
			IV acetaminophen	Placebo		
Yin et al. (2022)[13a]	SR with meta-analysis (1 relevant RCT[a])	Total morphine consumption within 24-hours postsurgery in mg, mean (SD)	5.53 (4.49)	7.85 (4.17)	MD = −2.32 (−4.69 to 0.05)	—
Aksoy et al. (2023)[15]	RCT	Total morphine consumption, mean (SD)	10.64 (3.53)	16.04 (3.99)	—	< 0.05

CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; SD = standard deviation; SR = systematic review.

[a]Findings reported from results of the 1 relevant RCT by Shimia and colleagues (2014).[16]

Appendix 5: References of Potential Interest

Previous CADTH Reports

Brett K, Severn M. CADTH Health technology review: IV acetaminophen for acute pain in emergency departments. *Can J Health Technol*. 2023;3(10). https://www.canjhealthtechnol.ca/index.php/cjht/article/view/RC1508/RC1508 PubMed

Unclear Intervention and/or Comparator – Potential Intraoperative Opioid Use

Fillingham YA, Hannon CP, Erens GA, et al. The efficacy and safety of acetaminophen in total joint arthroplasty: Systematic review and direct meta-analysis. *J Arthroplasty*. 2020;35(10):2715-2729. PubMed

Hilleman DE, Malesker MA, Aurit SJ, Morrow L. Evidence for the efficacy of an opioid-sparing effect of intravenous acetaminophen in the surgery patient: A systematic review. *Pain Med*. 2020;21(12):3301-3313. PubMed

Alternative Population – Intensive Care Unit

Archer VA, Samiee-Zafarghandy S, Farrokyhar F, Briatico D, Braga LH, Walton JM. Intravenous acetaminophen for postoperative pain in the neonatal intensive care unit: A protocol for a pilot randomized controlled trial (IVA POP). *PLoS One*. 2023;18(11):e0294519. PubMed

Higashitsuji A, Tomioka Y, Tanabe T, Ami N, Tei I. Intravenous acetaminophen reduces the length of intubation and rescue analgesics in intensive care unit patients after cardiovascular surgery in Japan: A retrospective analysis. *J Opioid Manag*. 2023;19(4):291-299. PubMed

Torres CM, Geneslaw AS, Svoboda L, Smerling AJ, Schlosser Metitiri KR. Effect of standing intravenous acetaminophen on postoperative opioid exposure in a pediatric cardiac intensive care unit. *J Pediatr*. 2023;255:236-239.e232. PubMed

Taylor BM, Chakraborty SR, Harthan AA, Tripathi S, Wang H, Swayampakula AK. Effect of IV acetaminophen usage on opioid requirements, outcomes and costs of care for postoperative children in a pediatric intensive care unit. *J Pediatr Pharmacol Ther.* 2020;25(6):514-520. PubMed

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